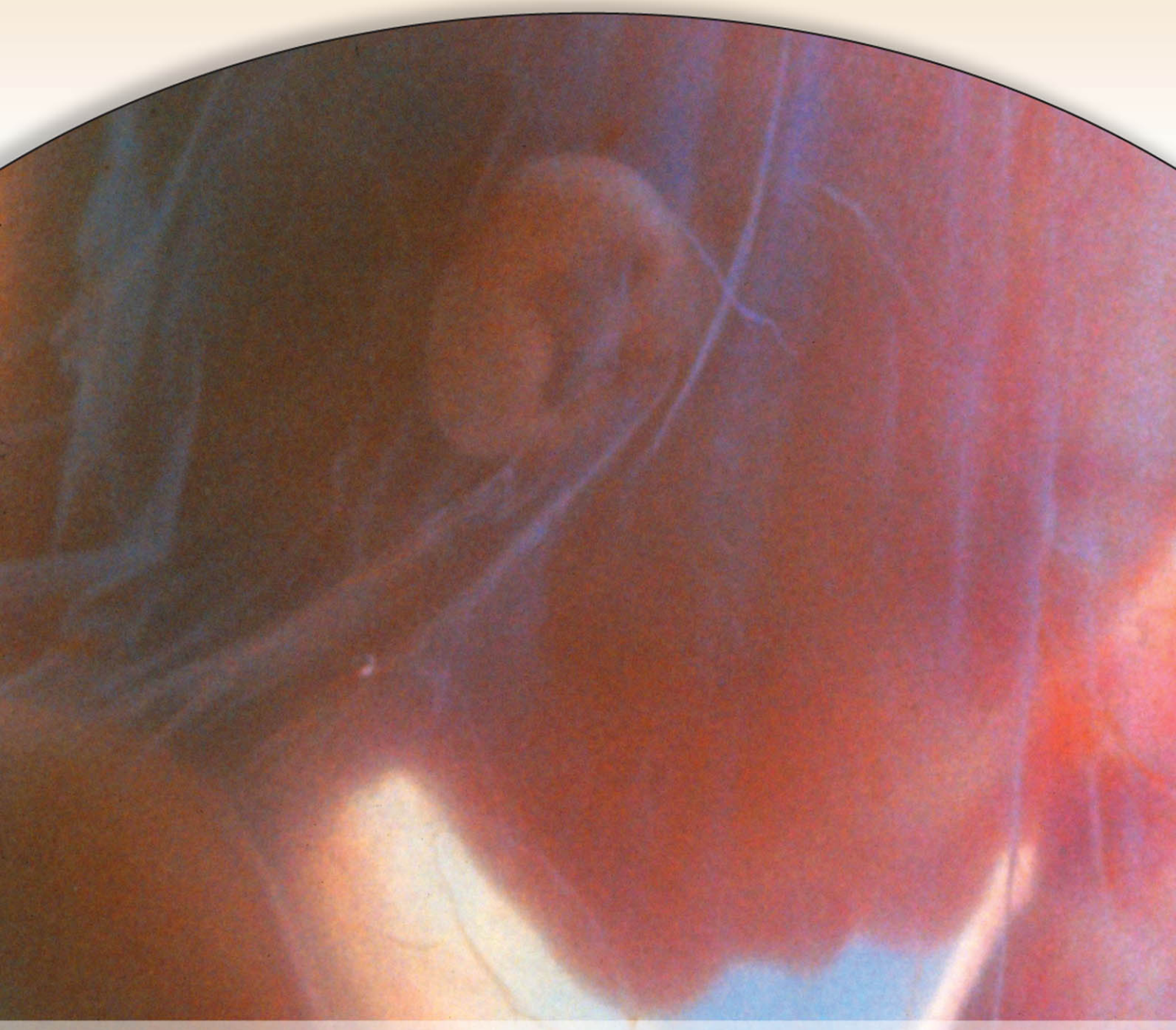
second edition

FETOLOGY

Diagnosis and Management of the Fetal Patient



Diana W. Bianchi / Timothy M. Crombleholme / Mary E. D'Alton / Fergal D. Malone

Fetology

Diagnosis and Management of the Fetal Patient

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Fetology

Diagnosis and Management of the Fetal Patient

Second Edition

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Summary: “This book was written to provide a multidisciplinary approach to the full implications of a fetal sonographic or chromosomal diagnosis–from prenatal management to long-term outcome–for an affected child. This book’s intended audience consists of practioners who care for fetuses or neonates with sonographically detected anomalies, and who seek prenatal and postnatal information regarding specific conditions”–Provided by publisher.

Dedicated to

John, Josh, and Elliott (Diana)

Peg, Caitlin, Hayley, and Kye (Tim)

Richard, Joseph, Conor, and Emer (Mary)

Marie, Ciara, Emma, Sarah, and Rachel (Fergal)

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Contents

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Preface to the First Edition

We wrote this book to provide a multidisciplinary approach to the full implications of a fetal sonographic or chromosomal diagnosis—from prenatal management to long-term outcome—for an affected child. We believed that what we, our colleagues, our trainees, and our patients needed was a compilation of available information to answer many of the questions that parents ask when a fetal anomaly is diagnosed.

In our experience, pregnant patients frequently receive conflicting information about the prognosis for the infant, depending on the sometimes narrow perspective of a subspecialist. The diagnosis and management of a fetus with an anomaly requires that an expertise be developed outside the traditional boundaries of the existing specialties of obstetrics, pediatrics, and surgery. These traditionally defined disciplines do not serve us well in addressing problems that exist outside our usual practice. By convention, pediatric care begins with the birth of an infant; however, we believe that pediatricians and pediatric surgeons can significantly contribute to the care of the fetus, their future patient. Similarly, obstetricians who do not generally provide medical care to the infant after delivery might enhance their antenatal care by being better informed about pediatric prognoses and outcomes. Pediatric surgeons who operate on fetuses or infants with congenital anomalies have more in common with perinatologists and neonatologists than with their other surgical colleagues. The problem-oriented multidisciplinary team approach has analogies in other specialties, such as cardiology, where the cardiologist, cardiac surgeon, and radiologist all focus on heart disease.

This book's intended audience consists of practitioners who care for fetuses or neonates with sonographically detected anomalies, and who seek prenatal and postnatal information regarding specific conditions. Included in this audience are general obstetricians, perinatologists, genetic counselors, neonatologists, pediatricians, pediatric subspecialists, and pediatric surgeons. We have also included information on some of the common chromosomal aneuploidies that may be detected when karyotyping is performed for a sonographic abnormality. Although the book is directed toward a medical audience, prospective parents were never far from our minds while we were writing. Most of the chapters were written by imagining that the prospective parents were in our offices seeking advice regarding the abnormal fetal finding. We have attempted to provide a balanced, scholarly, nondirective approach to management, which may differ significantly from what prospective parents may find on the Internet. Each chapter has a consistent format to facilitate locating specific kinds of information.

We have personally treated patients with most if not all of the conditions described within the following chapters as part of our collaborative work that began in the Fetal Diagnosis and Treatment Program at New England Medical Center and Tufts University School of Medicine in Boston in 1993. While the three of us brought to each case our individual approaches based on our different subspecialty training, we collectively recognized the need to present a coordinated and comprehensive plan to parents faced with a diagnosis of a fetal abnormality. Dr. Bianchi is a pediatrician, neonatologist, and medical geneticist who is interested in the correlation of pediatric outcome with prenatal sonographic findings; Dr. Crombleholme is a pediatric surgeon who has also trained in fetal surgical intervention. He writes extensively on the possibilities for surgical treatment of these diverse conditions and provides important information on long-term outcome. Dr. D'Alton is an obstetrician and perinatologist with expertise in antenatal sonographic diagnosis of anomalies.

Because our approach was unique, we felt that a multiauthored textbook would not specifically address the multiplicity of expertise necessary to care for the fetal patient. In establishing our Fetal Treatment Program we worked collaboratively to bring our individual training, experience, and knowledge base to each fetal patient on whom we consulted and whom we treated. We wanted this book to be more than a mere collation of facts; we wanted a cohesive approach to diagnosis, management, and in some cases, treatment of the fetal patient. We felt that in order for this book to reflect this approach it would be best for the three of us to have input into each chapter.

Finally, we must share with the reader that the most difficult aspect of writing this book was selecting a title. Although

we, as the authors, were in complete agreement regarding the body of knowledge and clinical information we wanted to convey, it did not fit simply or neatly into a single existing medical specialty. While it is the general obstetrician or perinatologist who first suspects (and diagnoses) an abnormality in the fetus, it is the pediatric medical or surgical specialist who will ultimately treat the newborn infant. In many medical settings, however, prospective parents of a fetus with an abnormality never meet with any pediatric specialists, let alone members of a fetal treatment team. After much debate, we selected the title, *Fetology: Diagnosis & Management of the Fetal Patient* to indicate that the focus of this book is on the diagnosis and the overall management of the fetal patient. No one medical specialty is devoted to the care of the fetus. By definition, therefore, *fetology* requires a multidisciplinary team approach. We wrote this book as a summary of available information for ourselves, our colleagues, our trainees, and our patients to answer many of the questions that are asked when a fetal anomaly is diagnosed.

Fetology, however, is an evolving field. Many of the subtle prenatal sonographic findings in this book have only recently been described. We therefore await future clinical research to provide further information on the long-term clinical significance of many of the fetal findings reviewed here. We hope that this reference serves to increase recognition of the unique aspects of caring for the fetal patient. We hope that by viewing conditions from both the prenatal and postnatal perspective, we will foster collaboration between the existing medical specialties, and ultimately benefit the care of fetal patients and their families.

Diana W. Bianchi, MD
Timothy M. Crombleholme, MD
Mary E. D'Alton, MD

Preface to the Second Edition

We are delighted to introduce this updated edition of our original textbook, which was intended to provide a multidisciplinary approach to the full implications of a fetal sonographic or chromosomal diagnosis—from prenatal management to long-term outcome—for an affected child.

Over the last decade since the publication of the first edition we have received considerable feedback from both patients and our colleagues regarding the strengths and areas needing improvement in the original text. Efficient access to a compilation of available information to answer many of the questions that parents ask when a fetal anomaly is diagnosed has been warmly embraced. Our colleagues have found the layout of the text to be helpful to extract the relevant pieces of information that they seek during a patient consultation. Frequently this may involve a rapid review of the sonographic features of a particular abnormality, while at other times it may require a synopsis of current surgical approaches to the repair of a complex malformation. Since 2000, the field of obstetric imaging has advanced rapidly, making many of the images in our original text dated and not reflective of contemporary imaging capabilities. This has required a complete review of all supplied images and we are grateful to our colleagues and patients for their assistance in providing the significantly improved illustrations in this latest edition. Another novel feature of this edition is the availability of succinct Key Points at the beginning of each chapter. This allows for rapid review of a particular condition when perhaps only a few moments are available for review between patient visits during a busy clinic.

As with the first edition of *Fetology*, we remain convinced that the diagnosis and management of a fetus with an anomaly requires that an expertise be developed outside the traditional boundaries of the existing specialties of obstetrics, pediatrics, and surgery. The problem-oriented multidisciplinary team approach, as illustrated by *Fetology*, has analogies in other specialties, such as cardiology, where the cardiologist, cardiac surgeon, and radiologist all focus on heart disease.

This book's intended audience remains practitioners who care for fetuses or neonates with sonographically detected anomalies, and who seek prenatal and postnatal information regarding specific conditions. Included in this audience are general obstetricians, maternal-fetal medicine subspecialists, genetic counselors, neonatologists, pediatricians, pediatric subspecialists, and pediatric surgeons. As well as including information on some of the common chromosomal aneuploidies that may be detected when karyotyping is performed for a sonographic abnormality, we have also included new chapters summarizing contemporary approaches to first and second trimester screening for aneuploidy. First trimester screening, in particular, has undergone marked changes in standards and potential over the last decade. This includes sonographic techniques, serum markers, and novel ways of combining these approaches.

Although the book is directed toward a medical audience, prospective parents remained in our thoughts while we were updating the text. Most of the chapters were written by imagining that the prospective parents were in our offices seeking advice regarding the abnormal fetal finding. We have attempted to provide a balanced, scholarly, nondirective approach to management, which may differ significantly from what prospective parents may find on the Internet. Each chapter has a consistent format to facilitate locating specific kinds of information.

Fetology began as a collaborative work at the Fetal Diagnosis and Treatment Program at New England Medical Center and Tufts University School of Medicine in Boston in 1993. By 2000, the original Boston team had dispersed to various academic medical centers throughout the United States, and today the authors represent a diverse international team of fetal medicine experts, spanning maternal-fetal medicine, neonatology, genetics and pediatric surgery. While the four of us brought to each case our individual approaches based on our different subspecialty training, we collectively recognized the need to present a coordinated and comprehensive plan to parents faced with a diagnosis of a fetal abnormality. Dr. Bianchi is a pediatrician, neonatologist, and medical geneticist who is interested in the correlation of pediatric outcome with prenatal sonographic findings; Dr. Crombleholme is a pediatric surgeon who has also trained in fetal surgical intervention. He

writes extensively on the possibilities for surgical treatment of these diverse conditions and provides important information on long-term outcome. Dr. D'Alton is an obstetrician and maternal-fetal medicine specialist with expertise in antenatal sonographic diagnosis of anomalies. Dr. Malone is also a maternal-fetal medicine specialist who has spearheaded the development of new approaches to aneuploidy screening, as well as directing an international multidisciplinary fetal therapy program.

We have remained loyal to our original premise that a multi-authored textbook would not specifically address the multiplicity of expertise necessary to care for the fetal patient. Each section of our Fetal Treatment Program has been developed collaboratively by the four of us to bring our individual training, experience, and knowledge base from each fetal patient whom we have consulted on and treated. We hope that our book remains more than a mere collation of facts, but instead is a cohesive approach to diagnosis, management, and treatment of the fetal patient. Each of the four of us therefore have had input into each chapter.

As with the first edition of *Fetology*, we hope that this reference serves to increase recognition of the unique aspects of caring for the fetal patient. We hope that by viewing conditions from both the prenatal and postnatal perspective, we will foster collaboration between the existing medical specialties, and ultimately benefit the care of fetal patients and their families.

Diana W. Bianchi, MD
Timothy M. Crombleholme, MD
Mary E. D'Alton, MD
Fergal D. Malone, MD

Acknowledgments (First Edition)

Diana W. Bianchi, MD: In addition to the faculty and fellows in maternal–fetal medicine and neonatology listed by Dr. D'Alton, I would like to acknowledge the collaboration, support, and expertise of the medical genetics faculty at Tufts University, which during the past six years has included Janet Cowan, Patricia Wheeler, Rosemarie Smith, Janey Wiggs, and Mira Irons. I am enormously grateful to the genetic counselors listed by Dr. D'Alton, who not only provided outstanding and compassionate care when a fetal anomaly was diagnosed, but alerted us to the existence of cases that would present useful teaching examples for this book. I would also like to acknowledge the perinatal genetics fellows who worked in my research laboratory during this time period, who read chapter drafts, and provided me with helpful feedback. They include Antonio Farina, JiYi Wang, Akihiko Sekizawa, Osamu Samura, Barbara Pertl, Satoshi Sohda, Kirby Johnson, Paula Farrell, Nancy Weinschenk, and Bharath Srivatsa.

I would also like to thank current or former Tufts faculty members who critically read sections of the manuscript, including Dr. Joseph Semple of Pathology, who supplied many photographs; Dr. Michael Lewis of Plastic Surgery; Dr. Michael Goldberg of Orthopedic Surgery; Drs. Gerald Marx, Ziyad Hijazi, and Jonathan Rhodes of Pediatric Cardiology; Dr. George Klauber of Urology; and Dr. N. Paul Rosman of Pediatric Neurology. In addition, I would like to thank Dr. Deborah Levine for her expertise in fetal MRI, Dr. Marjorie Treadwell for supplying additional illustrations, and Drs. Wolfgang Holzgreve and Roberto Romero for illustrations and helpful discussions. I would also like to thank my secretarial staff for their help and support in the writing and researching of the manuscript, including Lynne Aufiero, Maria McCarthy, and Glenn Christie. I would also like to thank Jane Licht, our orignal editor at Appleton & Lange, who guided me through the process of putting together a large textbook. I would like to give a special acknowledgment to Dr. Mary Ellen Avery, who not only provided moral support but helpful information on the origin of the term *neonatology,* as background for selecting the title of this book. Last but by no means least, I would like to thank Dr. Alan Guttmacher, who originally suggested the title for this book: *Fetology.* Although we as authors initially did not *bond* to this term, in the end, we decided that it was the most appropriate way to describe the body of knowledge in what is arguably a new field of medicine.

Timothy M. Crombleholme, MD: During the writing of this book, our understanding and approach to diagnosis and management of many fetal conditions has continued to evolve. Progress has only been possible through the supportive interactions of numerous professional colleagues in many disciplines who bring their unique expertise to bear on the fetus. I would like to acknowledge my research fellows and colleagues who have contributed to the development of the field of fetal surgery and fetology: at Tufts University, Sarah Garmel, Frank Robertson, Kevin Moriarty, and E. Kerry Gallivan, and at The Children's Hospital of Philadelphia, Darryl Cass, Karl Sylvester, Kenneth Liechty, Harold Lovvorn, Heung Bae Kim, Aimen Shaaban, Colette Pameijer, Danielle Walsh, Yoshihiro Kitano, Adina Knight, Ross Milner, Natalie Rintoul, Holly Hedrick, and Oluyinka Olutoye.

I wish to acknowledge the loyal support and guidance of Lori Howell, who has been instrumental in the development of fetal treatment programs, both at The University of California, San Francisco, and at The Children's Hospital of Philadelphia. The support and encouragement during the writing of this book of N. Scott Adzick and Alan Flake, my partners in fetal surgery at The Children's Hospital of Philadelphia, is gratefully acknowledged as is Michael R. Harrison, who as the father of fetal surgery was practicing fetology before it had a name. I would particularly like to thank my colleagues in other disciplines who have taught me so much and contributed to our understanding of the fetal patient, including Mark Johnson, Beverly Coleman, Stephen Horii, Jill Langer, Harvey Nisenbaum, and Mary King for their sonographic skill and enthusiastic support of fetal surgery; Anne Hubbard and Larissa Bilaniuk for their pioneering work on fetal MRI; Zhi-Yun Tien, Jack Rychik, Meryl Cohen, Marie Gleason, and Bill Mahle for their excellent echocardiographic support; and Elaine Zackai and Stefanie Kasperski for genetic evaluation and counseling at The Children's Hospital of Philadelphia.

In the operating room at the Hospital of the University of Pennsylvania and The Children's Hospital of Philadelphia, I would like to acknowledge the contributions of Ted Cheek, Bob Gaiser, Dean Kurth, David Cohen, and Jeff Galinkin, who have done so much to advance the anesthetic management of fetal surgical patients. Also, acknowledged in the operating room are Joy Kerr, Marianne Daskalakis, and Helen Lewis and, most particularly, in the postnatal care and evaluation of our fetal patients, Kelli Burns and Sue Von Nessen. Lastly, for their ability to decipher my hieroglyphic writing and secretarial support, I give special thanks to Dee Caton and Noreen Mulholland.

Mary E. D'Alton, MD: The years that I spent working with Dr. Diana Bianchi and Dr. Tim Crombleholme were some of the most rewarding years of my academic life. During this time, we worked collectively to create a seamless, multidisciplinary approach to prenatal diagnosis and therapy for our patients. Our collaboration is reflected in this manuscript. I wish to acknowledge the support of my former fellows and residents. All of these individuals in their unique way helped shape the Division of Maternal Fetal Medicine, initially at Tufts University School of Medicine, and now at Columbia University College of Physicians and Surgeons. Some former fellows stayed on as faculty, initially at Tufts, and more recently at New York Presbyterian Hospital, and others are practicing in many other areas of the world. They include Drs. Achilles M. Athanassiou, Emily R. Baker, Juan Castaner, Sabrina D. Craigo, Annette Perez Delboy, Karen Davidson, Patricia Devine, Marla Eglowstein, Sara Garmel, Martin Gillieson, Laura Goetzel, Gary Kaufman, Fergal D. Malone, Teresa Marino, Lucie Morin, Jose A. Nores, Steven Ralston, Dale P. Reisner, Rebecca Elliot Rigsby, Lynn Simpson, Julia Elizabeth Solomon, and Theresa Stewart. Other faculty members at New England Medical Center who helped create a multidisciplinary team include Drs. John Fiascone, Ivan Frantz, Michael Goldberg, Karen Harvey Wilkes, Ziyad Hijazi, George Klauber, Michael Lewis, Gerald Marx, Heber Nielsen, N. Paul Rosman, Joseph Semple, and Ralph Yarnell. I owe an enormous gratitude to the obstetric sonographers, Jean Crowley, Rachel Duguay, Peg Meyers, and Pam Sullivan, and to the genetic counselors, Beth Berlin, Mona Inati, DeeDee Lafayette, Emily Lazar, and Michele Murray, for their excellence and devotion to patient care. I extend a special thank you to a model mentor, Dr. John Hobbins, who is widely considered to be the father of obstetric ultrasound. In the program he initially established at Yale University, ultrasound assumed an integral role in patient care. This program became a model for many perinatal units throughout the United States. He irreversibly changed the way in which I considered the practice of maternal fetal medicine. In particular, I wish to acknowledge the contributions of Drs. Richard Berkowitz, Fergal D. Malone, and Lynn Simpson, who critically read many of the chapters. The loyal support and personal and professional encouragement provided by Dr. Fergal Malone on an ongoing basis is deeply acknowledged and much appreciated. My part of this manuscript could not have been completed without the superb editorial skills of Star Poole, virtuoso word processor, who served as a medical editor in the Division of Maternal Fetal Medicine at Tufts University.

Acknowledgments (Second Edition)

Diana W. Bianchi, MD: Since the publication of the first edition of *Fetology*, I have jokingly referred to it as my "third child". It weighs 7 pounds and it is never far from my mind! Alternatively, I refer to it as my "external hard drive", because it is a convenient compilation of all the facts I need or want to know when I perform a prenatal genetic consultation for a fetus with an anomaly or an abnormal karyotype. However, in the past 10 years, many sections of the book have become outdated. We seriously questioned whether we had the time or energy to perform a thorough revision for a second edition. In the end, Drs. Crombleholme, D'Alton, and I decided that we could do it only if we added a fourth author. The choice of Fergal Malone was a natural one, given his long association with Tufts and his expertise in prenatal diagnosis and fetal medicine. In contrast to the first edition, when Drs. Crombleholme, D'Alton, and I would meet for coffee in one of our offices at Tufts to review and discuss the chapters, we are now scattered across the US and Ireland. Thus, most of the writing and editing for the second edition was done via email, with occasional "marathon" meetings at the McGraw-Hill offices in Manhattan. Thanks to our editors, Alyssa Fried and Karen Davis, we received food, shelter, and administrative support during those sessions.

In addition to the people I thanked in the first edition I would like to specifically acknowledge Linda Keys, who helped me immensely with reference retrieval and typing the revised chapters. Dr. Nick Guerina transferred original color slides to digital files so that we could add color to this edition. I would also like to thank the staff at the Prenatal Diagnosis Center at Women and Infants' Hospital in Rhode Island, where I provided prenatal genetic consultations from 2000–2007. In particular, the genetic counselors Jacquelyn Halliday, Carolyn Slack and Kerry Lurix identified cases of interest for images and discussion. I would also like to thank Drs. François Luks, Steven Carr and Marshall Carpenter for referring interesting cases to me. At Tufts Medical Center I would also like to acknowledge the invaluable help of the genetic counselors Beth Berlin, Paula Delerme, Amy Sachs, Denise Lafayette, and Lauren Lichten for their help in proofreading and making editing suggestions. Similarly, Drs. Michael House, Terri Marino, Steven Ralston, and Sabrina Craigo have been enormously helpful in making the second edition even better than the first! I would also like to thank the Tufts maternal-fetal medicine fellows who have worked in my research laboratory, specifically Drs. Barbara O'Brien, Neeta Vora, Linda Kleeman, and Adam Urato, who have always stimulated me by asking great questions. Lastly, I would like to express my profound appreciation to my family, in particular my husband John, who have been understanding of the fact that the "third child" is a demanding one, and requires individual time and attention.

Timothy M. Crombleholme, MD: During the writing of this second edition, (which my children fondly refer to as "Fetology II: The Fetus Strikes Back") our understanding and approach to diagnosis and management of many fetal conditions has continued to evolve. Progress has only been possible through the supportive interactions of numerous professional colleagues in many disciplines who bring their unique expertise to bear on the fetus. I would like to acknowledge my past and present research fellows and colleagues who have contributed to the development of the field of fetal surgery and fetology: at Cincinnati Children's Hospital in the Center for Molecular Fetal Therapy, Elliott Kozin MD, Anna Katz MD, Jignesh Parvadia MD, Ahmed Marwan MD, Suzi Demiberg MD, Arturo Maldonado MD, PhD, Ursula Harkness MD, Sachin Vaikunth MD, Maria Ripberger, Fernando Vuletin-Solis MD, Lee Morris MD, Shuichi Katayama MD, Swathi Balaji PhD, Datis Alaee MS, Chuck Klanke MS, Helen Jones PhD, Louis Le MD, and Kim Lyons RN, BSN. In the Fetal Care Center of Cincinnati, Emmie Blayer, Rachel Jones, Cheryl Snell, Jenni Mason RN, Gina Sharp RN, Deborah Voet RN, Karen McGirr RN, CNM, Christine Spaeth MS, Diana Smith MS, and Erin Hillman MSW, Judith Hostiuck RNC-OB, Steven Imhoff RNC, our obstetrical nurses in The Fetal Care Center: Gina Allaire RN, Melissa Brewington RN, Judy Bryant RN, Kasey Casson RN, Kasey Duffens RN, Elizabeth Geiger RN, Deborah Kocis RN, Kelly LaFlamme RN, Lori Macke RN, Pam Mitchell RN, Monica Newman RN,

Lisa Pickett RN, Amanda Thacker RN, Autum Thompson RN, Susan Turner RN, Michelle Wesselman RN, and Lisa Wisby RN.

I wish to acknowledge the loyal support and guidance of Richard Azizkhan MD, Foong-Yen Lim MD and Kelli Young RN MS APN, and who have been instrumental in the development of the Fetal Care Center of Cincinnati. I would like to acknowledge my partners in the Fetal Care Center of Cincinnati from whom I learn from every day for their support and encouragement during the writing of this book: Sundeep G. Keswani MD, Mounira Habli MD, Jeffrey Livingston MD, William Polzin MD, Ray Bahado-Singh MD, Ronald Jaekle MD, David Lewis MD, James Van Hook MD and Kim Brady MD. I would like to acknowledge Michael R. Harrison MD, mentor and friend, who as the father of fetal surgery was practicing fetology before it had a name. I would particularly like to thank my colleagues in other disciplines who have taught me so much and contributed to our understanding of the fetal patient, including Erik Michelfelder MD, James Cnota MD, William Gottliebson MD, William Border MD, and Russell Hirsch MD in Pediatric Cardiology; Beth Kline-Fath MD, Eva Rubio MD, Maria Calvo MD, and Kyuran Choe MD in Radiology; Tariq Siddiqi MD in Maternal Fetal Medicine; James Greenberg MD, Beth Haberman MD, Paul Kingma MD, Amy Nathan MD, Tanya Cahill MD, and Kurt Schibler MD in Neonatology; Robert Hopkin MD in Genetics; Pramod Reddy MD, and Paul Noh MD in Pediatric Urology; Karin Bierbrauer MD, Francesco Mangano MD and Todd Maugans MD in Neurosurgery; Ravi Elluru MD in Pediatric ENT; Connie Bitters, Kristina Stenger, Linda Faulkner-Snyder, and Michelle King for their sonographic skill and enthusiastic support of fetal surgery; In the operating room I would like to acknowledge the contributions of Ik Lee MD, Dean Kurth MD, Anne Boat MD, Ximena Soler MD, Mohamed Mahmoud MD, Margaret Linker, and Bonnie Hugus RN, who have done so much to advance the anesthetic management of fetal surgical patients. Also, acknowledged in the operating room are Missy Ritter RN, Tracy Heidrich RN, Doug Dunbar, Britany Freeman, Todd Forte, Mary Ratliff, Latressa Rector, Curtis Johnson, Teco Gaines and most particularly, in the postnatal care and evaluation of our fetal patients, the fellows: Ala Stanford-Frey MD, Shawn Rangel MD, Sean Barnett MD, Timothy Lee MD, and Mubeen Jafri MD. Lastly, for their ability to decipher my hieroglyphic writing and secretarial support, I give special thanks to Marsha Corbett, Anne Riestenberg, Bonnie Killen and Tammie Day.

Finally, I am indebted to my co-authors Mary D'Alton MD, Diana Bianchi MD and Fergal Malone MD for the opportunity to continue a collaboration that has been the most rewarding of my professional career and continues to provide new opportunities to learn, teach and grow the field of Fetology.

Mary E. D'Alton, MD: Since coming to Columbia University Medical Center, our team has worked to create a system of seamless prenatal diagnosis and therapy for our patients described in the first edition of Fetology.

With support from New York Presbyterian Hospital and Columbia University College of Physicians and Surgeons, we have created the Center for Prenatal Pediatrics, a program focused specifically on providing multidisciplinary care to patients carrying pregnancies with fetal anomalies. Under the superb leadership of Dr. Lynn Simpson this center now sees over 500 families every year. Other physicians integral to success of the center are the other directors of the Center for Prenatal Pediatrics including Dr. Charles Kleinman, Dr. Richard Polin, Dr. Wendy Chung, Dr. Charles Stolar, and Dr. Ron Wapner. Their experience, camaraderie, and vision keep pushing us to strive for greater results. The staff of the Center act as the glue for our patients and include Ushta Davar Canteenwalla, Anne Van der Veer, Rosalie Perez, Angel Otero, and Kimberly Cordero.

It is fitting that this 2nd edition of *Fetology* will be published the same year that our Center for Prenatal Pediatrics moves to its new space. This state-of-the-art facility has been made possible by a naming gift from Carmen and John Thain and with additional funding from Sally and Mike Martell and the Klingenstein-Martell Foundation as well as ongoing support from New York Presbyterian Hospital and Columbia University College of Physicians and Surgeons.

I also wish to acknowledge the support of my current and former fellows who have played an integral role in preparing and presenting the new cases at our weekly multidisciplinary Prenatal Pediatrics conference. They include Patricia Devine, Annette Perez-Delboy, Joshua Weiss, Jane Cleary-Goldman, Tracy Shevell, George Graham, Dorothy Przydzial-Smok, Andrew Healy, Alexandra Spadola, Heather Lipkind, Young Mi Lee, Blair Wylie, Russell Miller, Danny Wai Fu Wu, Clarissa Bonanno, Karin Fuchs, Samuel Bauer, Fadi Mirza, Freddy Montero, Shai PriPaz, Jaclyn Coletta, and Joy Vink. In particular I wish to acknowledge the contributions of Dr. Richard Berkowitz, Dr. Jane Cleary-Goldman, and Dr. Karin Fuchs who critically read many of the chapters and who provided input, support, and encouragement throughout the revision process.

As I did in the first edition, I would like to extend a special thank you to Dr. John Hobbins. Dr. Hobbins not only served as a model mentor to me early in my career, but also is rightfully considered the father of obstetric ultrasound who irreversibly changed the way in which maternal fetal medicine is practiced today.

Fergal D. Malone, MD: I am indebted to my co-authors, Drs. Bianchi, D'Alton and Crombleholme, for their encouragement and support during the long process of developing and rewriting this edition. In particular, I would like to especially acknowledge Mary D'Alton for giving me my start in obstetrics, steering my career development in maternal-fetal medicine, and spurring my interest in prenatal screening and fetal therapy. Without her constant advice and mentoring, I would likely not have pursued an academic career in

maternal-fetal medicine. Despite moving to Ireland in 2005 to establish a new fetal treatment program, I remain in close contact with my colleagues in the United States. In this era of globalized medicine, I believe that continued international collaboration across continents represents the way forward for advancing the original goals of *Fetology* for all of our patients.

Finally, I would like to particularly acknowledge the never-failing support, loyalty, and inspiration of my wife, Marie. From traveling across continents in unwavering support, to being the gel that holds personal and professional lives together, I could not have achieved any of my accomplishments without her constant presence.

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PART

I

Introduction

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Prenatal Imaging

CHAPTER 1

Key Points

- In most cases, ultrasound is the method of choice for imaging the fetus, and the majority of pregnant women in the United States undergo at least one ultrasound.
- Sonographer skill and experience play a great role in the accuracy of ultrasound.
- Ongoing quality assurance is important.
- There have been exciting advances in the field of prenatal imaging within the past few years including three-dimensional ultrasound and fetal magnetic resonance imaging, and the future holds the promise of great breakthroughs.
- It is expected that imaging modalities will continue to improve, and it is hoped that techniques utilized in the fields of noninvasive prenatal diagnosis will continue to advance.
- Accurate prenatal diagnosis of fetal abnormalities improves patient care by optimizing patient counseling and allowing for informed patient and physician decision-making.

INTRODUCTION

The development and practice of fetology has been dependent on advances in the field of prenatal imaging. Without the ability to accurately visualize the structure and well-being of the fetus within its own intrauterine environment, it would not be possible to diagnose or treat the range of abnormalities that can now be addressed by the multidisciplinary fetal health care team. Rapid advances in the technologic basis of two imaging methods—ultrasonography and magnetic resonance imaging (MRI)—have resulted in highly accurate visualization of the fetal anatomy.

PRENATAL ULTRASONOGRAPHY

Development

Ultrasonography in obstetrics was first introduced in the late 1950s and has since become the method of choice for imaging the fetus. Gray-scale imaging became available in 1973 and resulted in an enhancement of the ability to differentiate the appearance of various organs and tissue interfaces. The advent of real-time sonographic scanning during the 1970s was vital for the accurate visualization of the constantly moving fetus. The subsequent development of higher frequency transabdominal and transvaginal transducers in the late 1970s resulted in vast improvements in the resolution of fetal images and also pushed back the gestational age barrier for accurate prenatal diagnosis into the late first and early second trimesters (D'Alton, 1998).

The 1980s saw innovations in obstetric sonographic technology, including the use of pulsed and color Doppler sonography, which allowed for detailed analysis of fetal perfusion and improvements in the visualization of fetal cardiac anatomy. More recent advances include the development of power Doppler, which displays the strength of a Doppler signal rather than the direction of flow. This technique is useful in fetal imaging for low-flow states and may aid in the

definition of fetal tumors and assessing placental function (Ogle and Rodeck, 1998). Three-dimensional ultrasonography is now also available for fetal imaging and has revolutionized the field of prenatal imaging by allowing simple sonographic acquisition of a "block" of fetal tissue (Timor-Tritsch and Platt, 2002). Postacquisition computer processing allows reconstruction of any number of planes through the organ of interest as well as producing real-time surface rendering images of the fetus.

Controversies

Ultrasonographic imaging is an integral part of obstetric practice today. In the United States, it is performed in the majority of all pregnancies (Horger and Tsai, 1989; Goncalves and Romero, 1993; Martin et al., 2002). Sonography has been used routinely for accurate dating of pregnancy, confirmation of pregnancy location and number of gestations, prenatal diagnosis of congenital malformations, and assessment of fetal well-being (American College of Obstetricians and Gynecologists, 2008). With the increasing availability of ultrasound equipment, the performance of obstetric ultrasonography has grown to the point that, in some countries, one or more ultrasound examinations are recommended during all pregnancies (Royal College of Obstetricians and Gynaecologists, 1994).

Studies evaluating the performance of ultrasonography in pregnancy have yielded conflicting results. A comprehensive meta-analysis of more than 30 studies assessing the performance of routine prenatal ultrasound in screening for fetal malformations reported detection rates ranging from 13% to 82% with a mean of 27.5% (Levi, 2002). Detection rates have been shown to vary according to the nature and severity of the anomaly with higher detection rates achieved for major structural malformations than for minor malformations (Grandjean et al., 1999). The inconsistent performance of the second trimester anatomic survey may also be explained by variations in the populations screened and differences in the facilities at which the ultrasounds are performed. For example, both the Helsinki and RADIUS trials demonstrated significantly higher detection rates when screening ultrasounds were performed at tertiary care facilities than when the ultrasounds were performed at community-based facilities (Crane et al., 1994; Saari-Kemppainen et al., 1994).

Apart from the detection of congenital abnormalities, obstetric ultrasonography can be expected to be beneficial in other aspects of pregnancy management. The routine use of obstetric ultrasonography has been shown to reduce the rate of postterm pregnancies and to reduce the use of tocolytic medications, both because of an improvement in the accuracy of pregnancy dating (Saari-Kemppainen et al., 1990; LeFevre et al., 1993). In addition, the routine use of obstetric ultrasonography has been shown to significantly increase the early detection of multiple gestations, which is essential if appropriate modifications in pregnancy management are to be applied (LeFevre et al., 1993).

While the RADIUS Trial did not demonstrate any improvement in overall perinatal outcome from routine obstetric ultrasonography, this study has been criticized because of its poor performance in the detection of anomalies (Ewigman et al., 1993; Goncalves and Romero, 1993). Other studies have demonstrated a significant reduction in perinatal mortality following routine obstetric ultrasonography, mostly because of an increase in the rate of pregnancy termination for congenital anomalies (Saari-Kemppainen et al., 1990). While an initial meta-analysis of four randomized clinical trials of routine versus indicated ultrasonography also confirmed a significantly lower perinatal mortality rate in patients allocated to routine scanning (Bucher and Schmidt, 1993), another more recent review failed to confirm a perinatal mortality advantage in the general population from routine obstetric ultrasonography (Neilson, 1998).

Impact of Skill and Experience

Perhaps the most likely reason for the significant discrepancy in the sensitivities of ultrasonography for the detection of anomalies is the effect of the skill and experience of the sonographer. There is undoubtedly wide variation in the skill levels of sonographers between different centers that practice obstetric ultrasonography. In the RADIUS Trial, for example, there was a significant difference in the rates of anomaly detection between participating tertiary and nontertiary level centers (Crane et al., 1994). Nontertiary level centers detected only 13% of congenital anomalies in the RADIUS Trial and were unable to detect any craniofacial, cardiac, gastrointestinal, or skeletal malformations. Tertiary level centers performed significantly better, detecting 35% of anomalies (Goncalves and Romero, 1993). Other studies have also demonstrated that in expert hands, second trimester ultrasound can detect more than 70% of fetal malformations (Boyd et al., 1998; Van Dorsten et al., 1998).

In a retrospective study from Vienna, the impact of sonographer experience was demonstrated by a wide variation in rates of anomaly detection between different centers with different skill levels (Bernaschek et al., 1996). In that study, the overall anomaly detection rate was only 22% for obstetric ultrasonography performed in private obstetricians' offices, 40% in general hospitals, and 90% for ultrasonography performed by experts in fetal imaging.

Because of the clear association between the skill or experience of the sonographer and rates of anomaly detection, it has been suggested that obstetric ultrasonography should be performed only in tertiary level centers, where up to four times as many fetuses with anomalies may be detected (DeVore, 1994). However, it is not clear that all pregnant patients will have equal access to tertiary level centers, which may be especially problematic in rural or other underserved areas.

Accreditation and Maintenance of Standards

Given the influence of the sonographer's skill and experience on the rate of anomaly detection for obstetric

ultrasonography, it is logical to expect that basic standards and requirements for the performance of ultrasonography be delineated. However, in the United States there is no mandatory requirement for licensure or accreditation for practitioners who provide obstetric ultrasonography services. Minimum standards are described only in the form of suggested guidelines, and any form of accreditation is entirely voluntary in nature.

The American Institute of Ultrasound in Medicine has suggested minimum qualifications for all practitioners involved in obstetric ultrasonography (American Institute of Ultrasound in Medicine, 1993). One of the key components of such qualification is the completion of an approved residency program, or the performance and interpretation of at least 500 obstetric ultrasound examinations. Furthermore, the American Institute of Ultrasound in Medicine now accredits obstetric ultrasonography practices, which involves evaluation of the credentials of sonographers, quality of fetal images, type of ultrasound equipment, methods of data storage, and presence of quality control measures in place (Abuhamad et al., 2004; American Institute of Ultrasound in Medicine, 2005).

Safety

Theoretical safety risks from ultrasound energy include thermal damage or cavitation, with subsequent tissue injury. Most prenatal ultrasound examinations produce energies of 10 to 20 mW/cm^2, which is well below the arbitrarily defined safe cutoff level of 100 mW/cm^2 (American College of Obstetricians and Gynecologists, 2008). Newer prenatal imaging methods, such as those that use power Doppler, may be associated with higher energy outputs, which reinforce the need to continuously monitor power output during prenatal ultrasonography and to achieve the lowest possible energy exposure.

Randomized trials on the safety of diagnostic ultrasonography in pregnancy have demonstrated no significant differences in developmental, neurologic, or psychologic outcomes, with up to 12 years of follow-up (Stark et al., 1984). One study did demonstrate a nonsignificant increase in the frequency of dyslexia in the group exposed to ultrasound in utero, as compared with the group with no ultrasound exposure (Stark et al., 1984). A subsequent study evaluating school performance and dyslexia in groups exposed and not exposed to ultrasound in utero found no differences in any outcome measures, although there was an association between left-handedness and in utero ultrasound exposure (Salvesen et al., 1992, 1993). One study has also suggested an association between frequent ultrasound exposure in utero (five ultrasound examinations) and growth restriction, although this has not been confirmed by other investigators (Newnham et al., 1993).

Overall, it appears that routine ultrasonography in pregnancy is not associated with any adverse outcome for the fetus. Repeat ultrasound examinations should be performed only as indicated.

Current Role

The four main roles of prenatal ultrasonography in contemporary obstetric practice are

1. to confirm fetal gestational age and number;
2. to search for fetal malformation;
3. to confirm fetal well-being; and
4. to aid in the performance of invasive diagnostic and therapeutic fetal procedures.

The ability of prenatal ultrasonography to accurately confirm fetal gestational age and number of fetuses is self-evident. The RADIUS Trial demonstrated a significantly decreased chance of postterm induction of labor following accurate sonographic dating of pregnancy and a significant increase in the prenatal detection of multiple gestations (LeFevre et al., 1993).

The ability of prenatal ultrasonography to diagnose fetal malformations, both as a screening tool and for targeted examinations, has also been confirmed. In expert hands, screening ultrasonography can be expected to detect approximately 70% of all fetal malformations (Boyd et al., 1998; Van Dorsten et al., 1998). However, the detection rate for individual anomalies varies significantly. While almost all spinal, renal, and abdominal wall malformations are detected by screening prenatal ultrasonography, the detection rate for isolated cardiac defects is only approximately 50% (Boyd et al., 1998; Flood and Malone, 2008). Efforts to increase the second trimester detection rate of Down syndrome by including soft markers for aneuploidy (such as short femur, short humerus, echogenic bowel, nuchal thickening, and choroid plexus cysts) may be successful, although it is likely that any such improvement will be accompanied by an increase in the false-positive rate (Nyberg et al., 2001; Bromley et al., 2002; Filly et al., 2004). See Chapters 2 and 3 for further discussion of first and second trimester screening for Down syndrome.

Prenatal ultrasonography also plays a crucial role in the confirmation of fetal well-being, especially following the identification of a fetal abnormality or a condition associated with a high risk of adverse fetal outcome. Fetal biophysical profile and pulsed Doppler assessment of fetal arterial flow may be used for identifying fetuses with compromised reserve that may benefit from either intensive surveillance or elective premature delivery (American College of Obstetricians and Gynecologists, 2008).

The ability to perform invasive prenatal diagnostic procedures safely, as well as fetal therapy, has been significantly improved by real-time ultrasonography (American College of Obstetricians and Gynecologists, 2008). Diagnostic procedures during the first trimester, such as chorionic villus sampling and embryofetoscopy, are now commonly performed under ultrasound guidance. Amniocentesis, fetal blood sampling, vesicocentesis, thoracentesis, and fetal biopsies are also possible because of the availability of real-time ultrasonography. The ability to treat the fetus using blood transfusions, drug infusions, and shunt placement is now also possible as a result of advances in sonographic technology and availability.

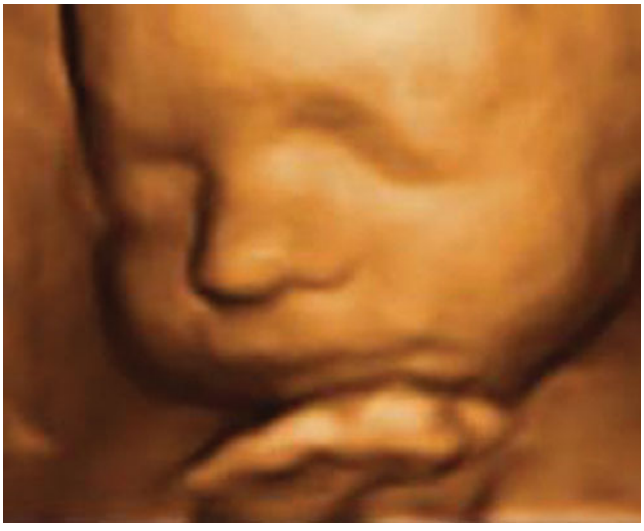

Figure 1-1 3D image of a fetal face at 24 weeks' gestation.

Three-dimensional ultrasound

Three-dimensional (3D) ultrasound allows for multiplanar imaging enabling the examiner to move back and forth between different planes due to the capability of viewing the fetus in three rather than two spatial planes (Figure 1-1). Images can be reconstructed and the examiner can move the fetus into ideal desired positions that are often not possible with conventional ultrasound. In addition, 3D scanning enhances imaging capabilities by permitting surface rendering of a structure. Acquisition of data points through the entire volume of interest is required to produce 3D ultrasound pictures. Acquisition quality depends on acquisition speed. Slow speeds result in more scanned slices and are used for nonmoving organs. Fast speeds are preferable for moving structures. The "four-dimensional" (4D) real-time imaging technique requires ultrafast acquisition. 4D ultrasound displays a continuously updated and newly acquired volume in any rendering modality. This creates the impression of a moving structure (Timor-Tritsch and Platt, 2002).

Previously, it was thought that 3D ultrasound provides only aesthetic images without contributing to prenatal diagnosis. There are no accepted indications for 3D ultrasound in obstetric practice at this point. Few outcome studies have confirmed whether or not this technology changes practices or clinical outcomes (Lee, 2003; American College of Obstetricians and Gynecologists, 2008). Nonetheless, this technology is rapidly advancing and has been shown to be helpful. It appears to be useful as an adjunct to 2D ultrasound in fetal echocardiography and in the diagnosis and further evaluation of certain fetal anomalies such as cleft lip and palate and skeletal anomalies (Dyson et al., 2000; Garjian et al., 2000; Johnson et al., 2000; Sepulveda et al., 2003; Roman et al., 2004; Sklansky et al., 2004; Merz and Welter, 2005). Goncalves et al. (2006) recently conducted a study that evaluated whether or not conventional ultrasound adds important information to 3D/4D imaging (Goncalves et al., 2006). Fifty-four fetuses without abnormalities and 45 fetuses with 82 abnormalities diagnosed by 2D ultrasound were evaluated. Agreement between 3D/4D and 2D ultrasound occurred in 90.4% of cases. Six anomalies were missed by 3D/4D when compared to 2D ultrasound. There were also two discordant diagnoses. There was one abnormality suspected by 3D/4D ultrasound, which was not confirmed by 2D ultrasound. The sensitivity and specificity of 3D/4D ultrasound and 2D ultrasound was 92.2% and 76.4% and 96.1% and 72.7%, respectively. This was not found to be a statistically significant difference. The authors concluded that the findings of 3D/4D ultrasound are consistent with the findings from 2D ultrasound.

PRENATAL MAGNETIC RESONANCE IMAGING

Development

While ultrasound remains the imaging modality of choice for the fetus due to its widespread availability and reasonable cost, it has several limitations. These include small field of view, limited soft tissue acoustic contrast, poor image quality in pregnancies complicated by oligohydramnios, beam attenuation by adipose tissue, and limited visualization of certain fetal structures at later gestational ages, for example, the posterior fossa after 33 weeks of gestation due to bone calcification (Garel et al., 1998; Coakley et al., 2004). MRI is now being used in conjunction with ultrasound to provide additional information for prenatal diagnosis. The advantages of MRI include the use of multiple planes for reconstruction and a large field of view making the visualization of complicated anomalies easier.

MRI has been available for clinical use for more than 20 years, but in more recent times its role in prenatal diagnosis has increased significantly. Use of MRI was first described in pregnancy in 1983 (Smith et al., 1983). Its initial application was for maternal and placental abnormalities. The potential for MRI in prenatal diagnosis was recognized early on, with reports of imaging of fetal abnormalities (Lowe et al., 1985; McCarthy et al., 1985; Weinreb et al., 1985). A serious limitation of these early attempts at prenatal MRI was the long acquisition times of standard spin echo images. The amount of fetal movement that would occur during image acquisition degraded the images obtained. The noise associated with MRI scanning made the likelihood of a fetus sleeping motionless during the study very small. The quality of the images that were possible prompted the use of paralyzing agents administered either by intramuscular injection into the fetus or umbilical cord injection to obtain motion-free spin echo images (Daffos et al., 1988). The invasive nature of this approach dampened the initial enthusiasm for prenatal MRI.

During the early 1990s, ultrafast MRI sequences and fast scanners, such as echo planar MRI, were developed (Johnson et al., 1990; Mansfield et al., 1990). Fetal MRI became practical due to the development of single-shot rapid acquisition sequence with refocused echoes. This high quality T_2-weighted sequence has a slice acquisition time of less than 1 second and essentially "freezes" fetal motion (Kiefer et al., 1994; Semelka et al., 1996; Levine, 2001). The ultrafast

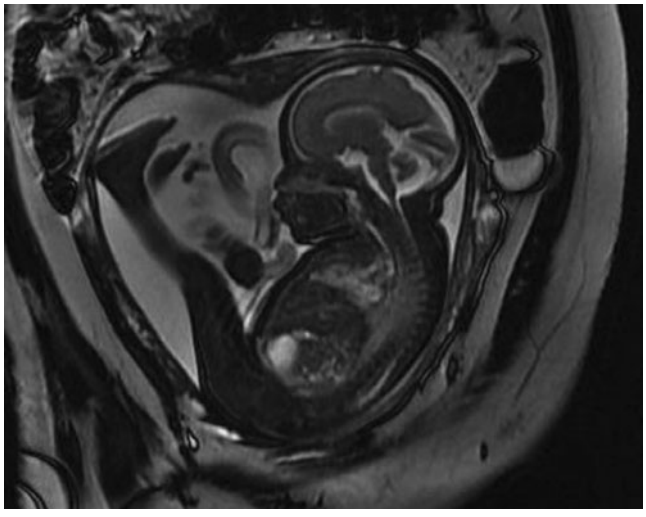

Figure 1-2 Fetal MRI demonstrating a normal fetus at 28 weeks' gestation.

scanning technique eliminates, or significantly reduces, the artifacts caused by fetal movement, making fetal sedation or paralysis unnecessary for prenatal MRI (Hubbard and Harty, 1999; Levine, 2001) (Figure 1-2).

These ultrafast sequences are now being successfully employed in imaging the human fetus (Garden et al., 1995; Levine et al., 1996; Hubbard et al., 1997a, 1997b, 1998; Yamashita et al., 1997; Quinn et al., 1998; Hubbard and Harty, 1999; Levine, 2003a). Fetal anatomy has been well visualized by MRI scanning in fetuses more than 18 weeks of gestation and is increasingly being used as an adjunct to prenatal ultrasound examination in the evaluation of structural fetal anomalies, facilitating appropriate prenatal counseling, and guiding fetal therapy (Levine et al., 1996; Quinn et al., 1998; Hubbard and Harty, 1999). The main indication for fetal MRI is further evaluation of inconclusive ultrasound findings. It is also useful for evaluation prior to fetal surgery (Levine, 2004). Definitive indications for fetal MRI have not been established and recommendations are based on case reports, small case series, and expert opinion (Coakley et al., 2004).

Safety

Provided that there is no maternal contraindication, most studies suggest that MRI is safe in pregnancy as it allows the acquisition of excellent soft tissue contrast without using ionizing radiation (Levine, 2001). To date there are no known harmful effects in the developing fetus with the use of scanners at field strengths of 1.5 T or less (Hubbard and Harty, 1999). Guidelines for patient safety were issued by the Safety Committee of the Society of Magnetic Resonance Imaging. However, several animal studies have suggested the possibility of teratogenetic effects in early pregnancy (Wolff et al., 1980; Schwartz and Crooks, 1982; Heinrichs et al., 1988; Beers, 1989; Tyndall and Sulik, 1991; Mevissen et al., 1994; Yip et al., 1994). While these studies may not be applicable to humans, they indicate that MRI should be used with caution in the first trimester. The risk of acoustic damage to the fetus is thought to be negligible (Baker et al., 1994; Gover et al., 1995). Patients can be informed that according to the Safety Committee of the Society for Magnetic Resonance Imaging, MRI is reasonable when other nonionizing forms of radiation are inadequate, or when the examination would provide information that would otherwise require exposure to ionizing radiation. While there is no evidence that MRI can harm the fetus (American College of Obstetricians and Gynecologists, 2008), it is important to note that the United States Food and Drug Administration asserts that the safety of fetal MRI "has not been established," and the majority of centers using this imaging technique in pregnancy limit its use to after the first trimester and require informed consent prior to the procedure (United States Food and Drug Administration, 1988; Levine, 2001).

MRI of the Fetal Central Nervous System

MRI had been used to characterize the developing brain as early as 1983 (Gilles et al., 1983). Ultrasound examination remains the primary method of prenatal imaging but, especially in the brain, MRI is becoming an invaluable adjunct, providing superior characterization of fetal brain maturation and morphology. In most instances, MRI is used for fetuses in which a CNS abnormality has already been demonstrated or is suspected by ultrasonography (Bilaniuk, 1999; Levine, 1997). The most common CNS abnormalities diagnosed by ultrasound examination and referred for evaluation by MRI include cysts, Dandy–Walker malformation or variant, agenesis of the corpus callosum, hydrocephalus, vein of Galen aneurysm, encephaloceles, and otherwise malformed brains.

Ventriculomegaly is a common indication for fetal MRI. T_2-weighted sequences provide excellent imaging of the size and configuration of the ventricles. Criteria for ventriculomegaly in fetal MRI is based on ultrasound data demonstrating ventricles of a width of at least 10 mm. However, the size of the ventricles tends to be slightly larger when obtained by MRI than the measurements obtained in the same fetus by ultrasound examination. Once ventriculomegaly is identified, a detailed examination of the entire fetus should be performed to detect associated anomalies (see Chapter 16). When ventricular enlargement is due to a myelomeningocele, MRI is particularly good for demonstrating the Chiari II malformation, the extent of the neural tube defect, and the level of the sac (Bilaniuk, 1999).

MRI provides excellent tissue discrimination in defining congenital CNS abnormalities such as calvarial defects, differentiating hemangioma or lymphangioma from encephalocele or meningocele, and demonstrating partial or complete agenesis of the corpus callosum. The finding of an abnormality of the corpus callosum is often not isolated and frequently indicates the presence of other cerebral abnormalities (Atlas et al., 1986; Barkovich and Norman, 1988) (see Chapter 6). Occasionally, ultrasound examination may have difficulty in differentiating partial agenesis of the corpus callosum from normal anatomy. MRI can be helpful in further delineating this anatomy.

Vein of Galen aneurysm is a vascular malformation that may be misdiagnosed as a cyst or a mass if not examined

using color Doppler on ultrasound (see Chapter 22). MRI can demonstrate not only the vascular anatomy, but also the condition of the brain, which is of concern because these lesions can be associated with encephalomalacia and macrocrania. The presence of encephalomalacia in cases of vein of Galen aneurysm indicates a poor prognosis (Bilaniuk, 1999).

In addition, MRI has changed the diagnosis and aided in the management of many cases of suspected CNS abnormalities on ultrasound (Levine et al., 2003, Sharma et al., 2003). MRI can better clarify a prenatal diagnosis and help patients make decisions such as whether or not to continue with the pregnancy. Levine et al. compared 242 ultrasound studies and 242 MRI studies of the CNS in 214 fetuses with suspected CNS abnormalities or at high risk for CNS abnormalities (Levine et al., 2003). At confirmatory ultrasound, 69 fetuses had normal CNS imaging. Approximately 80% of fetuses in the study (171/242) had postnatal follow-up. MRI imaging provided additional information in 50% (72/145) of cases and actually found a new major finding in 32% (46/145) of fetuses with abnormal ultrasound findings. In patients with previable fetuses, this information was utilized to help patients decide whether to continue or terminate the pregnancy. In patients with viable fetuses, this information was used to help determine the mode of delivery and the location of delivery (community hospital vs. tertiary care center).

MRI of the Fetal Neck

Fetal MRI may be particularly useful in evaluating fetal neck masses. Distinguishing between lymphangioma and a cervical teratoma may be difficult based on ultrasound images alone (see Chapters 32 and 110). In addition, the risk of a compromised airway at birth is high with each of these lesions. MRI can help with the assessment of the fetal airway so that proper precautions are taken at delivery. MRI of cervical fetal masses allows for more global imaging of the mass than with ultrasound because of the larger field of view. In a report by Hubbard et al. (1998), fetal MRI was able to accurately diagnose the nature of the mass and define the anatomy of the airway. In each case, as compared with ultrasound examination, fetal MRI provided better detail about the size and position of the mass and its relationship to the airway. MRI provides the best anatomic definition of the normal fetal cranial structures and their relationship to the mass (Semelka et al., 1996).

Lymphangiomas appear to be complex masses with cystic and solid components that may compress or surround the airway (Benacerraf and Frigoletto, 1987; Zadvinskis et al., 1992; Hubbard et al., 1998). Cervical teratomas arise from the anterolateral neck and tend to cross the midline (Sherer et al., 1993). These tumors can be solid and cystic with areas of calcification and hemorrhage (Rothschild et al., 1994). On more T_2-weighted fast sequences, cystic components can be evaluated. The oropharynx and trachea are filled with amniotic fluid, which is bright and can be differentiated from the tumor. Areas of acute hemorrhage can be identified by sequences that have more T_1-weighting, which helps delineate teratoma from lymphangioma (Hubbard et al., 1998). Hemorrhage and calcification can be identified on either gradient echo or echo planar images.

MRI of the Fetal Chest

The most common thoracic abnormalities identified on prenatal ultrasound examination include congenital diaphragmatic hernia (CDH), congenital cystic adenomatoid malformation (CCAM) of the lung, bronchopulmonary sequestration (BPS), and fetal hydrothorax (Morin et al., 1994; Levine et al., 2003b; Coakley et al., 2004). CDH has been recognized by herniation of the stomach to the level of the four-chamber view of the heart and a shift of the mediastinum away from the hernia (Chinn et al., 1983). Although the sonographic features of CDH are well described (see Chapter 37), the diagnosis of CDH has been missed in a significant number of fetuses that have been studied by prenatal ultrasound (Lewis et al., 1997). Even in cases in which CDH is correctly diagnosed by ultrasound examination, determination of the presence or absence of liver herniation may be difficult. Herniation of the liver has been found to be a predictor of poor postnatal outcome in CDH (Metkus et al., 1996). Ultrasound examination relies on indirect indicators of liver herniation, such as kinking of the umbilical vein as it enters the sinus venosus (Bootstaylor et al., 1995). Fetal MRI can directly identify the position and degree of herniation of the liver in CDH (Hubbard et al., 1997a). The fetal liver has high signal intensity on fast gradient echo sequences with T_1-weighting, making it easily identifiable relative to the diaphragmatic ridge and the compressed ipsilateral lung. The lung is intermediate to high in signal intensity, which allows differentiation from mediastinal structures and herniated viscera (Hubbard et al., 1997b). With T_2-weighting, the fluid filled stomach is high in signal intensity, equal to the signal intensity in amniotic fluid. The selection criteria for fetal surgery for CDH includes herniation of the liver, making accurate delineation of this anatomy all the more important (Shaaban et al., 1999).

MRIs in CCAM vary in appearance, depending on their size and number and size of cysts (see Chapter 35). The larger the size and number of cysts, the higher the signal intensity of the CCAM on sequences with T_2-weighting. MRI is able to distinguish CCAM from normal compressed lung and determine the lobe of the lung from which the tumor arises. BPS has very high signal intensity as compared with normal lung and is very homogeneous, with discrete margins (Hubbard et al., 1997). BPS in late gestation can become isoechogenic with adjacent lung and may seem to disappear on ultrasound examination (see Chapter 34). These lesions show up distinctly from adjacent normal lung on MRI (Hubbard and Harty, 1999). One disadvantage of fetal MRI in evaluating fetal chest masses has been the inability to demonstrate systemic feeding vessels to BPS. This is a distinct advantage of color flow Doppler over MRI in evaluating BPS or hybrid CCAM lesions, which also have a direct aortic blood supply. Because of its larger field of view, fetal MRI may be especially helpful in evaluating unusual chest lesions such as neurenteric

cysts, laryngotracheal or bronchial obstruction, or mediastinal masses (Hubbard et al., 1997b) (see Chapter 36).

MRI of the Fetal Abdomen and Pelvis

In most instances, ultrasound examination is excellent to evaluate anomalies of the fetal abdomen and pelvis. There are instances, however, when MRI can be helpful. In fetuses with oligohydramnios, ultrasound evaluation can be extremely difficult, whereas fetal MRI is unaffected by a lack of amniotic fluid. It is often difficult to distinguish proximal from distal small-bowel obstruction on prenatal ultrasound examination. There are different MRI signal characteristics that are helpful in these cases, distinguishing proximal from distal small bowel (Hubbard and Harty, 1999). Proximal bowel will have high to intermediate signal intensity on T_2-weighted sequences, similar to amniotic fluid, while distal bowel has intermediate to low signal intensity. Conversely, distal bowel has a high signal intensity on T_1-weighted sequences because of meconium filling the bowel lumen. Using these sequences, dilated loops of bowel may be distinguished as either proximal or distal (Hubbard and Harty, 1999). Because of the large field of view, complex anomalies such as persistent cloaca or cloacal exstrophy may be better imaged on MRI.

The imaging of the fetal urinary tract with ultrasound examination is excellent and rarely improved on by MRI. Exceptions to this include cases of obstructive uropathy complicated by oligohydramnios, polycystic kidneys, and renal tumors. This is also true of sacrococcygeal teratomas, which arise from Hensen's node at the tip of the coccyx. Sacrococcygeal teratomas are most commonly exophytic, but can also extend into the pelvis or abdomen with compression of bladder and intestines.

MRI in a Multiple Gestation

In monochorionic twin pregnancies complicated by intrauterine fetal demise (IUFD), fetal MRI can be used to diagnose multicystic encephalomalacia, a devastating neurologic disorder that may occur in up to 20% of monochorionic twins complicated by single IUFD (Coakley et al., 2004; Weiss et al., 2004) (see Chapter 118). Fetal MRI is usually performed 2 weeks following demise. A normal MRI following single IUFD in a monochorionic twin pregnancy is thought to be reassuring. In addition, fetal MRI has been used in other complicated monochorionic twins at risk for a possible neurologic ischemic episode such as cases complicated by the twin–twin transfusion syndrome and cases that have undergone invasive prenatal techniques such as selective reduction using cord ablative techniques (Coakley et al., 2004; Shevell et al., 2004). The imaging modality may also be helpful in the diagnosis of conjoined twins (Malone and D'Alton, 2000) (see Chapter 121).

Fetal MRI is not indicated as a primary imaging method in any fetal anomaly or condition. As discussed above, however, there are instances in which the information provided by fetal MRI complements that obtained by prenatal ultrasound examination. The role of MRI in prenatal diagnosis is still evolving. At present, MRI is best used selectively in cases in which prenatal sonography is unable to make a definitive diagnosis, where a larger field of view is required, or in acquiring specific information necessary for selection for fetal intervention.

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First Trimester Screening for Aneuploidy

2

CHAPTER

Key Points

- Nuchal translucency measurement in the first trimester is the most powerful marker for fetal Down syndrome.
- Combination of nuchal translucency with serum markers in the first trimester detects up to 87% of cases of Down syndrome for a 5% false-positive rate.
- Septated cystic hygroma, or simple nuchal translucency of 3.0 mm or greater, are indications for chorionic villus sampling (CVS) without need to await serum marker results.
- First trimester absence of the nasal bones, reversal of flow in the ductus venosus, and tricuspid regurgitation may have a limited role as second-line screening tests for select high-risk patients by expert sonologists.
- These second-line screening tests are unlikely to have any value for routine general population screening.

INTRODUCTION

The ideal time to screen for fetal aneuploidy is now during the first trimester of pregnancy. This evolution in screening policy is due to the significant advances that have been made in serum and sonographic markers for fetal chromosomal abnormalities over the past 20 years.

FETAL NUCHAL TRANSLUCENCY

The single most powerful marker available today for differentiating Down syndrome from euploid pregnancies is the first trimester sonographic measurement of the fetal nuchal translucency space. Nuchal translucency refers to the normal subcutaneous fluid-filled space between the back of the fetal neck and the overlying skin (Figure 2-1). Figure 2-2 demonstrates an increased nuchal translucency observed in a fetus subsequently shown to have Down syndrome. By adhering to a standard ultrasonographic technique, it is possible to obtain accurate measurements of this area in the vast majority of fetuses between 10 and 14 weeks' gestation. When performing nuchal translucency sonography, it is absolutely essential to ensure optimal technique, which can be attained by focusing on the following criteria (Abuhamad, 2005):

- Fetus should be imaged in the midsagittal plane, ideally with the fetal spine down.
- The image should be adequately magnified so that only the fetal head, neck, and upper thorax fill the viewable area.

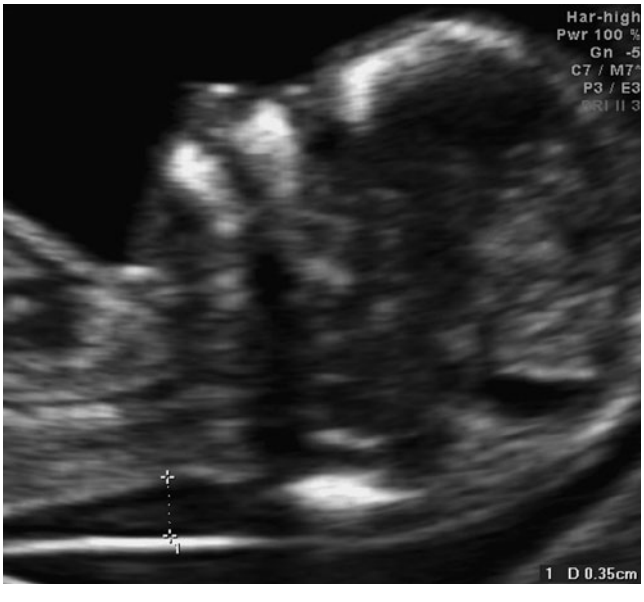

Figure 2-1 Optimizing the technique for first trimester nuchal translucency sonography: Nuchal translucency measurement in a normal fetus at 12 weeks' gestation. Components of a good sonographic screening protocol are evident, including adequate image magnification, midsagittal plane, neutral fetal neck position, and correct caliper placement.

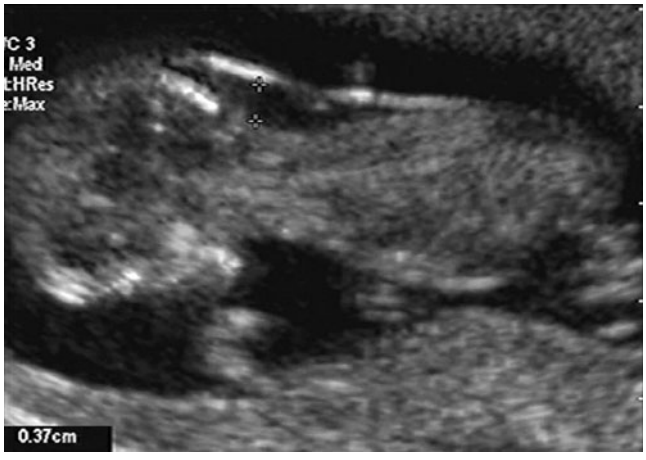

Figure 2-2 Increased nuchal translucency measurement of 3.7 mm in a fetus at 12 weeks' gestation with Down syndrome.

- Fetal neck should be neutral, with care being taken to avoid measurements in the hyperflexed or hyperextended positions.
- The skin at the fetal back should be clearly differentiated from the underlying amniotic membrane, either by visualizing separate echogenic lines or by noting that the skin line moves with the fetus.
- Measurement calipers should be placed on the inner borders of the echolucent space, and should be perpendicular to the long axis of the fetus.
- Ultrasound and transducer settings should be optimized to ensure clarity of the image and of the borders of the nuchal space in particular. This may require transvaginal sonography in certain situations.

There is a direct correlation between increasing nuchal translucency measurement and risk for Down syndrome, other aneuploidies, major structural malformations, and adverse pregnancy outcome (Malone et al., 2000, 2005b; Nicolaides et al., 2002; Wald et al., 2003b). Possible etiologies for the development of this increased fluid-filled space include cardiac failure secondary to structural malformation, abnormalities in the extracellular matrix, and abnormal or delayed development of the lymphatic system (Moscoso, 1995).

NUCHAL TRANSLUCENCY SCREENING FOR DOWN SYNDROME

Nuchal translucency sonography is the most powerful marker for general population screening for Down syndrome (Malone and D'Alton, 2003). The largest study of this form of screening was performed by the Fetal Medicine Foundation based in London (Snijders et al., 1998). This prospective study of 96,127 unselected patients at 22 centers required nuchal translucency sonography to be performed between 10 and 14 weeks' gestation by specially trained sonographers who utilized a standardized technique. The overall Down

syndrome detection rate was 77%, for a 5% false-positive rate. Another large prospective study from the United Kingdom that evaluated the role of nuchal translucency sonography in general population screening was the SURUSS Trial (Wald et al., 2003b). A total of 39,983 patients had nuchal translucency sonography obtained between 10 and 14 weeks' gestation, and the Down syndrome detection rate was 63%, for a 5% false-positive rate. The largest prospective trial of all forms of Down syndrome screening yet performed, the FASTER Trial, has also validated the important role of nuchal translucency sonography. This was a multicenter prospective study from 15 centers in the United States in which 36,306 patients from the general population had first trimester nuchal translucency sonography performed (Malone et al., 2005b). The detection rate for nuchal translucency with maternal age ranged from 70% to 64% at 11 and 13 weeks' gestation respectively, for a 5% false-positive rate. These large studies from varied centers and geographic locations confirm that nuchal translucency sonography must be a key component of first trimester screening programs for fetal Down syndrome.

COMBINED FIRST TRIMESTER SERUM AND SONOGRAPHIC SCREENING

Together with the clear role of nuchal translucency sonography, research in first trimester screening has consistently shown that pregnancies with fetal Down syndrome are associated with altered levels of certain maternal serum markers, including elevated levels of total human chorionic gonadotropin (hCG) and of the free β subunit of hCG (with a median multiple of the median [MoM] of 1.83 in affected cases) and lower levels of pregnancy-associated plasma protein A (with a median MoM of 0.38 in affected cases) (Canick and Kellner, 1999). Studies of the combination of free β subunit of hCG, pregnancy-associated plasma protein A, and maternal age uniformly demonstrate a sensitivity for Down syndrome of approximately 60% with a 5% false-positive rate.

These first trimester serum markers are largely independent of nuchal translucency, which has resulted in the development of a combined serum and sonographic screening protocol that would be more effective for screening than either component alone. The FASTER study evaluated 38,033 patients and demonstrated very high Down syndrome detection rates, and showed that performance varied significantly by gestational age. For a 5% false-positive rate, the Down syndrome detection rates using combined serum and sonographic screening were 87%, 85%, and 82% at 11, 12, and 13 weeks' gestation respectively (Malone et al., 2005b). For a 1% false-positive rate, the Down syndrome detection rates were 73%, 72%, and 67% at 11, 12, and 13 weeks' gestation respectively.

Figure 2-3 summarizes the comparative performance of the various screening options from the FASTER Trial, and demonstrates that first trimester combined screening has very similar performance to second trimester Quad marker serum screening (Malone et al., 2005b). Only when performed at 11 weeks' gestation does first trimester combined screening have a significantly better performance than second trimester Quad marker serum screening (87% vs. 81% Down syndrome detection, respectively, at a 5% false-positive rate). Additionally, the combined first trimester screening test has the lowest false-positive rate, compared with either first trimester component used alone or compared with second trimester serum screening. It is also important to realize that only the combination of first trimester nuchal translucency sonography

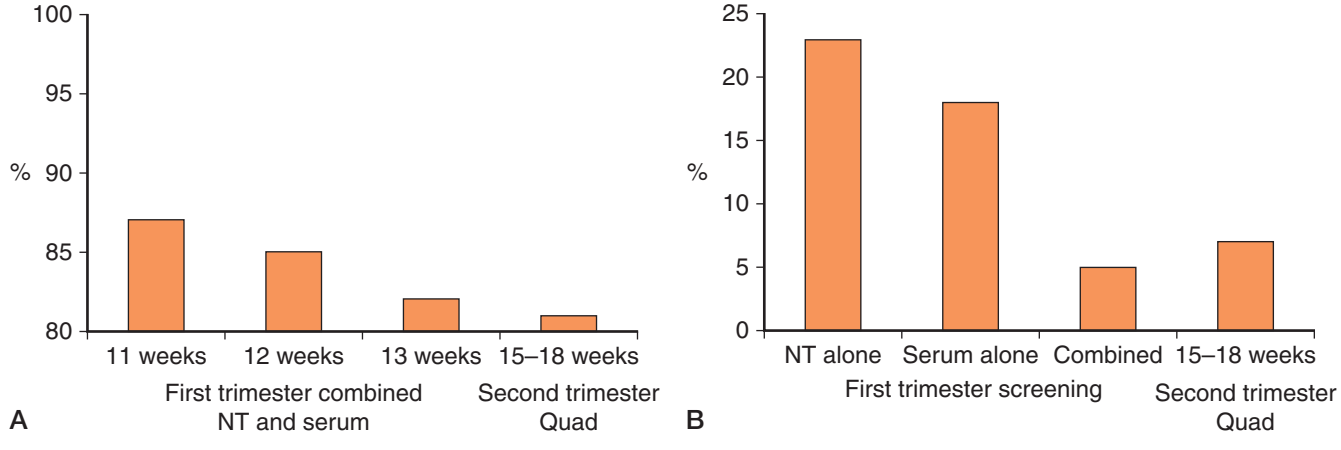

Figure 2-3 **A**. Comparison of first and second trimester screening for Down syndrome: Detection rates of combined first trimester screening at 11, 12, and 13 weeks' gestation, compared with second trimester Quad marker serum screening performed at 15 to 18 weeks' gestation (each at 5% false-positive rate). **B**. Comparison of first and second trimester screening for Down syndrome: False-positive rates of first trimester nuchal translucency alone, PAPP-A and fβhCG alone, and first trimester combined screening at 12 weeks' gestation, compared with second trimester Quad marker serum screening performed at 15 to 18 weeks' gestation (each for 85% detection rate).

with first trimester serum markers comes close to the performance of second trimester Quad marker serum screening. Nuchal translucency alone, without being combined with serum markers, has significantly inferior performance characteristics.

ENLARGED NUCHAL TRANSLUCENCY AND CYSTIC HYGROMA IN THE FIRST TRIMESTER

It is now clear that a subset of fetuses with very large nuchal translucency measurements can be effectively identified in the first trimester that have an extremely high risk of fetal aneuploidy or other adverse pregnancy outcomes. This finding has been described as septated cystic hygroma, and is present when the nuchal translucency space is enlarged extending along the entire length of the fetus, and in which septations are clearly visible (Figure 2-4) (Malone et al., 2005a). Septated cystic hygroma is seen in more than 1 in 300 first trimester pregnancies. In a recent prospective study of routine first trimester sonographic screening, septated cystic hygroma was shown to have a 50% chance of being associated with fetal aneuploidy, with most cases being Down syndrome, as well as cases of Turner syndrome and trisomy 18. Additionally, among cystic hygroma cases confirmed as being euploid, approximately 50% had a major structural fetal malformation, with most cases including cardiac malformations, as well as other malformations such as skeletal dysplasias. When compared with simple increased nuchal translucency, septated cystic hygroma cases were 5 times more likely to be aneuploid, 12 times more likely to have cardiac malformations, and 6 times more likely to result in fetal or neonatal demise.

The practical benefit of being able to counsel patients in the first trimester following the identification of septated cystic hygroma is that there is no need to delay decision-making while awaiting serum marker results or using computerized risk calculation algorithms. When faced with a 50% chance of fetal aneuploidy, it is reasonable to offer such patients the immediate option of CVS, and if fetal aneuploidy has been excluded, a detailed fetal anatomical evaluation, including fetal echocardiography, should be performed at 18 to 20 weeks' gestation.

Debate has also occurred regarding the differentiation between septated cystic hygroma and simple enlarged nuchal translucency, with some investigators believing that they are both part of a spectrum of a similar sonographic feature (Molina et al., 2006). However, the FASTER Trial, a prospective study of more than 38,000 pregnancies, has also now demonstrated that whenever a simple nuchal translucency measurement of 3.0 mm or greater is noted, CVS should be offered immediately because of a minimum risk of aneuploidy of 1 in 6 (Comstock, 2006). With such nuchal translucency measurements, there is no role for delaying decision-making while awaiting serum marker results, as such additional information does not meaningfully alter the original aneuploidy risk. This finding therefore suggests that debating the presence or absence of septations in cases of enlarged nuchal translucency is a moot point, as the risk of aneuploidy either when a nuchal translucency measurement of 3.0 mm or greater is noted, or when a septated cystic hygroma is noted, is sufficiently high to warrant immediate diagnostic testing.

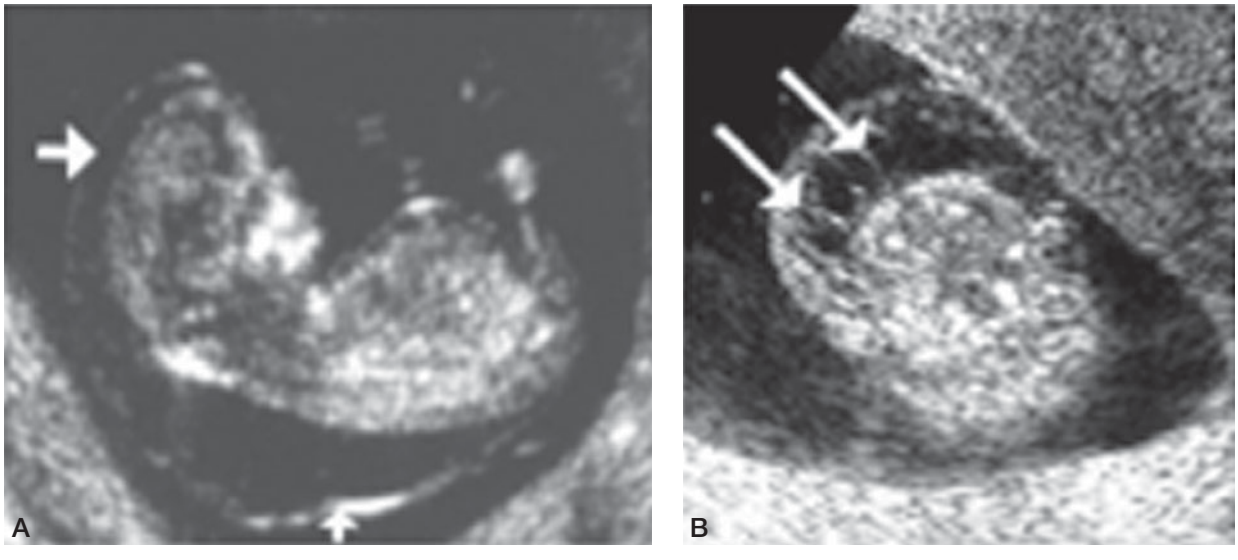

Figure 2-4 **A**. Septated cystic hygroma at 12 weeks of gestation: midsagittal sonographic view of a fetus with septated cystic hygroma, demonstrating increased nuchal translucency space extending along the entire length of the fetus. **B**. Septated cystic hygroma at 12 weeks of gestation: transverse view through the fetal neck of the same fetus demonstrating obvious septations (arrows). (*From Malone FD, Ball RH, Nyberg DA, et al. First trimester septated cystic hygroma: prevalence, natural history, and pediatric outcome.* Obstet Gynecol. *2005a;106:288-294.*)

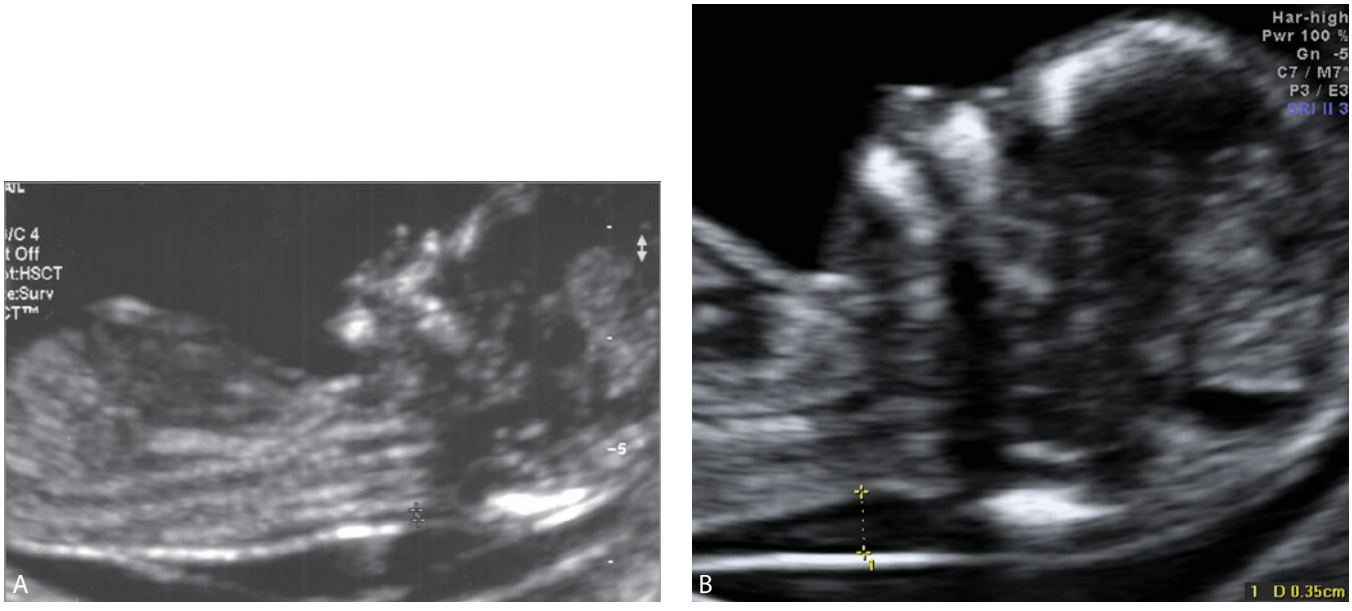

Figure 2-5 **A**. First trimester ultrasound examination of a fetus at 13 weeks' gestation, with normal nasal bones. Features of good nasal bone imaging technique are evident, including midsagittal plane, fetal profile facing upward, adequate magnification, and visualization of two parallel lines at the level of the fetal nose, one representing fetal skin (short arrow) and the deeper line representing nasal bones. **B**. First trimester ultrasound examination of a fetus at 13 weeks' gestation, with absent nasal bones and enlarged nuchal translucency thickness, in which karyotype was confirmed as trisomy 18.

NASAL BONE SONOGRAPHY IN THE FIRST TRIMESTER

There appears to be a clear association between the absence of the fetal nasal bones on first trimester ultrasound examination and Down syndrome. In a study conducted by Cicero et al. (2001), 701 fetuses with increased nuchal translucency were evaluated for the presence or absence of the nose bones during first trimester ultrasonography. The fetal nasal bones could not be visualized in 73% of Down syndrome fetuses (43 of 59) and in only 0.5% of unaffected fetuses (3 of 603). The authors also felt that the absence of the fetal nose bone was not related to nuchal translucency thickness and therefore could be combined into a single ultrasound screening modality, with a predicted sensitivity of 85% for a 1% false-positive rate. This study was subsequently expanded to a larger series of 3829 high risk, first trimester pregnancies, in which the detection rate for Down syndrome using absent nasal bones was 67%, for a 2.8% false-positive rate (Cicero et al., 2003).

Adequate imaging of the fetal nasal bones can be technically challenging in the first trimester, and careful attention to correct technique should therefore be paid to ensure consistency in technique. The nasal bones should be visualized on ultrasound along the midsagittal plane with a perfect fetal profile. The fetal spine should be down, with slight neck flexion. Two echogenic lines at the fetal nose profile should be visualized; the superficial echogenic line is the nasal skin, and the deeper echogenic line represents the nasal bones. This deeper echogenic line representing the nasal bones should be more echolucent at its distal end (Figure 2-5A). Care should be taken not to perform this evaluation with the ultrasound beam parallel to the plane of the nasal bones, because this might erroneously lead to the conclusion of absent nasal bones (Figure 2-5B).

While several other studies evaluating the role of first trimester nasal bone sonography as a screening test for fetal Down syndrome have also been published, all were limited by being derived from high-risk patient populations or lacking adequate pregnancy outcome ascertainment. The largest study of first trimester fetal nasal bone sonography published to date, and in which an unselected general patient population has been evaluated, did not confirm a useful role for this form of screening (Malone et al., 2004). In a prospective study of 6324 patients having nasal bone sonography by trained and experienced sonographers, adequate views of the fetal profile were obtained in only 76% of cases, and none of the 11 cases of fetal Down syndrome were found to have absent nasal bones. Two further studies of the role of first trimester nasal bone sonography as a screening tool in the general population have also recently been published, and have confirmed these findings that there is only a limited role of this form of screening. One study screened 7116 unselected patients from the general population including 12 cases of Down syndrome, and screened a further 510 high-risk patients including 23 cases of Down syndrome (Prefumo et al., 2006). Absent nasal bones in the first trimester was noted in only 17% of cases in the general population and in 48% of cases in the high-risk population. A further study screened 1800 consecutive patients from the

general population, and absent nasal bones was noted in only 2 of 7 (29%) of Down syndrome cases (Ramos-Corpas et al., 2006).

While it is possible that there may be a role for first trimester fetal nasal bone sonography in the hands of select experts as a second-line screening tool in high-risk patients, current data suggest that this form of sonography should not be used as a general population screening tool.

FIRST TRIMESTER DUCTUS VENOSUS SONOGRAPHY

First trimester Doppler sonographic evaluation of ductus venosus blood flow has been described as an adjunctive test for fetal aneuploidy screening. Forward triphasic pulsatile ductus venosus flow, as illustrated in Figure 2-6, is normal, while reversed flow at the time of the atrial contraction has been associated with aneuploidy and fetal cardiac malformations (Matias et al., 1998). In a series of early studies evaluating this association, between 59% and 93% of aneuploid fetuses had abnormal first trimester ductus venosus flow velocities (Malone and D'Alton, 2003). Abnormal ductus venosus flow velocities were also found in as few as 3% or as many as 21% of normal fetuses. It may therefore be possible that fetal ductus venosus flow velocity waveform analysis may be useful to modify a patient's final risk for aneuploidy following completion of the nuchal translucency measurement. This could be used to either improve the detection rate or alternatively to reduce the false-positive rate.

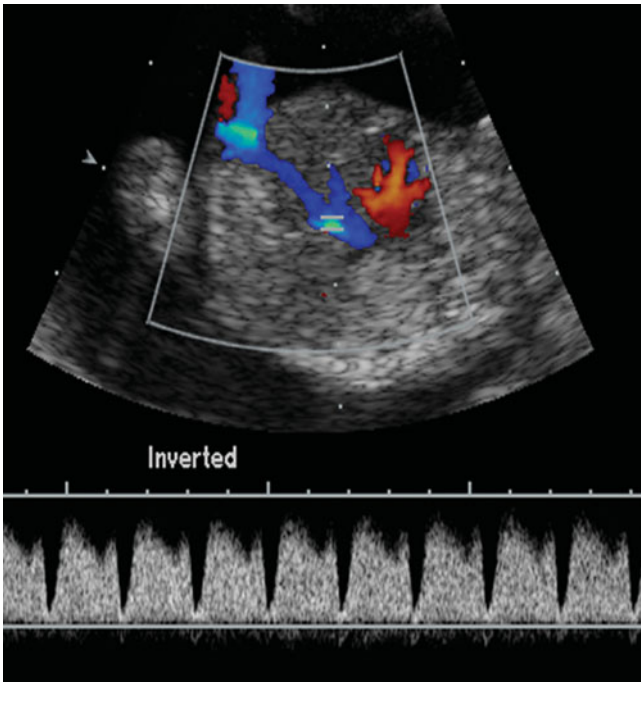

Figure 2-6 Pulsed Doppler sonography image of a normal ductus venosus waveform at 12 weeks' gestation. Of note, the ductus venosus can be identified using color flow as a small vessel with turbulent flow. The nadir of flow during the "a" wave remains forward flowing (arrow).

While it appears that there is some association between abnormal ductus venosus flow studies and aneuploidy in the first trimester, there are several pitfalls that must be considered. The ductus venosus vessel itself may be as small as 2 mm at 10 to 14 weeks, making it difficult to obtain accurate flow velocity waveforms from such a tiny vessel without contamination of the waveform from neighboring vessels. For example, if the Doppler gate is placed too proximally near the umbilical sinus, the normal continuous venous flow from the umbilical vein may obscure absence of flow during the atrial contraction in the ductus venosus. Alternatively, placement of the Doppler gate too far distally, near the insertion of the ductus venosus into the inferior vena cava may lead to the erroneous diagnosis of reversal of flow at the atrial contraction, as such reversal of flow is commonly seen in the inferior vena cava. The current consensus appears to be that first trimester ductus venosus Doppler flow studies should be performed only as a secondary screening test in the hands of experienced sonologists at referral centers, either to modify the final risk for aneuploidy or to help predict the prognosis of fetuses with normal chromosomes and an increased nuchal translucency measurement (Hecher, 2001; Nicolaides et al., 2005).

FIRST TRIMESTER TRICUSPID REGURGITATION EVALUATION

An association has been suggested between fetal aneuploidy and abnormal tricuspid regurgitation noted during first trimester sonography (Nicolaides et al., 2005). To perform this assessment, the fetus should be oriented so that the chest wall is anterior and the fetal heart should be insonated parallel to the ventricular septum. A pulsed Doppler gate of approximately 3 mm size is then placed across the tricuspid valve, with care to ensure that the angle to the direction of flow is as close to zero as possible (Figure 2-7). Significant tricuspid regurgitation is considered to be present if a regurgitant jet of at least 60 cm/s is noted extending to more than half of systole (Falcon et al., 2006).

In a series of 1557 high-risk pregnancies at 11 to 13 weeks' gestation, significant tricuspid regurgitation was noted in only 4% of chromosomally normal fetuses, but was present in 77 of 114 cases (68%) of Down syndrome and 14 of 42 cases (33%) of trisomy 18 (Falcon et al., 2006). These investigators were able to obtain adequate Doppler waveforms of the tricuspid valve in 99% of cases and there was low interobserver variability of measurements.

While these data are encouraging regarding an association between first trimester tricuspid regurgitation and chromosomal abnormalities, like ductus venosus assessment, it is unclear whether this form of screening will have any role in general population screening. Extrapolation of the results of a screening test from a high-risk population, performed in the hands of experts, to implementation in the general population

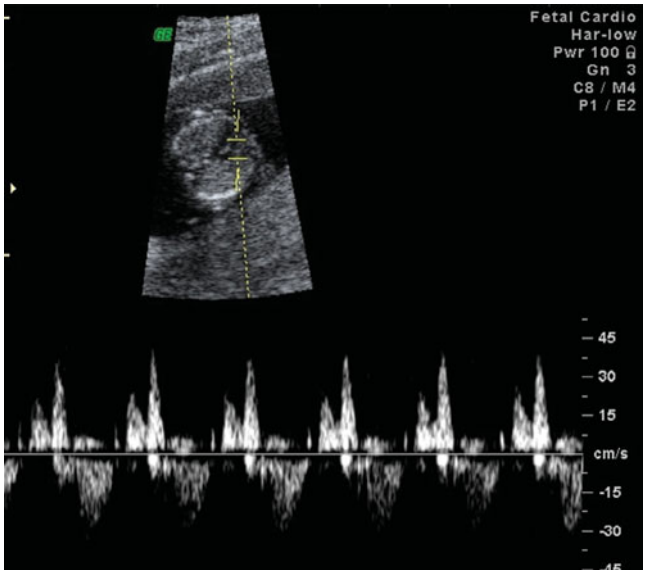

Figure 2-7 First trimester sonographic evaluation for tricuspid regurgitation in a fetus at 11 weeks' gestation. Note the pulsed Doppler gate placed across the tricuspid valve, with the angle to the direction of flow close to zero. There is no regurgitation greater than 60 cm/s.

will likely overstate the true performance of the test. It is likely that first trimester sonography for tricuspid regurgitation may have a role as a second-line test, following an initial high-risk nuchal translucency and serum screen. In this setting, it may have a role in reducing the false-positive rate of screening. In one series of 75,821 first trimester pregnancies, addition of tricuspid regurgitation as a second-line screening test following nuchal translucency and serum screening resulted in a Down syndrome detection rate of 92% for a false-positive rate of only 2.7% (Nicolaides et al., 2005).

NUCHAL TRANSLUCENCY SCREENING IN MULTIPLE GESTATIONS

Prenatal risk assessment for Down syndrome in multiple gestation pregnancies has been quite limited before the advent of nuchal translucency-based screening. Maternal serum screening has not been widely utilized in the setting of multiple gestations because of the potential for discordancy between twins and the impact of different placentas on the various analytes. Nuchal translucency measurements are broadly similar between singleton and twin pregnancies, implying that the Down syndrome detection rates should be similar. The false-positive rate of nuchal translucency screening might be higher in monochorionic twins because some complications unique to monochorionic gestations, such as twin-to-twin transfusion syndrome, might present with increased nuchal translucency measurement (Sebire et al., 2000).

Options for first trimester screening for Down syndrome therefore include providing either a fetus-specific risk based on nuchal translucency alone, or providing an overall pregnancy risk based on combined serum and sonographic markers. In one series of 448 twin pregnancies, nuchal translucency yielded an 88% detection rate for a 7% false-positive rate (Sebire et al., 2000). In another series of 206 twin pregnancies screened using nuchal translucency and first trimester serum markers, the Down syndrome detection rate was estimated to be approximately 75% for a 5% false-positive rate (Spencer and Nicolaides, 2003). To provide a pregnancy-specific risk in twins, a likelihood ratio is calculated for each fetus' nuchal translucency measurement; these two likelihood ratios are then added together, and this is then multiplied by the biochemistry likelihood ratio to provide a final "pseudorisk" calculation (Wald et al., 2003a). Although additional research on the efficacy of this combined first trimester screening in multiple gestations is still needed, nuchal translucency measurement should at least represent an improvement over serum screening in multiple gestations. Currently, some centers use nuchal translucency sonography to assist in selecting fetuses for reduction in higher order multiple gestations.

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CHAPTER 3

Second Trimester Screening for Aneuploidy

Key Points

- Quad marker serum screening is the most effective form of Down syndrome screening in the second trimester (81% detection rate at a 5% false-positive rate).
- Presence of a major structural malformation at second trimester sonographic fetal anatomy survey is an indication for genetic amniocentesis.
- A range of minor markers at second trimester sonographic fetal anatomy survey can be utilized with likelihood ratios to adjust the risk of Down syndrome.
- Absence of major or minor markers at second trimester sonographic fetal anatomy survey reduces the risk of fetal Down syndrome by 60%.
- Combinations of screening tests in both first and second trimesters, such as integrated, stepwise, and contingency screening, may be more efficient than screening in either trimester alone.

INTRODUCTION

While tremendous advances have been made in recent years regarding screening for fetal aneuploidy in the first trimester of pregnancy, the mainstay of screening for aneuploidy has been second trimester serum and sonographic screening. Despite the increasing popularity of first trimester screening, there will always be a role for second trimester aneuploidy screening given that some patients do not present for antenatal care sufficiently early in pregnancy to avail of nuchal translucency and given that a second trimester fetal anatomical survey has become an almost routine aspect of general antenatal care. Additionally, since first trimester screening requires the availability of chorionic villus sampling (CVS) to provide a first trimester diagnosis, in areas in which CVS is not available there will be a continued requirement for second trimester screening protocols leading to amniocentesis.

Options for second trimester screening include serum screening using the Quad test (alphafetoprotein, human chorionic gonadotropin, unconjugated estriol, and inhibin-A), sonographic screening using the so-called Genetic Sonogram, and combinations of serum and sonographic screening.

SECOND TRIMESTER SERUM SCREENING

Maternal serum levels of alphafetoprotein (AFP) and unconjugated estriol (uE3) are both approximately 25% lower in pregnancies complicated by Down syndrome, compared with euploid pregnancies (Wald et al., 1994; Malone et al., 2005). By contrast, levels of hCG and inhibin-A are approximately twice as high in pregnancies complicated by Down syndrome (Wald et al., 1994; Malone et al., 2005). Maternal serum levels of AFP, uE3, and hCG all tend to be decreased in pregnancies complicated by trisomy 18. The combination of AFP, uE3, and hCG, commonly known as the triple screen, can detect 69% of cases of Down syndrome, for a 5% false-positive rate (Wald et al., 2003; Malone et al., 2005). When inhibin-A is added to this test, commonly known as the Quad screen, the Down syndrome detection rate increases to 81%, for a 5% false-positive rate (Wald et al., 2003; Malone et al., 2005). Based on these results, if a second trimester serum sample is obtained for aneuploidy risk assessment, optimal performance will be obtained by measuring the four serum markers, rather than any double or triple marker combination.

Performance of serum screening tests can be maximized by accurate ascertainment of gestational age, and wherever possible, sonographic dating should be used instead of menstrual dating. It is optimal to provide serum screening between 15 and 16 weeks' gestation, thereby allowing the results to be available at the time of second trimester sonographic evaluation. Subsequently, if this sonographic evaluation reveals any markers for aneuploidy, the Down syndrome risk quoted from serum screening can be used with the ultrasound findings to determine the most precise final Down syndrome risk. Adequate time should then be available for diagnostic genetic amniocentesis if indicated by the screening results.

SECOND TRIMESTER SONOGRAPHIC SCREENING

Sonographic evaluation of the fetal anatomy at 18 weeks' gestation has become a routine aspect of antenatal care in most developed countries. When this methodical evaluation for fetal malformations is used to assess the risk for fetal aneuploidy, the term Genetic Sonogram is commonly used. Risk for fetal aneuploidy can be assessed by the detection of either major structural malformations known to be associated with aneuploidy, or by the detection of a range of minor sonographic markers that increase the chances of fetal aneuploidy (Table 3-1).

The detection of certain major structural malformations that are known to be associated with aneuploidy should prompt an immediate consideration for genetic amniocentesis. Major structural malformations that are associated with Down syndrome include cardiac malformations (AV canal defect [Figure 3-1], ventricular septal defect, tetralogy of Fallot), duodenal atresia (Figure 3-2), cystic hygroma (Figure 3-3), and hydrops fetalis (see Chapter 131). The major malformations associated with trisomy 18 include cardiac malformations (AV canal defect, ventricular septal defect, double outlet right ventricle), meningomyelocele, omphalocele, esophageal atresia, rocker bottom feet, cleft lip or palate, cystic hygroma, and hydrops fetalis (see Chapter 130). While the Genetic Sonogram can be performed at any time during the second and third trimesters, the optimal time is likely to be at 17 to 18 weeks' gestation, which is late enough to maximize fetal anatomical evaluation, yet early enough to allow for amniocentesis results to be obtained. When a major structural malformation is found, such as an AV canal defect or a double-bubble suggestive of duodenal atresia, the risk of Down syndrome in that pregnancy can be increased by approximately 20- to 30-fold (Nyberg et al., 1998). For almost all patients, such an increase in their background risk for aneuploidy will be sufficiently high to justify immediate genetic amniocentesis.

Second trimester sonography can also detect a range of minor markers for aneuploidy. The latter are not considered structural abnormalities of the fetus per se, but when noted, may be associated with an increased probability that the fetus is aneuploid. The minor markers that have been commonly linked to Down syndrome include nuchal fold thickening (Figure 3-4), nasal bone hypoplasia (Figure 3-5), mild ventriculomegaly, short femur or humerus, echogenic bowel (Figure 3-6), renal pyelectasis (Figure 3-7), echogenic intracardiac focus (Figure 3-8), clinodactyly (Figure 3-9), sandal gap toe (Figure 3-10), and widened iliac angle (Nyberg et al., 2001). The minor markers that are associated with trisomy 18 include nuchal fold thickening, mild ventriculomegaly, short femur or humerus, echogenic bowel, enlarged cisterna magna, choroid plexus cysts (Figure 3-11), micrognathia, single umbilical artery (Figure 3-12), clenched hands, and fetal growth restriction. It should be noted that almost all data supporting the role of second trimester sonography for minor markers for aneuploidy are derived from high-risk populations, such as patients of advanced maternal age or with abnormal maternal serum screening results. It is still unclear what the relative contribution of screening for such minor markers will be in lower risk patients from the general population.

The sonographic approach to establishing the presence or absence of each of the commonly utilized minor markers is summarized below:

1. *Nuchal fold.* Sonographic measurement of the nuchal fold is performed by imaging the fetal head in an axial plane passing through the posterior fossa (Figure 3-4). Calipers should be placed on the outer aspect of the occipital bone and the outer aspect of the skin. When measured between 15 and 21 weeks' gestation, a cutoff of 5 mm is commonly used to define an abnormally thickened nuchal fold. The finding of an isolated nuchal fold greater than 5 mm is associated with an 11-fold increase in background risk for Down syndrome (Benacerraf and Frigoletto, 1987; Nyberg et al., 2001).

Table 3-1

Major Structural Malformations and Minor Sonographic Markers Associated with Down Syndrome, Trisomy 18 and Trisomy 13

Feature	Down Syndrome	Trisomy 18	Trisomy 13
Major structural malformations	Cardiac defects: – AV canal defect – Ventricular septal defect – Tetralogy of Fallot Duodenal atresia Cystic hygroma Hydrops	Cardiac defects: – Double outlet right ventricle – Ventricular septal defect – AV canal defect Meningomyelocele Agenesis corpus callosum Omphalocele Diaphragmatic hernia Esophageal atresia Clubbed or rocker bottom feet Renal abnormalities Orofacial clefting Cystic hygroma Hydrops	Holoprosencephaly Orofacial clefting Cyclopia Proboscis Omphalocele Cardiac defects: – Ventricular septal defect – Hypoplastic left heart Polydactyly Clubbed or rocker bottom feet Echogenic kidneys Cystic hygroma Hydrops
Minor sonographic markers	Nuchal thickening Mild ventriculomegaly Short humerus or femur Echogenic bowel Renal pyelectasis Echogenic intracardiac focus Hypoplastic nasal bones Brachycephaly Clinodactyly Sandal gap toe Widened iliac angle Growth restriction	Nuchal thickening Mild ventriculomegaly Short humerus or femur Echogenic bowel Enlarged cisterna magna Choroid plexus cysts Micrognathia Strawberry-shaped head Clenched or overlapping fingers Single umbilical artery Growth restriction	Nuchal thickening Mild ventriculomegaly Echogenic bowel Enlarged cisterna magna Echogenic intracardiac focus Single umbilical artery Overlapping fingers Growth restriction

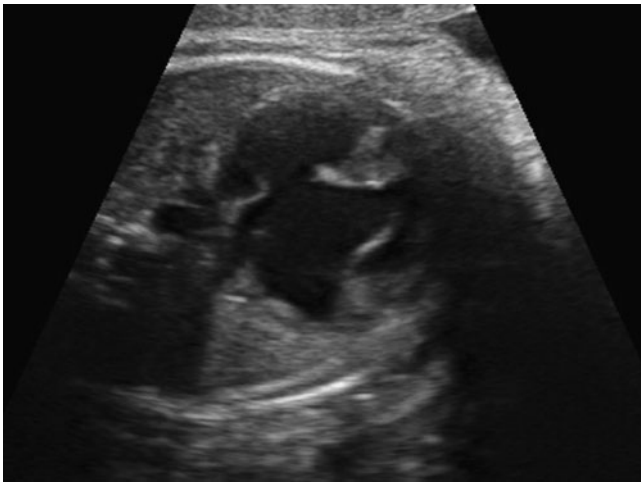

Figure 3-1 Down syndrome fetus at 21 weeks' gestation with atrioventricular canal defect (AVCD).

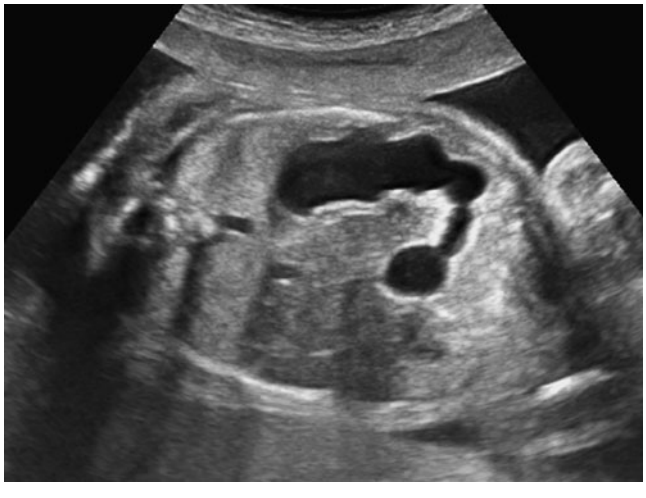

Figure 3-2 Down syndrome fetus at 24 weeks' gestation with double-bubble secondary to duodenal atresia.

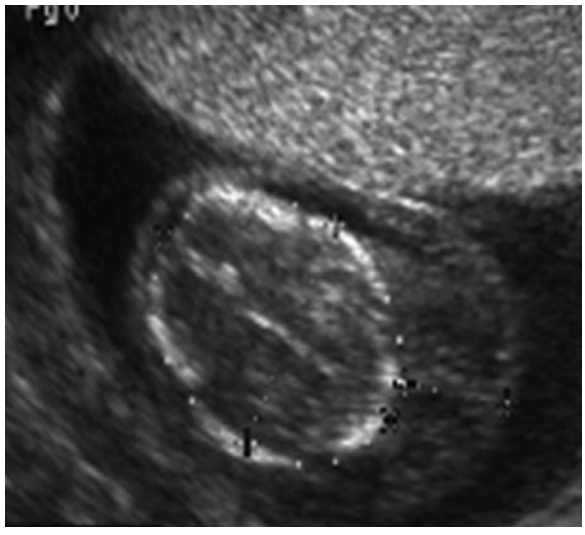

Figure 3-3 Cystic hygroma in fetus with Down syndrome at 15 weeks' gestation. This axial view through the fetal head demonstrates the marked skinfold thickening together with obvious septated appearance.

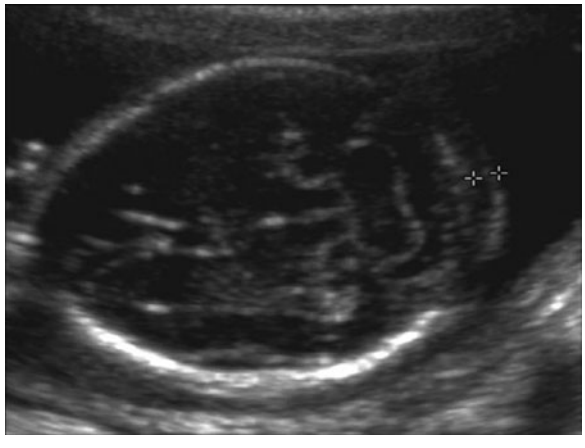

Figure 3-4 Second trimester sonographic measurement of the fetal nuchal fold in a normal fetus. Measurement is taken in the axial plane at the level of the posterior fossa, with calipers placed from the outer skull edge to the outer skin edge.

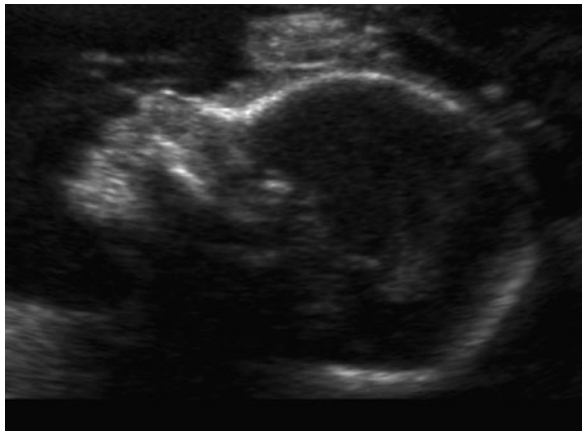

Figure 3-5 Normal fetal nasal bone evaluation at 16 weeks' gestation. A perfect midsagittal plane is demonstrated with echogenicity of the fetal nasal bones visible.

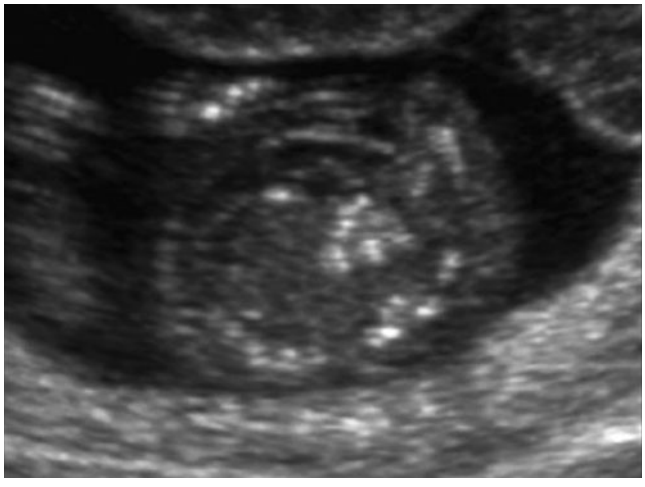

Figure 3-6 Fetal echogenic bowel at 15-week ultrasound evaluation. Transverse view through the fetal abdomen reveals bowel echogenicity as bright as fetal bone.

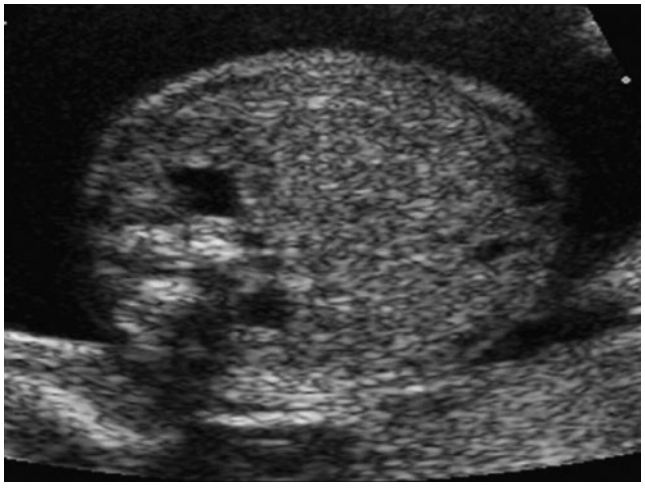

Figure 3-7 Sonographic evaluation of fetus at 17 weeks' gestation revealing bilateral pyelectasis with both renal pelves measuring greater than 3 mm in anteroposterior diameter.

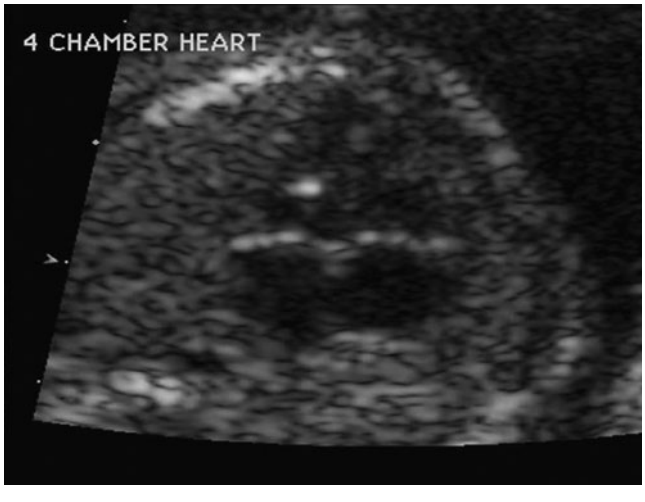

Figure 3-8 Second trimester fetal anatomic evaluation demonstrating echogenic intracardiac focus in the left ventricle of the fetal heart.

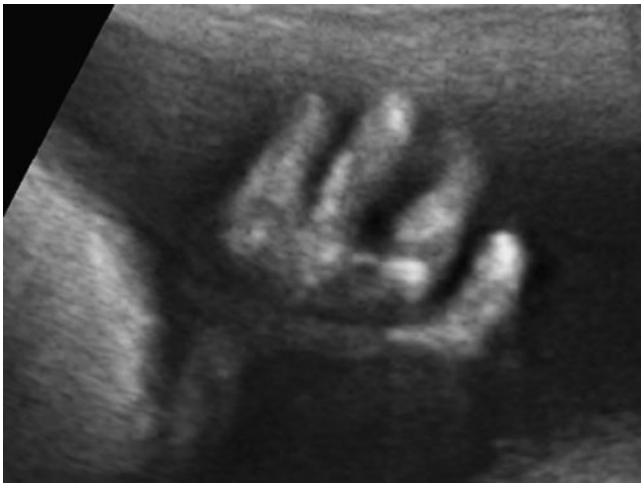

Figure 3-9 Clinodactyly in a fetus at 23 weeks' gestation with Down syndrome. The fifth digit is significantly smaller than expected with middle phalanx hypoplasia.

2. *Echogenic bowel.* Sonographic visualization of bright bowel in the fetal abdomen is considered abnormal if the echogenicity is similar to that of fetal bone (Figure 3-6) (Nyberg et al., 1990b). A common pitfall with this minor marker is to overdiagnose the finding because of inappropriately high sonographic gain settings. When present, it is associated with a 6.7-fold increase in background risk for Down syndrome.
3. *Humerus and femur length.* The expected humerus and femur lengths can be estimated after a measurement of the fetal biparietal diameter (BPD) is obtained, and can be calculated using the formula $\{-7.9404 + 0.8492 \times \text{BPD}\}$ for the humerus, or $\{-9.645 + 0.9338 \times \text{BPD}\}$ for the femur. A ratio of observed to expected humerus or femur lengths less than 0.90 is considered abnormal (Nyberg et al., 1990a, 1993). It is likely that separate norms will be needed to interpret long bone length in certain populations, such as biometry tends to be shorter amongst Asian fetuses (Shipp et al., 2001). The isolated finding of a short humerus or a short femur is associated with a fivefold and a 1.5-fold increase in background risk for Down syndrome respectively.
4. *Echogenic intracardiac focus.* Calcification of the papillary muscle in the intracardiac ventricles can be demonstrated by sonography as a discrete echogenic dot within the left or right ventricle (Figure 3-8) (Brown et al., 1994). The majority of cases are present in the left ventricle, and care should be exercised in imaging the fetal heart from multiple angles to avoid overdiagnosis due to specular reflection. Additionally, echogenic intracardiac focus may be

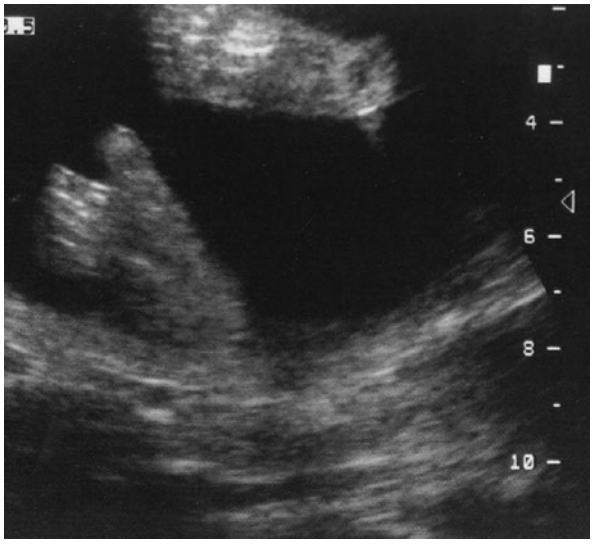

Figure 3-10 Prenatal sonographic image demonstrating the sandal gap.

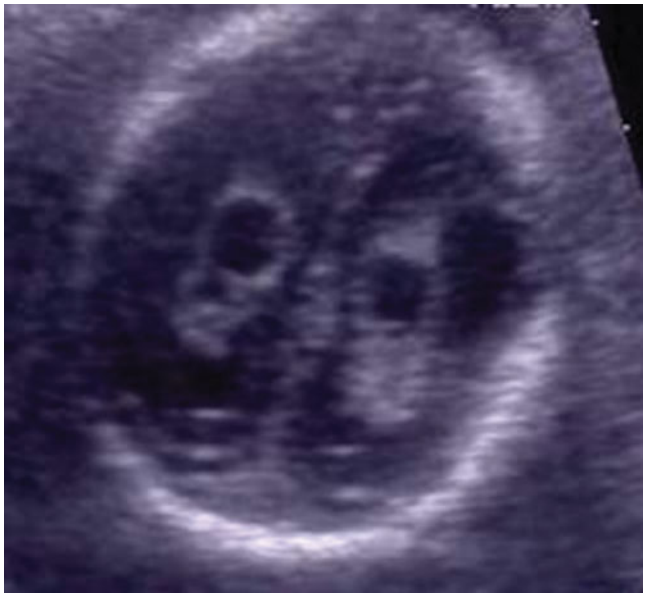

Figure 3-11 Bilateral choroid plexus cysts in a fetus with trisomy 18 at 18 weeks' gestation.

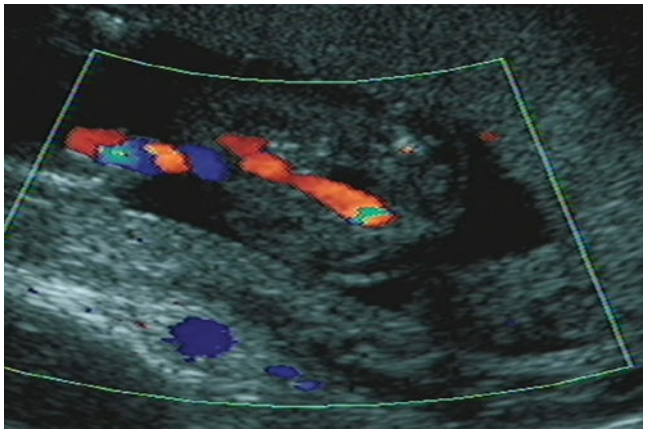

Figure 3-12 Single umbilical artery in a fetus at 23 weeks' gestation with trisomy 18. Color Doppler evaluation at the umbilical cord insertion site into the fetal abdomen, angled caudally to include the fetal bladder demonstrates only one umbilical artery at the dome of the bladder. The right umbilical artery is absent.

considered a normal variant in certain populations, being present in up to 30% of normal Asian fetuses (Shipp et al., 2000). When an echogenic intracardiac focus is detected, the background risk for Down syndrome can be increased by a factor of 1.8.

5. *Pyelectasis.* Sonographic measurement of the anteroposterior diameter of the renal pelves from 15 to 20 weeks' gestation should normally reveal a diameter of 3 mm or less (Figure 3-7) (Benacerraf et al., 1990). Bilateral pyelectasis, in which both renal pelvises measure 4 mm or greater, is associated with a 1.5-fold increase in background risk for Down syndrome.
6. *Nasal bones.* Failure to visualize the nasal bone, on a perfect sagittal fetal profile during the second trimester, or visualization of hypoplastic nasal bones, has recently been suggested as a powerful screening tool for Down syndrome (Figure 3-5) (Bromley et al., 2002; Vintzileos et al., 2003). It is likely that this second trimester approach may not be as subjective as first trimester nasal bone evaluation. Very limited data exist to date assessing the strength of this association during the second trimester. It is possible that the absence or hypoplasia of nasal bones may increase the background risk for Down syndrome by up to a factor of 8.
7. *Choroid plexus cyst.* Sonographic evaluation of the choroid plexus, using an axial view through the upper portion of the fetal head, can frequently reveal the presence of one or more discrete cysts (Figure 3-11). While debated extensively in the past, it does not appear that isolated choroid plexus cysts represent markers for Down syndrome, although they have been described as being associated with trisomy 18 (American College of Obstetricians and Gynecologists, 2001). It is possible that the detection of an isolated choroid plexus cyst might increase the background risk for trisomy 18 by a factor of 7. However, since the background risk for trisomy 18 is generally very low, it is unlikely that the finding of an isolated cyst in a low-risk patient is of any clinical significance. Additionally, it does not appear that the number, size, or evolution of choroid plexus cysts has any impact on trisomy 18 risk assessment.

USING SECOND TRIMESTER SONOGRAPHIC MARKERS FOR COUNSELING

To objectively counsel patients following the prenatal diagnosis of a minor sonographic marker, likelihood ratios can be used to create a more precise risk assessment for the patient that their fetus might be affected with Down syndrome. Table 3-2 summarizes the likelihood ratios that can be used to modify a patient's risk for Down syndrome, depending on which minor marker is detected. If no markers are present, the patient's a priori risk can be multiplied by 0.4, effectively reducing their chances of carrying a fetus with Down syndrome by 60% (Nyberg et al., 2001). The likelihood ratio values listed for each marker assume that the marker is an isolated finding. By contrast, when more than one minor marker is noted in the same fetus different likelihood ratios must be used, with the risk for Down syndrome being increased by a factor of 10 when 2 minor markers are detected and by a factor of 115 when 3 or more minor markers are found (Nyberg et al., 2001).

It should also be noted that the 95% confidence interval values for each marker's likelihood ratios are rather wide. These values should therefore be used only as a general guide for counseling patients, and care should be exercised to avoid implying too much precision in the final risk estimates. Accuracy of risk estimates however can be maximized by using the best available a priori risk value for a particular patient, such as the results of maternal serum marker screening or first trimester combined screening, rather than maternal age, when available. For example, if a 35-year-old patient has an age-related risk of Down syndrome of 1 in 250, and has had a second trimester serum Quad screen done that reveals a reduced risk of 1 in 1000, the finding of an echogenic intracardiac focus on genetic sonography should result in a final Down syndrome risk of 1 in 555 and not 1 in 140 (i.e., 1:1000 multiplied by 1.8, rather than 1:250 multiplied by 1.8).

Table 3-2

Likelihood Ratios for Down Syndrome When an Isolated Minor Sonographic Marker Is Detected. The Patient's A Priori Risk Is Multiplied by the Appropriate Positive Likelihood Ratio to Yield an Individualized Post-Test Risk for Fetal Down Syndrome

Minor Marker	Likelihood Ratio	95% Confidence Intervals
Nuchal fold >5 mm	11	6–22
Echogenic bowel	6.7	3–17
Short humerus	5.1	2–17
Short femur	1.5	0.8–3
Echogenic intracardiac focus	1.8	1–3
Pyelectasis	1.5	0.6–4
Any two minor markers	10	6.6–14
Any three or more minor markers	115	58–229
No markers	0.4	0.3–0.5

COMPARATIVE ROLE OF FIRST AND SECOND TRIMESTER SCREENING

As demonstrated in Figures 2-3A and 2-3B in the preceding chapter, second trimester serum screening for Down syndrome is similarly effective to first trimester combined screening using nuchal translucency sonography, PAPP-A and free ßhCG. Only when performed at 11 weeks' gestation does first trimester combined screening have a significantly better performance than second trimester Quad marker serum screening (87% vs. 81% Down syndrome detection, respectively, at a 5% false-positive rate). Additionally, first trimester combined screening has the lowest false-positive rate, compared with second trimester Quad marker serum screening.

COMBINED FIRST AND SECOND TRIMESTER SCREENING

Given the excellent performance characteristics of both first trimester combined screening and second trimester Quad marker serum screening, it is logical to assume that improved screening results could be obtained by performing screening tests in both trimesters in the same patient. However, with the increasing range of Down syndrome screening tests now available, confusion will likely develop when patients have more than one screening test performed.

It is not valid to perform separate Down syndrome risk assessments at different gestational ages by providing independent estimations of risk on each test. For example, if a particular population has been subjected to first trimester screening, approximately 80% of the cases of Down syndrome will have already been discovered and terminated prior to 15 weeks' gestation (Wapner et al., 2003; Malone et al., 2005; Nicolaides et al., 2005). If the remaining population is then subjected to second trimester screening with risks calculated independently, the positive predictive value of an abnormal second trimester screen will be significantly reduced. The individual risk calculation provided to such patients will be inaccurate. Additionally, since both screening tests carry their own false-positive rate, the overall population false-positive rate at the completion of all screening tests may be extremely high. In one recent study, such an independent sequential screening policy (nuchal translucency, PAPP-A, fβhCG in the first trimester, followed by triple screen performed independently in the second trimester) suggested a 98% Down syndrome detection rate, but at an unacceptably high 17% false-positive rate (Platt et al., 2004).

If screening tests are to be performed at different gestational ages in the same patient population, it is essential to ensure that earlier marker results are incorporated into the interpretation of later tests. Options that can be used to accurately combine both first and second trimester screening tests include integrated screening, stepwise sequential screening, and contingent screening.

Integrated Screening

This form of risk assessment refers to a two-step screening protocol, with results not being released until all screening steps are completed. Sonographic measurement of nuchal translucency, together with serum assay for PAPP-A, is obtained between 10 and 13 weeks' gestation, followed by a second serum assay for AFP, hCG, uE3, and inhibin-A obtained between 15 and 16 weeks' gestation. A single risk assessment is then calculated at 16 weeks' gestation. This "fully integrated" test has a Down syndrome detection rate of 95%, for a 5% false-positive rate (Wald et al., 2003; Malone et al., 2005). A variant of this approach, referred to as the "serum integrated" test, involves blood tests only, including PAPP-A in the first trimester, followed by AFP, hCG, uE3, and inhibin-A in the second trimester. This latter test, which does not require an NT ultrasound assessment, has a Down syndrome detection rate of 86%, for a 5% false-positive rate (Wald et al., 2003; Malone et al., 2005).

For some patients who are anxious to receive rapid screening results, or for those who might wish to avail of a first trimester CVS, it is possible that such integrated screening tests might not be acceptable, as a delay inevitably exists between the time of first trimester screening measurements and release of results in the second trimester. However, for patients who may not be interested in, or have access to, first trimester CVS, the efficiency of being provided with a single Down syndrome risk assessment result, which maximizes detection and minimizes false-positives, may make such integrated screening tests appear attractive.

Stepwise Screening

In contrast to integrated screening, stepwise screening refers to multiple different Down syndrome screening tests being performed, with risk estimates being provided to patients upon completion of each step. With this approach, patients undergo first trimester risk assessment using nuchal translucency, PAPP-A, and fβhCG, but immediate risk results are only provided to the highest risk patients (e.g., the highest 2.5% risk values). All other patients return at 15 weeks' gestation, at which time the Quad serum markers are obtained, and are combined with nuchal translucency and PAPP-A values to provide a final risk estimate. In the FASTER Trial, such a stepwise sequential screening program detected 95% of Down syndrome cases at a 4.9% false-positive rate (Malone et al., 2005). The benefit of this screening approach is detection and false-positive rates similar to integrated screening. A potential advantage over integrated screening is that it allows patients in the first trimester to avail of an immediate CVS, should their risk estimate justify this test, without having to wait until 16 weeks when the integrated screening results are provided. Patients could possibly get the benefit of early diagnosis associated with first trimester screening, as well as the higher detection rate for Down syndrome associated with integration of both first and second trimester screening tests (Malone, 2005).

Contingent Screening

A further refinement to stepwise sequential screening is the option of contingent screening. With this approach first trimester risk results are divided into three groups. The highest risk group of patients (e.g., risk greater than 1 in 100) is offered CVS immediately and obtains a definitive diagnosis. The lowest risk group (e.g., risk lower than 1 in 1000) is reassured in the first trimester and has no further Down syndrome screening tests performed. The intermediate risk group (e.g., risk between 1 in 100 and 1 in 1000) returns at 15 weeks' gestation, at which time the Quad serum markers are obtained and are combined with earlier markers to give a more precise final Down syndrome risk estimation.

The advantage of this approach, compared with integrated and stepwise screening, is that it may have similar detection and false-positive rates, but with only a small percentage of patients having to undergo further second trimester testing (Wright et al., 2004; Cuckle et al., 2008). In the FASTER Trial, a contingent screening protocol detected 91% of Down syndrome cases at a 4.5% false-positive rate (FPR) using cutoffs of >1 in 30 to define positive screens and 1 in 30 to 1500 to define borderline (Cuckle et al., 2008). At a fixed false-positive rate, contingent screening achieved comparable detection rates as stepwise and integrated screening, but substantially reduced the number of women needing to return for second trimester serum screening (Cuckle et al., 2008).

SECOND TRIMESTER SCREENING IN MULTIPLE GESTATIONS

As with the case for first trimester screening, prenatal risk assessment for Down syndrome in multiple gestation pregnancies is more limited than with singletons. Sonographic evaluation of each individual fetus in the second trimester for major structural malformations or minor markers will allow for the calculation of fetus-specific risks for aneuploidy. There does not appear to be any evidence that the performance of these sonographic markers is any less efficient in twin or higher order multiple gestations, other than the technical challenge in obtaining adequate imaging in such cases.

Interpretation of maternal serum screening, however, can be difficult because of the potential for discordancy between twins and the impact of different placentas on the various analytes. On average, second trimester levels of the commonly utilized biochemical markers are twice as high as in singleton pregnancies (Cuckle, 1998). In dichorionic pregnancies, if one fetus is euploid and another is aneuploid, the opposite direction in which biochemical markers from individual placentas go may be masked by the overall maternal serum levels. Maternal serum markers may be interpretable however using the "pseudorisk" approach. This involves dividing the observed multiple of the median (MoM) values found in each twin pregnancy being evaluated, by the median value found in normal singletons. Minimal data are available from twin pregnancies complicated by Down syndrome to validate this approach. The limited studies performed to date have suggested that second trimester serum screening in twins may have Down syndrome detection rates of 50% to 60% at false-positive rates of 7% to 10% (Spencer et al., 1994; Muller et al., 2001). For this reason, most prenatal diagnosis centers continue to rely on sonographic evaluation to provide aneuploidy risk assessment for multiple gestations in the second trimester.

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CHAPTER 4

Prenatal Diagnostic Procedures

Key Points

- Prenatal diagnostic procedures allow prenatal detection of an ever-expanding list of fetal abnormalities by obtaining genetic, biochemical, and physiologic information about the fetus.
- The specific procedure selected depends upon the gestational age and the information needed.
- Genetic consultation should be available to help patients choose which diagnostic procedure is optimal for them.
- Earlier prenatal diagnostic methods have become increasingly more common and are likely to increase in popularity. The most studied of these is CVS. Transcervical and transabdominal techniques are equally effective.
- Early amniocentesis is not recommended now that compelling evidence regarding its disadvantages has been published.
- Advances in molecular techniques have led to a declining number of reasons for using percutaneous umbilical blood sampling. It is now rarely the procedure chosen for determining fetal karyotype.
- Percutaneous umbilical blood sampling is the most direct method of evaluating fetal anemia secondary to severe Rh_o(D) disease.
- The majority of invasive diagnostic procedures are associated with low rates of complications commensurate with provider skill and experience.

AMNIOCENTESIS

Amniocentesis was first used during the 1880s for decompression of polyhydramnios (Lambl, 1881). In 1930, placental localization was achieved after the intra-amniotic injection of contrast medium (Menees et al., 1930). Aburel (1937) described the termination of a pregnancy by the intra-amniotic injection of hypertonic saline. During the 1950s, the role of amniocentesis and measurement of bilirubin concentrations in monitoring rhesus disease was reported (Bevis, 1950; Walker, 1957).

Amniocentesis for fetal chromosome analysis was also initiated in the 1950s. (Until 1956, the number of human chromosomes was not known.) The first reported application was for fetal sex determination (Fuchs and Riis, 1956). The feasibility of culturing and karyotyping amniotic fluid cells was demonstrated by Steele and Breg in 1966. The first prenatal diagnosis of an abnormal karyotype, a balanced translocation, was reported in 1967 by Jacobson and Barter. Trisomy 21 was detected prenatally by Valenti et al., in 1968. During the same year the first diagnosis of the metabolic disorder galactosemia was reported by Nadler (1968).

Indications

Indications for amniocentesis include (1) increased risk for fetal aneuploidy, (2) increased risk for known fetal genetic or

biochemical abnormalities, (3) increased risk for fetal open neural tube defect (ONTD), (4) evaluation for fetal infection, and (5) documentation of fetal lung maturity.

In the United States, while it had been considered standard practice to offer genetic counseling and prenatal cytogenetic analysis to all women of advanced maternal age, (age 35 years or older at their expected date of delivery), these recommendations have changed. Most recent guidelines from the American College of Obstetricians and Gynecologists emphasize that all patients, regardless of age, should have the option for invasive prenatal cytogenetic analysis if they prefer (ACOG, 2007). It is no longer considered acceptable clinical practice to limit or recommend invasive testing of fetal karyotype purely on the basis of maternal age. Amniocentesis is the most common invasive test used for this indication. The risk of numerical chromosomal abnormalities (aneuploidy) increases with advancing maternal age as a result of nondisjunction, which occurs during maternal meiosis. The relationship between maternal age and the estimated risk of chromosomal abnormalities is shown in Table 4-1 (Hook, 1981; Hook et al., 1983). It is now also standard practice to offer invasive prenatal diagnosis to patients with increased risk for aneuploidy according to the results of first and/or second trimester screening for aneuploidy (see Chapters 2 and 3 for more details on the various methods of maternal screening for aneuploidy).

Similar to patients with singletons, invasive prenatal diagnosis should be considered in all patients with multiple fetuses with an increased risk for aneuploidy (Meyers et al., 1997; American Academy of Pediatrics and The American College of Obstetricians and Gynecologists, 2002; The American College of Obstetricians and Gynecologists, 2004).

Invasive prenatal diagnosis is also indicated when there is a need to obtain fetal material for cytogenetic, biochemical, or DNA studies. Increasingly, the DNA abnormalities responsible for the etiology of many disorders are being identified. A list of some of the common genetic conditions for which DNA-based prenatal diagnosis is available is given in Table 4-2, although this list is far from complete. More than 100 abnormalities of lipid, mucopolysaccharide, amino acid, and carbohydrate metabolism are also amenable to prenatal diagnosis through the biochemical analyses of cultured amniotic fluid cells. Note, however, that the substantially larger amount of tissue obtained by chorionic villus sampling (CVS) makes CVS the preferred method of diagnosing single gene biochemical disorders in which the DNA abnormality is known.

Established screening tests for fetal ONTDs include measurement of maternal serum alpha fetoprotein levels (MSAFP) during the second trimester, followed by amniocentesis in patients with elevated results (UK Collaborative Study, 1979), or sonographic screening for brain and spine malformations. The ultrasound diagnosis of fetal ONTD has been greatly enhanced by the recognition of associated abnormalities in the skull and brain. These abnormalities include cerebral ventriculomegaly, microcephaly, frontal bone scalloping (lemon sign), and obliteration of the cisterna magna with either an "absent" cerebellum or abnormal posterior curvature of the cerebellar hemispheres (banana sign) (see Chapter 19) (Nicolaides et al., 1986). Van den Hof et al. (1990) have reported on the diagnosis of ONTD in 130 fetuses among 1561 patients at high risk for fetal neural tube defects who were referred for detailed ultrasound examination. The examinations revealed associated abnormalities of the skull and brain in 129 of the 130 fetuses with ONTD. As a result of this evidence of the accuracy of ultrasound in the diagnosis of neural tube defects, the need for amniocentesis in the evaluation of an elevated MSAFP has been questioned.

Table 4-1

Relation Between Maternal Age and the Estimated Rate of Chromosomal Abnormalities*

Age	Risk of Down Syndrome	Risk of Chromosomal Abnormality
20	1/1667	1/526
25	1/1250	1/476
30	1/952	1/385
35	1/385	1/202
36	1/295	1/162
37	1/227	1/129
38	1/175	1/102
39	1/137	1/82
40	1/106	1/65
41	1/82	1/51
42	1/64	1/40
43	1/50	1/32
44	1/38	1/25
45	1/30	1/20
46	1/23	1/16
47	1/18	1/13
48	1/14	1/10
49	1/11	1/7

**Ages are at the expected time of delivery.*
From D'Alton ME, DeCherney AH. Prenatal diagnosis. N Engl J Med. *1993;328:114-120.*

Table 4-2

List of Conditions Amenable to DNA Analysis

Disorder	Mode of Inheritance	Chromosome	Disorder	Mode of Inheritance	Chromosome
α_1-Antitrypsin deficiency	AR	14	Marfan syndrome	AD	15
α_1-Thalassemia	AR	16	Multiple endocrine neoplasia type I	AD	11
Adult polycystic kidney disease (type 1)	AD	16	Multiple endocrine neoplasia type IIA	AD	10
β-Thalassemia	AR	11	Myotonic dystrophy	AD	19
Congenital adrenal hyperplasia	AR	6	Neurofibromatosis (type 1)	AD	17
Cystic fibrosis	AR	7	Neurofibromatosis (type 2)	AD	22
DiGeorge syndrome	AD	22	Norrie disease	XLR	X
Duchenne/Becker muscular dystrophy	XLR	X	Ornithine transcarbamylase deficiency	XLR	X
Familial Alzheimer disease	AD	21	Phenylketonuria	AR	12
Familial hypercholesterolemia	AD	19	Retinoblastoma	AD	13
Familial polyposis coli	AD	5	Sickle cell anemia	AR	11
Fragile X syndrome	XLR	X	Spinal muscular atrophy	AR/AD	5
Gardner syndrome	AD	5	Tay–Sachs disease	AR	5
Hemoglobin Sc	AR	11	von Hippel–Lindau syndrome	AD	3
Hemophilia A (factor IX deficiency)	XLR	X	Wiskott–Aldrich syndrome	XLR	X
Huntington disease	AD	4			

AR = autosomal recessive; AD = autosomal dominant; XLR = X-linked recessive.
From D'Alton ME. Prenatal diagnostic procedures. Part 1—Diagnosis and treatment of fetal disease. Semin Perinatol. *1994;18:140-162.*

Many centers no longer offer either stand-alone MSAFP screening or amniocentesis for an elevated MSAFP level, given the significant advances in obstetric sonographic precision for this abnormality. At centers adept at diagnosing ONTD sonographically, amniocentesis can be reserved for patients with suspicious ultrasound findings or large MSAFP elevations despite a normal scan or when it is impossible to adequately visualize fetal anatomy. At such specialized centers, patients can be counseled that with a normal ultrasound examination, in which optimal views are obtained of the fetal head and spine, the risk of ONTD can be reduced by up to 95%, and therefore patients may elect not to undergo amniocentesis (American College of Obstetricians and Gynecologists, 1996). Patients who are at increased risk for neural tube defects (i.e., who have elevated MSAFP levels), who have a history of neural tube defects, or who are taking antifolate medications should be referred to centers with ultrasonographers experienced in diagnostic ultrasound. If ultrasound examination

demonstrates a normal spine, cranium, and cerebellum, the chance of an undetected spinal abnormality is low. Therefore, amniocentesis, with a procedure-related risk of 0.1% up to 1%, is probably unnecessary. Some centers have calculated a revised risk of neural tube defects on the basis of the MSAFP value and normal results on ultrasound examination at their particular center (Richards et al., 1988; Nadel et al., 1990). For example, in our reference laboratory in a Caucasian patient with an a priori risk for ONTD of 1 in 1000, an MSAFP of 2.8 multiples of the median (MoM) gives a risk of 1 in 170. When an adequate ultrasound examination is performed by competent ultrasonographers and is interpreted as a normal scan, this risk may be reduced by 95%, giving a reassigned risk of approximately 1 in 3400. In our center, amniocentesis is reserved for cases in which there is incomplete visualization of the fetus (as a result of maternal obesity or fetal position), serum levels of MSAFP greater than 3.5 MoM in the presence of normal sonographic examination, or suspicious ultrasound findings.

Premature delivery is one of the leading causes of perinatal death and long-term handicap. The association between intrauterine infection and premature labor, in the presence and absence of ruptured membranes, has stimulated research into amniocentesis for the diagnosis of subclinical intrauterine infection (Romero et al., 1989; Shim et al., 2004). Amniocentesis in the clinical management of preterm labor or preterm premature rupture of membranes (PPROM) may be utilized for cases in which there is a suspicion of intrauterine infection.

Measurement of the amniotic fluid lecithin: sphingomyelin ratio (Gluck et al., 1974) and phosphatidylglycerol (Hallman et al., 1976) level is useful for the assessment of fetal lung maturity. The need for these tests has declined because of improved neonatal care and the introduction of better methods of ultrasound assessment of gestational age and fetal surveillance. Elective preterm delivery should only be performed for a significant maternal or fetal indication. Nonetheless, amniocentesis in the third trimester is a safe procedure (Hodor et al., 2006).

Assessment of the severity of Rh disease and the need for fetal blood transfusion or early delivery had previously been based on the results of amniocentesis and the interpretation of the results of spectrophotometric estimation of amniotic fluid bilirubin (Liley, 1961). However, Doppler measurements of the middle cerebral artery peak systolic velocity have now replaced amniocentesis for this indication. MCA Dopplers can now be used to noninvasively diagnose anemia in fetuses without hydrops who are at risk for anemia secondary to conditions such as Rh_o(D) sensitization and parvovirus B19 infection (Mari et al., 2000; Cosmi et al., 2002) (Figure 4-1). This noninvasive method of detecting fetal anemia decreases the number of amniocenteses and percutaneous umbilical blood sampling (PUBS) procedures needed in these high-risk patients. The value of the middle cerebral artery peak systolic velocity is expressed as MoM. Middle cerebral artery peak systolic velocity >1.50 MoM is considered to be suggestive of anemia and is considered an indication for PUBS (Table 4-3). In the assessment of severe Rh sensitization in

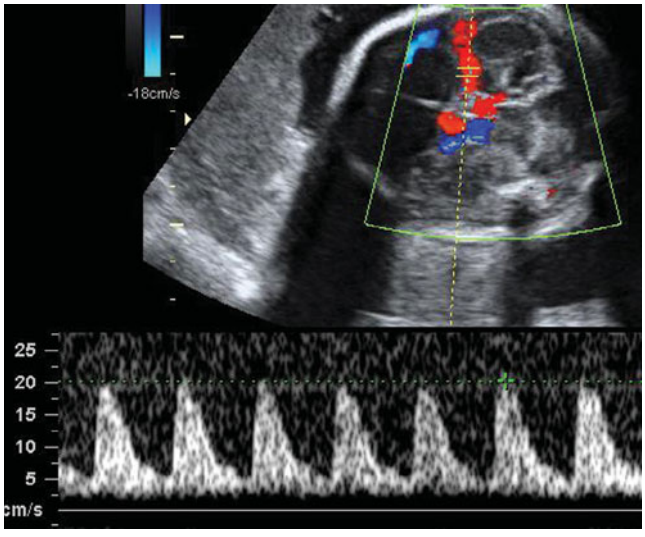

Figure 4-1 Middle cerebral artery peak systolic velocity measured in a case of fetal parvovirus exposure.

Table 4-3

Expected Middle Cerebral Artery Peak Velocity of Systolic Blood Flow by Gestational Age (cm/s)

Gestational Age	1.00 median	1.29	1.50	1.55
18	23.2	29.9	34.8	36.0
20	25.5	32.8	38.2	39.5
22	27.9	36.0	41.9	43.3
24	30.7	39.5	46.0	47.5
26	33.6	43.3	50.4	52.1
28	36.9	47.6	55.4	57.2
30	40.5	52.2	60.7	62.8
32	44.4	57.3	66.6	68.9
34	48.7	62.9	73.1	75.6
36	53.5	69.0	80.2	82.9
38	58.7	75.7	88.0	91.0
40	64.4	83.0	96.6	99.8

From Mari G, Deter RL, Carpenter RL, et al. Collaborative Group for Doppler Assessment of the Blood Velocity in Anemic Fetuses. Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization. N Engl J Med. *2000;342:9-14.*

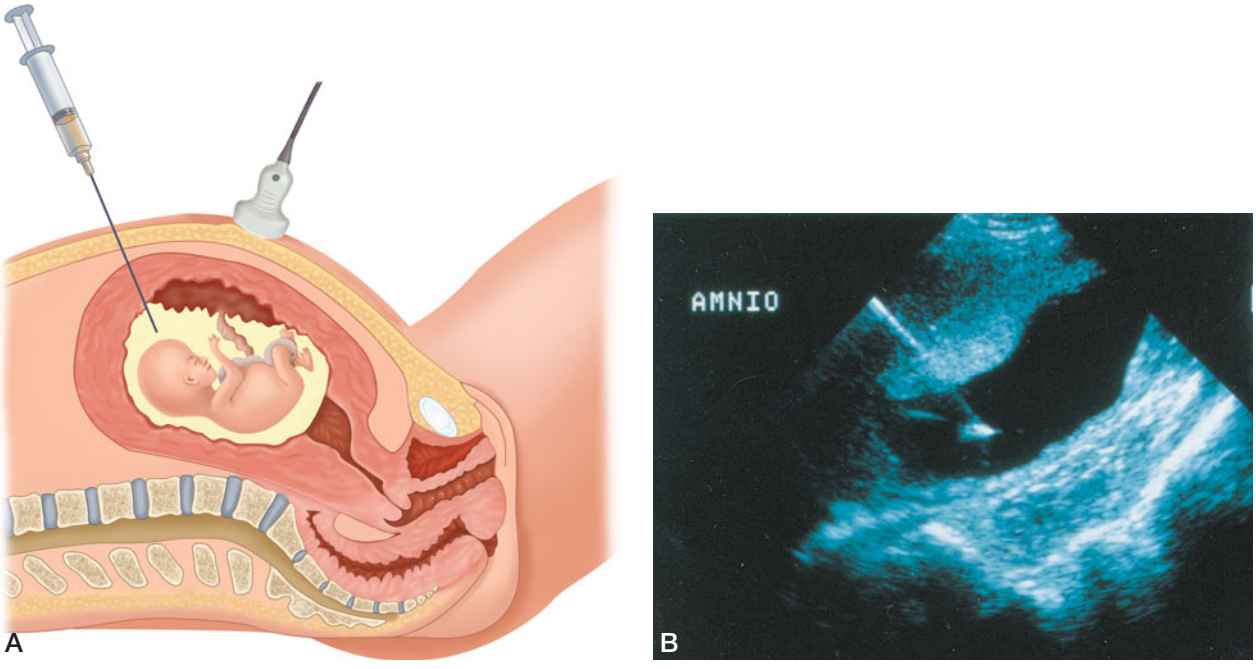

Figure 4-2 **A.** Diagrammatic representation of amniocentesis. **B.** Ultrasound image of amniocentesis.

the midtrimester, the only accurate method for predicting the severity of the disease is measurement of the hemoglobin concentration.

Technique

Early attempts at genetic amniocentesis were made transvaginally. Subsequently, the transabdominal approach has been shown to be the only acceptable approach. During the 1960s amniocentesis was performed "blindly." During the 1970s and early 1980s, ultrasonography was used to identify a placenta-free area for entry into a pocket of amniotic fluid. This position was marked on the maternal abdomen, and after a variable length of time, the operator would blindly insert the needle.

In contemporary practice, amniocentesis is always performed with continuous ultrasound guidance. An ultrasound scan is first performed to determine the number of fetuses present, to confirm gestational age and fetal viability, and to document normal anatomy. The maternal abdomen is washed with antiseptic solution; it is unnecessary for the technician to scrub and gown. Continuously guided by ultrasound, a 22-gauge needle is introduced into the amniotic cavity (Figures 4-2A and 4-2B). While the procedure may be performed either freehand or with needle guides, the vast majority of centers currently use a freehand technique (Jeanty et al., 1983; Lenke et al., 1985). The freehand technique is generally preferred because it allows easier manipulation of the needle if the position of the target is abruptly altered by a uterine contraction or fetal movement. Furthermore, this technique can be easily adapted to all ultrasound-guided diagnostic or therapeutic procedures, such as PUBS. Fetal heart rate and activity is documented immediately following the procedure.

Technique in Twins

Amniocentesis is a safe and accurate procedure for sampling twin pregnancies between 15 and 20 weeks' gestation. Amniocentesis in multiples was first described by Elias et al. in 1980 (Elias et al., 1980). Under ultrasound guidance, a spinal needle is introduced into one sac. After aspirating fluid, a blue dye (indigo carmine) is injected into that sac to serve as a marker before removing the initial needle. A second needle is then inserted into the other sac and the aspiration of clear fluid indicates that the second sac had been successfully entered (Figure 4-3). This technique is recommended when sampling either dichorionic or monochorionic twin pregnancies (but is not necessary in monoamniotic gestations). Likewise, the procedure can be used in triplets and higher order multiples. It is essential to map and document the location of each fetus and placenta at the time of amniocentesis. If discordant results are obtained and the patient desires selective termination, the appropriate fetus can then be targeted.

While use of a marker dye is extremely helpful in performing amniocentesis on patients with multiples, the instillation of some material has been associated with toxicity. For example, methylene blue has been linked to fetal hemolysis, multiple ileal obstructions, and jejunal atresia when injected into the amniotic fluid (Cowett et al., 1976; Nicolini and Monni 1990; Van der Pol et al., 1992). Indigo carmine has been evaluated and has not been shown to be associated with abnormal fetal outcomes (Cragan et al., 1993).

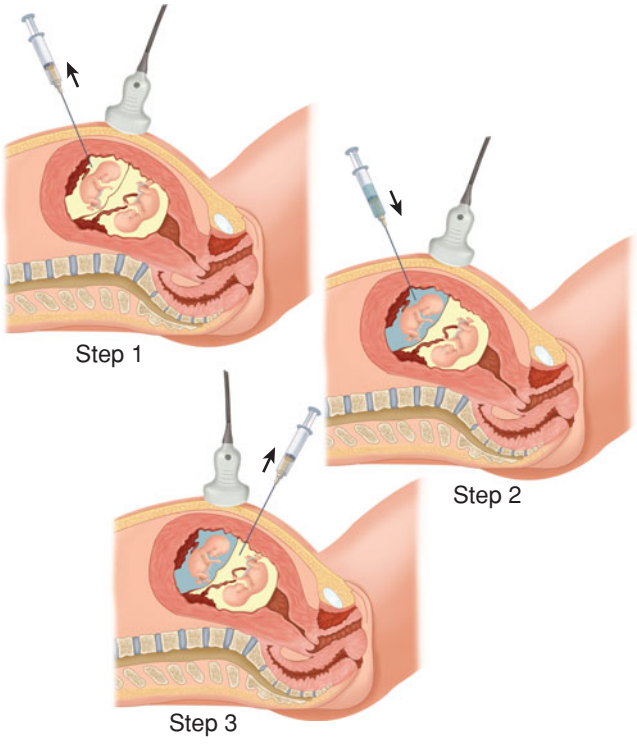

Figure 4-3 Diagrammatic representation of one method of performing amniocentesis in twins. In Step 1, the fluid is aspirated from the first amniotic sac. In Step 2, indigo carmine is injected into the first sac. In Step 3, clear fluid is aspirated from the second sac.

Alternative techniques have been described that do not use dye instillation to be sure that both sacs have been successfully sampled (Jeanty et al., 1990; Sebire et al., 1996). Sebire et al. described a technique utilizing single entry in 176 twin pregnancies (Sebire et al., 1996). After amniotic fluid is aspirated from the sac of one twin, the syringe is removed, the stylet replaced, and the needle is then advanced through the intertwin membrane into the sac of the second twin under continuous ultrasound guidance. When aspirating fluid from the second sac, the authors recommend discarding the first 1 mL in order to avoid possible contamination from amniotic fluid of the first sac. While this method is feasible, we continue to recommend the technique described earlier, using a separate needle insertion for each sac along with instillation of indigo carmine into the first in order to eliminate any chance of contaminating the samples.

Laboratory Considerations

Failure to culture amniocytes occurs in less than 1% of cases. Chromosomal mosaicism occurs in approximately 0.5% of cases. Chromosomal mosaicism is the presence of two or more cell lines with different karyotypes in a single person. This occurs as a result of postzygotic nondisjunction. The observation of multiple cell lines in a prenatal sample does not necessarily mean that the fetus has mosaicism. The most common type of mosaicism detected by amniocentesis is pseudomosaicism (Hsu and Perlis, 1984). This phenomenon should be suspected when an abnormality is evident in only one of several cultures of an amniotic fluid specimen. The abnormal cell lines arise during in vitro division; therefore, they are not present in the fetus and are not clinically important. Contamination by maternal cells can be minimized by discarding the first few drops of aspirated amniotic fluid. True fetal mosaicism, diagnosed when the same abnormality is present on more than one cover slip, is rare (0.25%) but clinically important (Hsu and Perlis, 1984). The question of whether true mosaicism is present is best resolved by karyotyping fetal lymphocytes obtained by PUBS (Gosden et al., 1988). PUBS can provide results within 48 hours. Detailed ultrasound examination is also recommended to assess fetal growth and exclude the diagnosis of structural anomalies. If both ultrasound and fetal blood sampling results are normal, the parents can be reassured that the major chromosomal abnormalities have been excluded (Gosden et al., 1988).

Complications

Serious maternal complications, such as maternal hemorrhage and sepsis, are virtually unheard of with amniocentesis in contemporary practice. Amnionitis occurs in 0.1% of cases (Turnbull and Mackenzie, 1983). The development of rhesus isoimmunization (Golbus et al., 1979; Hill et al., 1980) can be avoided by prophylactic administration of anti-D immunoglobulin to Rh_o(D)-negative women who are about to undergo amniocentesis. Amniotic fluid leak or vaginal blood loss, noted after amniocentesis by 2% to 3% of patients, is usually self-limiting, although occasionally leakage of amniotic fluid persists throughout pregnancy (NICHD Amniocentesis Registry, 1976; Simpson et al., 1981). Other common postprocedure symptoms include abdominal/pelvic cramping for 1 to 2 hours and lower abdominal discomfort for up to 48 hours after the procedure.

The safety and accuracy of midtrimester amniocentesis was documented in the mid-1970s by three collaborative studies performed in the United Kingdom, United States, and Canada (NICHD Amniocentesis Registry, 1976; Medical Research Council, 1977; Working Party on Amniocentesis, 1978). However, the only prospective, randomized, controlled trial is a study by Tabor et al. (1986), who reported on 4606 low-risk, healthy women. Patients, aged 25 to 34 years old, were randomly allocated to a group that would have amniocentesis or to one that would have ultrasound examination. The total rate of fetal loss in the patients who underwent amniocentesis was 1.7% and in the control patients 0.7% ($P < 0.01$). The conclusions of this study were initially criticized because an 18-gauge needle (which is associated with higher risks than smaller needles) was documented as having been used. Tabor et al. (1988) subsequently reported that they had been mistaken in citing the use of an 18-gauge needle and had, in fact, used a 20-gauge needle for most of the procedures. The Danish study also demonstrated that there were significant associations between pregnancy loss and puncture of the placenta, high MSAFP levels, and discolored amniotic fluid (Tabor et al., 1986).

Both the UK and Danish studies (Working Party on Amniocentesis, 1978; Tabor et al., 1986) found an increase in respiratory distress syndrome and pneumonia in neonates from the amniocentesis groups. Other studies have not found this association. The UK study showed an increased incidence of talipes and dislocation of the hip in the amniocentesis group (Working Party on Amniocentesis, 1978).

Much debate has centered on the current loss rates for amniocentesis, as anecdotal reports suggested that a 1% procedure-related loss rate appeared higher than what was seen in clinical practice. It was felt by many that the loss rate of 1% reflected clinical practice in the 1980s when ultrasound equipment and skill was significantly less advanced than contemporary practice, and when needle sizes were also different from contemporary practice. However, another randomized trial of amniocentesis will never occur due to ethical concerns. The only other option to provide contemporary data on amniocentesis safety is from large-scale prospective observational trials from the general population, and in which detailed pregnancy outcome data are available. The FASTER Trial (see Chapter 2) provided an ideal opportunity to obtain such updated safety data on amniocentesis (Malone et al., 2005). This study demonstrated a much lower procedure-related loss rate of 1 in 1600 (0.06%) (Eddleman et al., 2006). While the publication of this study has provoked much debate about the true procedure-related loss rate from amniocentesis, it is now commonly accepted that the loss rate is somewhere between the initial 1% quoted by Tabor (Tabor et al., 1986) and 0.06%, perhaps closer to 1 in 1000. The most recent ACOG statement on this topic describes the loss rate as being "less than 1 in 300–500" (ACOG, 2007).

Needle puncture of the fetus, reported in 0.1% to 3.0% of cases (NICHD Amniocentesis Registry, 1976; Karp and Hayden, 1977), has been suggested as the cause of exsanguination (Young et al., 1977), intestinal atresia (Swift et al., 1979; Therkelsen and Rehder, 1981), ileocutaneous fistula (Rickwood, 1977), gangrene of a fetal limb (Lamb, 1975), uniocular blindness (Merin and Beyth, 1980), porencephalic cysts (Youroukos et al., 1980), patellar-tendon disruption (Epley et al., 1979), skin dimples (Broome et al., 1976), and peripheral-nerve damage (Karp and Hayden, 1977). Continuous use of ultrasound to guide the needle minimizes needle puncture of the fetus. Finegan et al. (1990) have reported an increased incidence of middle ear abnormalities in children whose mothers underwent amniocentesis.

Complications in Multiple Gestation

Early studies suggested a higher fetal loss rate in twin pregnancies than in those with singletons (Pijpers et al., 1988; Anderson et al., 1991). These studies, however, did not address whether the fetal wastage following amniocentesis is attributable to the procedure or to the twin gestation itself. Patients with multiples are at increased risk for fetal loss. In a case–controlled study, Ghidini et al. (1993) reported similar loss rates between sampled twins and unsampled matched twin controls (3% vs. 2.8%). They concluded that second trimester amniocentesis in twins was not associated with excess pregnancy loss and that the likelihood of fetal wastage secondary to this procedure is probably the same as that in singletons. More recent studies, however, have contradicted this finding. In a retrospective study of 476 twins who underwent amniocentesis and 477 who did not, Yukobowich et al. (2001) found statistically different loss rates 4 weeks after the procedure, 2.7% versus 0.6%. Toth-Pal et al. (2004) compared pregnancy loss in 175 twin pregnancies that underwent amniocentesis to 300 controls. The loss rate between 18 and 24 weeks' gestation was 3.87% in the amniocentesis group versus 2.39% in the control group. Although these results were not statistically significant, the authors concluded that genetic amniocentesis slightly increases the loss rate in women carrying twins.

Early Amniocentesis

As the technique of midtrimester amniocentesis gained rapid acceptance, interest developed in the use of the same diagnostic technique at earlier gestational ages. The term "early amniocentesis" was used to describe the performance of amniocentesis at less than 14 weeks' gestation. An assumption was made that since amniocentesis was shown to be a safe and effective procedure in the second trimester of pregnancy, it would be equally safe and effective during the first trimester. However, with the completion of the CEMAT study (Canadian Early and Midtrimester Amniocentesis Trial) in 1998, it has become clear that EA from 11 weeks to 12 weeks 6 days is associated with significant disadvantages (CEMAT Group, 1998).

In the CEMAT study, 4374 patients were randomized to either EA (defined as amniocentesis from 11 weeks to 12 weeks 6 days) or midtrimester amniocentesis (defined as amniocentesis from 15 weeks to 16 weeks 6 days). It was found that EA was significantly more likely to be a technically difficult or unsuccessful procedure when compared with midtrimester amniocentesis (1.6% vs. 0.4%), and it was twice as likely that EA would require more than one needle insertion (Johnson et al., 1999). In addition, it was found that EA was significantly more likely to result in karyotype culture failure (2.4%) when compared with midtrimester amniocentesis (0.25%) (Winsor et al., 1999).

The CEMAT investigators also demonstrated significant safety concerns with the EA technique. There was a significantly higher rate of total pregnancy loss in the EA group (7.6%) versus the midtrimester group (5.9%) (CEMAT Group, 1998). Also of concern was a significantly higher rate of clubfoot in the EA group (1.3%) versus the midtrimester group (0.1%). EA was also associated with a significantly higher chance of postprocedural amniotic fluid leakage (3.5%) when compared with midtrimester amniocentesis (1.7%). The CEMAT study effectively ended the controversy on the role of EA, and suggested that this technique should generally be avoided before the 13th week of gestation. The safety of amniocentesis between 13 and 14 weeks is unknown.

Consequently, it is best to delay amniocentesis until 15 weeks' gestation.

Summary

Indications for amniocentesis have changed considerably in recent years and are likely to evolve even further. The most common indication for amniocentesis is to obtain a fetal karyotype in pregnant women with an increased risk for fetal aneuploidy. The use of amniocentesis in the investigation of elevated MSAFP is declining. The use of amniocentesis to test for fetal lung maturity has decreased because ultrasound dating of pregnancy is now obtained in many cases, and premature deliveries are performed only if there are maternal or fetal indications. For the assessment of fetal anemia in severe red-cell isoimmunized pregnancies in the second trimester, amniocentesis has been replaced by Doppler ultrasound of the middle cerebral artery. Contemporary loss rates secondary to amniocentesis are quite low, likely approaching 1 in 1000.

CHORIONIC VILLUS SAMPLING

With conventional amniocentesis, karyotype results may be received as late as the middle second trimester. This is a drawback because of the medical risks of performing pregnancy termination using dilation-and-evacuation procedures late in the pregnancy. In addition, delaying such procedures until after fetal movement is perceived may be emotionally difficult for the patient. Using chorionic villi as a source for fetal karyotyping during the 10th week of pregnancy was introduced experimentally by Hahnemann and Mohr in 1969, and the use of an endoscopic transvaginal approach (Figure 4-4) was evaluated by Hahnemann in 1974. Clinical use of chorionic villi for fetal sex determination was described in 1975 by a group from China. They performed blind transvaginal aspiration without ultrasound examination (Tietung Hospital, 1975). Once an ultrasound-guided technique for aspiration was introduced, CVS became accepted for more widespread use.

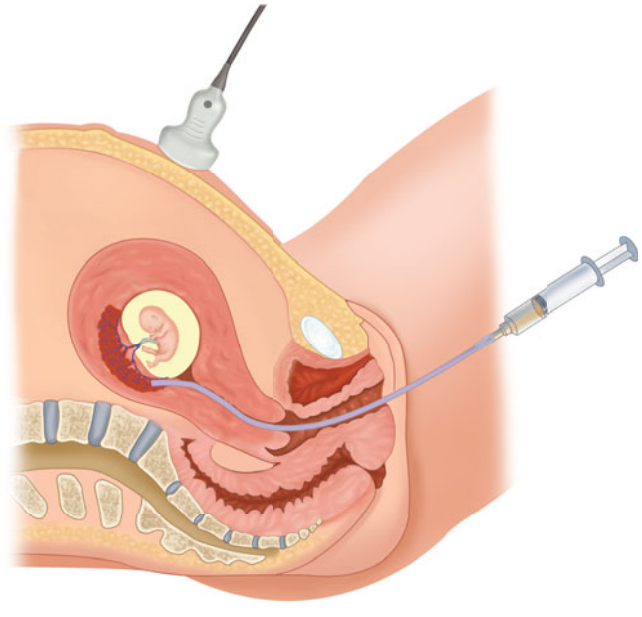

Figure 4-4 Diagrammatic representation of transcervical chorionic villus sampling.

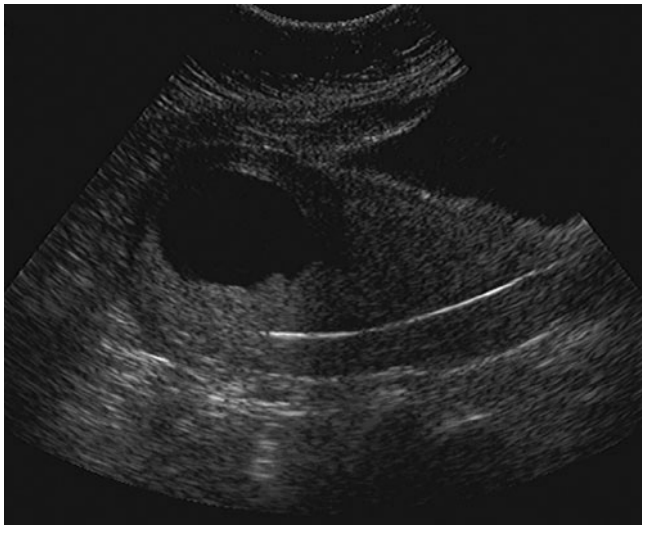

Figure 4-5 Ultrasound image of transcervical chorionic villus sampling demonstrating the catheter in a posterior placenta.

Transcervical CVS

Ultrasound examination immediately before the procedure confirms fetal heart activity, appropriate growth, and location of the placenta (Figures 4-4 and 4-5). The position of the uterus and cervix is determined, and the anticipated catheter path is mentally mapped. If the uterus is severely anteverted, filling of the bladder frequently straightens its position. If a uterine contraction occurs it could interfere with passage of the catheter, and a decision may be made to delay the procedure until the contraction dissipates. When the uterine condition and location are favorable, the patient is placed in the lithotomy position; and the vulva, vagina, and cervix are aseptically prepared. A speculum is inserted, and the anterior lip of the cervix may be grasped with a tenaculum to aid in manipulating the uterus. The distal 3 to 5 cm of the catheter is molded into a slightly curved shape and then gently passed through the cervix until a loss of resistance is felt at the endocervix. The operator then waits until the ultrasonographer visualizes the tip of the catheter.

The catheter is inserted parallel to the placenta and passed almost to its distal end (Figures 4-4 and 4-5). The stylet is then removed and a 20-mL heparinized syringe containing nutrient medium is attached. The syringe is used to apply negative pressure. The catheter and attached syringe are then pulled back slowly, and the syringe is visually inspected for villi, which are easily seen with the naked eye as white branching structures. Once an adequate sample is obtained, the patient is discharged. The patient is instructed to inform her physician if she develops heavy bleeding, fever, or

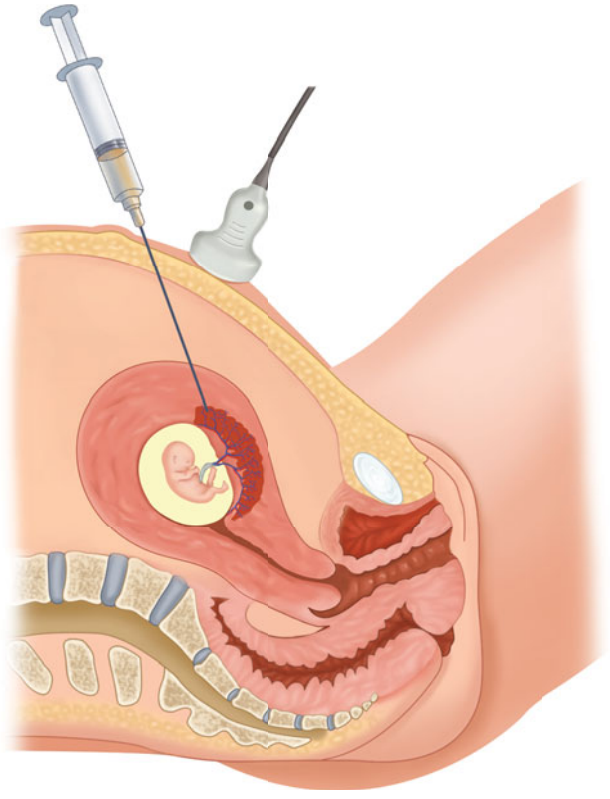

Figure 4-6 Diagrammatic representation of transabdominal chorionic villus sampling.

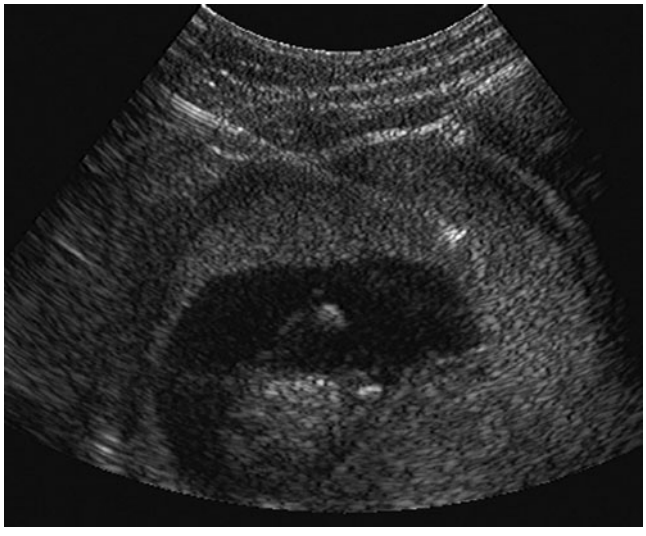

Figure 4-7 Ultrasound image of transabdominal chorionic villus sampling demonstrating the needle in an anterior placenta at 12 weeks.

unusual vaginal discharge. A follow-up scan and MSAFP assay are performed at 16 weeks of gestation.

Alternative approaches to transcervical CVS include use of a reusable biopsy forceps, rather than a disposable plastic catheter. There are no comparative data available guiding which transcervical instrument is optimal.

Transabdominal CVS

Continuous ultrasound imaging is used to direct a 19- or 20-gauge spinal needle into the long axis of the placenta (Figures 4-6 and 4-7). After removal of the stylet, villi are aspirated into a 20-mL syringe containing tissue culture medium. It may be a reasonable alternative to amniocentesis or PUBS if karyotype evaluation is needed later in pregnancy when special circumstances may exist, such as severe oligohydramnios.

Multiple Gestation

CVS is considered a safe alternative to amniocentesis in multiple gestations (Brambati et al., 1991b; Pergament et al., 1992; Wapner et al., 1993). Chorionic villi for chromosome or DNA analysis can be obtained either by transcervical catheter or by transabdominal needle approaches under ultrasound guidance. The advantage of CVS over amniocentesis is the earlier availability of results and, if discordant results are obtained, selective termination can be performed early in gestation when it is associated with a lower risk of adverse outcomes. First trimester diagnosis by CVS is particularly important for women with multiple gestations who may be considering multifetal pregnancy reduction. These patients can verify that specific fetuses are euploid prior to multifetal pregnancy reduction. Similar to amniocentesis, the location of each fetus and placenta should be carefully mapped and documented at the time that CVS is performed (Appelman and Furman, 2005).

CVS in multiple gestation can be technically challenging. Both the physician and sonographer should be adequately experienced to ensure proper placement of the sampling instrument because there are no markers to confirm that each sample has been obtained from a distinct placenta. Early studies suggested that contamination from one placenta to another occurs in up to 4% of cases (Pergament et al., 1992; Wapner et al., 1994). However, more recent studies have suggested that cross-contamination between placentas is far less frequent (DeCatte et al., 2000; Brambati et al., 2001). De Catte et al. (2000) described 262 twin pregnancies that underwent CVS with 99% of the placentas being sampled adequately (DeCatte et al., 2000). In two pregnancies, the same placenta was sampled twice, and in three others there was cross-contamination between placentas. Brambati et al. (2001) described 198 sets of twins and 9 sets of triplets undergoing CVS. Sampling was successfully performed in all cases, and no evidence of incorrect sampling was reported. Methods to decrease contamination errors include collecting samples near the cord insertion site when placentas are adjacent, avoiding the dividing membrane, and using both the transabdominal and transcervical approach in certain clinical situations.

CVS appears to be an accurate diagnostic procedure in multiple gestation. The diagnostic precision of CVS and amniocentesis in twins and triplets was reviewed by van den Berg et al. (1999). Two hundred and ninety-eight women with twins underwent second trimester amniocentesis, and 163

others were sampled by CVS. Four women with triplets underwent CVS and 11 had amniocentesis. Amongst the twins, uncertain results in one or both samples requiring additional sampling was more frequent in the CVS group compared to the amniocentesis group (8/163 (5%) vs. 1/298 (0.3%)). Erroneous sampling (sampling the same placenta twice) was only seen once in the CVS group and cross-contamination was present in two of seven pregnancies that underwent CVS and DNA analysis. Uncertain results were present in eight pregnancies undergoing CVS, five of which were secondary to confined placental mosaicism. No diagnostic errors occurred in the CVS group. In the amniocentesis group, the one uncertain result was likely due to a sampling error. In the triplet group, one patient who underwent amniocentesis and one who underwent CVS needed an additional amniocentesis procedure because of abnormal results. Although CVS is associated with a higher risk of uncertain results and cross-contamination in patients with multiples, the authors concluded that clinical diagnostic uncertainties are minimal.

Laboratory Aspects

The average sample from a transcervical aspiration contains 15 to 30 mg of villous material. The villi identified in the syringe are carefully and aseptically transferred for inspection and dissection under a microscope. Visually confirming that the appropriate tissue has been aspirated is mandatory to minimize maternal decidual contamination. Clean, decidua-free villi are then transferred to petri dishes for further preparation. Villi are processed for cytogenetic analysis in two ways: Results of direct preparation are available within 3 to 4 days of the procedure; results of tissue culture are usually available within 6 to 8 days. Most laboratories wait to report both results at the same time.

It is recommended that both the direct and culture methods be used with all samples. The direct method gives rapid results on the cytotrophoblast and minimizes maternal decidual contamination. Tissue culture, which is subject to potential contamination from maternal cells, is a better means of identifying and evaluating discrepancies that may exist between the cytotrophoblast and the fetal state (Bianchi et al., 1993).

Most biochemical diagnoses that can be made from amniotic fluid or cultured amniocytes can also be made from chorionic villi (Poenaru, 1987). In many cases, the results are available more rapidly and efficiently when villi are used because enzymes are present in sufficient quantity to allow direct analysis rather than requiring the products of tissue culture.

Pregnancy Loss Following CVS

The advantage of earlier diagnosis must be weighed against any increased risk of fetal loss associated with CVS. For statistical purposes, procedure-related spontaneous loss has generally been defined as spontaneous miscarriage or diagnosed intrauterine fetal death occurring up until 28 completed weeks of gestation. Calculating such procedure-related losses is complicated by background pregnancy loss rates, since 2% to 5% of pregnancies viable at 7 to 12 weeks of gestation are either nonviable when rescanned at 8 to 20 weeks or will undergo spontaneous miscarriage before 28 weeks of gestation (Wilson et al., 1984; Gilmore and McNay, 1985; Liu et al., 1987). The background rate of spontaneous loss increases with maternal age and is therefore highest in the same age range in which women are likely to present for prenatal diagnosis (Wilson et al., 1984; Gilmore and McNay, 1985).

Data evaluating the safety of CVS come primarily from three collaborative reports (Table 4-4). In 1989, the Canadian Collaborative CVS/Amniocentesis Clinical Trial Group reported its experience with a prospective randomized trial comparing the safety of CVS to that of amniocentesis. During the study period, patients across Canada were able to undergo CVS only as part of this randomized protocol. The results from the Canadian group confirmed the safety of CVS as a first trimester diagnostic procedure. There was a 7.6% rate of fetal loss (spontaneous loss, induced abortions, and late losses) in the CVS group, and a 7.0% rate of loss in the amniocentesis group. This excess rate of loss of 0.6% for CVS over amniocentesis was not statistically significant. Surprisingly, there was a tendency toward later losses (28 weeks) in the CVS group. No significant differences were noted between the two groups in the incidence of preterm birth or low birth weight. Maternal complications were equally uncommon in each group.

The U.S. report involved a prospective, though nonrandomized, trial of 2235 women who chose either transcervical CVS or second trimester amniocentesis (Rhoads et al., 1989). An excess rate of loss of 0.8% in the CVS group over the amniocentesis group was calculated, which was not statistically significant. The rates of loss were lowest in those cases in which relatively large amounts of tissue were obtained. Repeated catheter insertions were significantly associated with pregnancy loss. Cases requiring three or more catheter insertions had a 10.8% rate of pregnancy loss, as compared with a rate of 2.9% in cases that required only one pass.

A prospective, randomized, collaborative comparison of more than 3200 pregnancies, sponsored by the European Medical Research Council, demonstrated that CVS was associated with a 4.6% greater rate of pregnancy loss than amniocentesis (95% confidence interval, 1.6% to 7.5%) (MRC Working Party, 1991). This difference reflected more spontaneous deaths before 28 weeks of gestation (2.9%), more terminations of pregnancy for chromosomal anomalies (1.0%), and more neonatal deaths (0.3%). In this study, CVS was performed by both the transcervical and transabdominal routes. The number of repeat procedures was significantly higher in the CVS group as compared with the amniocentesis group.

Exactly what factors contribute to the discrepant results between the European and North American studies remains uncertain. Variability in operator experience might account for part of this discrepancy. The U.S. trial included 7 centers and the Canadian trial 11, whereas the Medical Research

Table 4-4

Total Pregnancy Loss Rates of Chorionic Villus Sampling (CVS) and Amniocentesis (AC) in Three Collaborative Trials

Stydy	Eligible or Attempted (no.)		Total Loss Rate (%)		CVS Excess Loss Rate (%)
	CVS	AC	CVS	AC	
Canadian Collaborative CVS-Amniocentesis Clinical Trial Group (1989)	1191	1200	7.6	7.0	0.6
Rhoads et al. (1989)	2235	651	7.2	5.7	0.8*
MRC Working Party (1991)	1609	1592	13.6	9.0	4.6

** Corrected for difference in maternal age and gestational age.*
From D'Alton ME. Prenatal diagnostic procedures. Part 1—Diagnosis and treatment of fetal disease. Semin Perinatol. *1994;18:140-162.*

Council Trial involved 31 participating centers contributing various numbers of cases and using different sampling and cytogenetic procedures. There were, on average, 325 cases per center in the U.S. study, 106 in the Canadian study, and only 52 in the European trial. The pregnancy losses in the European series tended to occur before 20 weeks of gestation, as compared with the Canadian study, in which losses occurred significantly later. There is no apparent explanation for these findings, although some feel that the larger number of centers and operators in the European trial reflect fewer per-operator procedures and the therefore less experienced technique.

Transcervical Versus Transabdominal Approach to CVS

Brambati et al. (1991a) reported the results of a randomized trial of transabdominal versus transcervical CVS by a single operator in 1194 patients. More than 110 cases deviated from the allocated procedure, and more than 80% of the deviations occurred in the transcervical arm of the trial. Moreover, the proportion of cases in which the operator chose to deviate from the allocated procedure increased in each of the 3 years of the study (4.6%, 9.7%, and 15.5%, respectively). More chorionic tissue was obtained by the transcervical method, but the proportion of cases in which less than 10 mg was obtained was similar in both groups. Bleeding was more common following transcervical CVS, whereas cramping was more common with the transabdominal approach. No significant difference was detected in the overall rate of fetal loss (transabdominal approach, 16.5%; transcervical, 15.5%). The transabdominal technique required a significantly smaller proportion of repeat needle insertions (3.3% vs. 0.3%), although this did not seem to affect pregnancy outcome. There were also no differences in birth weight, gestational age at delivery, or congenital malformations. The authors commented that a limitation of this study was the operator's eventual preference for the transabdominal approach. They conclude that the two techniques seem equally safe and effective, and the choice to perform one particular technique may depend largely on the operator's preference.

Jackson et al. (1992) conducted a randomized comparison of transcervical and transabdominal CVS at 7 to 12 weeks of gestation. Of 3999 eligible patients, 94% in each arm of the study underwent the allocated procedure. Only one needle insertion was required in 94% of transabdominal CVS cases, and one catheter pass was required in 90% of transcervical CVS procedures. The rate of fetal loss, excluding elective terminations of pregnancy, was 3% in each group.

Smidt-Jensen et al. (1992) published their randomized comparison of routine amniocentesis, transabdominal CVS, and transcervical CVS in 3706 low-risk patients. Patients were randomly assigned to one of the three procedures. The proportion of patients for whom a cytogenetic diagnosis was successfully obtained at the first attempt was 99.7% for amniocentesis, 98.1% for transabdominal CVS, and 96.0% for transcervical CVS ($P < 0.0001$). Total rates of fetal loss were 10.9% for transcervical CVS, 6.3% for transabdominal CVS, and 6.4% for amniocentesis, a statistically significant difference. A large difference was noted between the transabdominal and transcervical CVS groups in the proportion of postprocedural losses of cytogenically normal pregnancies (3.7% for transabdominal and 7.7% for transcervical CVS). The authors concluded that although transabdominal CVS and amniocentesis carry similar risks of fetal loss, transcervical CVS is associated with an overall higher rate of fetal loss, estimated to be in excess of 4.0%.

It is reasonable to speculate that the rate of fetal loss will equilibrate in most centers once equivalent expertise is gained with either approach (Brambati et al., 1987b). Integration of both transcervical and transabdominal methods of CVS into any program offers the most practical and safe approach to first trimester diagnosis.

Other Complications with CVS

Vaginal bleeding or spotting is relatively uncommon after transabdominal CVS procedures, occurring in 1% or less of cases (Rhoads et al., 1989). Most centers report postprocedure bleeding in 7% to 10% of patients sampled by transcervical CVS (Rhoads et al., 1989). Minimal spotting is more common than bleeding and may occur in almost one-third of women sampled by the transcervical route (Rhoads et al., 1989). A subchorionic hematoma may be visualized immediately after sampling in up to 4% of patients sampled transcervically (Brambati et al., 1987b). The hematoma usually disappears before the 16th week of pregnancy and is usually not associated with an adverse outcome.

Since the initial development of transcervical CVS there has been concern that transvaginal passage of an instrument would introduce vaginal flora into the uterus, thereby increasing the risk of infection. Cultures have isolated bacteria in 30% of catheters used for CVS (Brambati and Varotto, 1985; Garden et al., 1985; McFadyen et al., 1985; Wass and Bennett, 1985; Brambati et al., 1987a). The reported incidence of post-CVS chorioamnionitis, however, is low; it occurs following both transcervical and transabdominal procedures. In the U.S. collaborative trial, infection was suspected as a possible cause of pregnancy loss in only 0.3% of cases (Rhoads et al., 1989). It has been demonstrated that, at least in some cases, infection that occurs after transabdominal CVS is a result of bowel flora introduced by inadvertent puncture by the sampling needle. Early in the development of transcervical CVS, two life-threatening pelvic infections were reported (Blakemore et al., 1985; Barela et al., 1986). A practice of using a new sterile catheter for each insertion has subsequently been universally adopted, and there have been no additional reports of serious infections resulting from the procedure.

Acute rupture of membranes within hours of the procedure can occur but is rare (Rhoads et al., 1989); in 0.3% of cases, rupture has been reported days to weeks after the procedure (Hogge et al., 1986). An acute rise in MSAFP levels after CVS has been consistently reported, implying a detectable degree of fetomaternal bleeding (Blakemore et al., 1986; Brambati et al., 1986; Shulman et al., 1990). The elevation in MSAFP levels is not related to the technique used to retrieve villi but seems to depend on the quantity of tissue aspirated (Shulman et al., 1990). Levels will return to normal ranges by 16 to 18 weeks of gestation, thus allowing serum screening to proceed according to usual prenatal protocols. All Rh-negative, nonsensitized women who are undergoing CVS should receive Rh_o(D) immune globulin after the procedure. Exacerbation of Rh immunization following CVS has been described. Existing Rh sensitization therefore represents a contraindication to the procedure (Moise and Carpenter, 1990).

Risk of Fetal Limb Abnormality Following CVS

Concern has been raised that CVS might cause severe limb deficiencies. This was first reported by Firth et al. (1991). Their series of 289 CVS pregnancies identified five infants with severe limb abnormalities. Oromandibular limb hypogenesis syndrome was present in four of the five, and the fifth had a terminal transverse limb-reduction defect. The oromandibular limb hypogenesis syndrome occurs in 1 of 175,000 livebirths (Hoyme et al., 1982); therefore, the occurrence of this abnormality in more than 1% of pregnancies in which CVS was performed strongly suggested an association. In Firth's initial report, all of the limb abnormalities followed transabdominal sampling performed: between 55 and 66 days of gestation. Burton et al. (1992) also reported transverse limb abnormalities after CVS. Apart from these two reports, most other series have found the incidence of limb-reduction defects to be not significantly different from the expected rates. Using records of the experience of the eight centers participating in the U.S. collaborative evaluation of CVS, Mahoney (1991) reported no cases of oromandibular limb hypogenesis syndrome and no increased incidence of transverse limb defects. Monni et al. (1991) reviewed their experience of CVS procedures performed before the 66th day of gestation and reported no severe limb defects in the selected population. Two mild finger abnormalities were seen in their series. Defects have also been observed when CVS is performed after 66 days. Reports of limb abnormalities after CVS procedures and population-based studies are summarized in Table 4-5 (see also, Froster-Iskenius and Baird, 1989; Froster and Baird, 1992).

A variety of mechanisms by which CVS could potentially lead to fetal malformations has been proposed. The occurrence of placental thrombosis with subsequent fetal embolization has been raised as a potential cause. Inadvertent entry into the extraembryonic coelom, resulting in amniotic bands, has also been suggested. This seems unlikely because actual bands have not been observed in any cases. The most plausible proposed mechanism is a form of vascular insult leading to underperfusion of the fetus (Brent, 1990). CVS could cause disruption of the vessels supplying the extracorporeal fetal circulation. This disruption would result in the release of vasoactive peptides, producing fetal vasospasm and hypoperfusion of the fetal peripheral circulation. Limb defects have been demonstrated in animal models after exposure to cocaine (Brent, 1990; Webster and Brown-Woodman, 1990). Theoretically, an overly vigorous technique during the CVS procedure could lead to significant placental damage, with resulting vasospasm and hypovolemia.

Using transcervical embryoscopic visualization of the first trimester embryo, Quintero et al. (1992) demonstrated the occurrence of fetal facial, head, and thoracic ecchymotic lesions following a traumatic CVS. Although these lesions consistently appeared following significant physical trauma to the placental site, the researchers were not able to produce them by the passage of a standard CVS catheter. Furthermore, these lesions were demonstrated only after the development of a subchorionic hematoma.

The most current data suggest that performance of CVS in the usual gestational age time period of 10 to 13 weeks is not associated with an increased risk of limb defects but that

Table 4-5

Incidence of Limb-Reduction Defects in Groups Undergoing Chorionic Villus Sampling and Population-Based Studies

Chorionic Villus Sampling Series

Study	55 to 66 Days*	Defect	>66 Days*	Defect
Firth et al. (1991)	5/289	1 Transverse limb-reduction defect, 4 combined limb-reduction defects with micrognathia or microglossia	0/250	—
Burton et al. (1992)†	—	—	4/394	3 Finger-and-toe abnormalities, 1 finger abnormality
Monni et al. (1991)	0/525	—	2/2227	2 Finger abnormalities
Mahoney (1991)‡	1/1025	Longitudinal limb-reduction defect	6/8563	1 Longitudinal limb-reduction defect, 5 transverse limb-reduction defects (2 of the 5 were limited to fingers or toes)
Jackson et al. (1992)‡	1/2367	Bilateral aplasia of the thumbs	4/10,496	
Schloo et al. (1992)	1/636	Microglossia and hypodactyly	3/2200	3 Finger abnormalities (2 of the 3 had a family history of limb defects)

Population-based Studies

Study	Defect	Incidence
Froster-Iskenius and Baird (1989)	Combination of limb-reduction defects and micrognathia or microglossia	1/175,000
	Limb-reduction defects	1/1692
	Terminal longitudinal defects	1/2857
	Terminal transverse defects	1/6250
Froster and Baird (1992)	Hand	1/11,035
	Fingers	1/7016
	Foot	1/39,158
	Toes	1/43,354

* *The number of days after the beginning of the last menstrual period at the time the procedure was performed.*
† *The number of procedures performed before 67 days was not reported.*
‡ *There was some overlap between the series studied by Mahoney and by Jackson et al.*
From D'Alton ME. Prenatal diagnostic procedures. Part 1—Diagnosis and treatment of fetal disease. Semin Perinatol. *1994;18:140-162.*

performance of the procedure prior to this time may be associated with a risk of severe limb defects as high as 1% to 2% (Jenkins and Wapner, 1999). The frequency of oromandibular-limb hypogenesis syndrome seems to be more common among infants from pregnancies that underwent CVS earlier than 7 weeks of gestation (ACOG, 2007).

Accuracy of CVS Cytogenetic Results

The overall incidence of chromosomal mosaicism in CVS specimens is estimated to be approximately 1% (Vejerslev and Mikkelsen, 1989). Generalized chromosomal mosaicism originates from a mutational event in the first or second postzygotic division, and all tissues of the fetus are affected

(Kalousek and Dill, 1983). Confined placental mosaicism (CPM), defined as a dichotomy between the chromosomal constitution of placental and fetal tissues, results from nondisjunction that occurs in the trophoblast or extraembryonic mesoderm progenitor cells (Kalousek et al., 1991). In most cases of mosaicism diagnosed by CVS, the cytogenetic abnormality is confined to extraembryonic tissue (Vejerslev and Mikkelsen, 1989; Johnson et al., 1990; Breed et al., 1991).

Several studies have reported a higher incidence of adverse perinatal outcomes, including increased rates of fetal loss and intrauterine growth restriction (IUGR) in pregnancies complicated by CPM (Johnson et al., 1990; Kalousek et al., 1991; Wilkins-Haug et al., 2006). Kalousek et al. (1991) confirmed CPM in only half of placentas studied after birth. IUGR was found only in cases of CPM mosaicism confirmed in term placentas. Wapner et al. (1992) found a significantly higher rate of fetal loss (8.6%) among the 2.5% of patients with CPM, in comparison with patients with a normal karyotype (3.4%). Patients with pseudomosaicism had a rate of pregnancy loss and perinatal outcome similar to that of the normal population. It is interesting to note that the long-term health and development of children with CPM diagnosed prenatally is not thought to be adversely affected (Amor et al., 2006). Amor et al., compared 36 children with antenatally diagnosed CPM to 195 matched controls with a normal karyotype diagnosed antenatally. All children were between the ages of 4 and 11, and outcome information was obtained through maternal questionnaire. No major health problems were detected among the CPM group. There was no increase in IUGR but postnatal growth was slowed compared to controls ($p = 0.047$). Issues that still need to be investigated are the exact contribution of CPM to IUGR, the significance of the specific chromosome involved in the mosaic aneuploidy, and the significance of specific tissue sources (i.e., direct cytotrophoblast preparations or mesenchymal tissue cultures) on pregnancy outcome.

Summary

CVS is considered a viable alternative to second trimester amniocentesis for prenatal diagnosis. Its immediate and long-term safety has been demonstrated. Evaluation of transcervical and transabdominal CVS has demonstrated their comparable safety and efficiency. The techniques are complementary and offer the choice of early prenatal diagnosis to patients who have the appropriate indications for the procedure. Counseling before CVS requires a discussion of the frequency and significance of CPM and the potential need for follow-up studies, including ultrasound, amniocentesis, and PUBS (Miny et al., 1991).

PERCUTANEOUS UMBILICAL BLOOD SAMPLING

In 1983, Daffos et al. described a method of obtaining fetal blood using ultrasonographic guidance. This involved the passage of a 20-gauge spinal needle through the maternal abdomen into the umbilical cord. This technique offered considerable advantage over the fetoscopic methods previously used to obtain fetal blood. The techniques are variously described as PUBS, fetal blood sampling, cordocentesis, or funipuncture.

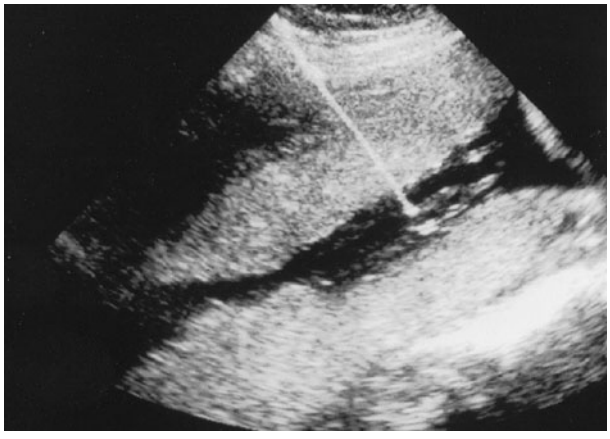

Figure 4-8 Ultrasound image of PUBS demonstrating the needle above the umbilical vein. (*From D'Alton ME. Prenatal diagnostic procedures. Part 1—Diagnosis and treatment of fetal disease.* Semin Perinatol. *1994;18:140-162.*)

Technique

The main differences in the techniques of fetal blood sampling are related to whether the operator uses a needle guide or uses a "freehand" technique. A variety of needle guides that attach to the transducer can be used. The advantage to this approach is that the needle will be directed precisely to a specific target. The disadvantage is that if the fetus moves or a contraction occurs while the needle is in the uterus, redirection of the tip may be difficult or impossible and will necessitate a repeat procedure. Because of these drawbacks, most centers performing this procedure use the freehand technique. Fetal vessels can be accessed within the cord or the fetus itself. It is easier to enter the cord at the placental insertion site because it is anchored at this location (Figure 4-8). Color Doppler imaging significantly enhances the ease of visualization of the cord insertion site (Figure 4-9) and is especially useful when oligohydramnios is present. The hepatic vein is the most accessible vessel for blood sampling within the fetal body.

Once a sample of blood has been aspirated, it is essential to verify that it is fetal in origin. The most definitive way to do this is to compare the mean corpuscular volume (MCV) of the red cells to that of a sample of maternal blood. This is easily performed on small aliquots of blood by a standard channeling instrument. It is preferable to either have this instrument in the procedure room, or alternatively have a system to allow immediate access to the instrument in an adjacent laboratory. Fetal red cells are considerably larger than those of an adult and therefore afford rapid differentiation.

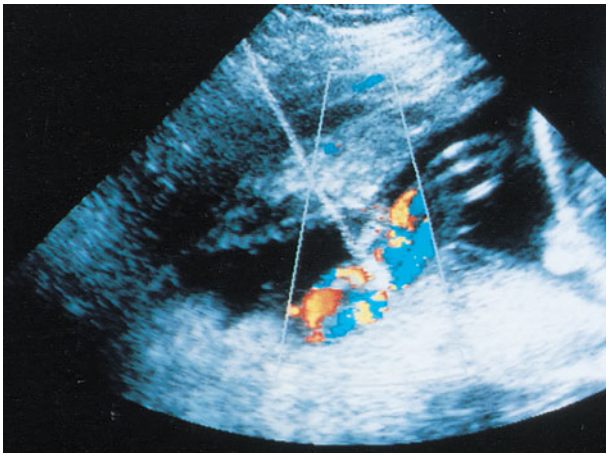

Figure 4-9 Ultrasound image of the same case shown in Figure 4-8, demonstrating the use of color Doppler to enhance visualization of the umbilical cord.

Success Rates and Safety

The rate of fetal loss after PUBS is approximately 2% higher than the background risk for that particular fetus (Daffos et al., 1985; Shulman and Elias, 1990). Because many of the fetuses studied have severe congenital malformations, the background loss rate is high in comparison with that of the generally lower risk population of women who undergo CVS amniocentesis.

The North American PUBS registry, which was maintained at Pennsylvania Hospital in Philadelphia, University of Pennsylvania, collected data from 16 centers in the United States and Canada. As of 1993, information on 7462 diagnostic procedures performed on 6023 patients was available (Ludomirsky, 1993). The most common needle used for procedures was a 22-gauge spinal needle. Fetal loss was defined as intrauterine fetal death within 14 days of the procedure. The rate of fetal loss was calculated to be 1.12% per procedure and 1.33% per patient. There were 84 pregnancies that were considered to be lost as a direct consequence of the fetal blood sampling. The major causes for fetal loss were chorioamnionitis, rupture of membranes, bleeding from the puncture site, severe bradycardia, and thrombosis. The range of losses for participating centers varied from 1% to 6.7%; this range reflects differing levels of experience of the operators. These figures are subjective, relying on the operator's impression that a pregnancy loss was directly related to the procedure itself and not to the underlying fetal condition that necessitated the procedure. Because many of these fetuses were already compromised at the time of PUBS, it is certainly possible that an in utero death following the procedure might have been entirely unrelated. Nevertheless, this assessment is subjective and could be responsible for an underestimation of the true rates of loss for PUBS. The authors concluded that the intrahepatic vein is an alternative site of sampling or transfusion when access is difficult or failure occurs at the placental cord insertion site. Nicolini et al. (1990b) described their experience with 214 fetal blood sampling procedures performed from the fetal hepatic vein and reported success rates of 91% and 90% for diagnostic and therapeutic procedures, respectively. Rates of fetal loss comparable to those for blood sampling procedures performed at the placental cord insertion site were reported. Because PUBS entails a substantially greater risk of pregnancy loss than does amniocentesis, it should be reserved for situations in which rapid diagnosis is essential or in which diagnostic information cannot be obtained by safer means (D'Alton and DeCherney, 1993).

Indications

Approximately two-thirds of the cases of diagnostic fetal blood sampling procedures reported to the PUBS registry were performed either to determine a rapid karyotype or to evaluate hematologic status in pregnancies at risk for red-cell isoimmunization (Ludomirsky, 1993). One-third of the procedures were performed to rule out fetal infection or to evaluate nonimmune hydrops, fetal acid–base status, twin-to-twin transfusion syndrome, or fetal platelet count.

Chromosome analysis

The ultrasonographic detection of fetal morphologic malformations is one of the most common indications for rapid fetal karyotyping in the United States (Table 4-6). With PUBS, fetal karyotypes are usually available from fetal white cells within 48 to 72 hours. The main advantage of PUBS is that it gives rapid results. Its disadvantage is that it entails a greater risk of pregnancy loss than does amniocentesis. We rarely use PUBS for rapid diagnosis of fetal karyotype, due to the easy availability of amniocentesis supplemented with fluorescence in situ hybridization (FISH) or polymerase chain reaction (PCR).

Table 4-6

Indications for PUBS

Most frequent
Rapid karyotyping
When ultrasound detects anatomic malformation
When mosaicism is reported from amniotic fluid or CVS specimens
Less frequent
Fetal red cell isoimmunization
Nonimmune hydrops fetalis
Fetal platelet assessment
Fetal infection
Fetal acid–base status
Diagnosis of twin–twin transfusion
Hemoglobinopathies
Coagulation factor deficiencies
Immunologic deficiencies

From D'Alton ME. Prenatal diagnostic procedures. Part 1—Diagnosis and treatment of fetal disease. Semin Perinatol. *1994;18:140–162.*

An exception is in the late second trimester, if karyotype information is needed urgently in order to make a decision regarding termination of pregnancy. Karyotyping fetal white cells may also occasionally be indicated for mosaicism detected in material obtained from amniotic fluid or chorionic villi. Although most cases of mosaicism found in chorionic villi can be effectively ruled out by amniocentesis, there have been reports of trisomy 21 mosaicism in which the chorionic villus culture revealed two cell lines. In this study, the amniotic fluid culture was entirely normal, yet true mosaicism was demonstrated in fetal blood (Ledbetter et al., 1990).

DNA analysis

Most inherited hematologic disorders can now be diagnosed by the study of fetal DNA obtained from amniocytes or chorionic villi. Therefore, the antenatal detection of most congenital coagulopathies, hemoglobinopathies, white cell disorders, and immune disorders does not usually require direct analysis of fetal blood specimens. In some of these cases, family studies are uninformative and PUBS is necessary for diagnosis. This is now the exception rather than the rule.

Fetal anemia

Assessment of fetal anemia in cases of red cell isoimmunization requires direct measurement of these parameters in fetal blood. Therefore, in severely affected cases of Rh isoimmunization, determination of the fetal hemoglobin level is the most accurate way to determine the fetal status and the optimal timing of a transfusion before.

Fetal blood sampling for determination of fetal anemia in red cell isoimmunization is a common reason for this procedure. It accounted for 23% of all cases reported to the PUBS registry (Ludomirsky, 1993). Fetal blood may also be obtained in cases of red cell isoimmunization to determine the antigen status of the fetus when the father is heterozygous for the discordant antigen. A single invasive procedure can rule out the disease, and no further diagnostic testing will be necessary. Amniocentesis initially replaced PUBS as the safest method for fetal Rh_o(D)type determination, while currently, analysis of fetal DNA in a maternal blood sample has effectively replaced all invasive tests for fetal Rh_o(D) type determination (Bennett et al., 1993; Lo et al., 1998; van der Schoot et al., 2003; Bianchi et al., 2005).

Fetal thrombocytopenia

Alloimmune thrombocytopenia is the platelet equivalent of Rh disease. In this disorder, the mother makes antibodies to antigens on the fetal platelets, and transplacental passage of these antibodies results in fetal thrombocytopenia. This disorder is associated with a marked depression of the fetal platelet count. Intracranial hemorrhage may occur in utero long before the onset of labor. Because severe thrombocytopenia and intracranial hemorrhage have been documented in this disorder as early as at 20 weeks of gestation, prolonged antenatal therapy is necessary to protect the fetus against the possibility of spontaneous bleeding. Intravenous gamma globulin at a dose of 1 g per kilogram with or without steroids is suggested to increase fetal platelet count and to decrease the risk of severe fetal hemorrhage (Bussel et al., 1988, 1996; Lynch et al., 1992).

The fetal platelet count should be obtained by PUBS prior to delivery. The risk of PUBS is higher in patients with alloimmune thrombocytopenia than in the general population. In these patients, blood sampling should be performed in a facility with access to rapid automated platelet counts at the time of the procedure, and a count should be determined before the sampling needle is withdrawn. A concentrate of washed maternal platelets should be available. If the fetal platelet count is found to be lower than 40,000 to 50,000 per cubic millimeter, a transfusion of maternal platelet concentrate can then be given.

Infectious disease diagnosis

Evaluation for fetal infection was the third most common indication for fetal blood sampling in the PUBS registry (8% of all cases). Daffos et al. (1988) reported on more than 700 pregnancies exposed to *Toxoplasma gondii* infection and demonstrated that 95% were not infected. Although PUBS has been used for *T. gondii* in the United States, screening for Toxoplasma is not routinely offered to pregnant women; therefore, PUBS is rarely performed for this diagnosis in the United States. Direct isolation of the organism from fetal blood or amniotic fluid is the most reliable evidence of fetal infection. Technical difficulties and the length of time necessary for culture of the organism often make this approach impractical. Another method is to evaluate the fetal antibody response. Production of specific IgM antibodies is gestational-age dependent and also seems to depend on the organism involved. Almost 100% of fetuses with congenital rubella infection produce specific IgM antibodies after 22 weeks of gestation (Daffos et al., 1984), whereas only 15% of those infected with *T. gondii* tested between 24 and 29 weeks produce specific IgM antibodies against the parasite (Daffos et al., 1988). Therefore, although detection of specific IgM antibodies in fetal blood is reliable evidence of fetal infection, their absence does not rule it out. Nonspecific evidence of infection includes fetal thrombocytopenia, erythroblastosis, leukocytosis, eosinophilia, elevated levels of γ-glutamyltransferase, lactic dehydrogenase, interferon (Lebon et al., 1985; Raymond et al., 1990), and total IgM antibodies.

More recently, PCR analysis has been highly reliable in detecting cytomegalovirus in amniotic fluid. Data suggest that PCR analysis of amniotic fluid is both highly sensitive and specific for the Toxoplasma organism, affording a diagnosis in a few hours (Grover et al., 1990). For this reason, amniocentesis and molecular techniques have effectively replaced PUBS for the confirmation of fetal infection.

Fetal well-being

Because cord blood pH at the time of delivery is a well-accepted indicator of neonatal status, it was hoped that fetal blood sampling for blood gases would also accurately predict

the fetal condition. Theoretically, PUBS could prove to be useful when more conventional forms of fetal assessment (nonstress testing, biophysical profile) were either equivocal or conflicting. Nicolaides et al. (1989) found significantly more hypoxemia, hypercapnia, hyperlactacidemia, and acidosis when 196 growth-restricted fetuses were compared with 208 who were appropriate in size for gestational age. However, Nicolini et al. (1990a) found that acid–base determination did not predict perinatal outcome in a group of growth-restricted fetuses. In their study, 26 growth-restricted fetuses with normal anatomy and karyotypes and absent end-diastolic flow on Doppler examination of the umbilical artery were compared with 20 similar fetuses, with end-diastolic flow evident on Doppler examination. The perinatal mortality was 65.4% in the first group and 0% in the latter. Significant differences in fetal blood values of Po_2, Pco_2, base equivalents, and nucleated red cell counts were demonstrable between the groups. However, these measurements did not discriminate between surviving fetuses and those who died perinatally. The values in fetuses who survived were similar to those in fetuses who died in the perinatal period. The authors concluded that PUBS has a limited role in monitoring fetal well-being. Appreciable fetal acidosis and hypoxia are found only when the umbilical-artery Doppler waveform and the fetal heart rate pattern are abnormal (Nicolini et al., 1990a; Pardi et al., 1993). Doppler velocimetry of the fetal vessels seems to be a much more powerful predictor than PUBS of the compromised fetus with IUGR. Furthermore, there is a high incidence of nonreassuring fetal testing necessitating emergency cesarean section when PUBS is performed in IUGR fetuses. There is a 15% incidence of fetal bradycardia reported when PUBS is performed in IUGR (Ludomirsky, 1993). Because of this, amniocentesis is the preferred technique when determination of fetal karyotype is indicated in the workup of the growth-restricted fetus.

Summary

Access to the fetal circulation has led to important contributions to the understanding of fetal physiology and disease states. PUBS has an overall rate of fetal loss of 2%. There has been a continued decline in the indications for fetal blood sampling because of advances in molecular and cytogenetic techniques, which allow for diagnosis from amniotic fluid and chorionic villi. Performance of less invasive procedures that provide the same information is encouraged. PUBS should be reserved for situations in which diagnostic information cannot be obtained by safer methods.

OTHER ADVANCES IN PRENATAL DIAGNOSIS

Preimplantation Genetic Diagnosis

In the field of reproductive endocrinology, preimplantation genetic diagnosis (PGD) is one of the most exciting recent advances (Sermon et al., 2004). It is the earliest form of antenatal diagnosis for cytogenetic and Mendelian disorders. This technique allows for genetic testing prior to embryo transfer in patients undergoing assisted reproductive technology (ART). One or two cells are biopsied from embryos at the 6 to 8 cell stage and are analyzed for chromosomal abnormalities or for single-gene disorders. Alternatively, polar bodies can be biopsied from oocytes.

PGD has been used by couples at risk for having pregnancies affected by single-gene disorders, increased risk for aneuploidy, and for couples in which one partner carries a balanced chromosomal rearrangement (Sampson et al., 2004). At the time of transfer, only embryos without the genetic abnormalities under evaluation are replaced. The main drawback to this procedure is that patients must undergo conception by in vitro fertilization (IVF) in order to have PGD even if they are not infertile. IVF has inherent risks, such as ovarian hyperstimulation and multiple gestation. In addition, the technique is expensive and not necessarily covered by insurance. At this point, PGD is reserved for patients at high risk for inherited single-gene disorders or chromosome abnormalities.

Fetal cells and nucleic acids in the maternal circulation

Noninvasive prenatal genetic diagnosis is an important area of research, as it would be preferable to invasive methods such as amniocentesis and CVS, which carry a small risk for fetal loss. Isolating fetal cells or cell-free fetal DNA from maternal plasma is currently an exciting and promising area of research that is transitioning to clinical care (Jackson, 2003). Current applications for analysis of fetal cells and of cell-free fetal DNA in maternal circulation include noninvasive detection of fetal gender and noninvasive detection of fetal Rh (D) genotype (Maron et al., 2007). Noninvasive fetal genotyping is useful for the management of Rh (D) negative women whose partners are heterozygous for the Rh (D) gene because no further diagnostic or therapeutic procedures would be necessary if the fetus was confirmed Rh (D) negative. In X-linked genetic disorders in which half of the fetuses will be female and unaffected, noninvasive determination of fetal gender could reduce the number of invasive procedures required for the diagnosis of X-linked genetic disorders by 50%. It could also guide treatment decisions regarding maternal steroids in fetuses at risk of inheriting congenital adrenal hyperplasia (Jackson, 2003). Additional clinical applications for fetal nucleic acids in maternal circulation may include screening for aneuploidy (Wataganara et al., 2003; Lo and Chiu, 2008), pre-eclampsia (Levine et al., 2004), or preterm labor (Farina et al., 2003).

CONCLUSIONS

Midtrimester amniocentesis created the field of invasive prenatal diagnosis and has become the standard by which

all other methods are judged. Earlier prenatal diagnostic methods have increasing appeal for many patients. The most studied of these methods is CVS. Transcervical and transabdominal techniques are equally effective; individual operator experience and placental location are usually the criteria used to choose between the two approaches. EA is not recommended now that compelling evidence regarding its disadvantages has been published. Advances in molecular techniques have led to a declining number of reasons for using PUBS. It is now rarely the procedure chosen for determining fetal karyotype. It is, however, the most direct method of evaluating fetal anemia secondary to severe $Rh_o(D)$ disease.

While there have been exciting advances in the field of prenatal diagnosis, the future holds the promise of more breakthroughs. It is expected that imaging modalities will continue to improve, and it is hoped that techniques utilized in the fields of noninvasive prenatal diagnosis and in PGD will continue to advance. Accurate prenatal diagnosis of fetal abnormalities improves patient care by optimizing patient counseling and allowing for informed patient and physician decision-making.

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CHAPTER 5

Fetal Intervention

Key Points

- The range of interventional procedures continues to grow with refinements in criteria for treatment, technique, and instrumentation.
- Shunts work well to decompress thoracic fluid collections such as pleural effusions and cysts in congenital pulmonary airway malformation (CPAM; formerly known as congenital cystic adenomatoid malformation [CCAM]).
- Shunts work less well for treating bladder outlet obstruction; despite restoring amniotic fluid, renal outcomes are often compromised.
- Balloon valvuloplasty for aortic stenosis remains an unproven therapeutic innovation aimed at preventing progression to hypoplastic left heart syndrome.
- Fetoscopic surgery has proven safe and effective in treating twin–twin transfusion syndrome as well as other conditions such as amniotic band syndrome.
- Intrafetal radiofrequency ablation has been shown to have fewer complications and better survival than fetoscopic cord occlusion in Twin Reversed Arterial Perfusion (TRAP).
- Open fetal surgery is an option in rare cases for hydropic CPAM, sacrococcygeal teratoma (SCT), pericardial teratoma, and—depending on results of the MOMS trial—meningomyelocele (MMC).
- EXIT procedures are indicated for the management of compromised airways due to cervical teratoma, CHAOS, intrathoracic mass, and severe micrognathia.
- EXIT-to-ECMO may be beneficial in some cases of CDH or hypoplastic left heart syndrome with restrictive or intact atrial system.

Table 5-1

Fetal Malformations Treatable by Needle Aspiration and Shunting Procedures

Fetal Malformation	Fetal Presentation	Fetal/Neonatal Consequence
Posterior urethral valves	Hydronephrosis Oligohydramnios	Renal dysplasia and renal insufficiency Pulmonary hypoplasia and respiratory insufficiency
Cystic adenomatoid malformation of the lung	Mediastinal shift Hydrops	Pulmonary hypoplasia
Aqueductal stenosis	Hydrocephalus	Neurologic damage
Fetal hydrothorax	Mediastinal shift, hydrops, polyhydramnios	Pulmonary hypoplasia
Ovarian cyst	Wandering cystic abdominal mass, polyhydramnios	Ovarian torsion

Prenatal diagnosis has become increasingly sophisticated, and technologic advances have enhanced not only our diagnostic abilities, but also our understanding of the natural history of lesions detected in the prenatal period. Invasive therapies have developed as a consequence of our expanded understanding of the natural history and pathophysiology of structural anomalies (Garmel and D'Alton, 1993; Adzick and Harrison, 1994b). Despite rapid progress in prenatal diagnosis in the 1960s and 1970s, few invasive therapies were considered, much less employed (Adamsons, 1966). If a fetal malformation was made prenatally, parents had only two alternatives: pregnancy termination (if the diagnosis was made prior to 24 weeks of gestation) or continuing to term (Harrison et al., 1981b). An additional option is arranging for delivery at a tertiary care facility where appropriate pediatric specialists would be available to immediately treat the newborn with a congenital anomaly. As the natural history of many prenatally diagnosed anomalies became better understood, early delivery was recognized as an option to avoid the continuing damage caused by the anomaly in utero (Adzick and Harrison, 1994a,b). Today there are more alternatives. In this chapter we describe the treatment options available, how they were developed, and new therapies that may be available in the future.

FETAL SHUNTING PROCEDURES

A new era in invasive fetal therapy began in the early 1980s, when several independent groups introduced shunting procedures for hydrocephalus and hydronephrosis (Clewell et al., 1982; Frigoletto et al., 1982; Golbus et al., 1982). These first few cases represented an extension of invasive fetal therapy from simple intrauterine blood transfusion for a medical illness to the first attempts at in utero treatment of structural anomalies (Table 5-1).

During this period, hydronephrosis and hydrocephalus were being recognized more frequently with ultrasound examination. The prenatal natural history of these lesions was established by serial sonographic observation of untreated cases (Chervenak et al., 1984; Glick et al., 1984a,b; Clewell et al., 1985; Nakayama et al., 1986; Crombleholme et al., 1988b; Cendron et al., 1994). Fetuses with high-grade obstructive uropathy followed to term were often born with advanced hydronephrosis, type IV cystic dysplasia, and pulmonary hypoplasia that were incompatible with life (Potter, 1976; Crombleholme et al., 1988b; Cendron et al., 1994). In the case of obstructive hydrocephalus, it was known that shunting during the newborn period improved neurologic outcome, and it was reasoned that decompression in utero might avert progressive brain damage (Lawrence and Coates, 1962; Lorber, 1969; Young et al., 1973). However, the poor outcomes observed with shunting for hydrocephalus resulted in a moratorium on the use of shunts in the treatment of obstructive hydrocephalus (Clewell, 1991). In other conditions, work in appropriate animal models helped to define the pathophysiology of these lesions and establish the theoretical basis for intervention (Adzick et al., 1970; Harrison et al., 1982d, 1983; Glick et al., 1983, 1984a, 1984b).

Hydronephrosis

The first case of a fetus with obstructive uropathy treated in utero by vesicoamniotic shunting was reported by Golbus et al. in 1982. Advances soon followed in diagnosis, technique, shunt design, and patient selection (Rodeck et al., 1988; Crombleholme et al., 1988a, 1991a; Harrison and Filly, 1991; Crombleholme, 1994; Johnson et al., 1995). The enthusiasm for treating fetal obstructive uropathy has continued unabated during the past two decades. The procedure

became widely implemented before stringent selection criteria for treatment were developed and the therapeutic efficacy of the procedure was established. The widespread use of vesicoamniotic shunts also had the effects of shifting cases away from the centers studying vesicoamniotic shunts to better define their role in the management of fetal obstructive uropathy.

The lack of a prospective randomized trial makes it difficult to address the efficacy of prenatal decompression of fetal obstructive uropathy. One of the few series that attempted to address this question, was a retrospective analysis reported by Crombleholme et al. (1991a). In fetuses predicted to have either good or poor prognoses by fetal urine electrolyte and ultrasound criteria, survival was greater among those who underwent decompression in utero, as opposed to those who did not undergo decompression. In the group of fetuses predicted to have a poor prognosis by selection criteria, 10 were treated; three of these pregnancies were electively terminated, 4 neonates died from pulmonary hypoplasia or renal dysplasia, and 3 survived. All three survivors had restoration of normal amniotic fluid (AF) levels and no pulmonary complications, but two of the three subsequently developed renal failure requiring renal transplantation. Among the 14 patients with no intervention, there were no survivors (11 terminations and 3 neonatal deaths from pulmonary hypoplasia). In the entire series, uncorrected oligohydramnios was associated with a 100% neonatal mortality rate. Normal or restored AF volume was associated with a 94% survival rate (Crombleholme et al., 1991a).

Although in utero decompression seems to prevent neonatal death from pulmonary hypoplasia, the effect on renal function is less clear. The severity of renal dysplasia at birth depends on the timing and severity of obstruction before birth (Harrison et al., 1981a,b, 1982a,c, 1987, 1990; Manning et al., 1986; Crombleholme et al., 1988b, 1991a). Experimental work suggests that relief of obstruction during the most active phase of nephrogenesis (20–30 weeks of gestation) may obviate further damage and allow normal nephrogenesis to proceed (Adzick et al., 1970; Beck, 1971; Harrison et al., 1982a, 1987; Glick et al., 1984a,b; Gonzalez et al., 1985; Salinas-Madrigal et al., 1988; Peters et al., 1991). The development of postnatal renal failure in two infants who were not treated because AF volume remained normal raises the question of whether to treat fetuses with obstruction before oligohydramnios develops. Because renal development or maldevelopment is complete at birth, relief of obstruction in infancy or childhood may not prevent the progression to end-stage renal failure (Warshaw et al., 1982). Müller et al. (1993) reported on a group of fetuses with obstructive uropathy, a favorable prognostic profile, and normal AF in whom renal insufficiency developed by 1 year of age. The only feature that distinguished this group of fetuses was a urinary level of β_2-microglobulin greater than 2 mg per liter suggesting that elevated fetal urinary levels of β_2-microglobulin may identify fetuses at increased risk for ongoing renal damage from obstruction, even if AF is normal. Other investigators have not found β_2-microglobulin levels to be as useful, although levels greater than 10 mg per liter can be a predictor of poor outcome in fetuses over 20 weeks of gestation (Freedman et al., 1997). It remains an open question whether or not in utero decompression could prevent long-term renal insufficiency in these patients.

The maternal morbidity associated with vesicoamniotic shunting has been reported to be minimal, but chorioamnionitis related to the procedure has been reported (Glick et al., 1985; Crombleholme et al., 1991a). In addition, there have been reports of shunt-induced abdominal wall defects with herniation of bowel through trochar stab wounds and maternal ascites from leakage of AF through the uterine wall into the maternal peritoneal cavity (Manning et al., 1986; Robichaux et al., 1991; Ronderos-Dumit et al., 1991).

The utility of vesicoamniotic shunts is limited by the brief duration of decompression, the risk of infection, the risk of catheter obstruction or dislodgment, fetal injury during placement, and potentially inadequate decompression of the fetal urinary tract (Glick et al., 1985; Crombleholme et al., 1988a, 1991a; Estes and Harrison, 1993). These factors make vesicoamniotic shunts less effective when placed early in gestation for long-term decompression of the urinary tract and are the impetus for development of open fetal surgical and fetoscopic techniques to treat obstructive uropathy in utero (Crombleholme et al., 1988a; Estes and Harrison, 1993; Crombleholme and Lim, in press).

Fetal Hydrothorax

Thoracentesis is a diagnostic maneuver to obtain pleural fluid for differential cell count and culture and to establish whether the effusion is chylous. But even repeated thoracentesis provides inadequate decompression of the fetal chest. There have been several reports of thoracentesis for fetal hydrothorax (FHT), performed with either complete resolution or a good outcome despite reaccumulation (Petres et al., 1982; Kurjak et al., 1985; Benacerraf et al., 1989). Others have had disappointing results with repeated thoracentesis for FHT, because of rapid reaccumulation of the effusion and neonatal death from respiratory insufficiency (Longaker et al., 1989; Nicolaides and Azar, 1990). Spontaneous resolution of FHT may occur in as many as 10% of cases, and resolution following thoracentesis may or may not be related to the procedure. Thoracentesis alone cannot adequately decompress the fetal chest to allow pulmonary expansion and prevent pulmonary hypoplasia (Laberge et al., 1991).

Thoracoamniotic shunting for FHT, first reported by Rodeck et al. in 1988, provides continuous decompression of the fetal chest, allowing lung expansion. If instituted early enough, this allows compensatory lung growth and prevents neonatal death from pulmonary hypoplasia. Nicolaides and Azar (1990) reported on 48 cases of thoracoamniotic shunting, but there was no attempt to distinguish isolated primary FHT from secondary FHT. Despite intervention, mortality was high. Four of the deaths were due to termination

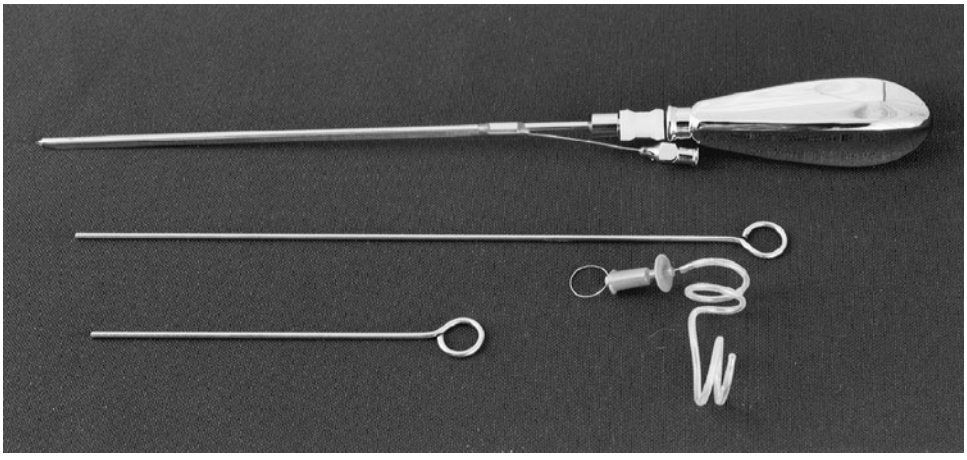

Figure 5-1 The trochar used for KCH catheter insertion, including the obturators and sheath with the KCH catheter for scale. Note the KCH catheter with the pigtail ends at 90° to each other.

of pregnancy when a chromosomal abnormality was diagnosed. In addition, there were 12 neonatal deaths despite thoracoamniotic shunt placement, but these fetuses seemed to have severe hydrops and secondary FHT. Two fetuses that died in utero also seemed to have had secondary FHT and severe hydrops. If the cases that appear to be secondary FHT are eliminated, the survival of isolated primary FHT treated with thoracoamniotic shunting is 38 of 41 (92%) cases (Nicolaides and Azar, 1990; Moran et al., 1994). A similar survival rate with thoracoamniotic shunting was found by Hagay et al. (1993) in their review of fetal pleural effusions. This is a striking improvement when compared with a survival of only 50% in untreated FHT.

The indications for thoracoamniotic shunting are not well defined. Most authors consider the presence of FHT-induced hydrops or polyhydramnios as indications for shunting (Rodeck et al., 1988; Longaker et al., 1989; Nicolaides and Azar, 1990). In addition, we recommend thoracoamniotic shunting for primary FHT with evidence of effusion under tension even in the absence of hydrops (Moran et al., 1994). Because spontaneous resolution has been observed even in severe cases of FHT, we reserve thoracoamniotic shunting for cases in which tension hydrothorax recurs after two thoracenteses.

The limited experience with thoracoamniotic shunting suggests that it is extremely effective in decompressing effusion and improving survival. The risks to mother and fetus of thoracentesis and shunt placement have been minimal and are far outweighed by the potential benefits. Few complications have been reported for either fetal thoracentesis or thoracoamniotic shunts. Procedure-related fetal death is rare, due to hemorrhage from an intercostal artery laceration or torsion of the umbilical cord (Longaker et al., 1989). Migration of the shunt under the fetal skin has also been reported, but required no intervention when the infant was born (Rodeck et al., 1988). There have been no maternal complications reported with either thoracentesis or thoracoamniotic shunting. However, it should be recognized that these procedures have the potential for significant complications, including infection, bleeding, premature rupture of membranes, preterm labor, and injury to the fetus (Moran et al., 1994).

There are currently two FDA-approved devices available for shunt placement in a broad range of applications including bladder outlet obstruction, pleural effusions, and cyst decompressions in congenital pulmonary airway malformation (CPAM). The Harrison catheter (Cook, Inc., IN) is available in a complete shunt insertion kit that includes not only the polyurethane shunt but also the trocar for insertion, the guide wire over which the double pigtail catheter is threaded and the pusher that deploys the shunt. The advantages of the Harrison catheter include the ease of insertion and the complete kit it comes with. The disadvantage of the Harrison catheter is that it is more easily dislodged.

The alternative catheter is the Rocket or KCH catheter (see Figure 5-1). The Rocket catheter requires a reusable trocar insertion device that is larger and somewhat more difficult to use compared to the Harrison catheter set. The advantage of the Rocket catheter is that it is less likely to be dislodged. The larger size of the Rocket trocar may make this less appealing for chest shunt insertion due to increased difficulty inserting the shunt and increased risk of laceration of the intercostal artery, especially in fetuses at less than 25 weeks gestation.

Miscellaneous Procedures and Other Indications for Shunts

Small ovarian cysts are common in neonates. They are typically small follicular cysts due to maternal hormonal stimulation and are rarely clinically significant. They usually regress spontaneously (Kirkinen and Jouppila, 1985). The prenatal diagnosis of an ovarian cyst should be considered in any female fetus with a cystic pelvic mass (see Chapter 67). Although they can be mistaken for mesenteric cysts, duplications, urachal cysts, or choledochal cysts, ovarian cysts are

usually simple pelvic cysts that disappear shortly after delivery. Occasionally, these cysts require surgery for complications due to size, rupture, or torsion (Kurjak et al., 1984; Kirkinen and Jouppila, 1985). Once an ovarian cyst becomes symptomatic, salvage of the ovary is unlikely.

Valenti et al. were the first to perform cyst decompression in utero, in 1975. A large (7 by 9 cm) ovarian cyst was aspirated to prevent intrapartum cyst rupture. Landrum et al. (1986) reported fetal ovarian cyst aspiration ostensibly to prevent pulmonary hypoplasia. While pulmonary hypoplasia from a pelvic mass is unlikely, aspiration to prevent in utero rupture or torsion and to preserve ovarian tissue is a more appropriate indication for treatment. Holzgreve et al. (1993) have reported their experience with 13 cases of fetal ovarian cysts. This group recommends ovarian cyst decompression if the cyst is large, rapidly increasing in size, or observed to be a "wandering mass" as cysts exhibiting these features are more likely to undergo torsion. Cyst tap revealing high levels of prostaglandin F21, progesterone, and testosterone in the fluid confirms the diagnosis. Giorlandino et al. (1990) have reported a case of ovarian cyst treated by cyst aspiration and sclerosis with tetracycline. While this treatment was successful, the use of tetracycline as a sclerosing agent in the fetus is not advised. This group has subsequently reported success in four cases of simple cyst aspiration (Giorlandino et al., 1993). Similarly, D'Addario (1990) aspirated ovarian cysts in two fetuses, but neonatal surgery was still needed. Crombleholme et al. have suggested criteria for intervention in fetal ovarian cysts with diameters of >4 cm, increasing 1 cm per week in size, or as Holzgreve suggested, noted to wander about the abdomen (Crombleholme et al., 1997). Although fetal ovarian cyst decompression seems a relatively benign procedure with the potential for ovarian preservation, the indications for fetal intervention are not uniformly accepted.

In 1987, Nicolaides et al. reported the first case of CPAM treated by shunt insertion in utero. Decompression of a large type I CCAM in a 20-week-old fetus by percutaneous placement of a thoracoamniotic shunt was subsequently reported by Clark in 1987. This procedure resulted in resolution of both mediastinal shift and hydrops and successful delivery at 37 weeks of gestation. Postnatally, the infant underwent uneventful resection of the CCAM. Recently, Wilson et al. (2006) reviewed the CHOP experience with thoracoamniotic shunts for cystic CCAMs demonstrating an average acute 70% reduction in CCAM volume with a 74% survival with thoracoamniotic shunting in the presence of hydrops, polyhydramnios or fetuses at increased risk for developing pulmonary hypoplasia. This experience is consistent with other reports of CCAMs with a dominant cyst that responded to thoracoamniotic shunt placement (Adzick, 2003, Wilson et al., 2004, 2006). There are however potential procedure-related complications including catheter dislodgment, catheter occlusion from thrombus, fetal hemorrhage, placental abruption, premature rupture of membranes or preterm delivery, and chest wall deformity (Dommergues et al., 1997; Mann et al., 2007; Merchant et al., in press). More commonly, it is the type III CCAM or microcystic lesions, which becomes enlarged, resulting in hydrops and intrauterine fetal death; in these cases, open fetal surgery and resection are indicated. However, in the rare instances in which there is a single large cyst in CCAM responsible for hydrops, thoracoamniotic shunting appears to be an appropriate treatment option (see Chapter 35).

FETAL CARDIAC PROCEDURES

Fetal Arrhythmias

Fetal arrhythmias are most often ventricular extrasystoles or tachyarrhythmias (see Chapter 41). But bradyarrhythmias account for 9% of cases reported to the Fetal Arrhythmia Registry, half of which occur in structurally normal hearts due to transplacental passage of antibody in mothers with collagen vascular disease (Kleinman and Evans, 1988) (see Chapter 42). The other half occur in structurally abnormal hearts, and bradyarrhythmia is almost uniformly fatal in that setting (Kleinman et al., 1982; Stewart et al., 1983). In structurally normal hearts in which complete heart block (CHB) develops in mothers with collagen vascular disease, hydrops will develop in 25% and is usually refractory to medical therapy (Altenburger et al., 1977; Carpenter et al., 1986; Machado et al., 1988). Based on the combined retrospective experience from the groups at Toronto Sick Kids and UCSF, fetuses with CHB may benefit from the combination of maternal steroids and β-mimetics (see Chapter 42). There is no expectation that steroids will improve the fetal heart rate but may reduce maternal Ab titer and transplacental passage and limit the ongoing injury to the fetal cardiac conduction system and the myocardium. If low-output fetal heart failure cannot be reversed by increasing heart rate with β-agonists then fetal cardiac pacing is the only alternative. Carpenter et al. (1986) reported the first fetus treated by implantation of a percutaneous transthoracic pacemaker. Unfortunately, the fetus was severely hydropic and despite successful ventricular capture and pacing the fetus died within hours. The obvious problems with the percutaneous transthoracic pacemaker are the risks of dislodgment, potential for infection (chorioamnionitis), and the temporary nature of the device in a fetus that will require pacing for the rest of gestation. These limitations prompted a group led by Michael Harrison at UCSF to attempt pacemaker placement by open fetal surgery (Harrison et al., 1993). Previous work by Crombleholme et al. (1990, 1991b) had developed the techniques for acute and chronic fetal cardiac pacing and studied the effects of CHB in fetal lambs. Based on this experimental work, Harrison et al. (1993) placed a unipolar epicardial pacemaker in a fetus at 22 weeks of gestation with CHB and hydrops. Similar to Carpenter et al.'s (1986) experience, although able to achieve ventricular capture and pacing, the heart was irreversibly damaged by 6 weeks of in utero cardiac failure and the procedure resulted in fetal death in the operation room (Harrison et al., 1993). More

recently, Crombleholme et al. performed open fetal surgery for placement of epicardial pacing lead with an implantable programmable pulse generator in VVI mode. The pacemaker was set at 65 beats per minute that doubled the combined ventricular output measured by echocardiography. The fetus expired on postoperative day 5 and autopsy was found to have extensive renal and hepatic ischemic injury that likely preceded the fetal surgery (Crombleholme et al., 2008). It is clear from these reports that a fetus with long standing CHB with severe hydrops may already have significant end organ injury that may be unsalvageable despite successful pacemaker placement. The survival of fetuses with CHB and ventricular escape rates of less than 50 beats per minute is poor (Schmidt et al., 1991). Placement of a pacemaker in the fetus with a ventricular response rate of less than 50 beats per minute before the development of hydrops may allow us to save these fetuses with an otherwise dismal prognosis.

Structural Fetal Heart Disease

Structural cardiac defects, such as pulmonic atresia with an intact ventricular septum (PAIVS) or severe aortic stenosis (AS) (see Chapters 49 and 50), may result in obstruction to blood flow, which in turn alters the development of the heart chambers as well as the pulmonic and systemic vasculature in utero (Vlahakes et al., 1981). The major morbidity from these congenital heart defects often results from the secondary alterations in heart development caused by the primary defect (i.e., hypoplasia of the right ventricle in PAIVS or hypoplastic left heart syndrome [HLHS] in AS). In theory, relief of the anatomic obstruction in utero may allow more normal cardiac development, thereby eliminating the need for corrective surgery postnatally.

AS diagnosed prenatally is frequently associated with intrauterine fetal death or neonatal death in fetuses that survive to term. Maxwell et al. (1991) reported a series of 28 fetuses diagnosed prenatally with AS either alone or associated with endocardial fibroblastosis. Only 12 mothers continued the pregnancy to term, and in 2 there was an intrauterine fetal death. None of the 10 neonates survived despite balloon valvuloplasty in 4 of them. Maxwell et al. also noted that in four fetuses the left ventricle failed to grow, resulting in hypoplastic left heart, which would make the neonate unsuitable for postnatal aortic valve reconstruction. This grim natural history for fetuses with prenatally detected AS, as well as poor outcomes with Norwood procedure in their institution, prompted Maxwell et al. (1991) to attempt the first in utero aortic balloon valvuloplasty. This procedure was performed by direct percutaneous puncture of the left ventricle under ultrasound guidance. A J-wire is passed through the stenotic valve, and the balloon catheter is passed over the wire and inflated. All three fetuses treated with this procedure survived to term; two died as neonates and one was doing well to a follow-up of 3 years of age (Maxwell et al., 1991). Two other fetuses were treated unsuccessfully by this technique by another group (Chouri et al., 1994).

More recently, the group at Boston Children's Hospital has reintroduced fetal balloon valvuloplasty in an effort to prevent progression of AS to HLHS (Mäkikallio et al., 2006). In their initial experience with 43 fetuses diagnosed with AS, they retrospectively identified a subset of patients that all progressed to HLHS postnatally. These fetuses all had AS associated with normal LV length, reversed flow in the transverse aortic arch or foramen ovale, and a monophasic mitral inflow pattern. Several centers soon followed with reports of attempts at fetal aortic valvuloplasty (see Table 5-2). Although most centers' experience is quite small, there appears to be a steep learning curve judging from the largest series reported thus far (Tworetzky and Marshall, 2004; Matsui and Gardiner, 2007). "Technical success," as defined as increased flow across the aortic valve, has been achieved in 75% of cases but only 1/3 of technically successful procedures achieve an eventual biventricular circulation postnatally (Matsui and Gardiner, 2007). This contrast between technical success and postnatal success suggests that current selection criteria do not accurately select fetuses that are likely to respond to balloon valvuloplasty.

Wright et al. (1994) have performed radiofrequency pulmonic valvotomy in a fetus with PAIVS. In the most severe forms of PAIVS, the primary valvular lesion causes secondary alteration in the intracardiac flow pattern, resulting in a hypoplastic right ventricle (Casteneda et al., 1994). In these instances, only palliative pulmonary valvotomy and systemic to pulmonary artery shunting can be performed. However, if flow can be reestablished across the pulmonic valve in utero, restoration of intracardiac blood flow may allow subsequent growth of the right ventricle and pulmonary outflow tract. The indications for fetal balloon valvuloplasty in PAIVS include a cardiovascular profile score of less than 7, decreased biventricular cardiac output, severe pulmonary stenosis and/or elevated RV pressure and/or hydrops (Matsui and Gardiner, 2007). In a 26-week-old fetus with PAIVS, no growth was observed in the right ventricle during 6 weeks of in utero observation. By direct puncture of the right ventricle, a pulmonary valvotomy was performed using a radiofrequency ablation catheter. Although only a minute hole with insignificant flow resulted, this procedure and those reported by Maxwell and Chouri et al. have established the feasibility of in utero treatment of structural heart disease. Although there have been technical successes, the outcomes have not been different from the natural history of PAIVS often due to growth failure of the pulmonic valve annulus (Matsui and Gardiner, 2007; Gardiner, 2008).

These procedures are certainly not without risk. One of Maxwell's patients died within hours of the procedure and pieces of balloon and guide wire were left within the fetal heart. All three centers have noted pericardial effusions at the conclusion of the procedure that required evacuation. In the series reported by Marshall et al. (2005), in 20 of 26 patients with technically successful procedures, 12 had at least mild regurgitation at the procedure. In a report from the same group, 45% of 83 fetuses experienced hemodynamic instability (Mizrahi-Arnaud et al., 2007) that was associated

Table 5-2

Compilation of All Fetal Balloon Valvoplasties Reported Including the Method, Technical Success, and Fetal and Neonatal Outcome

					Outcome		Neonatal Outcome	
Ref	**No.**	**GA**	**Method**	**Technical Success**	**Fetal Death**	**IUD/TOP**	**D**	**A**
Kohl et al.	12	26–33	P	8/12	4		6	2
Tulzer et al.	8	25–32	P	5/8	2			6
Tworetzky	38	20–32	P, TU	29/38	5	1	2	28
Gardiner/Kumar	4	23–27	P, F	4/4	1	1	1	1
Suh/Huhta	2	n/a-23	P	2/2	1		1	
Total	64			48/64	13	2	10	37

P = percutaneous; TU = transuterine; F = fetoscopy.
Adapted from Matsui H, Gardiner H. Fetal intervention for cardiac disease: the cutting edge of perinatal care. Semin Fetal Neonatal Med. *2007;12:482-489.*

with transventricular approach and the development of large hemopericardium. In 31 of the 37, resuscitation medications were used and—in all 37—the hemodynamic stability was restored. However, there were 5 fetal deaths (5 of 63, 8%) within 24 hours of the procedure (Mizrahi-Arnaud et al., 2007). Despite the risk of these procedures, the unfavorable outcomes for the fetuses with these structural heart defects argue in favor of continued efforts at developing safe and effective invasive fetal therapies.

FETOSCOPIC SURGERY

Diagnostic Fetoscopy

Embryoscopy was first performed via the transcervical approach early in gestation, prior to fusion of the chorion and amnion, to make a phenotypic diagnosis (Westin, 1954; Gallinat et al., 1978; Dubuisson et al., 1979; Roume et al., 1985; Dumez et al., 1988; Cullen et al., 1991; Ghirardini, 1991). Percutaneous techniques were then developed to introduce the fetoscope directly into the amniotic cavity transabdominally. Many of the initial indications for fetoscopic guidance are procedures that now are routinely performed with ultrasound guidance alone. In some instances, however, diagnostic fetoscopy can still be a useful adjunct to ultrasound, especially early in gestation. The suspicion of a significant fetal anomaly prior to 14 weeks' gestation may be difficult to definitively resolve with ultrasound alone and is too early in gestation for MRI (Deprest and Ville, 2001).

Duchenne muscular dystrophy (DMD), a progressive, degenerative muscle disease, is inherited as an X-linked recessive trait. It is one of the more common genetic diseases among all populations, affecting approximately one in 3500 liveborn male infants. DMD is caused by the deficiency of a protein component of muscle tissue called dystrophin. Dystrophin is part of the membrane cytoskeleton in normal muscle, and a deficiency leads to myofiber necrosis, presumably because of membrane instability. While 70% of cases are inherited through a carrier mother, approximately 30% of cases occur without previous family history, representing apparent de novo mutations in the dystrophin gene (Moser, 1984). Because of isolation of the dystrophin gene (Koenig et al., 1987) and its normal protein product (Hoffman et al., 1987), diagnosis of this disorder can now be made on a molecular basis. However, because of the tremendous size of the DMD gene and variation in molecular abnormalities, the underlying gene defect (usually a deletion) has been able to be identified in only 65% of affected individuals. In such a case, however, female carriers in such families can be identified with molecular testing and future male pregnancies can be tested for that specific familial gene defect.

In 1991, the first case of in utero fetal muscle biopsy for DMD diagnosis was described in a family in which the carrier status of the mother could not be determined for the reasons described above (Evans et al., 1991). Using a renal biopsy device directed into the fetal buttock under high-resolution ultrasound guidance, a satisfactory biopsy of skeletal muscle was obtained for analysis and was subsequently shown to contain normal amounts of the dystrophin protein. DMD

and other genetic conditions remain a rare but important indication for fetoscopic-guided biopsy.

Therapeutic Fetoscopy

Lower urinary tract obstruction

Fetal lower urinary tract obstruction can result in progressive oligohydramnios, pulmonary hypoplasia, and cystic renal dysplasia. Occurring mostly in males, common etiologies include posterior urethral valves, urethral atresia, and urethral hypoplasia. The presence of significant bladder dilation, bilateral hydronephrosis, and severe oligohydramnios prior to 20 weeks' gestation is almost universally associated with in utero or early neonatal death if left untreated. Experimental models of ureteral obstruction in sheep suggest that early reversal of obstruction in midgestation can prevent progression of renal damage and potentially improve postnatal survival and renal outcomes (Glick et al., 1983). This work led to the concept of in utero therapy either by open fetal surgery (Harrison et al., 1982b; Crombleholme et al., 1988a) or vesicoamniotic diverting shunts that drain urine from the bladder to the amniotic space (Harrison et al., 1981b).

However, shunt placement is a technically challenging, invasive procedure, and long-term shunt success is variable, largely due to shunt obstruction or displacement. Functional shunt failure has been reported to occur in 40% to 50% of cases after successful placement, mostly due to displacement of the shunt into the fetal abdomen or amniotic space (Hassan et al., 1997). Because of the displacement issue and the bladder dysfunction that results after catheter decompression, alternative approaches such as fetal cystoscopy have been attempted.

One approach has been based on postnatal therapy for such disorders that involves cystoscopic identification of the underlying etiology, and in cases of posterior urethral valves, destruction of the membranous obstruction. However, developing such an approach in an 18- to 20-week fetus has proven problematic. Engineering and manufacturing advances have produced successive generations of smaller fiberoptic endoscopes that have made the possibility of fetal cystoscopy a reality. Initially, using a variety of 1.7- to 2.2-mm endoscopes, Quintero et al. (1995b) were able to show that in utero diagnostic fetal cystoscopy was possible and later were able to identify proximal urethral obstructions. Several attempts at laser ablation of posterior urethral valves were technical successes, but postoperative obstetrical complications resulted in no long-term survivors from this early experience (Quintero et al., 1995a). Using a 1.2 × 2.4-mm double-lumen trocar sheath, it is possible to pass wire probes or laser fibers to assist in diagnostic evaluation and offer the possibility of laser ablation of posterior urethral valves. Design modifications and refinements to this system have recently allowed fetoscopists to more reliably visualize the source of proximal urethral obstruction and differentiate between urethral atresia and posterior urethral valves (Figure 5-2). Visualization of the posterior urethral valves may be difficult beyond 20 weeks due to increased angulation at the posterior urethra. Clifton et al. (2008) have added the placement of a transurethral stent to disrupt the valves with good renal function and bladder function at one year postnatally. It is hoped that by treating the source of the obstruction in midgestation, renal function will be preserved and the need for postnatal urologic surgery to correct secondary anatomic abnormalities may be eliminated. However, despite a compelling rationale for fetal cystoscopic treatment of posterior urethral valves and advances in fetoscopic techniques, this approach has yet to be shown to be a more effective treatment of lower urinary tract obstruction than vesicoamniotic shunting.

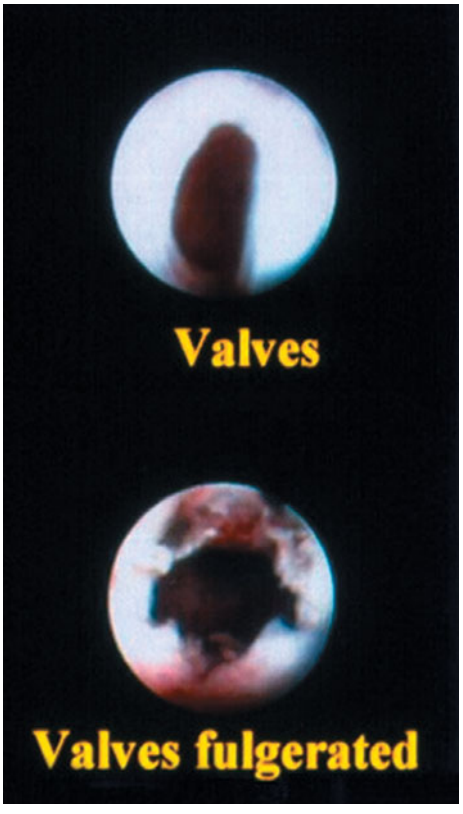

Figure 5-2 Fetal antegrade cystourethroscopy (top) prior to fulgeration of valves and immediately following (bottom).

Diaphragmatic hernia

Congenital diaphragmatic hernia (CDH) is a simple anatomic defect in the diaphragm, but in severe cases it may result in profound pulmonary hypoplasia precluding postnatal survival (Harrison et al., 1978; Harrison and deLorimier, 1981). This prenatal natural history of CDH has led to attempts to correct the diaphragmatic defect before birth, with some anecdotal success. It had been recognized in the physiology literature for decades that occlusion of the fetal trachea results in accelerated lung growth (Carmel et al., 1965; Alcorn et al., 1977). This technique was applied in animal models of CDH, demonstrating that tracheal occlusion can correct the pulmonary hypoplasia associated with CDH (DiFiore et al., 1994; Hedrick et al., 1994). This work was quickly replicated in other laboratories and was pioneered in clinical application

by Harrison and the University of California at San Francisco (UCSF) group using open fetal surgical techniques to occlude the trachea (Harrison et al., 1996). The survival using an open fetal surgical approach, however, was disappointing, and fetoscopic techniques of tracheal occlusion were developed in hopes of avoiding the problems of preterm labor and complications from tocolytic agents associated with hysterotomy (Adzick et al., 1985b; Harrison et al., 1990; Flake et al., 2000). The fetoscopic techniques used for tracheal occlusion have evolved with growing experience by the UCSF and Eurofetus group.

In their initial approach with the "fetendo" clip, Harrison et al. (1998) reported a 75% survival compared with 15% in the open fetal surgical approach to tracheal occlusion and a 38% survival with standard postnatal therapy. Not only did survival appear to be improved in this small series, but there was also a trend toward less preterm labor, less need for tocolysis, and a shorter hospital stay. The UCSF group further refined their technique, eliminating the multiple ports and the neck dissection entirely by performing an endoluminal balloon tracheal occlusion (Harrison et al., 2001). A single port is used to introduce a fetoscope into the amnion and the fetal oropharynx. The vocal cords are fetoscopically viewed for passage of a detachable balloon catheter through the vocal cords. The position in the trachea is determined sonographically before inflation and deployment of the balloon. This technique was piloted in several cases of right-sided CDH and was evaluated in a National Institutes of Health (NIH) sponsored prospective randomized clinical trial comparing fetoscopic endoluminal balloon tracheal occlusion to conventional postnatal therapy.

The NIH trial of fetoscopic tracheal occlusion was halted after randomization of only 24 subjects when it became apparent that there would be no significant difference in survival between the fetoscopic tracheal occlusion group and the conventional therapy group. The fetoscopic surgery group had a 73% (8 out of 11) survival, as predicted by preliminary data, but the conventional postnatal treatment group had a better than predicted survival of 77% (10 out of 13). The fetoscopically treated patients delivered significantly earlier compared to conventional treatment at a mean of 30.8 versus 37.0 weeks, respectively. The entry criteria for this study was LHR <1.4, which resulted in a number of patients included that would be expected to do well with conventional postnatal therapy. European centers that are a part of the Eurofetus FETO (Fetoscopic Endoluminal Tracheal Occlusion) in Leuven, Belgium, Barcelona, Spain, and London, United Kingdom have collaborated on fetoscopic tracheal occlusion for LHR <1.0 with liver herniation. This has resulted in survival of 55% that compared favorably to conventional postnatal therapy in their neonatal centers with 11% survival (Deprest et al., 2008). More recently, Deprest et al. (2008) has reported 83% survival with fetoscopic tracheal occlusion and reversal later in gestation. The reversal of tracheal occlusion is performed by either a second fetoscopic procedure for removal or by ultrasound-guided balloon puncture. The detachable balloon used in tracheal occlusion in Europe is not FDA approved. Recently, centers in the United States including UCSF and the Fetal Care Center of Cincinnati have obtained an investigational device exemptions (IDE) to perform fetoscopic tracheal occlusion in cases of severe CDH with liver herniation and a lung/head ratio (LHR) of <1.0 between 26 and 28 weeks' gestation.

Attempts at treating fetal SCT with minimally invasive fetoscopic techniques have met with mixed results. Hecher and Hackeloer (1996) reported the successful treatment of an SCT by fetoscopy using laser. The base of this SCT was unusually narrow, without distortion of the anorectal sphincter complex onto the mass. This is an important consideration, as most fetal SCTs distort the anorectal sphincter complex, and such a fetoscopic approach as described by Hecher might result in ischemic necrosis of the anorectal sphincter complex along with the SCT. In addition, the superficial vessels are the only ones accessible to the laser, while the deeper pelvic vessels, which may be more important in the development of high-output physiology, are inaccessible. These difficulties are highlighted by the UCSF experience with the use of radiofrequency ablation (RFA) (Paek et al., 2001). The goal was the coagulation of the feeding vessels to the SCT that are responsible for the high-output state. The power of the RFA in this ultrasound-guided technique could not be precisely controlled and the fetus sustained necrosis of the anus, vagina, and bladder, with injury to the sciatic nerve (Paek et al., 2001).

Myelomeningocele

In recent years, fetal surgery has moved from the treatment exclusively of life-threatening fetal anomalies such as CDH, SCT, or hydropic CPAMs to fetal anomalies that are severely debilitating, but not life threatening. Myelomeningocele (MMC) may be the most controversial of the current nonlethal indications for fetal surgery. While fetal repair of myelomeningocele is now performed using open fetal surgical techniques, it was first attempted using a fetoscopic approach by the group at Vanderbilt (Bruner, 1998; Bruner et al., 1999). The uterus was exteriorized and three fetoscopic ports were placed, one for the fetoscope and two operative ports (Bruner et al., 1999). A maternal split-thickness skin graft was placed over the myelomeningocele defect and secured using Surgicel and fibrin glue in four patients between 22 and 24 weeks' gestation. The results were disappointing: two fetal losses occurred, one from intrauterine fetal demise due to placental abruption and the other due to severe prematurity. Although the intent was palliative (i.e., providing cover and protection to the neural tube defect in utero to preserve neurologic function until a more definitive repair could be performed postnatally), none of the split-thickness skin grafts survived. The two survivors in this small series did not appear to benefit from this procedure, and the Vanderbilt group has abandoned this approach in favor of an open surgical technique until technical advances in fetoscopic instrumentation may make this a viable alternative approach (Tulipan and Bruner, 2001). More recently, Kohl and Gembruch (2008) have reported fetoscopic

closure using a gortex patch in myelomeningocele to protect the exposed spinal cord. It is not clear whether the approach offers any advantages over open techniques or the previously reported fetoscopic approach.

The MOMS (*M*anagement *o*f *M*yelomeningocele *S*tudy) trial is a National Institute of Child Health and Human Development sponsored study that began in *2003 to assess the outcomes* of prenatal and postnatal closure of myelomeningocele. This ongoing study is enrolling approximately 200 women from Fetal Surgery Units Network sites, and randomizing them either to prenatal surgery between 19 and 25 weeks of gestation or to postnatal surgery. Pediatric outcomes will be assessed at 12 months and at $2\frac{1}{2}$ years of age. When available, results of this study should provide additional information regarding the optimal timing of surgical intervention for prenatally diagnosed neural tube defects.

Amniotic band syndrome

The amniotic band syndrome (ABS) is another example of a usually nonlethal anomaly potentially treatable by fetoscopic surgery. ABS is a group of sporadic congenital anomalies (including the limbs, craniofacial regions, and trunk) ranging from constrictive bands to pseudosyndactyly to amputation, as well as multiple craniofacial, visceral, and body wall defects (Torpin, 1965; Jones et al., 1974; Higginbottom and Jones, 1979; Seeds et al., 1982; Ray et al., 1988; Lockwood et al., 1989; Seidman et al., 1989; Kulkarni and Gopal, 1990). Constrictive bands most commonly affect the extremities, but can also involve the umbilical cord and result in fetal demise (Torpin, 1965; Graf et al., 1987; Moerman et al., 1992; Kanayama et al., 1995). Recently, Crombleholme et al. (in press) successfully treated three fetuses with umbilical cord ABS, averting cord accident with survival in all three patients.

We have performed fetoscopic laser release of six cases of extremity amniotic bands, with impending limb amputation. Secondary lymphedema persisted postnatally in two fetuses, while atrophy of the hand occurred in another. One lower extremity in which the band was released before there was irreversible damage was completely normal by the time of delivery. The results of these few cases establish at least the feasibility and safety of performing fetoscopic release of amniotic bands with the potential to salvage the extremities. In cases of umbilical cord involvement, this approach also has the potential of being lifesaving.

Fetoscopic Treatment of Complications in Monochorionic Twins

Monochorionic twins discordant for anomaly

Twin gestations are at increased risk for the development of congenital anomalies. A range of congenital malformations such as anencephaly, omphalocele, hydrocephalus, and atresia/stenosis of the gastrointestinal tract are more common in twin gestations (Bajoria and Kingdom, 1997). Congenital heart defects are twice as prevalent in monozygotic twins than dizygotic twins or singleton pregnancies (Burn, 1995). In addition, it has been noted that twins discordant for anomaly deliver even earlier than the average twin delivery of 34 weeks (Malone and D'Alton, 1999). Therefore, there are increased risks for the healthy co-twin not only from intrauterine demise of the anomalous co-twin but also from the risks attendant to extremely premature delivery.

It is important to distinguish the chorionicity of a twin gestation when one of the twins has a structural or karyotypic abnormality. In a dichorionic pregnancy, it is possible to observe spontaneous intrauterine fetal demise or perform selective feticide by means of a potassium chloride injection without significant risk to the healthy co-twin (Golbus et al., 1988). This is not the case with monochorionic pregnancies in light of the vascular connections between the twins, or chorioangiopagus. In the past, because alternative interventions such as sectio parva or ultrasound-guided embolization have been unsuccessful, the usual recommendation has been to manage these pregnancies expectantly. In monochorionic gestations, however, this strategy leaves the healthy co-twin at risk for simultaneous intrauterine fetal demise or severe neurologic injury in the event of co-twin demise. Fetoscopic cord ligation or intrafetal RFA provides a viable therapeutic option under these circumstances. Crombleholme et al. (1996) reported the first use of fetoscopic cord ligation specifically to prevent neurologic injury in a surviving twin when death of a co-twin was anticipated, and several groups have since reported success with fetoscopic cord ligation or coagulation (Deprest et al., 2000; Nicolini et al., 2001; Johnson et al., 2002). A less invasive approach we currently favor is ultrasound-guided intrafetal RFA (Livingston et al., 2007) (see section on "Twin Reversed Arterial Perfusion Sequence" below).

Twin reversed arterial perfusion sequence

Twin reversed arterial perfusion (TRAP) sequence occurs only in the setting of a monochorionic pregnancy and complicates approximately 1% of monochorionic twin gestations, with an incidence of 1 in 35,000 births (James, 1977). In the TRAP sequence, the acardiac/acephalic twin receives all of its blood supply from the normal or so-called "pump" twin. The acardiac twin has a grossly anomalous circulation that is sustained in a parasitic manner by the normal co-twin ("pump" twin) through reversed perfusion of the arterial–arterial anastomoses. Because of the increased demand the abnormal circulation in TRAP sequence places on the heart of the "pump" twin, cardiac failure is the primary concern. If left untreated, the "pump" twin dies in up to 50% to 75% of cases. This is especially true when the acardiac/acephalic twin is greater than 50% of the size of the "pump" twin by estimated weight (Moore et al., 1990).

At least 33 cases of umbilical cord ligation or coagulation for TRAP sequence have now been reported (Porreco et al., 1991; McCurdy et al., 1993; Quintero et al., 1994, 1996; Hecher et al., 1995; Willcourt et al., 1995; Rodeck et al., 1998;

Deprest et al., 2000; Nicolini et al., 2001; Johnson et al., 2002) and an additional 7 cases have been treated by umbilical cord laser coagulation (Willcourt et al., 1995). Laser coagulation is not recommended after 21 weeks' gestation (Challis et al., 1999). The most common complication was the development of premature rupture of membranes, complicating up to 30% of cases (Porreco et al., 1991; McCurdy et al., 1993; Quintero et al., 1994, 1996; Hecher et al., 1995; Willcourt et al., 1995; Rodeck et al., 1998; Deprest et al., 2000; Nicolini et al., 2001; Johnson et al., 2002). Challis et al. (1999) reported a failure rate for cord coagulation of 10%, with fetal survival of 71%, and risk of preterm premature rupture of membranes of 30%.

In recent years, we have converted to the use of intrafetal RFAin TRAP sequence with 95% "pump" twin survival. This is consistent with the survival reported by UCSF (Tsao et al., 2002). The experience at Cincinnati and UCSF compare favorably with the experience of European groups who report an overall survival rate of 85% with fetoscopic bipolar electrocautery. Lee et al. (2008) reported the North American Fetal Therapy Network (NAFTNet) experience with intrafetal RFA at five centers. Not surprisingly, the centers with the most experience had the best survival and fewest complications (Lee et al., 2008).

Twin—twin transfusion syndrome

The natural history of severe twin–twin transfusion syndrome (TTTS) is well established, with mortality approaching 100% if left untreated, especially when it presents at less than 20 weeks' gestation (Weir et al., 1979; Cheung et al., 1995; Saade et al., 1997) (see Chapter 119).

The first treatment of TTTS that attempted to treat the underlying chorioangiopagus was reported by DeLia et al. (DeLia et al., 1995; Ville et al., 1995). Fetoscopic laser was used to photocoagulate vessels crossing the inter-twin membrane. In the first series of cases of TTTS, DeLia et al. (1995) reported a survival of 53% in 26 patients. While survival was not significantly better than previous reports with serial amnioreduction, the neurologic outcome was normal in 96%. Other groups from Europe have reported similar survival with fetoscopic laser photocoagulation. Ville et al. (1995) reported 53% survival with a nonselective laser technique, which was better than the survival observed with historical controls at the same center with serial amnioreduction (37%). There also appeared to be an improved neurologic outcome in fetuses treated by laser. Nonselective fetoscopic laser photocoagulation of all vessels crossing the inter-twin membrane may be problematic, as the inter-twin membrane often bears no relation to the vascular equator of the placenta. This may result in sacrifice of vessels not responsible for the TTTS, resulting in a higher death rate of the donor twin from acute placental insufficiency (Quintero et al., 1998). More recently a selective laser photocoagulation technique has been reported (Quintero et al., 1998). The selective technique does not photocoagulate every vessel crossing the inter-twin membrane; only direct, arterial–arterial and veno-venous, connections are photocoagulated, along with any unpaired artery going to a cotyledon with the corresponding vein (and vice versa) going to the opposite umbilical cord (Figure 5-3). In a nonrandomized comparison of patients treated by serial amnioreduction at one center and selective laser photocoagulation at another, the overall survival was not significantly different (61% for laser vs. 51% for serial amnioreduction) (Hecher et al., 1999). However, the survival of at least one twin with laser photocoagulation was 79%, while survival of at least one twin with serial amnioreduction was only 60% (Hecher et al., 1999). This was not a controlled trial, and patients were not randomized.

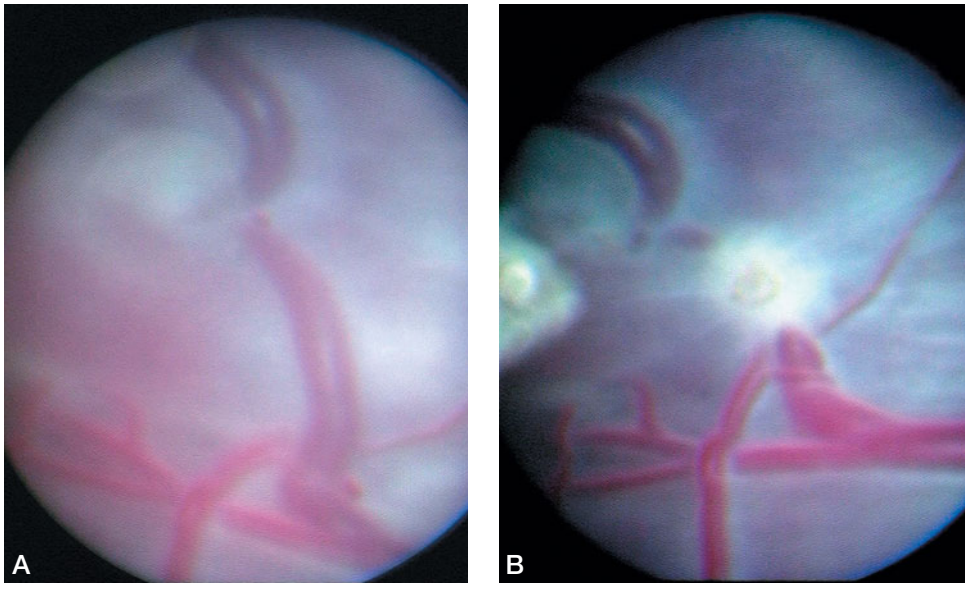

Figure 5-3 Fetoscopic view of chorioangiopagus on a monochorionic placenta before (**A**) and after (**B**) selective fetoscopic laser photocoagulation in a case of severe TTTS.

Quintero et al. (2003) retrospectively examined data from 78 patients treated by serial amnioreduction and 95 patients treated with selective laser photocoagulation with no significant difference in the distribution of patients by stage. Perinatal survival was not significantly different in the laser versus amnioreduction group (64.2% vs. 57.7%). However, there was an inverse relationship between fetal survival and stage in the amniocentesis group but not in the laser group. For stage IV disease, there was a significantly lower fetal survival in the amnioreduction group compared with the laser group (20.6% vs. 63.6%, $P = 0.001$). This information has important implications for evaluation of treatment options and the development of stage-based treatment protocols.

The Eurofoetus trial conducted by Senat et al. (2004) was the first prospective randomized trial that compared the efficacy and safety of treatment of twin-to-twin transfusion syndrome with laser therapy versus serial amnioreduction. Women presenting between 15 and 26 weeks' gestation with polyhydraminos in the recipient twin and oligohydramninos in the donor twin were allowed to participate. Fifty-two percent of patients were stage I or II, 47% were stage III, and 1% were stage IV. Enrollment was halted after a planned interim analysis revealed a significantly higher likelihood of survival of at least one twin to 28 days of age (76% vs. 56%, $P = 0.009$) and to 6 months of age (76% vs. 51%, $P = 0.002$) in the laser group compared to the amnioreduction group. More infants were alive without neurologic abnormalities detected on neuroimaging studies in the laser group as well (52% vs. 31%, $P = 0.003$). The overall survival in the laser arm was 57%. This is consistent with previous reports of nonselective fetoscopic laser (53%) (DeLia et al., 1995; Ville et al., 1995). This is significantly lower, however, than the survival reported with selective fetoscopic laser (64–68%) (Hecher et al., 2000; Fisk et al., 2004). Of particular concern is the poor survival that was observed in the amnioreduction arm. The overall survival was only 39%, which is significantly lower than previously reported (60–65%) (Elliott et al., 1991; Pinette et al., 1993; Dickinson and Evans, 2000; Mari et al., 2001). Antenatal, peripartum, and neonatal care were provided by the referring hospital and lack of standardization may explain some of these differences (Fisk et al., 2004). The decreased survival in the amnioreduction group may reflect the higher pregnancy termination rate in the amnioreduction group (16 patients vs. 0 patients in the laser group). The terminations were requested after the diagnosis of severe fetal complications; it would be instructive to know whether these women were offered cord coagulation as a means of rescuing one baby (Fisk et al., 2004). Reliable assessment of neurologic outcome is critical when assessing efficacy of treatment for TTTS. While there was a lower rate of abnormality on neurologic imaging in the laser group (7% vs. 17%), long-term neurodevelopmental assessment has revealed no difference in outcome between survivors treated by fetoscopic laser versus those treated by amnioreduction.

The NIH-sponsored TTTS trial is the only other prospective randomized trial comparing the survival with amnioreduction versus selective fetoscopic laser phtotocoagulation (Crombleholme et al., 2007). This trial differed from the Eurofetus trial in several important aspects. First, in order to qualify for the NIH Trial, the TTTS had to fail to respond to a qualifying amniocentesis. The rationale for this requirement was to eliminate subjects who were more likely to respond to amnioreduction, the so-called "single amnio paradox." Secondly, patients were only candidates if the TTTS presented earlier than 22 weeks and no stage I patients were candidates for the trial. These two requirements were quite different from the Eurofetus trial in which subjects were randomized up to 26 weeks' gestation, and 52% of those entered were stage I (Senat et al., 2004).

The study was stopped after 42 subjects were randomized because the Trial Oversight Committee detected a trend in adverse outcome affecting the recipient twin in one treatment arm. Based on this finding, the Trial Oversight Committee recommended to the Data Safety Monitoring Board that the trial be stopped early to allow biostatistical analysis of this adverse trend. The results of the NIH TTTS trial showed no statistically significant difference in overall neonatal survival to 30 days of life (60% vs. 43% p = NS) or neonatal survival of one or both twins in the same pregnancy (75% vs. 65%, p = NS) in cases of severe TTTS treated by either AR or selective fetoscopic laser photocoagulation (SFLP). Despite these overall results, there is a statistically significantly worse fetal survival observed among recipient twins in pregnancies treated by SFLP compared to those treated by AR. This apparent conundrum can be accounted for by recipient fetal losses in the SFLP arm being balanced by increased treatment failures among recipient subjects in the AR arm. These results suggest that, in these highly selected cases of severe TTTS, neither treatment is superior to the other. Once TTTS reaches this severity, the mortality among recipients will be considerable, but the losses may occur at different times depending on treatment. The impact of TTTS severity on fetal survival is further supported by the significantly worse fetal survival among recipient twins in stages III and IV compared to stage II. One of the strongest predictors of recipient demise is echocardiographic evidence of TTTS cardiomyopathy. The losses of fetal recipients treated by SFLP usually occur within 24 hours of the procedure. In contrast, the recipients treated by AR are not lost following the procedure, but there is progressive TTTS cardiomyopathy as reflected by more recipients in the AR arm meeting criteria to be declared treatment failures. Taken together these data suggest a disproportionate impact of TTTS cardiomyopathy on recipient survival in advanced stages of TTTS no matter what treatment they receive.

Recently, Rossi et al., reported a Cochrane review of TTTS with a meta-analysis including data from both the Eurofetus and NIH trials. The conclusion drawn from this analysis was that selective fetoscopic laser treatment of TTTS is preferred over amnioreduction when it is available and amnioreduction when it is not (Rossi and D'Addario, 2008). The results of this analysis are likely to be skewed toward fetoscopic laser based on the small numbers of subjects included from

Table 5-3

Comparison of Overall Survival (Number of Fetuses Treated Divided by Number of Surviving Newborns) and Percentage of Pregnancies with One or Both Twins Surviving in Reported Series Using Selective Fetoscopic Laser Photocoagulation*

	Year	Overall Fetal Survival (%)	At Least 1 Survivor (%)
Hecher	1999	61	79
Hecher	2000	68	81
Quintero	2000	61.3	83
Quintero	2003	64.2	83.2
Huber	2004	70	83
Huber	2006	71.5	83.5
Crombleholme	2007	77	91.7

** The overall survival trend has been improving indicating better outcomes as experience with this technique grows.*

the NIH trial ($n = 40$) compared to the number included from the Eurofetus trial ($n = 142$).

Amnioreduction is readily available, less costly and less invasive; laser therapy is only available at select institutions and requires specialized training. While it makes sense to use the former where treatment options give similar results, it would be prudent to move promptly to laser therapy if rigorous studies can prove laser has better short-term and long-term outcomes in the setting of advanced disease (see Table 5-3).

One potential limitation to the success of laser treatment is the presence of deep vascular AV anastomoses that cannot be identified endoscopically. In one study, vascular casts of 8 of 15 placentae (53%) demonstrated potentially significant atypical AV anastomoses such that two apparently normal cotyledons were actually communicating below the chorionic surface (Wee et al., 2005). A second type of atypical AV anastomoses was noted in 11 of the 15 placentae (73%) in which shared cotyledons arise within larger apparently normal cotyledons. One would be able to see these anastomoses as shared cotyledons on endoscopy; ablating these has the potential to destroy some surrounding normal cotyledon which, in the donor's territory, could contribute to placental insufficiency (Wee et al., 2005). It has also been recognized that in up to 20% of cases, communicating vessels on the chorionic plate are missed at the time of fetoscopic laser treatment (Lopriore et al., 2007). However, only 5% of these cases were associated with persistence of TTTS. These observations point to the necessity of a careful fetoscopic inspection of the chorionic plate to be certain that no vessel has been missed.

Open Fetal Surgery

The technical aspects of open fetal surgery were developed by Harrison and colleagues in extensive animal experiments using fetal sheep and rhesus monkeys (Harrison and Adzick, 1990). Using these experimental animal models, anesthetic, tocolytic, and surgical techniques were developed and applied clinically. Innovative techniques for opening and closing the gravid uterus were developed that minimize the risks to the mother's health and future reproductive potential (Harrison et al., 1993). This included the development of a uterine stapling device to minimize myometrial bleeding (Adzick et al., 1985a; Bond et al., 1989). The details of techniques used for specific diagnoses requiring fetal surgery are covered under the fetal intervention sections of the chapters on these topics. The approaches to entering the gravid uterus, fetal exposure, fetal and maternal monitoring, and anesthetic and tocolytic management are largely the same and are discussed below.

The maternal abdomen is exposed through a low transverse abdominal incision. The fascial incision is determined by the position of the placenta. In the case of a posterior placenta a midline fascial incision can be used, as the uterus will not need to be lifted out of the abdomen. In contrast, in an anteriorly placed placenta, the rectus muscles need to be divided in order to allow room to tilt the uterus out of the abdomen, facilitating a fundal or posterior hysterotomy. A large abdominal ring retractor (Turner-Warwick, V. Mueller, Berlin, Germany) is used to maintain exposure. Sterile intraoperative ultrasound examination is then used to map the fetal position and the placental location. The edge of the placenta is marked under ultrasound guidance using electrocautery. The position and the orientation of the hysterotomy is planned in order to stay parallel to the closest edge of the placenta and 4 to 5 cm from it.

Two different techniques have been used for performing the hysterotomy. A 2-cm incision is made through the myometrium and amnion using electrocautery. This hysterotomy incision is then extended using a specially developed absorbable Lactimer stapler (U.S. Surgical Corporation, Norwalk, CT) that is fast and hemostatic and seals the membranes to the myometrium (Adzick et al., 1985a; Bond et al., 1989). The second technique for performing a hysterotomy uses a trocar attached directly to the uterine stapling device. Two traction sutures are placed to elevate the membrane and myometrial wall from the fetus, and a specially designed trocar attachment that fits on the anvil of the uterine stapling device is inserted directly into the amniotic cavity under ultrasound guidance.

Once the hysterotomy is performed, it is necessary to infuse saline in order to avoid cord compression. A red rubber catheter attached to a Level I rapid volume infusion device is

inserted into the amniotic cavity, which delivers a continuous stream of normal saline warmed to 37°C. The appropriate fetal part is then exposed, leaving the rest of the fetus entirely within the womb. A miniaturized pulse oximeter is wrapped around the fetal palm and protected with a clear plastic adhesive, then shielded from extraneous light with sterile foil wrapping or Coban.

Once the specific defect has been repaired, the fetal part is then returned to the uterus. Full-thickness number 1 PDS stay sutures are then placed along the length of the hysterotomy. As the staples are made of polyglycolic acid and are absorbable, they are left in place to avoid bleeding from the hysterotomy edges. A watertight three-layer uterine closure is then performed, using a running O PDS. Just prior to completing the first layer, 400 to 500 mL of warm normal saline containing 500 mg of oxacillin is instilled into the amniotic cavity to restore the AF volume to a deepest vertical pocket of 3 to 5 cm. After the hysterotomy has been closed, the stay sutures are tied and the maternal laparotomy incision is closed in layers. A subcuticular maternal skin closure is used with a transparent adhesive dressing to facilitate postoperative monitoring by a tocodynamometer and ultrasound examination.

Tocolysis is administered as soon as the uterus is closed with a 6 g load of magnesium sulfate over 1 hour, which then continues at 2 g per hour, or at a higher dose, as clinically indicated by uterine irritability. As the mother emerges from deep anesthesia with isoflurane, there is a tendency for uterine tone to return and for uterine contractions to be observed. To supplement the magnesium sulfate, rectal indomethacin on a schedule of 50 mg every 4 to 6 hours is also used for the first 48 hours. When using indomethacin in this setting, it is our practice to perform daily fetal echocardiography to evaluate for ductal constriction. Patient-controlled analgesia is also an essential part of the tocolytic management. If the mother is having pain, this will be reflected in increased uterine irritability. We currently use a continuous fentanyl infusion supplemented by bupivacaine for postoperative pain control, delivered through an epidural catheter, with patient-controlled rescue doses. The systemic levels of fentanyl achieved with the use of this epidural technique are sufficient to cross the placenta and provide fetal analgesia as well.

Far and away the most difficult problem in the management of the maternal–fetal patient following fetal surgery is the control of preterm labor. The large hysterotomy necessary for these procedures uniformly results in preterm labor. This has led to the development of an aggressive tocolytic regimen that often includes combinations of indomethacin, isoflurane anesthesia, magnesium sulfate, terbutaline, calcium channel blockers, and most recently intravenous nitroglycerin as a nitric oxide donor (Adzick and Harrison, 1994b). Despite aggressive tocolytic therapy, the median interval from fetal surgery to delivery is only 8 weeks, with a range of 1 to 15 weeks (Harrison, 1993).

Although the benefits to the fetus with an otherwise lethal congenital malformation are obvious, there are no direct benefits to the mother, who must assume the risks of fetal surgery and obligatory delivery by cesarean section. Unlike any other procedure, with the possible exception of organ transplantation from a living donor, fetal surgery exposes two patients—the mother and the fetus—to the risks of anesthesia, surgery, hysterotomy, and postoperative tocolysis.

There have been no reports of maternal deaths related to open fetal surgery, but the potential for maternal morbidity is formidable. Among the 42 cases reported by Harrison, 5 patients have required perioperative blood transfusions. AF leaks were observed in five patients, two via the hysterotomy site requiring reoperation and three via the vagina. Preterm labor was uniformly observed, and the majority of the morbidity occurred as a result of aggressive treatment of preterm labor, including pulmonary edema induced by tocolytic agents (Harrison et al., 1993). In addition to these short-term complications, women undergoing fetal surgery also face long-term consequences as a result of fetal surgery. Specifically, the hysterotomy used in fetal surgery is not in the lower uterine segment and remains a weakened area in the myometrium. Accordingly, these women are at risk for rupture during active labor with subsequent pregnancies. Because of the nature of the hysterotomy used in all open fetal surgeries, it is mandatory that women undergoing open fetal surgery be delivered by cesarean section prior to onset of labor in the index pregnancy as well as in all future pregnancies.

Given the maternal risks associated with fetal surgery, careful monitoring of maternal status—including arterial blood pressure and pulse oximetry—is necessary in the postoperative period. In addition, appropriate fetal monitoring includes telemetric fetal heart monitoring, serial sonography, and surveillance of preterm labor by external tocodynamometer. Optimal monitoring of both patients can best be managed in a fetal–maternal intensive care unit that combines the capabilities and expertise of both an intensive care unit and a labor floor (Jennings et al., 1993).

The specific anatomic malformations in which open fetal surgery has already been employed are listed in Table 5-4. Detailed discussions of these specific conditions are reviewed in the chapters that follow.

Ex utero Intrapartum Treatment (EXIT procedure)

The central principle of the EXIT procedure is to maintain controlled uterine hypotonia and preserve uteroplacental circulation while performing a fetal procedure. The ex utero intrapartum technique (EXIT) procedure was initially described for reversal of tracheal occlusion in fetuses with severe CDH (Mychaliska et al., 1997). These cases required neck exploration for the removal of the tracheal clips, with maintenance of uteroplacental blood flow until the fetal airway was secured by endotracheal intubation. Experience with the EXIT technique demonstrated the ability to maintain fetal and maternal hemodynamic stability, and soon led to expanded indications for its use. Indications for EXIT procedures now include giant fetal neck masses, fetal mediastinal

Table 5-4

Fetal Malformations Treatable by Open Fetal Surgery

Fetal Malformation	Fetal Presentation	Fetal/Neonatal Consequences
Posterior urethral valves	Hydronephrosis and oligohydramnios	Renal dysplasia and renal insufficiency Pulmonary hypoplasia and respiratory insufficiency
Cystic adenomatoid malformation of the lung	Chest mass with mediastinal shift and hydrops	Pulmonary hypoplasia and respiratory insufficiency
Congenital diaphragmatic hernia	Herniated viscera in chest	Pulmonary hypoplasia and respiratory insufficiency
Twin–twin transfusion syndrome	Oligohydramnios and polyhydramnios	IUFD, heart failure, MLE
Acephalic-acardiac twin	IUFD	
Sacrococcygeal teratoma	High-output failure hydrops	IUFD, prematurity, hemorrhage
Complete heart block	Hydrops	IUFD
Fetal neck mass	Polyhydramnios	Inability to ventilate due to lack of airway

IUFD = intrauterine fetal death; MLE = multifocal leukoencephalomalacia.

or lung masses, congenital high airway obstruction syndrome (CHAOS), as well as congenital heart disease requiring immediate ECMO (see Table 5-5).

A common misconception is that an EXIT procedure is merely a cesarean section. The goals of a cesarean delivery are to (1) maximize the uterine tone to prevent postpartum hemorrhage; and (2) minimize the transplacental diffusion of inhalational anesthetic agents to avoid neonatal depression (if performed under general anesthesia). In contrast, the goals during the EXIT procedure are to (1) achieve a state of uterine hypotonia so to maintain the uteroplacental circulation using deep general anesthesia; (2) preserve uterine volume so to prevent placental abruption; (3) reach a deep plane of maternal anesthesia but maintain normal maternal blood pressure; and (4) achieve a surgical level of fetal anesthesia without cardiac depression. In addition, the EXIT procedure requires synchronized team work involving multiple disciplines, including at least one or two pediatric surgeons or a pediatric otolaryngologist, a maternal–fetal medicine specialist or obstetrician, an echocardiographer, a neonatologist, two anesthesiologists, two circulating nurses, and two scrub nurses. Unlike standard obstetric anesthetic practice in which regional anesthesia is the rule, general anesthesia is the technique of choice for patients undergoing the EXIT procedure.

As with any fetal surgical procedure, the EXIT procedure involves the treatment of two patients: the mother and her baby. For this reason, we usually have one anesthesiologist for the mother and another for the baby. There are a number of maternal and fetal anesthesia considerations that must be managed. The physiology of pregnancy contributes to a number of maternal and fetal anesthetic risks. The mother is at increased risk for aspiration pneumonitis due to pregnancy-related reduction of lower esophageal sphincter pressure, the increased pressure of the gravid uterus on the stomach, and increased gastric acid production. The cardiovascular system is also affected during pregnancy. A decrease in the preload during supine positioning can cause maternal hypotension, decreased uterine artery perfusion, and thus fetal hypoxia. It is therefore important to position the mother with a left uterine displacement to maximize venous return to the heart and preserve an adequate maternal cardiac output. In pregnancy there is an expanded blood volume, but a lower hematocrit and an increase in peripheral venous capacity. Pregnancy also affects pulmonary function, with a decrease in functional residual capacity that puts the mother at an increased risk for hypoxia. For these reasons, maternal anesthesia is induced through a rapid-sequence technique using a combination of thiopental (5 mg/kg), succinylcholine (2 mg/kg), and fentanyl (1–2 mg/kg) administered intravenously. This is followed by immediate endotracheal intubation. Paralysis is maintained using intravenous vecuronium titrated by peripheral nerve stimulation.

Support of the fetus during the EXIT procedure depends entirely on the preservation of uteroplacental gas exchange. Both uterine and umbilical artery blood flow influence fetal oxygenation. Uterine artery blood flow is affected by maternal systemic blood pressure and myometrial tone. Volatile anesthetics used during the EXIT procedure not

Table 5-5

Current Indications for the EXIT Procedure at the Fetal Care Center of Cincinnati

Reversal of Tracheal Occlusion
Following tracheal clip or endoluminal balloon procedures
Fetal Neck Masses
Cervical teratoma
Hemangioma
Goiter
Neuroblastoma
EXIT-to-Resection
Lung Masses
Congenital cystic adenomatoid malformation (CCAM)
Bronchopulmonary sequestration (BPS)
Mediastinal Mass
Teratoma
Lymphangioma
EXIT-to-ECMO
CDH with lung/head ratio (LHR) <1.0, and liver up
Congenital heart disease (CHD)
Hypoplastic left heart syndrome (HLFS) with intact/restrictive atrial septum
Aortic stenosis with intact/restrictive atrial septum
CHD + CDH, LHR <1.2
EXIT-to-Separation for Conjoined Twins
CHAOS
Tracheal atresia
Laryngeal atresia
EXIT-to-Airway for micrognathia

only decrease myometrial tone but also tend to decrease both maternal blood pressure and placental blood flow. This can result in a decrease in fetal oxygenation (Luks et al., 1996). Maintenance of maternal blood pressure within 10% of baseline is therefore critical for adequate fetal oxygenation during the EXIT procedure. Maintenance of maternal blood pressure is achieved using ephedrine to counterbalance the hypotensive effects of the high concentrations of inhalational agents used in EXIT procedures. Ephedrine acts selectively on peripheral vascular resistance and sparing placental circu1ation (Gaiser and Kurth, 1999). Uteroplacental gas exchange is also dependent on umbilical artery blood flow, which is influenced by fetal cardiac output and placental vascular resistance. Preservation of fetal cardiac output is thus important in maintaining fetal oxygenation.

The cardiovascular physiology of the fetus is different from that of full-term neonates in that the cardiac output is more dependent on heart rate rather than on stroke volume. In addition, high vagal tone and low baroreceptor sensitivity cause the fetus to respond to stress with a decrease in heart rate. The fetus primarily relies on increased heart rate to increase cardiac output and blood flow redistribution in response to stress. This preserves oxygenation for the brain at the expense of the rest of the body. In addition to the peculiar characteristics of fetal physiology, inhalational anesthetics also cause a direct fetal myocardial depression, vasodilatation, and changes in arteriovenous shunting, all of which can lead to fetal hemodynamic instability (Biehl et al., 1983). These physiologic differences and responses to anesthetic agents require continuous fetal monitoring to ensure uncompromised uteroplacental gas exchange and fetal well-being.

The inhalational anesthetic regime used during the EXIT procedure passes through two different stages. Anesthesia is at first maintained with 0.5 MAC (minimal alveolar concentration) of desflurane, isoflurane, or sevoflurane in oxygen, and is then increased to 2 MAC before maternal incision. More recently, we have used total intravenous anesthesia (TIVA) to prevent transplacental passage of inhalational agent that may act as a fetal myocardial depressant. Inhalational agent is used only at time of hysterotomy to achieve the desired relaxation of uterine tone. Occasionally, a tocolytic is given to augment the uterine relaxation. A number of tocolytic agents can be used as an adjunct to inhalational agents, including indomethacin, terbutaline, or nitroglycerine. Indomethacin may also prevent prostaglandin-mediated increases in placental resistance independent of its effects on uterine tone (Holcberg et al., 2001). Maintenance of uterine volume is also important to prevent uterine contraction. This is accomplished by preventing the fetus from completely delivering and by the use of amnioinfusion with warm Ringer's lactate solution administered via a rapid infuser to prevent cord compression.

The second critical stage of the anesthetic technique comes just before clamping of the cord and ending the EXIT procedure. During this stage, coordination between the surgical and anesthesia teams is crucial to prevent uterine atony and excessive maternal bleeding. The volatile anesthetic is decreased to 0.5 MAC or turned off entirely to allow uterine tone to return to normal. This is followed by administration of oxytocin 20 units in 500 mL of normal saline intravenously as a bolus followed by 10 units in a 1000-mL drip titrated to enhance uterine contraction. If required, further measures are taken to decrease the risk of uterine atony. These measures include uterine massage and administration of 0.25 mg Methergine and 250 mg carboprost (F2-alpha prostaglandin) via intramuscular or intravenous injection. After skin closure, the inhalational anesthetic is discontinued and 100% oxygen is administered. Maternal paralysis is reversed by the use of glycopyrrolate (10 mg/kg) and neostigmine (0.7 mg/kg), and the patient is extubated after spontaneous breathing is observed (Bouchard et al., 2002).

Fetal anesthesia is provided primarily through the transplacental passage of the volatile anesthetics. However, this takes about an hour to reach 70% of the maternal levels. As such, before fetal incision, a cocktail comprising 10 to 20 mg/kg fentanyl, 20 mg/kg atropine, and 0.2 mg/kg vecuronium is administered intramuscularly to supplement anesthesia and provide for postoperative analgesia.

Close maternal and fetal monitoring during the EXIT procedure are aimed at the early recognition and management of problems as they arise. Maternal monitoring includes invasive arterial blood pressure monitoring (arterial line) to recognize possible maternal hypotension that will jeopardize fetal oxygen transport, as well as continuous maternal electrocardiography, pulse oximetry, and end-tidal CO_2 monitoring.

Continuous fetal monitoring is also of paramount importance during the EXIT procedure. Fetal arterial saturation is monitored by a reflectance pulse oximeter placed on the fetal hand and wrapped with foil to decrease ambient light exposure (Dassel et al., 1992). Normal fetal arterial saturation is 60% to 70%, although values greater than 40% represent adequate fetal oxygenation. Continuous intraoperative fetal echocardiography is also used to monitor fetal cardiovascular function (Rychik et al., 2004). The use of fetal echocardiography helps to identify early problems such as decreased filling, fetal bradycardia, decreased myocardial contractility, ductal constriction, and atrioventricular valve incompetence (Figure 5-4). These are all signs of fetal distress that require prompt treatment. Fetal arterial or venous blood gases may be obtained through umbilical vessel puncture during periods of fetal distress to guide in therapy. An intravenous access is essential to allow administration of fluids, blood, or medications for inotropic support when needed.

The decision to enter the abdomen through a low transverse skin incision or through a midline fascial incision is based on the placental location, predicted site of hysterotomy, and the indication for performing the EXIT procedure. The incision of choice is usually a low transverse abdominal incision unless the anterior position of the placenta necessitates a posterior hysterotomy. In the latter case, a midline laparotomy is required. After laparotomy, the uterus is examined for adequacy of myometrial relaxation, and concentration of inhalational agents is adjusted as necessary. Before fashioning the hysterotomy, precise sonographic mapping of the placental edge is crucial to avoid placental injury and hemorrhage. A sterile intraoperative ultrasound is used to map the placental borders. This is performed while considering the position of the fetal head and neck to avoid excessive fetal manipulation after hysterotomy. The position of the hysterotomy is dictated by the placental location. A low anterior placental site precludes a low transverse hysterotomy and may necessitate a posterior approach for the hysterotomy. Special considerations are important in cases of severe polyhydramnios. Amnioreduction in these cases is necessary to avoid underestimation of the proximity of the placental edge to the hysterotomy. To adequately manipulate the fetus, it is sometimes necessary to decompress any accompanying fetal ascites or cystic mass. This can be achieved by using a 20- or 22-gauge spinal needle under U.S. guidance. In some instances, the use of amnioinfusion and fetal version before hysterotomy facilitate the exposure (Hedrick, 2003). During EXIT procedures, hysterotomy is performed using a specially designed uterine stapler (U.S. Surgical Corporation, Norwalk, CT) to decrease the incidence of bleeding (Bond et al., 1989). Following hysterotomy, maintenance of uterine volume is one of the most important steps in an EXIT procedure. This is done to decrease the likelihood of uterine contraction and placental abruption, thus maintaining continuous maternal–fetal oxygen transfer. Warm Ringer's lactate solution is infused after the hysterotomy to maintain the uterine volume and prevent cord compression. Limited exposure of the fetus during the EXIT procedure also helps in maintaining the uterine volume and fetal temperature. Only the head, neck, and shoulders are exposed while keeping the remainder of the fetus and the cord intrauterine.

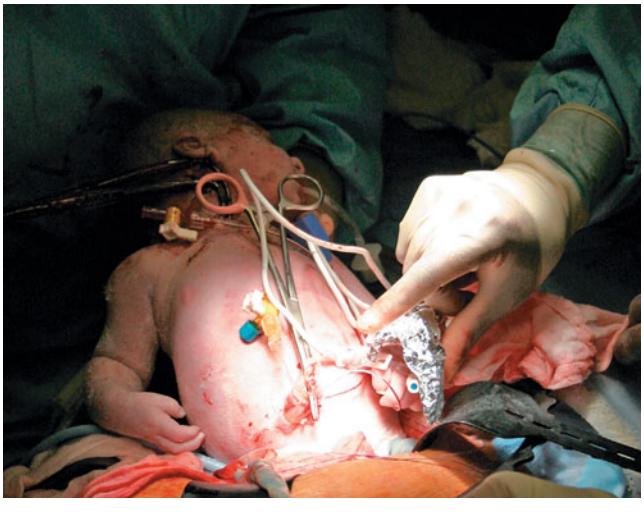

Figure 5-4 An intraoperative view during an EXIT procedure demonstrating continuous fetal monitoring using a sterile echocardiography, reflectance pulse oximetry, and IV access lines.

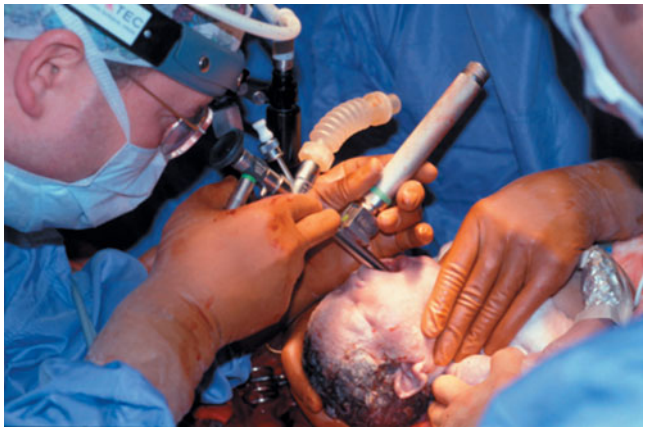

Figure 5-5 Bronchoscopy during an EXIT procedure to secure a fetal airway.

The most important aspect of fetal airway management during an EXIT procedure is preparedness for every contingency. In that one can never assume that the fetus will only require direct laryngoscopy and intubation, we have developed an airway algorithm. In addition to the basic instruments and setup, the following items should be available on a separate airway table managed by a second scrub nurse: direct laryngoscopy supplies with Miller 0 and 00 blades, armored endotracheal tubes (ETTs) appropriate for the size of the fetus, endotracheal tube exchangers, 2.5 and 3.0 Fr feeding tubes for surfactant administration, 2.5 or 3.0 rigid bronchoscope, a flexible bronchoscope, and a major neck tray for formal tracheostomy or mass resection.

Direct laryngoscopy and endotracheal intubation should be the first option for securing a fetal airway during EXIT procedures (Figure 5-5). In cases in which there is distortion of the normal anatomy, flexible and/or rigid bronchoscopy may be necessary to visualize and diagnose

Table 5-6

Pitfalls of the EXIT Procedure

Failure to achieve adequate uterine relaxation	Compromise uteroplacental gas exchange
Failure to treat polyhydramnios	Inaccurate mapping of placental edge—hemorrhage
Failure to plan for fetal position relative to hysterotomy	Difficult exposure for delivery of head
Failure to use uterine staples	Maternal hemorrhage
Failure to use deep inhalational anesthesia	Inadequate uterine relaxation—poor uteroplacental gas exchange
Failure to maintain adequate maternal blood pressure	Poor uterine artery perfusion or compromised uteroplacental gas exchange
Failure to recognize cord compression	Fetal bradycardia
Failure to recognize placental abruption	Fetal hemorrhage
Failure to make airway first fetal priority	May have to end EXIT acutely due to abruption, or persistent fetal bradycardia
Failure to prepare for every airway challenge	Fetal death. Must not assume that laryngoscopy will be successful. Must be prepared for bronchoscopy, tracheostomy, and/or mass resection
Failure to allow sufficient time for return of uterine tone	Uterine atony and maternal hemorrhage
Failure to use armored endotracheal tube (ETT)	Collapse of fetal endotracheal tube by tumor compression
Failure to confirm ETT tip position bronchoscopically	Malpositioned ETT. This is especially important with cervical or mediastinal tumors
Failure to maintain uterine volume	Acute loss of uterine volume may predispose to placental abruption
Failure to perform adequate intrapartum fetal monitoring	Unrecognized fetal distress or bradycardia
Failure to recognize maternal indications for terminating EXIT	Maternal hemorrhage
Failure to recognize fetal indications for terminating EXIT	Fetal bradycardia or arrest, fetal hemorrhage, or hypoxic brain injury

abnormal airway anatomy. The glottis is sometimes displaced cephalad above the level of the soft palate; in such cases, flexible bronchoscopy via the nares may be helpful. In other cases, mass effect may shift the glottis severely from its normal midline position. An ETT can be placed over the flexible bronchoscope or rigid lens and can be used to place the ETT beyond the level of obstruction. If this fails to secure an airway, then retrograde intubation becomes the next option in which a tracheotomy is performed through limited neck dissection. Using a Seldinger technique, an ETT exchanger is passed retrograde until seen in the oropharynx. The ETT is passed antegrade over the ETT exchanger and the tracheotomy repaired. In the case of large neck masses, traction by an assistant may lift the mass off the airway. This permits an armored ETT to be passed beyond the level of obstruction. If there is severe compression, release of the strap muscles may be required to permit passage of an armored ETT beyond the area of airway obstruction. Airway control is sometimes impossible even after all these techniques have been attempted. In these cases, reflection of the mass off the airway or resection of the mass to facilitate formal surgical tracheostomy may be necessary. Proper positioning of the tracheostomy is extremely important, especially in cases of giant neck masses in which the trachea is pulled out of the chest by neck hyperextension. It is not uncommon to find the carina at the level of the thoracic inlet due to the opisthotonic position of the head caused by a neck mass. Care should be taken to place the tracheostomy tube no lower than the second to third tracheal rings.

After securing the airway, it is prudent to confirm the position of the ETT or tracheostomy tube relative to the carina using flexible bronchoscopy. This is particularly important in patients with cervical or mediastinal masses. If required, surfactant can then be administered by a feeding tube passed through the ETT. The fetus is then ventilated by hand. Finally, umbilical arterial and venous access catheters can be placed and the cord clamped. Coordination between the surgical team and the anesthesiologists is of paramount importance at this moment to ensure adequate return of the uterine tone and proper hemostasis. The newborn is either taken to an adjoining operating room for further resuscitation and completion of the neck mass resection or to the neonatal intensive care unit for further resuscitation and stabilization.

The EXIT procedure is associated with an increased potential risk of maternal bleeding due to uterine hypotonia induced by high concentrations of inhalational agents. These high levels may also induce maternal hypotension. It is important to ensure the prompt return of uterine tone at the conclusion of the EXIT procedure to minimize maternal hemorrhage. Although uterine atony remains a significant risk and there is the potential need for hysterectomy, in our experience, the mean blood loss with EXIT procedures has been equivalent to that observed in cesarean sections. Early in our experience, we had to transfuse a patient in whom polyhydramnios caused us to underestimate the proximity of the placenta to the hysterotomy. In a review of the experience of clinicians at the UCSF, a slightly higher incidence of wound infection was reported with EXIT procedures than with cesarean sections. Although the EXIT procedure is specifically designed to optimize outcomes for the fetus, if it is not performed appropriately, there is also the potential for fetal complications. These are primarily related to failure to preserve uteroplacental gas exchange due to cord compression, placental abruption, or loss of myometrial relaxation (Table 5-6).

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PART

II

Management of Fetal Conditions Diagnosed by Sonography

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Agenesis of the Corpus Callosum

CHAPTER 6

Key Points

- The corpus callosum is a major pathway connecting the two hemispheres of the brain. By the 17th week of gestation, the mature corpus callosum is formed.
- In agenesis of the corpus callosum (ACC), the commissural fibers do not cross the midline but rather form thick bundles of fibers called Probst bundles, which course in a posterior direction along the medial walls of the lateral ventricles. These bundles indent and separate the anterior horns of the lateral ventricles.
- ACC may be isolated, but often is associated with other malformations and genetic syndromes.
- ACC occurs in <1% of the general population and in 2% to 3% of the developmentally disabled population.
- The finding of mild ventriculomegaly during routine prenatal ultrasound examination should prompt a targeted search to confirm the presence of the corpus callosum.
- The most consistent and easy-to-identify finding is the teardrop configuration of the lateral ventricles.
- Prenatal magnetic resonance imaging (MRI) and three-dimensional ultrasound examination may be helpful in confirming the diagnosis. MRI may also be useful in identifying other subtle brain abnormalities that may not be apparent on sonogram but may have an impact on the long-term prognosis.
- The natural history of antenatally detected ACC is not known due to the fact that there have been relatively few case series reported.
- Fetal karyotype should be considered when ACC is diagnosed antenatally due to its association with chromosomal abnormalities.
- Patients prenatally diagnosed with ACC can be managed according to routine prenatal care guidelines.
- The neonate with suspected ACC should be examined carefully. MRI is the radiologic examination of choice.
- ACC in addition to other abnormalities is often associated with poor neurologic outcomes. The long-term outcome of isolated ACC has not yet been elucidated.
- The recurrence risk of ACC depends on the underlying cause.

CONDITION

The corpus callosum is a major pathway connecting the two hemispheres of the brain. The development of the corpus callosum begins during the 5th week of fetal life with the formation of the primitive lamina terminalis, which thickens to form the commissural plate. Glial cells coalesce to form a bridge-like structure that serves as a guide for the callosal fibers crossing the longitudinal cerebral fissure to their targets on the contralateral side of the brain (Rakic and Yakovlev, 1968). The mature corpus callosum is formed by the 17th week of gestation. In agenesis of the corpus callosum (ACC), the commissural fibers do not cross the midline; instead they form thick bundles of fibers, called "Probst bundles," which course in a posterior direction along the medial walls of the lateral ventricles. These bundles indent and separate the anterior horns of the lateral ventricles.

ACC may be an isolated finding; however, it is frequently associated with other malformations and genetic syndromes including chromosomal aberrations and inborn errors of metabolism (Parrish et al., 1979; Jeret et al., 1987; Dobyns, 1989). Associated central nervous system (CNS) abnormalities include Chiari malformations, anomalies of neuronal migration including lissencephaly, schizencephaly, pachygyria and polymicrogyria, encephaloceles, Dandy–Walker malformations, holoprosencephaly, and olivopontocerebellar degeneration (Barkovich and Norman, 1988). Extracranial malformations include abnormalities of the face and of the cardiovascular, genitourinary, gastrointestinal, respiratory, and musculoskeletal systems (Parrish et al., 1979; Franco et al., 1993; Kozlowski and Ouvrier, 1993).

INCIDENCE

ACC has been estimated to occur in 0.3% to 0.7% of the general population and in 2% to 3% of the developmentally disabled population (Freytag and Lindenberg, 1967; Grogono, 1968; Jeret et al., 1986). In a large series of patients diagnosed with a metabolic disease, 17% were shown to have an abnormality of the corpus callosum by computed tomography (CT), ultrasound, or autopsy examination (Bamforth et al., 1988).

In a series of 4122 perinatal or neonatal autopsy specimens, the incidence of CNS malformations was 8.8%, and of the 363 CNS malformations diagnosed, ACC accounted for 4.1% (Pinar et al., 1998).

SONOGRAPHIC FINDINGS

Usually only midsagittal and midcoronal scans of the fetal brain allow clear visualization of the corpus callosum. Such views can be obtained with standard transabdominal ultrasound examination of most fetuses in breech position or transverse lie. For fetuses in the vertex position, transvaginal sonography is the preferred technique.

On sagittal scan, the corpus callosum appears as a sonolucent band, demarcated superiorly and inferiorly by two echogenic lines. The superior line arises from the pericallosal cistern; the inferior line derives from the fornix and roof of the cavum septum pellucidum. Color Doppler sonography can demonstrate the pericallosal artery, a branch of the anterior cerebral artery that sweeps in a circular pattern over the corpus callosum. In a coronal scan, the corpus callosum appears to form the roof of the cavum septum pellucidum and frontal horns.

Classic neuroradiologic signs for the diagnosis of ACC on pneumoencephalography were described by Davidoff and Dyke (1934). Their criteria have been applied to the CT diagnosis and also can be applied to sonography (Skidmore et al., 1983). The findings include the absence of the corpus callosum and cavum septum pellucidum and a variety of indirect findings, including

1. increased separation of the frontal horns and bodies of the lateral ventricles;
2. relative dilatation of the occipital horns of the lateral ventricles;
3. concave medial border of the lateral ventricles due to protrusion of the Probst bundles;
4. general dilatation and upward displacement of the third ventricle;
5. abnormal radial orientation of the medial cerebral gyri (Comstock et al., 1985; Bertino et al., 1988; Sandri et al., 1988; Pilu et al., 1993; Maheut-Lourmiere and Paillet, 1998).

In a series of 141 cases of fetal cerebral ventriculomegaly, ACC was noted in 16 cases (11%) (Valat et al., 1998). In another series of 82 cases of mild ventriculomegaly, there were 7 cases (9%) of ACC (Vergani et al., 1998). The finding of mild ventriculomegaly during routine prenatal sonography should, therefore, prompt a targeted search to confirm the presence of the corpus callosum.

Ultrasound diagnosis of ACC is more difficult prenatally than postnatally. The earliest prenatal diagnosis has been made at 19 weeks of gestation (Pilu et al., 1993). Because the corpus callosum is not normally formed until 18 weeks, most reported cases have been diagnosed in the third trimester (Bertino et al., 1988; Bennett et al., 1996). This difficulty in prenatal diagnosis is usually due to the fact that the characteristic ventricular abnormalities can be quite subtle on the axial views of the fetal cranium that are most commonly obtained. It is preferable to use coronal and sagittal views to diagnose the characteristic ventricular abnormalities; however, these views are not as commonly used prenatally.

Routine sonography of the fetal brain is usually performed with axial scans that do not allow visualization of the corpus callosum. However, enlargement of the atria of the lateral ventricles is readily appreciated with these views. In the largest series of prenatally diagnosed ACC, 34 of 35 fetuses had atrial measurements 10 mm (Pilu et al., 1993). Once atrial enlargement has been observed, other sonographic findings

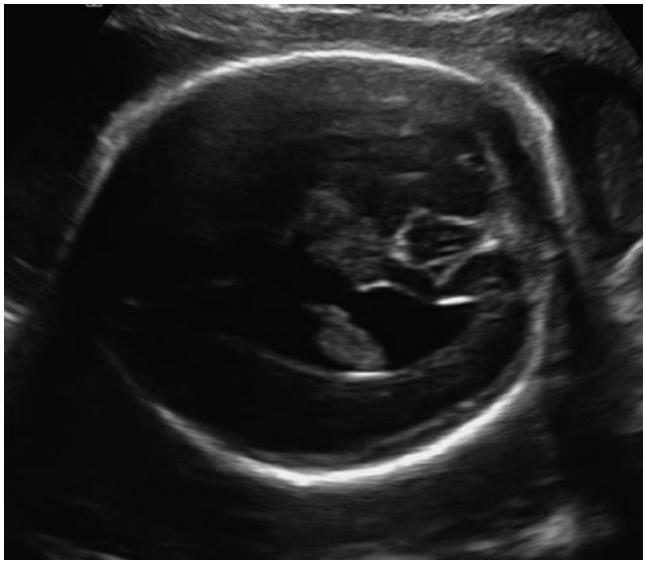

Figure 6-1 Transaxial ultrasound image demonstrating the classic teardrop configuration of the lateral ventricle.

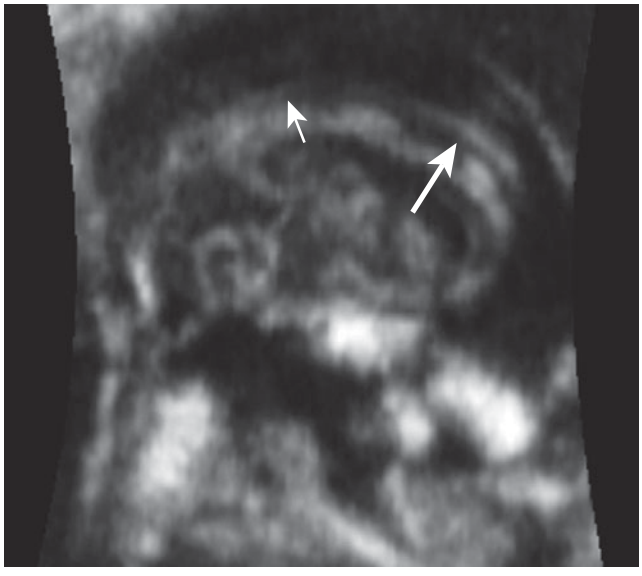

Figure 6-2 Three-dimensional ultrasound image, using VCI-C plane, of fetus at 22 weeks' gestation with partial posterior agenesis of the corpus callosum. Thick arrow demonstrates normal anterior corpus callosum fibers. Thin arrow demonstrates disappearance of this band posteriorly.

may identify possible ACC. The most consistent and easy-to-identify finding is the teardrop configuration of the lateral ventricles (Figure 6-1). In the axial plane, enlargement of the atria and occipital horns and separation of the bodies combine to generate a pattern that is readily recognizable. The teardrop configuration of the ventricles has not been documented in conditions other than ACC, and it is believed to be a specific sign for the diagnosis of callosal agenesis (Pilu et al., 1993). In order to document the callosal lesion directly, it is important to obtain midcoronal and midsagittal scans when a dilated atrium or teardrop ventricle is identified.

Prenatal diagnosis of partial ACC has been reported (Figure 6-2) (Lockwood et al., 1988; Pilu et al., 1993). The natural history of partial ACC is uncertain, and cerebral findings associated with it are probably more subtle than with the complete form. It is expected that antenatal diagnosis will not be possible in many cases. The cavum septum pellucidum is not identified in cases of complete ACC but may be visualized in cases of partial agenesis. Sonographic evaluation of the structure is potentially helpful in routine screening, alerting the sonologist to perform more coronal and sagittal scans for direct visualization of the corpus callosum. Widening of the interhemispheric fissure and upward displacement of the third ventricle can be documented in approximately half of the prenatal cases. Radial arrangement of the medial cerebral sulci has been seen only in third trimester studies. This is presumably because the surface of the hemispheres is smooth in the second trimester, with secondary sulci appearing only at the onset of the third trimester. In many cases of ACC, prenatal ultrasound examination may only cause one to suspect the diagnosis, while prenatal magnetic resonance imaging (MRI) may be needed to accurately confirm the diagnosis (Glenn et al., 2005). In one series of 14 cases of ACC, ultrasonography confirmed the diagnosis in only 4 cases, while MRI confirmed the diagnosis in 13 cases (d'Ercole et al., 1998). In another series of 20 cases of ACC, prenatal MRI made a positive diagnosis in 19 cases (Brisse et al., 1998). In a recent series of 10 cases of callosal abnormalities suspected by ultrasound examination, 8 cases were confirmed by MRI and 2 cases were found to have a normal corpus callosum (Glenn et al., 2005). MRI was also useful in identifying additional brain abnormalities that were not apparent by sonography such as abnormal sulcation. Sixty-three percent of cases (5/8) with confirmed callosal abnormalities on both ultrasound examination and MRI were found to have additional abnormalities on MRI. These occult findings were confirmed on postnatal MRI or autopsy in three of five patients. The information obtained by MRI is invaluable for patient counseling since additional brain abnormalities have been associated with worse long-term outcomes. In addition, three-dimensional ultrasound examination may also be useful to confirm the diagnosis (Kalache et al., 2006; Pilu et al., 2006).

DIFFERENTIAL DIAGNOSIS

Dilatation of the atria and occipital horns is often the most prominent sonographic finding; therefore, anything that causes hydrocephalus is also within the differential diagnosis for ACC (see Chapter 16). In ACC there is usually greater enlargement of the occipital horns, as compared with the remaining ventricular system, than is observed in other forms of hydrocephalus. When a dilated third ventricle is present, differential diagnosis includes other midline cystic spaces such as a cavum septum pellucidum, cavum vergae, interhemispheric arachnoid cyst, and medial porencephalic cyst.

ACC is associated with many recognizable genetic syndromes (see Table 6-1) (Bamforth et al., 1988; Paul et al., 2007). ACC has also been associated with abnormalities

Table 6-1

Genetic Syndromes Associated with ACC

Syndrome	Clinical Findings
With identified genes	
Andermann syndrome *(KCC3)*	ACC, progressive neuropathy, and dementia
XLAG *(ARX)*	Lissencephaly, ACC, intractable epilepsy
Mowat Wilson syndrome (*ZFHX1B*)	Hirschsprung disease, ACC
ACC with fatal lactic acidosis (*MRPS16*)	Complex I and IV deficiency, ACC, brain malformations
HSAS/MASA syndromes (*L1CAM*)	Hydrocephalus, adducted thumbs, ACC, MR
ACC seen consistently, no gene yet identified	
Acrocallosal syndrome	ACC, polydactyly, craniofacial changes, MR
Aicardi syndrome	ACC, chorioretinal lacunae, infantile spasm, MR
Chudley–McCullough syndrome	Hearing loss, hydrocephalus, ACC, colpocephaly
Donnai–Barrow syndrome	Diaphragmatic hernia, exomphalos, ACC, deafness
FG syndrome	MR, ACC, craniofacial changes, macrocephaly
Genitopatellar syndrome	Absent patellae, urogenital malformations, ACC
Temtamy syndrome	ACC, optic coloboma, craniaofacial changes, MR
Toriello–Carey syndrome	ACC, craniofacial changes, cardiac defects, MR
Vici syndrome	ACC, albinism, recurrent infections, MR
ACC seen occasionally (partial list)	
ACC with spastic paraparesis (*SPG11*)	Progressive spasticity and neuropathy, thin corpus callosum
Craniofrontonasal syndrome	Coronal craniosynostosis, facial asymmetry, bifid nose
Fryns syndrome	CDH, pulmonary hypoplasia, carniofacial changes
Marden–Walker syndrome	Blepharophimosis, micrognathia, contractures, ACC
Meckel–Gruber syndrome	Encephalocele, polydactyly, and polysystic kidneys
Microophthalmia with linear skin defects	Microopthalmia, linear skin marking, seizures
Opitz G syndrome	Pharygneal cleft, craniofacial changes, ACC, MR
Orofaciodigital syndrome	Tongue hamartoma, microretrognathia, clinodactyly
Pyruvate decarboxylase deficiency	Lactic acidosis, seizures, severe MR, and spasticity
Rubinstein–Taybi syndrome	Broad thumbs and great toes, MR, microcephaly
Septo-optic dysplasia (DeMorsier syndrome)	Hypoplasia of septum pellucidum and optic chiasm
Sotos syndrome	Physical overgrowth, MR, craniofacial changes
Warburg micro syndrome	Microcephaly, microophthalmia, microgenitalia, MR
Wolf–Hirschhorn syndrome	Microcephaly, seizures, cardiac defects, 4p-

Modified from Paul LK, Brown WS, Adolphs R, et al. Agenesis of the corpus callosum: genetic, developmental and functional aspects of connectivity. Nat Rev Neurosci. *2007;8:287-299.*

of chromosomes 8, 13, and 18 (Jeret et al., 1987). ACC also may be found in association with several inborn errors of metabolism, including nonketotic hyperglycinemia, Zellweger syndrome, adenylosuccinase deficiency, pyruvate dehydrogenase deficiency, neonatal adrenoleukodystrophy, Menkes disease, Leigh syndrome, and glutaric aciduria type II (Dobyns, 1989; Kolodny, 1989; Blum et al., 1990). Various teratogens have also been implicated as a possible cause of ACC, including alcohol, valproate, cocaine, rubella, and influenza virus (Table 6-1) (Friedman and Cohen, 1947; Cornover and Roessmann, 1990; Dominguez et al., 1991; Lindhout et al., 1992).

ANTENATAL NATURAL HISTORY

Little is known about the natural obstetric history of ACC when it occurs as an isolated finding because there have been relatively few case series reported. In one series of 37 pregnancies with prenatally diagnosed ACC, 28 resulted in elective termination of pregnancy, and in the remaining 9 cases liveborn infants were delivered (Hatem-Gantzer et al., 1998). Four of these 9 infants died in the postnatal period. It seems unlikely that the presence of isolated ACC should alter the antenatal course of pregnancy.

MANAGEMENT OF PREGNANCY

Identification of ACC demands a careful search of fetal anatomy for other intracranial and extracranial abnormalities. The association between ACC and chromosomal abnormalities has been addressed by Serur et al. (1988), who reviewed 100 cases. Identification of ACC demands a careful search of fetal anatomy for other intracranial and extracranial abnormalities. MRI is of value for confirming the diagnosis and ensuring no other intracranial malformations coexist (Brisse et al., 1998; d'Ercole et al., 1998; Glenn et al., 2005). Three-dimensional ultrasound may also be useful (Kalache et al., 2006; Pilu et al., 2006).

In the report of Serur et al., trisomy 18 was found in 29 cases, full or mosaic trisomy 8 in 21 cases, trisomy 13 in 20, and a variety of other conditions in the remaining cases. It is therefore postulated that chromosomes 8, 13, and 18 have a direct influence on the development of the corpus callosum. In Pilu et al.'s (1993) review of fetal diagnosis of ACC, three fetuses with abnormalities of chromosome 8 had ACC as the only sonographic finding. Therefore, it is our practice to offer amniocentesis for fetal karyotyping independently of the presence of other sonographically detectable abnormalities.

If an isolated ACC is detected and the chromosomes are normal, there is no indication to change the standard of obstetrical care. This diagnosis does not necessitate delivery at a tertiary care hospital. One should consult with genetics and pediatric neurology specialists. However, the presence of other associated structural abnormalities should prompt referrals to the appropriate pediatric subspecialists, and in this situation the patient should be delivered at a tertiary care hospital.

Vaginal delivery is recommended unless there is significant hydrocephalus with macrocephaly. Delivery prior to term is not recommended unless an obstetrical indication exists.

FETAL INTERVENTION

There is no fetal intervention recommended for this condition.

TREATMENT OF THE NEWBORN

Detailed examination of the newborn is required. The radiologic procedure of choice postnatally is MRI, which allows detection of subtle abnormalities not seen by the other methods, including CT and ultrasound (Davidson et al., 1985; Barkovich and Norman, 1988). Additional metabolic investigations may be necessary if inborn errors of metabolism are suspected.

SURGICAL TREATMENT

There are no surgical issues for isolated ACC; however, surgery may be indicated for additional intracranial or extracranial lesions. Some infants may require ventriculoperitoneal shunts for treatment of progressive ventricular dilatation and accelerated head growth (Lacey, 1985).

LONG-TERM OUTCOME

Children with ACC and multiple major congenital abnormalities are at high risk for neurodevelopmental retardation, especially if craniofacial defects are present. The presence of either neonatal or infantile seizures is an ominous prognostic sign; most of these children are severely retarded or exhibit delayed development (Lacey, 1985). Children with additional intracerebral abnormalities also appear to have a poor prognosis, with most infants experiencing developmental delay. A diagnosis of ACC should alert the physician to the likelihood of severe neurodevelopmental delay and subsequent seizures.

No specific risk figures are available at present to counsel parents regarding neurologic development in children with isolated ACC. Vergani et al. (1988) reported that three infants with prenatal diagnosis of ACC had normal or borderline intelligence quotients at 3-year follow-up examination. In the series by Pilu et al. (1993), a normal developmental quotient was found in 9 of 11 nonfamilial cases with a follow-up ranging between 6 months and 11 years, and borderline development was found in the remaining two. The neurologic development of surviving infants was evaluated with the Brunet–Lezine test and the Stanford–Binet Intelligence Scale. Even in the presence of normal intelligence, ACC may be associated with subtle cognitive defects (Temple et al., 1989, 1990; Jeeves, 1991). A possible relationship between ACC and psychotic disorders has also been proposed (Swayze et al., 1990).

In a survey of ACC from the United Kingdom, two thirds of 59 affected patients had epilepsy, half of the adult cases had intellectual impairment, and one-third had a psychotic disorder (Taylor and David, 1998). However, this and other series may be biased by under-ascertainment of asymptomatic cases of ACC. In another series of 10 children who had a diagnosis of ACC made prenatally, all had normal developmental outcome at 3 years of follow-up, although febrile convulsions were reported to occur more frequently than expected (Moutard et al., 1998).

Goodyear et al. (2001) compared patients with prenatally diagnosed ACC (14) to those in whom the disorder was diagnosed in postnatal period (61). The patients were evaluated for developmental milestones as well as other clinical issues. ACC was more common in males than in females, and partial ACC was more common in the postnatally diagnosed group. Complete ACC had a worse prognosis compared to partial ACC, especially when it was associated with other abnormalities, particularly those of the CNS. The only

neurodevelopmentally normal patients were in the group with an isolated finding of partial ACC. Adverse neurological outcomes included seizures, developmental delay, and mental retardation, as well as a need for special help in school.

More recently, Francesco et al. (2006) evaluated 9 children, aged 2 to 16, who had been diagnosed with ACC during the prenatal period. The diagnosis was confirmed in the post partum period. Six children had had isolated ACC, three of whom had generalized hypotonia, while three others had normal neurological development. The three with other associated findings did not have normal neurological outcomes. The authors concluded that if ACC is associated with other abnormalities a poor outcome is likely. However, if it is not, it is difficult to predict if there will be a normal neurological outcome.

With regard to partial ACC, Volpe et al. (2006) recently evaluated 19 prenatally diagnosed cases. Ten cases occurred in association with other anomalies. Nine cases were initially thought to be isolated. One of the nine cases was found to have additional brain malformations following MRI, and this case was lost to follow-up. There were 11 livebirths, 6 voluntary terminations, and 2 perinatal deaths. Thirty-two (6/19) percent of cases had normal psychomotor follow-up. All of these cases had isolated partial ACC. Two cases of isolated partial ACC had less favorable outcomes, one of which had significant developmental delay and hypotonia. Similar to the cases of isolated complete ACC, isolated partial ACC may be associated with significant adverse neurological outcomes.

GENETICS AND RECURRENCE RISK

The recurrence risk of ACC, whether it is isolated or in addition to inborn errors of metabolism or genetic syndromes, depends on the underlying cause. If ACC is associated with aneuploidy, the recurrence risk is 1% or the maternal age–related risk for aneuploidy, whichever is greater. If there is an isolated ACC with no known cause, the recurrence risk is probably on the order of 2% to 3% (Young et al., 1985). ACC is a known criterion for the diagnosis of certain syndromes, such as Aicardi, Andermann, and acrocallosal syndromes (Philip et al., 1998). While ACC is generally considered to be sporadic, familial cases have been reported (Naritomi et al., 1997).

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7 CHAPTER

Anencephaly

Key Points

- Accounts for approximately one-half of all cases of neural tube defects.
- Incidence is approximately 0.3/1000 births. Maternal risk factors include Hispanic ethnicity, pregestational diabetes, obesity, and hyperthermia.
- First trimester sonographic findings include a reduced crown-rump length, and the "Mickey Mouse" sign in the coronal view. Second trimester findings include an absent upper cranial vault and no cerebral tissue above the level of the orbits.
- Differential diagnosis includes amniotic bands, ruptured encephalocele, and iniencephaly.
- Approximately a quarter of affected pregnancies are complicated by polyhydramnios.
- Consider prenatal karyotype if associated anomalies present. If anencephaly is isolated, consider postnatal karyotype.
- Condition is uniformly fatal postnatally. Only 7% of fetuses die in utero.
- Preconceptual folic acid (4 mg/day) significantly decreases recurrence if anomaly is isolated and not due to a chromosomal or single-gene disorder.

CONDITION

Anencephaly [congenital absence of a major portion of the brain, skull, and scalp (Medical Task Force on Anencephaly, 1990)] is the most severe and single most common prenatally detected neural tube defect (Goldstein and Filly, 1988). Although the cerebral hemispheres can develop in this condition, any exposed brain tissue is subsequently destroyed (see Chapter 13). This produces a hemorrhagic, fibrotic mass of neurons and glia, with no functional cortex. The brainstem and cerebellum may be spared. Despite the severe brain abnormalities, the facial bones and base of the skull are nearly normally formed. The frontal bone, however, is always absent and the brain tissue is always abnormal.

Anencephaly is sometimes divided into two subcategories. The milder form is known as meroacrania, which describes a small defect in the cranial vault covered by the area cerebrovasculosa. The more severe form is holoacrania, in which the brain is completely absent.

Van Allen et al. (1993) proposed that multisite neural-tube closure provides the best explanation for neural tube defects in humans. The closure sites are most likely controlled by separate genes expressed during embryogenesis. These authors hypothesized that the majority of neural tube defects could be explained by a failure of fusion of one of the closures or their contiguous neuropores. Anencephaly results from failure of closure site 2 for meroacranium and closures 2 and 4 for holoacranium. Folate deficiency is thought to affect the closures of sites 2 and 4. This hypothesis has been demonstrated in humans with more than one neural tube defect (Pantzar et al., 1993).

INCIDENCE

Anencephaly accounts for approximately one-half of all cases of neural tube defects (Chescheir et al., 2003). The incidence of anencephaly in livebirths and stillbirths has been estimated as 0.3 per 1000 by the Centers for Disease Control (Medical Task Force on Anencephaly, 1990). Female fetuses are more commonly affected. The ratio of affected females to males is 3:1 to 4:1 (Naidich et al., 1992). In one study, there was a 2.6 fold increased incidence of anencephaly in twins (Ben-Ami et al., 2005). There is also an increased incidence of anencephaly in Hispanic women, who are 45% more likely than white women to have an affected pregnancy (Feuchtbaum et al., 1999). Other risk factors include maternal pregestational diabetes, maternal obesity, and maternal hyperthermia (Mitchell, 2005). Unlike meningomyelocele, the risk of anencephaly is not increased in women who take valproic acid and/or carbamazepine (Mitchell, 2005). The most important environmental influence is diet. There is a well-documented protective effect of maternal periconceptual folic acid supplementation. Data from countries that have implemented mandatory folic acid fortification programs indicate a 30% to 50% reduction in the prevalence of neural tube defects postfortification (Mitchell, 2005).

In one study, Limb and Holmes (1994) documented that prenatal diagnosis and the availability of elective termination of pregnancy had significantly altered the birth status of infants with anencephaly. They noted a prevalence that varied between 1.0 and 0.4 per 1000 live and stillbirths during two different study periods (1972–1974 and 1979–1990, respectively). In the 1970s, half the infants with anencephaly were born alive at an average gestational age of 35.6 weeks. By 1988 to 1990, all affected infants were diagnosed by maternal serum α-fetoprotein screening or prenatal sonography. All parents elected to terminate, at an average gestational age of 19.6 weeks. These investigators, however, commented that their study population was potentially biased due to a higher percentage of mothers with epilepsy and diabetes delivering at their institution. More recent data, however, collected over the Internet, suggest that a larger proportion of women are opting to continue their pregnancies than would be suggested from the Limb and Holmes study (Jaquier et al., 2006).

SONOGRAPHIC FINDINGS

The first trimester sonographic appearance of anencephaly differs significantly from the second trimester (Chatzipapas et al., 1999). In the first trimester, the cerebral hemispheres are present and in direct contact with the amniotic fluid. In the coronal section of the head, the exposed cerebral lobes resemble the face of Mickey Mouse. In addition, the crown-rump length is significantly reduced in affected fetuses.

In the second trimester, the ultrasound diagnosis of anencephaly is made on the basis of the absence of the upper portion of the cranial vault (Figures 7-1 to 7-3). Above the level of the orbits, where the cerebral hemispheres are normally seen, no tissue is present or an ill-defined mass of heterogeneous density is observed. The abnormality is best demonstrated on coronal views of the fetal face (Figure 7-2). The sonographic diagnosis of this condition is very accurate and there are almost no false-positive diagnoses.

Anencephalic fetuses are usually normal in terms of body weight for gestational age (Melnick and Myrianthopoulos, 1987). Thus, intrauterine growth restriction is uncommon in isolated anencephaly. Another sonographic finding that may be present is polyhydramnios.

Goldstein and Filly (1988) reviewed the spectrum of prenatal sonographic findings in 20 fetuses with anencephaly. The sonographic diagnosis was based on the absence of brain and calvarium superior to the orbits on coronal views of the fetal head. In 45% of cases, echogenic tissue was seen superior to the orbits. This corresponded to the area cerebrovasculosa and was quite large in four fetuses. In 35% of their cases, frank polyhydramnios was seen. There were no cases of oligohydramnios. These authors stated that anencephaly can be distinguished from cranial defects associated with the amniotic band syndrome on the basis of symmetry of the

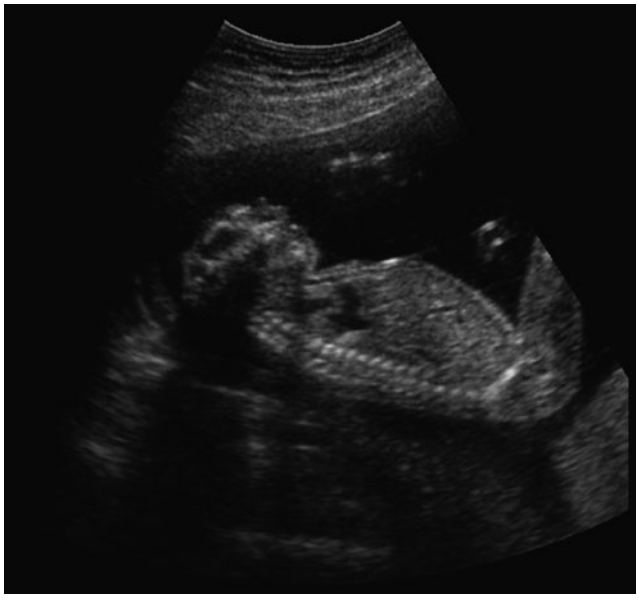

Figure 7-1 Sagittal view of fetal facial profile, demonstrating a lack of cranium above the easily visualized orbit. (Image courtesy of Prenatal Diagnosis Center, Women and Infants' Hospital).

cranial defects and the absence of limb, body wall, and spinal anomalies that generally accompany amniotic bands. In this report, prenatal diagnosis was 100% accurate after 14 weeks of gestational age. These authors missed one case initially studied at 12.5 weeks of gestation, but the defect was diagnosed on a repeat study performed at 26 weeks (Goldstein and Filly, 1988). As stated above, more recently it has become appreciated that the first trimester signs of anencephaly are different, so accuracy of detection earlier in gestation is likely to improve.

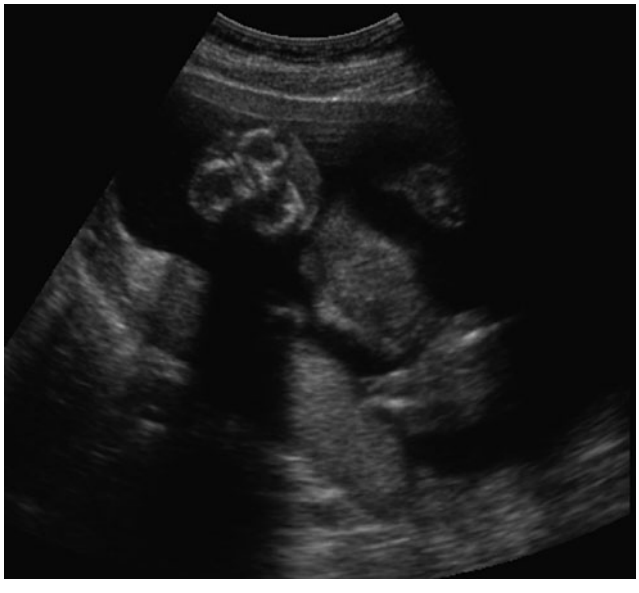

Figure 7-2 Coronal image through the face of a fetus with anencephaly, demonstrating lack of cranial structures above the orbits. (Image courtesy of Prenatal Diagnosis Center, Women and Infants' Hospital).

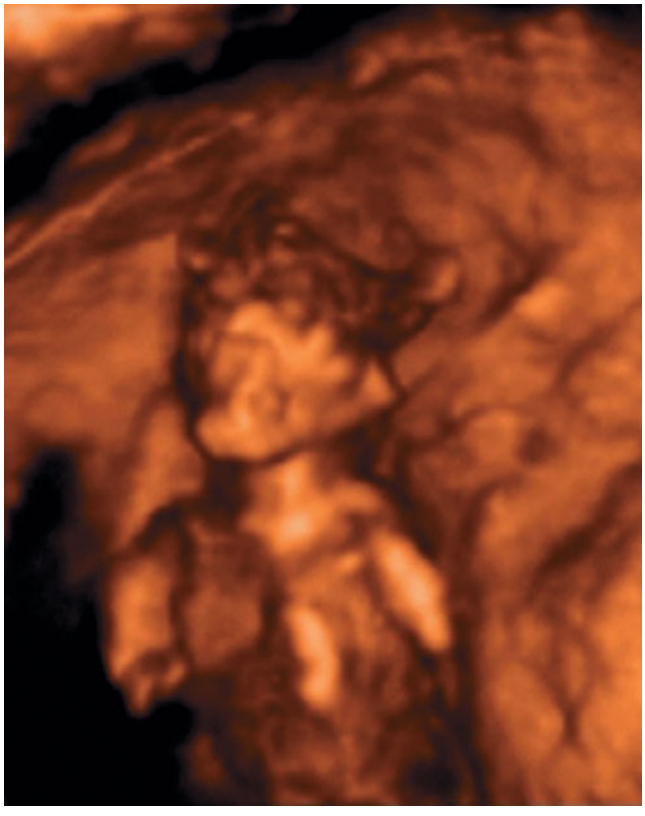

Figure 7-3 Three-dimensional ultrasound image at 12 weeks gestation of a fetus with anencephaly demonstrating lack of cranial bones above the orbits.

In postnatal studies, 13% to 33% of anencephalic infants have additional major congenital anomalies. These include congenital heart disease (4% to 15% of cases), hypoplastic lungs (5% to 34%), congenital diaphragmatic hernia (2% to 6%), malrotation of the gut (1% to 9%), renal malformations (25%) including polycystic or dysplastic kidneys (1% to 3%), hypoplasia of the adrenal glands (94%), and omphalocele (16%) (Melnick and Myrianthopoulos, 1987; Medical Task Force on Anencephaly, 1990). Additional minor anomalies that have been observed in fetuses with anencephaly include a single umbilical artery, a patent ductus arteriosus, and a patent foramen ovale, seen in 2% to 31% of cases. In one study, four-dimensional (4-D) sonography was used to study the hand and body movements of an anencephalic fetus at 19 weeks (Andonotopo et al., 2005). These were compared to a normal fetus at the same gestational age. Movement of the hand occurred in only one direction, and it was abnormal, forceful, and "jerky." In the normal fetus, movements were continuous and occurred in all directions. The anencephalic fetus showed a lack of positional changes.

DIFFERENTIAL DIAGNOSIS

The major consideration in the differential diagnosis is to distinguish anencephaly from the presence of amniotic bands. In

Table 7-1

Disorders Associated with Anencephaly

Folate deficiency
Maternal hypothermia
Trisomy 13
Trisomy 18
Turner syndrome
Triploidy
Amniotic band syndrome
Limb/body wall defects
Walker–Warburg syndrome

addition, scalp-covered lesions that include demineralization of the skull can occasionally be confused with anencephaly. It is important to note that the cranial defect associated with anencephaly is always symmetric. With amniotic bands, there should be evidence of other defects, such as limb or digital amputations, asymmetric ventral wall defects, or spinal defects. Amniotic bands are often associated with oligohydramnios, which is in contrast to anencephaly, which is often associated with polyhydramnios. Other conditions in the differential diagnosis include ruptured encephalocele (see Chapter 12) and iniencephaly. The latter condition does not involve the rostral skull or the forebrain. It is very important to distinguish between anencephaly and amniotic bands because of significant differences in their respective recurrence risks. Disorders that are associated with anencephaly are listed in Table 7-1.

ANTENATAL NATURAL HISTORY

In one recent study, data were collected via a personal website from 211 women who opted to continue their pregnancies after a prenatal diagnosis of anencephaly (Jaquier et al., 2006). These data showed that only 7% of cases resulted in intrauterine fetal demise, which was lower than expected. The stillbirth rate was 20%. Polyhydramnios complicated 26% of pregnancies. Additional externally visible malformations were present in 8% of neonates. Thirty-four percent of infants were delivered prematurely and delivery by cesarean section was performed in 26% of women. The most common indications for cesarean section were breech presentation, placenta previa, twin pregnancy, and parental request. Seventy-two percent (153) of infants were liveborn. Of these, 103 died within the first 24 hours, but 6 survived for 6 to 28 days.

MANAGEMENT OF PREGNANCY

Interestingly, although maternal serum α-fetoprotein (AFP) levels are elevated in approximately 90% of cases of anencephaly (Medical Task Force on Anencephaly, 1990), as a primary screen, routine sonography detects a higher percentage of cases than second trimester maternal serum screening (Norem et al., 2005). All cases of significantly elevated maternal serum AFP levels need to be followed with a sonographic examination to confirm dating of the pregnancy and evaluate fetal anatomy. Prospective parents confirmed to be carrying a fetus with anencephaly should be referred to a tertiary care center, with ultrasound technicians and physicians who are capable of definitive diagnosis of fetuses with anomalies. If additional fetal structural anomalies are detected, a prenatal karyotype should be offered, and if declined, a postnatal karyotype is recommended. If the anencephaly is isolated, a postnatal karyotype is also encouraged, although the yield is likely to be low. In one prospective study of 46 fetuses with acrania or anencephaly, chromosome analysis was normal in 45/46 cases (Sepulveda et al., 2004). Only one fetus with anencephaly was shown to have trisomy 18.

Because pregnancy with a fetus with anencephaly carries an increased medical risk for the mother, prospective parents should be offered the opportunity to terminate, if the diagnosis is made before 24 weeks of gestation, as the prognosis for the fetus is uniformly fatal. Because polyhydramnios is often associated with this condition, premature delivery is increased (Jaquier et al., 2006). Labor and delivery are frequently associated with an unstable fetal position, and common maternal complications include dysfunctional labor (poor dilatation or dystocia) and postpartum hemorrhage (Medical Task Force on Anencephaly, 1990). There is an increased incidence of placental abruption with anencephaly (Melnick and Myrianthopoulos, 1987).

A special situation exists for twins in which one fetus has anencephaly, as there is an increased risk of premature delivery of the unaffected fetus (Leeker and Beinder, 2004) In dichorionic pregnancies, selective termination of the anencephalic fetus may prevent polyhydramnios and decrease the chance of preterm labor. The selective termination is most safely performed prior to 16 weeks of gestation.

In a review of more than 181 consecutive infants born with anencephaly, Main and Mennuti (1986) found that more than half of the cases were stillborn and virtually all others died during the neonatal period. However, more than 40% were alive at 24 hours and 5% lived to at least 7 days. These numbers were very similar in the most recent study performed by Jaquier et al. (2006). Therefore, parents should not be counseled that the infant will die immediately after birth. They should, however, be advised that the prognosis is uniformly fatal for this condition.

FETAL INTERVENTION

There is no fetal intervention for anencephaly.

TREATMENT OF THE NEWBORN

The mean gestational age at delivery for infants with anencephaly is 36.7 ± 5 weeks (Melnick and Myrianthopoulos, 1987). The mean birth weight for fetuses with anencephaly, when corrected for the absence of the brain, is within normal limits. The diagnosis of anencephaly can be confirmed on physical examination when the following criteria are met: A large portion of the skull is absent, the scalp is absent over the skull defect, and a hemorrhagic, fibrotic mass of tissue is exposed to the environment (Figure 7-4). There are no recognizable cerebral hemispheres present.

Because affected infants lack functioning cerebral cortex, they are permanently unconscious, but brainstem function is present in varying degrees. These patients are not, however, comatose. All infants have spontaneous movements of the extremities and startle myoclonus, although their tone and deep tendon reflexes are increased. Their typical behavior pattern consists of increased extensor tone and spontaneous or stimulus-induced axial myoclonus of the upper and lower extremities (Peabody et al., 1989). They respond to noxious stimuli and exhibit the primitive reflexes associated with feeding and breathing.

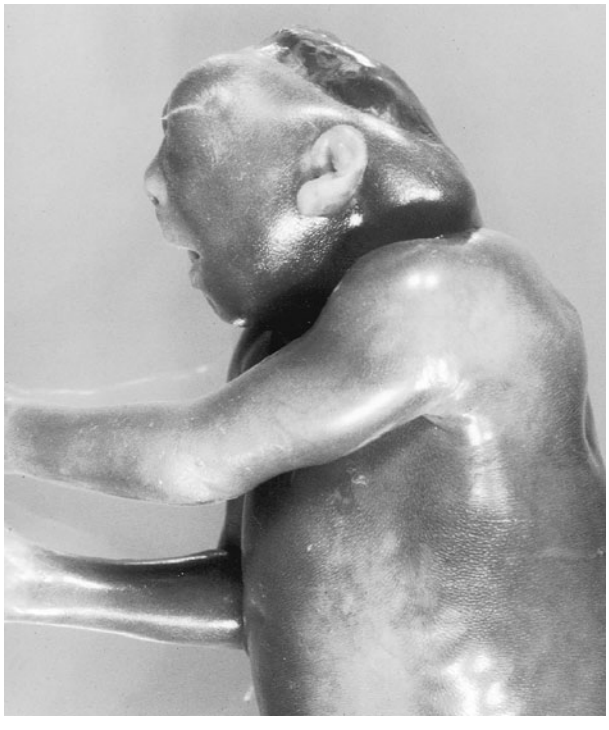

Figure 7-4 Sagittal view of a 20-week-old fetus with anencephaly. Note the total lack of cranial development above the orbits. The area cerebrovasculosa is easily seen. (*Photograph courtesy of Dr. Joseph Semple.*)

Most infants reported have died within the first few days of life, however, survival beyond 1 week of age has been reported in up to 9% of affected infants. The Medical Task Force on Anencephaly (1990) confirmed that one infant with anencephaly survived for 2 months.

SURGICAL TREATMENT

Surgical treatment is not applicable in anencephaly.

LONG-TERM OUTCOME

The major issue in long-term outcome is the potential use of anencephalic fetuses or infants as organ donors. This is a consideration because nationally 30% to 50% of children less than 2 years of age who are registered for organ transplantation die while waiting for donor organs to become available. Anencephalic infants have been considered as potential organ donors because they have a uniformly fatal prognosis. Difficulties exist, however, because of the traditional means of determining brain death for organ donors. Because anencephalic patients have no functioning cerebral cortex, the usual methods of determining brain death, such as cerebral blood flow testing and electroencephalograms (EEGs), are irrelevant to the diagnosis of anencephaly. For anencephalic patients, the diagnosis of brain death depends on documentation of disappearance of previously existing brainstem functions, such as a positive apnea test or loss of spontaneous movements.

Four different strategies have been suggested for the procurement of organs for transplantation from anencephalic patients.

The first is to place the infant on life support systems at birth and remove the organs as soon as technically possible without regard to the presence or absence of brainstem function. This strategy has been described by a group in Germany. Holzgreve et al. (1987) removed the kidneys from three infants with anencephaly and successfully transplanted them into four recipients. These authors argued that the anencephalic infants were "brain absent." Potential benefit was experienced not only by the organ recipients, but also by the parents of the anencephalic fetuses, who experienced psychologic benefits and additional moral purpose in carrying the anencephalic pregnancies to term (Holzgreve et al., 1987).

A second strategy is to place the anencephalic infant on life support systems at birth and observe the infant until all brainstem functions stop. This approach was tested by Peabody et al. (1989), who modified the medical care of 12 liveborn infants with anencephaly. For a period of 1 week, they tried to determine whether organ viability could be maintained and whether the criteria of total brain death could be met if these anencephalic infants were placed on life support for 1 week. Only 2 of the 12 infants met these criteria, and no solid organs were procured from these 12 infants. The authors concluded that most organs were suitable for

transplantation at birth and that organ function was maintained when intensive care was provided, but only one infant had conclusive evidence of brainstem death.

A third strategy is to give the infant with anencephaly only comfort care until signs of cardiorespiratory failure develop and then to place the infant on life support awaiting brain death. Peabody et al. (1989) concluded that when intensive care was delayed until brain death was imminent, most organs were damaged to the extent that they were no longer suitable for transplantation.

Most centers currently use a fourth strategy for organ donation from anencephalic infants. They provide standard comfort care until the infant dies. Then cadaver organs are removed, such as the corneas, heart valves, and kidneys.

It is important to note that most of the major organs from anencephalic infants are smaller than average for body size and have somewhat higher rates of malformation, but neither of these findings preclude their use in transplantation (Botkin, 1988).

GENETICS AND RECURRENCE RISK

A family history of spina bifida and/or anencephaly is one of the strongest risk factors for recurrence. Most cases of anencephaly are compatible with a multifactorial model, with a recurrence risk of between 2% and 5% following a single case (Medical Task Force on Anencephaly, 1990). For fetuses identified with multiple sonographic abnormalities, if a karyotype has not been performed prenatally, it should be obtained at delivery, as some cases of anencephaly are associated with chromosomal abnormalities, such as trisomies 13 and 18, and triploidy. In isolated populations, anencephaly has been described as a single-gene disorder. In Iranian Jews, who are highly inbred, anencephaly is inherited as an autosomal recessive condition (Zlotogora, 1995).

All women of reproductive age should take at least 400 mcg of folic acid daily to prevent neural tube defects. To be effective, folic acid must be consumed before conception and at least through the first 4 weeks of development. Folic acid is nontoxic even at very high doses and it is rapidly excreted in the urine. For women who have previously had a fetus or infant affected with anencephaly, the Centers for Disease Control and Prevention (CDC) recommends increasing the intake of folic acid to 4000 mcg (4mg) per day beginning at least 1 month prior to conception (Committee on Genetics, 1999). Prenatal diagnosis can be performed in a subsequent pregnancy, either by sonographic examination, or by maternal serum α-fetoprotein analysis.

The genetic basis of the interaction between folate metabolism and neural tube defects is under investigation. The conversion of homocysteine to methionine requires folate (Chescheir et al., 2003). Some—but not all—studies have shown that parents who have had a pregnancy complicated by a neural tube defect are more likely to be homozygous or a mutation in the gene for the enzyme methylenetetrahydrofolate reductase (MTHFR) than an unaffected population (Relton et al., 2003).

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8 CHAPTER

Arachnoid Cyst

Key Points

- Arachnoid cysts are rare central nervous system malformations that represent 1% of neonatal intracranial masses.
- Arachnoid cysts are diagnosed prenatally as a simple, echolucent area within the fetal head and in which no communication with the ventricular system is seen.
- The main differential diagnosis for a posterior fossa arachnoid cyst is between mega cisterna magna and Dandy–Walker malformation.
- Most arachnoid cysts remain stable antenatally, but some may cause hydrocephalus by their mass effect as the pregnancy progresses.
- Management of pregnancy is generally not altered with an arachnoid cyst, unless significant hydrocephalus is present. Careful head imaging in the neonatal period is required to confirm the diagnosis and exclude associated abnormalities.
- Prognosis depends on the presence of other malformations, parenchymal hemorrhage, rate of cyst growth, and progession of ventriculomegaly.
- Pediatric management is usually either expectant, for asymptomatic cysts, or open or endoscopic fenestration or obliteration of the cyst if symptomatic.

CONDITION

Arachnoid cysts represent collections of cerebrospinal fluid enclosed within layers of pia arachnoid, that do not communicate with the intracranial ventricular system (Osborn and Preece, 2006). They are lined by arachnoidal cells and collagen. Arachnoid cysts are unilocular, round, oval, or crescentlike in shape. They initially communicate with the subarachnoid space and have the potential to grow due to this continued communication. Fluid accumulates as a result of a ball-valve mechanism (Diakoumakis et al., 1986). Choroid plexus-like tissue can be present within the cyst wall. This ectopic tissue secretes cerebrospinal fluid, resulting in progressive distention of the cyst (Diakoumakis et al., 1986). These fluid-filled masses must be distinguished on prenatal sonographic evaluation from the fourth ventricle and vallecula. The cerebellar vermis, hemispheres, and brainstem are usually normal in this condition except when the cyst compresses these structures (Altman et al., 1992).

Two types of arachnoid cysts exist: the congenital type, which is considered to be the result of maldevelopment of the leptomeninges, and the acquired type, which is the result of hemorrhage, trauma, or infection (Meizner et al., 1988). Two-thirds of prenatally detected cases are supratentorial in location, whereas one-third are located within the posterior fossa (Estroff et al., 1995). In contrast, most postnatally detected cases are located within the posterior fossa (Hogge et al., 1995). Five percent of supratentorial interhemispheric arachnoid cysts are associated with agenesis of the corpus callosum (Lena et al., 1995).

Structural features of the arachnoid cyst wall that distinguish it from the normal arachnoid membrane include

1. splitting of the arachnoid membrane at the margin of the cyst;
2. a very thick layer of collagen present in the cyst wall;
3. absence of the traversing trabecular processes within the cyst;
4. presence of hyperplastic arachnoid cells located within the cyst wall that presumably participate in collagen synthesis (Rengachary and Watanabe, 1981).

Electron micrographic studies of arachnoid cysts reveal a striking and nearly invariable association of the arachnoid cyst with the normal subarachnoid cistern. Some investigators have demonstrated that in their early stages, arachnoid cysts communicate with the subarachnoid space, revealing

the exclusively intra-arachnoid nature of the cyst (Rengachary and Watanabe, 1981). Other investigators, however, postulate that the retrocerebellar arachnoid cyst may represent a persistent diverticulum of the fourth ventricle that fails to involute, the so-called Blake pouch (Altman et al., 1992). The precise cause for the development of arachnoid cyst is unknown. The factors responsible for the formation of the normal subarachnoid cistern, however, also produce splitting of the arachnoid membrane in that location. This results in a diverticulum or enclosed cystic space. Thus, arachnoid cysts are thought to be a developmental anomaly of the subarachnoid cistern (Rengachary and Watanabe, 1981).

INCIDENCE

The incidence of arachnoid cysts is unknown. They are rare in prenatal life. Arachnoid cysts represent 1% of all space-occupying masses in childhood (Estroff et al., 1995) and are an incidental finding in 0.5% of autopsy studies (Rafferty et al., 1998). Arachnoid cysts are more common in males than in females (Kollias et al., 1993; Lena et al., 1995). The left side of the brain is more commonly affected than the right.

SONOGRAPHIC FINDINGS

Sonographic diagnosis of arachnoid cyst relies on the finding of a sonolucent mass with smooth and thin walls within the brain (Figure 8-1). This cyst does not communicate with the lateral ventricles, but may be associated with hydrocephalus

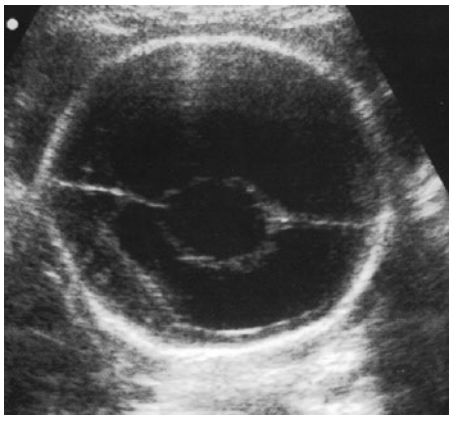

Figure 8-2 Transaxial image of a fetal head demonstrating an arachnoid cyst and associated hydrocephalus.

(Figure 8-2) due to a mass effect that obstructs the flow of cerebrospinal fluid. In this condition, the cerebellar vermis is normal in size. The cyst is usually completely echolucent, with the same signal intensity as CSF (Figure 8-2). Occasionally, hemorrhage into an arachnoid cyst may obscure its simple appearance (Osborn and Preece, 2006).

In 1986, Diakoumakis et al. described a fetal suprasellar arachnoid cyst that was detected on a routine antenatal sonographic examination at 32 weeks of gestation, and resulted in development of hydrocephalus. Postnatal cranial computed tomographic (CT) examination revealed a characteristic "head of the bunny" appearance with a midline cyst and two dilated lateral ventricles (Diakoumakis et al., 1986). In another case report, a fetus was described at 22 weeks of gestation with an isolated extraventricular supratentorial arachnoid cyst, which appeared as a rounded, fluid-filled cyst

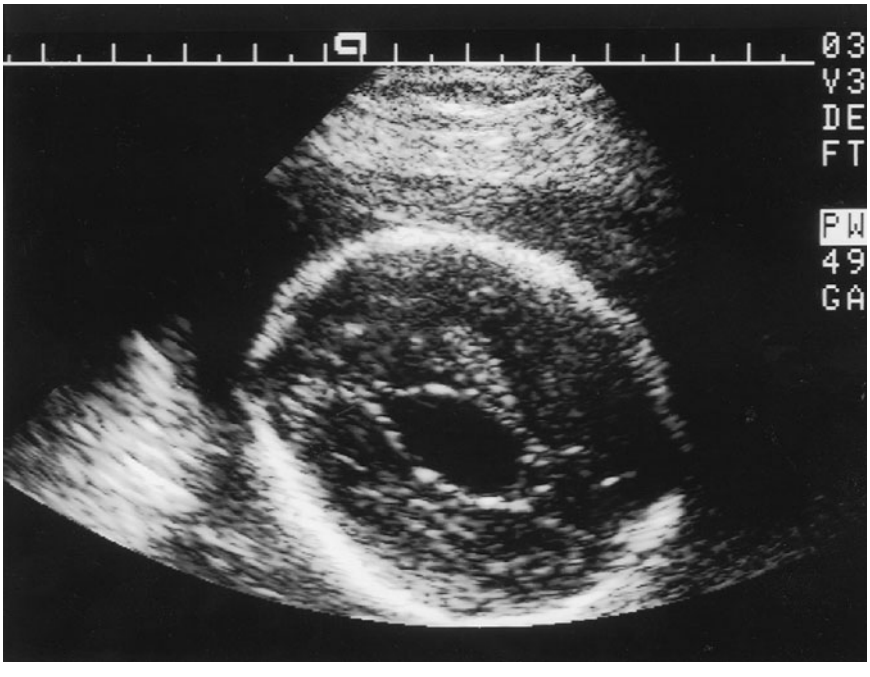

Figure 8-1 Transaxial image of fetal head demonstrating solitary arachnoid cyst.

in the right parieto-occipital lobe of the brain (Meizner et al., 1988). There was splaying of the right lateral ventricle due to a pressure effect, and the cyst enlarged progressively over the duration of pregnancy (Meizner et al., 1988).

Most cases of arachnoid cysts are detected at >20 weeks of gestation (Hogge et al., 1995; Rafferty et al., 1998). Only rarely are extracranial abnormalities detected. In one case report, a 1- by 1-cm posterior fossa cyst was detected at 18 weeks of gestation. The pregnancy was aborted because of associated chromosomal abnormalities (Hogge et al., 1995).

Estroff et al. (1995) described two cases of arachnoid cysts that, on the basis of prenatal sonographic findings, were suspected antenatally to be a Dandy–Walker malformation. These authors noted that sonographic distinction between the retrocerebellar arachnoid cysts and the Dandy–Walker cyst may be difficult. Both malformations may be associated with hydrocephalus. In arachnoid cysts, the underlying cerebellar hemispheres and vermis are normal, although they are displaced and compressed anteriorly. Typically, no extracranial abnormalities are present in arachnoid cysts (Estroff et al., 1995). At least 27 cases of fetal arachnoid cysts have been described in the literature (reviewed in Chen, 2007). Of these, 9 had prenatal MR imaging in addition to sonography. In a few cases, the diagnosis was made in the second trimester, but the majority were third trimester diagnoses. In one report, using transvaginal sonography, a posterior fossa arachnoid cyst was diagnosed at 13 weeks of gestation (Bretelle et al., 2002).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for arachnoid cysts is given in Table 8-1, and antenatal magnetic resonance imaging (MRI) may be needed for accurate evaluation (Golash et al., 2001). Mega cisterna magna can be confused with arachnoid cyst but, there is no mass effect on the cerebellar hemispheres nor hydrocephalus in the setting of mega cisterna magna (Estroff et al., 1995). Arachnoid cysts in the midline that lie wholly posterior to the cerebellum may be difficult to distinguish from the mega cisterna magna (Altman et al., 1992).

Dandy–Walker malformation can also be mistaken for an arachnoid cyst (see Chapter 11), as it is associated with a well-defined posterior fossa cyst that is separate from the ventricular system (Meizner et al., 1988). Anterior extension of an arachnoid cyst to the cerebellar hemispheres effectively rules out the Dandy–Walker malformation (Altman et al., 1992). It may be quite difficult to distinguish antenatally between Dandy–Walker malformation and posterior fossa arachnoid cysts. The determination of size, shape, and position of the fourth ventricle and cerebellar vermis is critical to accurate differentiation between arachnoid cyst and Dandy-Walker malformation (Estroff et al., 1995). The finding of associated agenesis of the corpus callosum may suggest a diagnosis of Dandy–Walker malformation. Postnatally, an invasive procedure, such as instilling radiographic contrast material into the ventricular system (cisternagram) may be necessary to distinguish among Dandy–Walker malformation and its variants (see Chapter 11), mega cisterna magna, or Blake pouch cyst (Estroff et al., 1995). La Torre et al. (1973) recommended angiographic distinction between Dandy–Walker malformation and arachnoid cysts by evaluation of the posterior inferior cerebellar artery and its vermian branch. In arachnoid cysts, all vessels are normal in size and are displaced forward and upward, while in the Dandy–Walker malformation, the posterior inferior cerebellar artery is miniature and the vermian branch of the inferior cerebellar artery and the inferior vermian vein are absent.

An additional consideration in the differential diagnosis of arachnoid cyst is a variant of normal. Knutzon et al. (1991) described a linear hyperechoic structure in the cisterna magna previously thought to be the straight sinus. This structure was identified in 92 to 95 of prenatal sonographic examinations. This structure appeared cystlike in 17 of 95 cases studied. On histopathologic correlation in aborted fetuses, this structure was shown to be formed by subarachnoid septa. It is most likely due to focal concentrations of arachnoid trabeculations in the subarachnoid space (Knutzon et al., 1991). Intrahemispheric arachnoid cysts can be confused with a dorsal cyst present in cases of alobar holoprosencephaly (see Chapter 14) (Lena et al., 1995). Porencephalic cysts are located within brain matter, communicate with the ventricular system, and do not exert a mass effect. They are often associated with prenatal or postnatal brain injury (Lena et al., 1995). Ependymal cysts occur less frequently than arachnoid cysts and tend to occupy the central white matter of the frontal or temporoparietal lobes (Rengachary and Watanabe, 1981). In ependymal cysts, the protein content of the cyst fluid is higher than that of the arachnoid cyst.

Table 8-1

Differential Diagnosis of Arachnoid Cyst

Mega cisterna magna
Dandy–Walker malformation
Normal variant
Alobar holoprosencephaly
Porencephalic cyst
Ependymal cyst
Schizencephaly
Infarct
Tumor

ANTENATAL NATURAL HISTORY

Little is known about the antenatal natural history of arachnoid cysts. Some increase in size and others resolve spontaneously. Two cases have been described in the medical literature of arachnoid cysts associated with increased maternal serum α-fetoprotein levels (Kwon and Jeanty, 1991; Hogge et al., 1995). It is not known if these are etiologically related or coincidental. From the limited number of prenatal cases reported, it appears that the cyst can grow in size during antenatal life (Diakoumakis et al., 1986; Meizner et al., 1988). In addition, hydrocephalus can develop from obstruction of the foramen of Monro and displacement of the aqueduct posteriorly with blocked basal cisterns.

MANAGEMENT OF PREGNANCY

When an arachnoid cyst is detected within the fetal brain, the patient should be referred to a center capable of complete anatomic sonographic fetal diagnosis. If differential diagnosis of a posterior fossa arachnoid cyst from Dandy–Walker malformation is difficult, prenatal MRI may be necessary. Serial sonographic examination should be performed to monitor potential enlargement of the cyst and subsequent development of ventriculomegaly (Hogge et al., 1995). It is important to seek evidence of associated malformations, as arachnoid cysts may be part of a multiple malformation syndrome. For example, one rare recessively inherited condition consists of absent tibia, polydactyly, cleft palate, and the presence of retrocerebellar cysts (Holmes et al., 1995). Rare cases of arachnoid cyst have been associated with tetralogy of Fallot and neurofibromatosis type 1.

Serious consideration should be given to performing amniocentesis to obtain a fetal karyotype, particularly if other anomalies are present. In one case, a fetus with a posterior fossa arachnoid cyst was shown to have an abnormal karyotype consisting of 46,X der(X),tX:9(q22;q22). Thus, this fetus had a partial trisomy of the long arm of chromosome 9 with partial monosomy of the long arm of the X chromosome. This was due to a balanced translocation occurring in the mother between chromosomes X and 9 (Hogge et al., 1995). Other chromosome abnormalites described in association with fetal arachnoid cyst include deletion of the distal long arms of chromosome 14 (Souter et al., 2003) and chromosome 16 (Arriola et al., 2005), trisomy 18 (Pilu et al., 1997), and triploidy (Elbers and Furness, 1999).

Prospective parents of a fetus demonstrated to have an arachnoid cyst should be offered the opportunity to consult with a pediatric neurologist, neurosurgeon, and medical geneticist. The presence of an isolated arachnoid cyst is not an indication for cesarean section (Meizner et al., 1988). However, because of the potential for development of ventriculomegaly, the patient should be followed by serial sonograms to determine if the fetal head size is small enough for a vaginal delivery. An additional consideration in the determination of route of delivery is the risk of trauma and hemorrhage within the cyst (Altman et al., 1992).

FETAL INTERVENTION

There is no fetal intervention recommended for arachnoid cyst.

TREATMENT OF THE NEWBORN

Newborns who have been diagnosed with an arachnoid cyst antenatally should have an evaluation with consultants in genetics and neurology. Depending on the location of the cyst, CT or MRI scanning is indicated to confirm the presence of the cyst. A careful measurement should be made of the newborn's head circumference, and the presence of asymmetry of the calvarium should be noted. The newborn should be observed for any changes in head circumference, as the potential exists for expansion of the cyst by hemorrhage due to trauma at delivery through the rupture of bridging veins (Altman et al., 1992). Clinical characteristics at birth will depend on the size of the cyst (Kollias et al., 1993). Associated hydrocephalus is present in 30% to 100% of cases (Kollias et al., 1993). In newborns in whom an arachnoid cyst is detected postnatally, the overwhelming presenting symptom is macrocephaly (71.5% of 67 cases reported) (Pascual-Castroviejo et al., 1991). Seizures may occasionally occur in infants with arachnoid cyst. Increased intracranial pressure is rarely a presenting clinical sign.

SURGICAL TREATMENT

The operative procedures for treatment of arachnoid cysts consist of cyst excision, fenestration, or drainage into an adjacent cistern, abdominal cavity, or atrium (Richard et al., 1989). Small asymptomatic cysts do not require any intervention. Surgical excision of the cyst is indicated in the rare cases in which increased intracranial pressure is detected. Craniotomy, however, may result in severe complications. The most common treatment consists of a cystoperitoneal shunt, which results in a high rate of regression of the cyst and rarely produces recurrence or complications. These shunts may need revision due to blockage or growth of the patient (Pascual-Castroviejo et al., 1991). Most neurosurgeons prefer to treat the patient initially with expectant management, as the avoidance of a shunt is the primary goal in management (Fewel et al., 1996). More recently, an endoscopic approach to cyst obliteration has been described (Choi et al., 1999; Golash et al., 2001). Additionally, endoscopic cyst fenestration may

also be used as a less invasive alternative to open surgical management (Nakamura et al., 2001).

LONG-TERM OUTCOME

The major complications in the long-term outcome for affected patients include hydrocephalus, seizures, and neurologic abnormalities (Altman et al., 1992; Hogge et al., 1995). Estroff et al., (1995) described normal developmental outcome for a fetus diagnosed at 28 weeks of gestation with hydrocephalus and a retrocerebellar cyst following cystoperitoneal shunt decompression (Estroff et al., 1995).

In a follow-up study of 16 children with symptomatic supratentorial interhemispheric cysts ascertained postnatally, Lena et al. (1995) demonstrated that no cyst became larger but none disappeared completely. These authors had a median follow-up period of 50 months. In 16 children, the preoperative symptoms disappeared completely in 7 and partially in 4. Two of the original patient group were asymptomatic and remained completely normal. Of the 16 children, 12 were entirely neurologically normal, 1 had moderate disability, 2 had severe disability, and 1 died from unrelated pneumonia 3 months after surgery. Seizures developed in 4 of the 16 children (Lena et al., 1995). Richard et al. (1989) followed affected children into adulthood over a 48-year period. These investigators demonstrated a favorable outcome for most patients, with 62% to 93% of all individuals followed over this period having had normal physical and social development and a satisfactory quality of life. The prognosis was also noted to be related to age at operation. Independent of the surgical method used over this 48-year period, the percentage of patients with any disability as compared with all due to arachnoid cyst ranged from approximately 11% to 14%. Patients who died in this study had causes of death unrelated to the arachnoid cyst (Richard et al., 1989).

In another series of 33 cases of supratentorial arachnoid cysts managed surgically and followed to a mean of 70 months, all patients were improved symptomatically, even though most still demonstrated persistence of the cyst (Galarza et al., 2002). One of these 33 children had developmental delay and 4 had epilepsy, although all 4 of these children were seizure free on medications following surgery.

GENETICS AND RECURRENCE RISK

Most cases of arachnoid cyst appear to be sporadic (Altman et al., 1992). Rare cases of arachnoid cyst are associated with neurofibromatosis type 1 or other multiple congenital anomaly disorders due to single gene mutations (Holmes et al., 1995). For example, an unexpectedly high number of asymptomatic intracranial arachnoid cysts were found in a group of 247 patients with autosomal dominant polycystic kidney disease who underwent high-resolution CT scanning or MR imaging (Schievink et al., 1995). If a prenatal karyotype analysis is performed and an unbalanced chromosome abnormality is detected, as in the cases cited here (Hogge et al., 1995; Souter et al., 2003; Arriola et al., 2005), parental chromosome analysis is strongly suggested.

Occasional families have been described with recurrence of arachnoid cysts. For example, Handa et al. (1981) reported the presence of bilateral arachnoid cysts in the middle cranial fossa in two brothers, aged 10 months and 3 years. Other reports of siblings affected with arachnoid cysts exist in the medical literature (Wilson et al., 1988; Pomeranz et al., 1991; Tolmie et al., 1997; Hendricks et al., 1999). Arriola et al. (2005) described two families that had three affected members each. Significantly, each family had individuals with arachnoid cysts in two generations. These reports suggest the possible existence of heritable factors that predispose individuals to the formation of arachnoid cysts.

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CHAPTER 9

Cerebral Calcifications

Key Points

- Cerebral calcifications are rare and are associated with fetal infections, such as CMV, rubella, toxoplasma, syphilis, and herpes, as well as with trisomies 21 and 13.
- Following the diagnosis, detailed sonographic evaluation for other markers of aneuploidy or intrauterine infection is warranted, together with maternal TORCH titers, followed by amniocentesis for the specific infectious agent as suggested by abnormal TORCH titers.
- Further pregnancy and pediatric management is dictated by the specific underlying etiology.

CONDITION

Cerebral calcifications are an unusual sonographic finding in the fetus. They are thought to occur late in gestation and result from localized neuronal-cell death. Intracranial calcifications are most commonly associated with the in utero infections due to the TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes virus) agents (Ghidini et al., 1989). This chapter covers three types of fetal cerebral calcifications: (1) focal, punctate parenchymal calcifications, (2) periventricular echogenicity, and (3) echogenic blood vessels demonstrated in the thalami and basal ganglia (Estroff et al., 1992).

INCIDENCE

Fetal intracranial calcifications are rare. Although congenital cytomegalovirus is common [affecting 30,000 to 40,000 infants each year in United States (Ross and Boppana, 2004)], most cases of congenital cytomegalovirus are not associated with cerebral calcifications. One study found fetal brain

abnormalities, including intracranial calcifications, in 10 of 39 (20%) of fetuses who were infected congenitally and had prenatal sonographic studies (Enders et al., 2001).

SONOGRAPHIC FINDINGS

Much of the information regarding the differential diagnosis and outcome for infants with intracranial calcifications derives from the postnatal pediatric radiographic literature. The use of postnatal cranial sonography as an effective means of visualizing intracranial calcifications in newborn infants with congenital infections was first described by Dykes et al. in 1982. She and her colleagues demonstrated the presence of multifocal, high-intensity echoes in infants with infection. What was unusual about this sonographic finding was that there was no acoustical shadowing from these echoes. Subsequently, Teele et al. (1988) noted the unique sonographic finding of bright, branching vessels in the thalami and basal ganglia of 12 newborn infants. This finding was strongly associated with the presence of congenital infection. In this group of 12 infants, 5 had congenital cytomegalovirus (CMV), 2 had congenital rubella, 1 had congenital syphilis, and 3 had trisomy 13 with no known evidence of infection. These findings later were extended by other investigators, including Ben-Ami et al. (1990), who studied 11 infants noted to have bright echogenic stripes in the thalami and basal ganglia. By using duplex sonography, these investigators demonstrated that the stripes derived from the lenticulostriate arteries in the basal ganglia (Figure 9-1). In their study group, 8 of 11 cases were infected in utero, and 1 additional patient had trisomy 13. In a retrospective review of 2320 neonatal cranial sonograms, 25 newborns were identified with these linear areas of echogenicity in the basal ganglia (Hughes et al., 1991). Three of the 25 newborns were shown to have abnormal chromosomes (2 had trisomy 21 and 1 had trisomy 13). An additional four patients had CMV, and eight had clinical evidence of either anoxia or other metabolic brain injury (Hughes et al., 1991).

Relatively few cases of fetal intracranial calcifications have been described in the literature on prenatal diagnosis (Ghidini et al., 1989). Fakhry and Khoury (1991) reported two cases of fetal intracranial calcifications associated with CMV. In one case, at 32 weeks of gestation, the fetus was also noted to have microcephaly (Figure 9-2). In the other case, the fetus had a completely normal sonographic examination at 17 weeks, but by 22 weeks was noted to have mild hydrocephalus and hyperechoic foci in the periventricular areas. The pattern of bilateral periventricular calcifications may be a specific finding for intrauterine CMV infection (Figure 9-3) (Tassin et al., 1991). A different fetal manifestation of congenital CMV infection has also been reported by Estroff et al. (1992). This included a hyperechoic rim in the periphery of the fetal cerebral cortex, with branching linear areas of echogenicity seen in the fetal thalami, which is likely to be the fetal equivalent of the lenticulostriate artery echogenicity

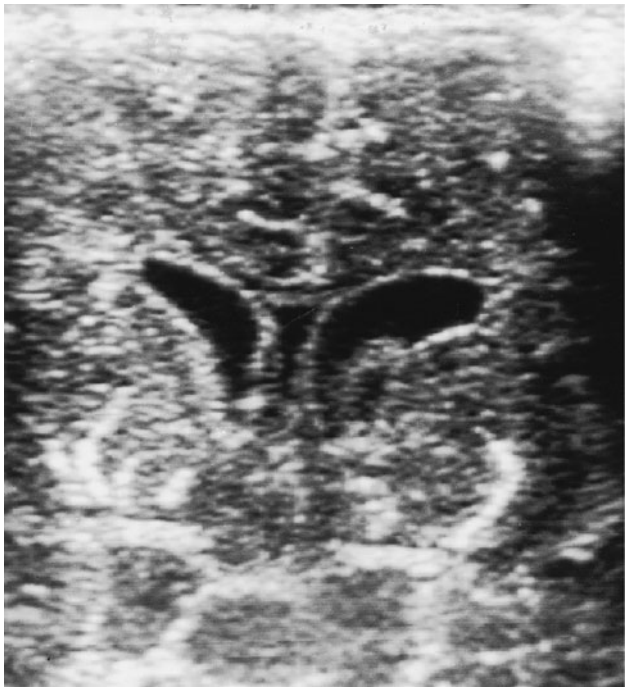

Figure 9-1 Coronal sonogram of a newborn with congenital cytomegalovirus infection, demonstrating branching, echogenic vessels in the basal ganglia. (*Reprinted, with permission, from Ben-Ami T, Yousef-zadeh D, Backus M, Reichman B, Kessler A, Hammerman-Rozenberg C. Lenticulostriate vasculopathy in infants with infections of the central nervous system: sonographic and Doppler findings.* Pediatr Radiol. *1990;20:575-579.*)

demonstrated postnatally in several studies (Teele et al., 1988; Ben-Ami et al., 1990; Hughes et al., 1991).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of fetal intracranial calcifications includes noninfectious and infectious causes. The noninfectious or structural causes include intracranial tumors (Sherer and Onyeije, 1998), the bilateral periventricular calcification of subependymal nodules seen in tuberous sclerosis (see Chapter 58), sagittal or transverse sinus thrombosis, Sturge–Weber syndrome, trisomy 13, and intracranial or intraventricular hemorrhage. Why echogenicity of the lenticulostriate arteries in the fetal thalami or basal ganglia is associated with trisomy 13 is currently not known. Case reports also exist that document the finding of fetal intracranial calcifications in rare autosomal recessive conditions such as carnitine palmitoyltransferase II deficiency (Elpeleg et al., 2001) and Aicardi–Goutières syndrome (Le Garrec et al., 2005).

The more common cause for fetal intracranial calcification is congenital infection (Degani, 2006). In many cases, the fetal intracranial calcifications are accompanied by other findings suggestive of infection, including intrauterine growth restriction, placental villitis, hepatosplenomegaly, ascites, hydrops fetalis, ventriculomegaly, or microcephaly (Ghidini et al., 1989; Enders et al., 2001). The infections likely to cause

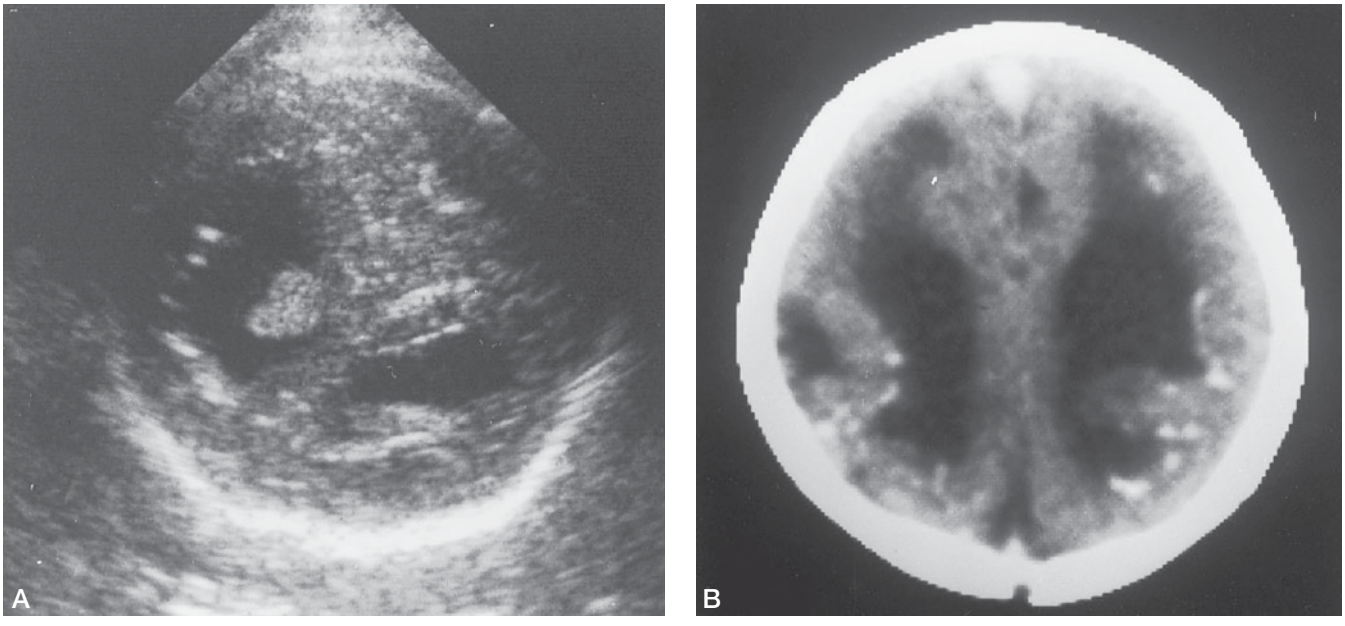

Figure 9-2 **A**. Axial scan of a fetal head at 32 weeks of gestation showing periventricular hyperechoic foci with absent acoustic shadowing. The choroid plexi are well seen in the moderately dilated ventricles. **B**. CT scan without contrast obtained after birth from the same infant, showing ventriculomegaly and periventricular and parenchymal calcifications. (*Reprinted, with permission, from Fakhry J, Khoury A. Fetal intracranial calcifications: the importance of periventricular hyperechoic foci without shadowing.* J Ultrasound Med. *1991;10:51-54.*)

intracranial calcifications include CMV (Hohlfeld et al., 1991; Estroff et al., 1992), rubella (Yamashita et al., 1991), toxoplasmosis, and herpes simplex, although CMV is overwhelmingly the most likely infectious cause (see Figures 7-1 to 7-3) (Fakhry and Khoury, 1991).

ANTENATAL NATURAL HISTORY

Toxoplasmosis, CMV, herpes simplex virus type 2, and rubella infections reach the fetal central nervous system via hematogenous dissemination. These viruses are known to have a predilection for rapidly growing subependymal or germinal matrix cells. Once the fetus is infected, these agents cause neuronal- or ganglia-cell necrosis. Necrotic cells may subsequently undergo calcification (Ghidini et al., 1989). Because of this sequence of events, cerebral calcification is rarely documented before the mid to late second trimester.

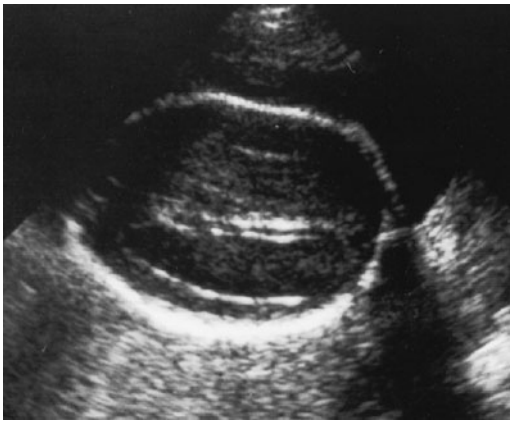

Figure 9-3 Axial scan of a fetal head in a fetus with cytomegalovirus demonstrating ventriculomegaly and bilateral periventricular calcifications. (*Reprinted, with permission, from Drose JA, Dennis MA, Thickman D. Infection in utero: US findings in 19 cases.* Radiology. *1991;178:369-374.*)

In several cases in which a neuropathologic examination was performed on infants who died with the postnatal sonographic finding of echogenic branching thalamic vessels, histopathology demonstrated thickened hypercellular walls with deposits of amorphous basophilic material, suggesting a perinatally acquired vasculitis (Teele et al., 1988). The pathophysiology behind the demonstration of echogenicity was likely due to a vascular injury resulting from a viral infection that affected the fetal central nervous system. Teele et al. concluded that postnatal sonography was helpful in detecting early noncalcific inflammation and mineralization in vasculitis due to infection. Fetuses with perinatally acquired infection are at increased risk of spontaneous abortion.

MANAGEMENT OF PREGNANCY

When fetal intracranial calcifications are documented, a careful search must be undertaken for associated structural anomalies, intrauterine growth restriction, and placental problems. The leading candidate in the differential diagnosis is CMV, so further management of pregnancy should include maternal TORCH titers. In some centers, TORCH titer testing has been replaced by testing only for CMV antibodies due to

the extremely low likelihood of finding positive results for toxoplasma, syphilis, or herpes virus (Abdel-Fattah et al., 2005). Primary CMV infection can be diagnosed if CMV-specific IgG antibodies are found in a patient previously known to be seronegative. The presence of both IgG and IgM however can be difficult to interpret, as CMV IgM can remain present following distant infection, or can be cross-reacting IgM from herpes virus infection. In such situations, CMV IgG avidity testing on maternal serum is recommended, with binding by antibodies less avidly during recent infection (Andrews, 2004). An amniocentesis is recommended for fetal karyotyping to rule out trisomies 13 and 21, and to obtain amniotic fluid for CMV analysis. Amniotic fluid can be analyzed for CMV using either viral culture, shell vial assay, PCR to quantify CMV DNA or amplification for CMV-specific RNA (Andrews, 2004). CMV culture, however, will be positive only 6 weeks after the onset of infection, and is generally only reliable after 21 weeks' gestation. In one series, two false-negative results from amniotic fluid CMV culture were reported following analysis less than 4 weeks following infection (Nicolini et al., 1994). After 18 to 20 weeks of gestation, cordocentesis can be performed to measure fetal immunoglobin M (IgM) to CMV, although this is rarely performed now due to the limited sensitivity for CMV and the improvements in amniotic fluid detection techniques. The finding of grossly abnormal liver-function tests and complete blood count has been associated with a rapidly fatal postnatal outcome (Hohlfeld et al., 1991).

One of the main challenges with identifying CMV in amniotic fluid is the lack of correlation with symptomatic congenital infection (Guerra et al., 2000). However, there does appear to be a correlation between CMV viral load and a higher likelihood of fetal infection. Serial sonograms are recommended to monitor fetal growth.

FETAL INTERVENTION

There is no known effective therapy to treat the fetus in utero (Guerina, 1994; Ross and Boppana, 2004). The results of treating newborns with ganciclovir have been encouraging, and prompt consideration may be given to fetal treatment with this antiviral agent. Because ganciclovir crosses the placenta by simple diffusion, maternal administration should be possible (Gilstrap et al., 1994). However, there are no prospective data to validate this approach.

TREATMENT OF THE NEWBORN

Because of the risk of anemia and cardiovascular complications associated with severe perinatal infection, consideration should be given to delivering potentially infected infants in a tertiary care center. After delivery, a complete physical examination is indicated, with careful attention to measurements of weight, head circumference, and length. A computed tomographic (CT) scan is useful to confirm the areas of intracranial calcification that were noted on prenatal sonography. However, if bright branching thalamic vessels were demonstrated antenatally, this finding will not be demonstrated on postnatal CT scans (Teele et al., 1988).

If amniocentesis was not performed antenatally, a neonatal urine sample should be obtained for CMV culture. Newborn TORCH titers should be drawn to pair with the maternal samples. The use of amplification techniques for CMV DNA in peripheral blood samples from the newborn may also be effective (Ross and Boppana, 2004). If the infection with CMV is confirmed, consideration should be given to treatment with ganciclovir over a 6-week course. Ophthalmologic examination may be useful to document the presence of chorioretinitis. Prior to discharge, the newborn infant should undergo hearing tests.

SURGICAL TREATMENT

There is no surgical treatment for cerebral calcifications.

LONG-TERM OUTCOME

The long-term outcome will depend on the cause of the cerebral calcifications. If the underlying diagnosis is trisomy 13, refer to Chapter 129. If the underlying diagnosis is congenital CMV infection, the prognosis is variable. The major complications include hearing loss, microcephaly, developmental delay, seizures, and visual impairment (Ben-Ami et al., 1990; Koga et al., 1990). In a review of 19 cases of prenatally acquired infection due to different agents, Drose et al. (1991) described 6 cases of CMV, 3 of which were detected prenatally by the presence of periventricular calcifications on sonography. An additional 3 were detected postnatally by CT scan or at autopsy. The outcomes for these 6 cases included 2 spontaneous losses at 23 and 24 weeks of gestation, 1 death in the neonatal period, 1 infant who survived with hydrocephalus, 1 infant who survived with hearing loss and abnormal development to 18 months of age, and 1 survivor with only hearing loss (Drose et al., 1991).

The postnatal history of intracranial calcifications in infants with treated congenital toxoplasmosis has been studied by computed tomography (Patel et al., 1996). In infants who were treated with appropriate doses of antibiotics, the majority (75%) of calcifications resolved or diminished.

GENETICS AND RECURRENCE RISK

Fetal intracranial calcifications due to an infectious cause presumably have a low risk of recurrence. Limited case reports exist of recurrence of fetal CMV, although reactivation of CMV infection in a subsequent pregnancy is much less likely to result in intrauterine infection. If echogenic branching

thalamic vessels were demonstrated due to trisomy 21 or 13, the recurrence risk is 1%, or the maternal age–related risk, whichever is greater.

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10 CHAPTER Craniosynostosis

Key Points

- Condition due to premature fusion of cranial sutures (sagittal, coronal, lambdoid, or metopic).
- Incidence is 1 in 2000 livebirths. One of the most common human malformations.
- Eighty to ninety percent of cases are isolated, 10%–20% are syndromic.
- Women with fetuses suspected of having craniosynostosis should be referred for a detailed fetal anatomic survey. Sonographers should pay attention to the fetal hands, midface, heart, and central nervous system.
- Differential diagnosis includes Muenke coronal craniosynostosis, Saethre–Chotzen syndrome,

Key Points (cont.)

Apert syndrome, Crouzon syndrome, Pfeiffer syndrome, and many others.

- DNA diagnosis is available to detect mutations in the causative genes associated with craniosynostosis, including *FGFR1, FGFR2, FGFR3, TWIST, and MSX2*.
- Newborns are at risk for difficulties with breathing, feeding, and vision. Consultation with genetics and neurosurgery is indicated.
- Long-term outcome and recurrence risk depend on identification of a genetic basis through DNA analysis.

CONDITION

The term *craniosynostosis* refers to the process of premature bony fusion of the cranial sutures. The term is frequently used interchangeably with the word *craniostenosis*, which technically refers to the aberrant skull shape that results from the process of craniosynostosis (Graham, 1981). The weight of the brain doubles during the first year of life, and enlargement of the skull vault is distributed among the main cranial sutures—sagittal, coronal, lambdoid, and metopic. Premature fusion of a suture leads to reduced growth in the direction perpendicular to the fused suture (Thompson et al., 1994). Compensatory growth occurs in the remaining normal sutures. Normally, the cranial sutures are open at birth and become interdigitated by 7.5 months of age. Cranial sutures do not fuse completely until the fourth decade of life (Graham, 1981).

It is important to determine whether craniosynostosis is primary or secondary. In primary craniosynostosis, abnormal skull development is genetically determined and alteration in sutural growth is present from birth (Flores-Sarnat, 2002). In primary craniosynostosis, the head of the affected individual is frequently asymmetric. The brain grows at a normal rate but must adjust to the confined space. The brain continues to grow in areas where the sutures are open but not in areas where the sutures are closed (Lyons-Jones et al., 1980). Most children affected with primary craniosynostosis are normal neurologically and benefit from surgery. In secondary craniosynostosis, brain growth is impaired and most affected children are neurologically abnormal. In secondary craniosynostosis, a metabolic, storage, hematologic, or structural disorder results in microcephaly or otherwise abnormal brain growth (Table 10-1). In evaluating the fetus with craniosynostosis, it is important to determine whether the craniosynostosis is isolated (80–90% of cases) or syndromic (10–20% of cases). More than 150 syndromes have been described that include craniosynostosis as an associated feature (Lajeunie et al., 1995; Warren and Longaker, 2001).

Isolated craniosynostosis generally presents during the first year of life, and severe neuropsychologic sequelae are unusual (Meilstrup et al., 1995). In most studies, the sagittal suture is the most common site for isolated craniosynostosis (Figure 10-1). This is called "scaphocephaly," and it results

Table 10-1

Classification of Craniosynostosis

Primary			Secondary
Single suture	Multiple sutures		
Nonsyndromic (simple)	Nonsyndromic	Syndromic (complex)	
Scaphocephaly (sagittal) Plagiocephaly (coronal or lambdoid) Trigonocephaly (metopic)	Brachycephaly (bicoronal)	Crouzon Apert Pfeiffer Saethre–Chotzen	*Storage disorders* Hurler syndrome Morquio syndrome *Metabolic disorders* Rickets Hyperthyroidism *Hematologic disorders* Polycythemia vera Thalassemia *Drug teratogens* Diphenylhydantoin Retinoic acid *Shunted hydrocephalus*

From Thompson D, Jones B, Hayward R, Harkness W. Assessment and treatment of craniosynostosis. Br J Hosp Med. *1994;52:17-24.*

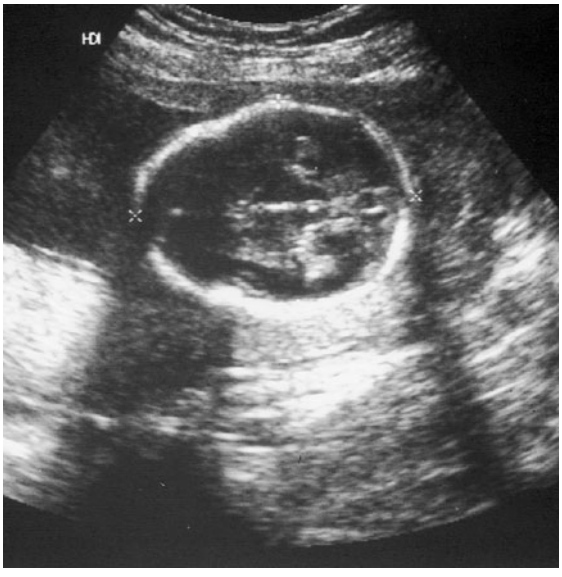

Figure 10-1 Prenatal transaxial sonographic image of an isolated suture synostosis, which gives a lemon-like shape to the cranium.

in a narrow, elongated head. Physical examination reveals a palpable ridge along the line of the fused suture. Bilateral coronal craniosynostosis (Figure 10-2) leads to "acrobrachycephaly" and a broad, short head (Flores-Sarnat, 2002). Unilateral coronal craniosynostosis, called "plagiocephaly," results in asymmetric flattening of the forehead with loss of the supraorbital ridge. This condition is best appreciated when viewed from above the patient. In most reported studies, the least commonly involved suture is the metopic. This is called "trigonocephaly," and produces a keel-shaped forehead and orbital hypotelorism (Thompson et al., 1994). The kleeblattschädel deformity, also described as a cloverleaf skull, has a more symmetric trilobar appearance, which results from premature synostosis of the coronal and lambdoidal sutures (Meilstrup et al., 1995).

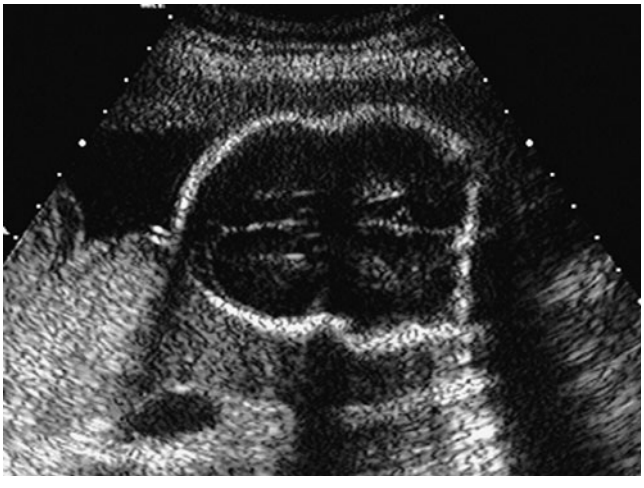

Figure 10-2 Prenatal sonographic image of a fetus at 24 weeks with bilateral coronal craniosynostosis.

INCIDENCE

Craniosynostosis is one of the most common human malformations, with an incidence of approximately 1 in 2000 livebirths (Shuper et al., 1985; Lajeunie et al., 1995; Van der Ham et al., 1995). Craniosynostosis is associated with advanced paternal age (Lajeunie et al., 1995), maternal smoking, and higher altitudes (Alderman et al., 1994, 1995). In a study of 154 patients at Johns Hopkins Hospital followed over a 2-year period, Van der Kolk and Beatty (1994) found that 78% of affected patients had only one suture involved, whereas 16% of patients had multiple sutures involved. Of these 154 patients, 94% had isolated craniosynostosis and 6% had complex or syndromic craniosynostosis. In this study, secondary synostosis occurred in four patients as a result of microcephaly or following complications of ventriculoperitoneal shunt placement (Van der Kolk and Beatty, 1994). Craniosynostosis occurs in all ethnic and racial groups.

Of the syndromic craniosynostoses, the most common are Saethre–Chotzen syndrome (Lewanda et al., 1994) and Muenke coronal craniosynostosis (Muenke et al., 1997). The next most common is Crouzon syndrome, with an incidence of 1 per 25,000 livebirths (Leo et al., 1991). Apert syndrome, with its distinctive craniofacial and digital abnormalities, occurs in 1 per 65,000 to 160,000 livebirths (Chenowith-Mitchell and Cohen, 1994; Moloney et al., 1996). Apert syndrome is associated with advanced paternal age (Moloney et al., 1996).

SONOGRAPHIC FINDINGS

Prenatal sonographic evaluation of the fetus in which craniosynostosis is suspected should include examination of

1. the symmetry of the calvarium contour (coronal views through temporal lobes and orbits);
2. the continuity of the calvarium to exclude encephalocele;
3. the size and shape of the orbits;
4. the cerebral ventricles;
5. the brain parenchyma;
6. the overall head size;
7. the remainder of fetal anatomy by detailed sonography (Meilstrup et al., 1995).

The most important consideration in the sonographic examination is the distinction between isolated and syndromic craniosynostosis. For most of the conditions associated with craniosynostosis, long-bone growth is within normal limits. It is particularly important to evaluate the fetal hands and feet, the central nervous system, and the heart.

In most published reports of prenatal diagnosis of craniosynostosis, the diagnosis was not made until the third trimester, unless a family history was present for one of the associated syndromes. In one report, 16 fetuses at risk for craniosynostosis were referred to a fetal medicine unit because of a positive family history (Delahaye et al., 2003). Serial

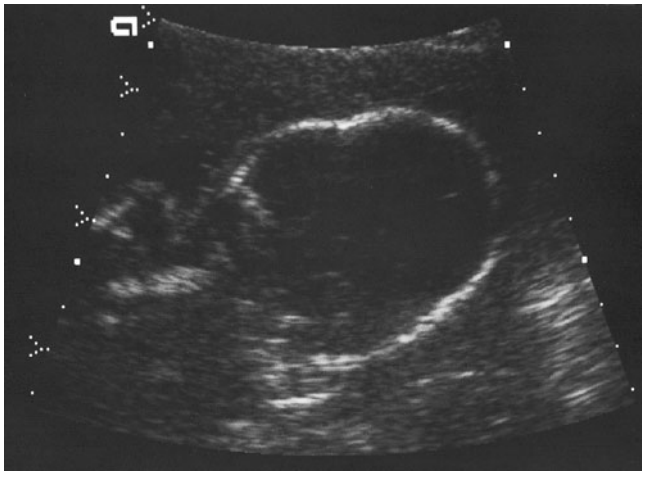

Figure 10-3 Prenatal sonographic image of a fetus at 23 weeks' gestation with Apert syndrome, demonstrating bilateral coronal suture synostosis and a tower-like shape of the skull (turricephaly).

sonographic examinations were performed at 12, 22, and 32 weeks of gestation. In all cases, postnatal diagnosis agreed with the third trimester (and, in a few cases, second trimester) diagnosis. Craniosynostosis was diagnosed when there was a loss of hypoechogenicity of the normal suture. Sutures were examined along their entire length. Dysmorphology and skull deformity preceded closure of the sutures by 4 to 16 weeks.

Fetuses at risk for Apert syndrome (Figure 10-3) should be evaluated for abnormalities of the hands (syndactyly), proptosis, congenital heart defects, agenesis of the corpus callosum, and abnormalities of the limbic structures of the brain (de León et al., 1987; Skidmore et al., 2003; Hansen et al., 2004). At least one case has been reported of Apert syndrome presenting as fetal hydrocephalus, although the presence of hydrocephalus is considered controversial (Kim et al., 1986). Some authors prefer to use the term *distortion ventriculomegaly* to indicate that the apparent abnormalities in fluid are the result of the misshapen brain (Cohen and Kreiborg, 1993b). One case of Apert syndrome presenting as nuchal-fold thickening as early as 12 weeks of gestation has been described (Chenowith-Mitchell and Cohen, 1994). This fetus did not demonstrate any additional sonographic abnormalities until after 26 weeks of gestation, when an abnormal head shape was first noted. By 29 weeks of gestation, the fetal skull was demonstrated to have prominent parietal lobes, and for the first time, lack of separate fetal finger movement was noted. This latter finding of the absence of distinct and separate movements of the fingers and toes is considered to be one of the hallmarks of Apert syndrome (Hill et al., 1987). Three-dimensional (3-D) sonographic imaging has been shown to be useful in the diagnosis of a sporadic case of Apert syndrome, specifically by demonstrating a widely open metopic suture and bilateral fusion of the coronal sutures (Esser et al., 2005).

Pfeiffer syndrome is characterized by coronal craniosynostosis, midface hypoplasia, and broad thumbs and great toes. There are three clinical subtypes: type I is the mildest presentation, type II is the most severe, and type III is intermediate. Type II is associated with a cloverleaf-shaped skull, severe ocular proptosis, midface hypoplasia, radially deviated digits, and occasional ventriculomegaly (Benacerraf et al., 2000). Several cases of the sonographic diagnosis of Pfeiffer syndrome, type II, with molecular confirmation, have been reported in the literature (Benacerraf et al., 2000; Blaumeiser et al., 2004; Gorincour et al., 2005).

DIFFERENTIAL DIAGNOSIS

Whenever craniosynostosis is considered in a fetus, an attempt should be made to rule out encephalocele (see Chapter 12) and the presence of an intracranial mass. Craniosynostosis is associated with abnormalities of chromosomes 5p, 7p, and 13q, single-gene disorders, and rare teratogens, such as aminopterin.

The most common conditions associated with syndromic craniosynostosis include Saethre–Chotzen syndrome, which includes craniosynostosis, facial asymmetry, low frontal hairline, ptosis, a deviated nasal septum, brachydactyly, and partial cutaneous syndactyly of the toes (Lewanda et al., 1994). Saethre–Chotzen syndrome is dominantly inherited, but in some families the features are so mild that they may go unrecognized.

A relatively recently identified syndrome, Muenke coronal craniosynostosis, has significant clinical overlap with Saethre–Chotzen syndrome (Vajo et al., 2000). It is also quite common. There is considerable phenotypic variability in this condition and mild cases may be missed. Affected individuals have coronal craniosynostosis, and mild abnormalities of the hands and feet, including carpal and tarsal fusion, brachydactyly, thimble-like middle phalanges, and cone-shaped epiphyses. Additional findings include sensorineural hearing loss and developmental delay (Muenke et al., 1997). This condition is also dominantly inherited.

The next most common syndrome associated with craniosynostosis is Crouzon syndrome, which includes coronal craniosynostosis, maxillary hypoplasia, shallow orbits, and ocular proptosis. This condition was first described in 1912 in an affected mother and daughter (Leo et al., 1991). Crouzon syndrome is distinguished from some of the other syndromes by the absence of abnormalities in the hands and feet. The essential features of this syndrome are limited to the skull and face, resulting in brachycephaly and orbital hypoplasia (Thompson et al., 1994).

Less common syndromes in the differential diagnosis include Jackson–Weiss, Pfeiffer (types I, II, III) and Carpenter. Jackson–Weiss syndrome was first described in an Amish kindred with more than 130 affected family members. The characteristic findings of Jackson–Weiss syndrome include craniosynostosis, maxillary retrusion, frontal prominence, hypotelorism, strabismus, and in general, anomalies of the feet but not the hands. The characteristic anomalies of the

feet include medial deviation of the big toes and partial syndactyly of the first web space (Stankovic et al., 1994). Pfeiffer syndrome has three forms. There is a relatively benign form, known as the type I, which consists of an acrocephalic skull due to bicoronal synostoses. Affected patients have broad thumbs and great toes and soft tissue syndactyly. Like many of the other syndromes associated with craniosynostosis, affected patients have hypotelorism, maxillary hypoplasia, low-set ears, and normal intelligence (Hill and Grzybeck, 1994). Two other subgroups of patients with Pfeiffer syndrome had extreme proctosis and hydrocephalus. These patients have a uniformly poor outcome and are distinguished from each other as the type II form with the cloverleaf skull deformity and the type III form without the cloverleaf skull deformity (Moore et al., 1995). The kleeblattschädel, or cloverleaf, skull deformity is also associated with thanatophoric dysplasia (see Chapter 90). Of all patients with the cloverleaf skull deformity, 20% are due to Pfeiffer syndrome and 40% are due to thanatophoric dysplasia (Hill and Grzybeck, 1994). In Carpenter syndrome, affected patients have acrocephaly, soft-tissue syndactyly, radial/tibial polydactyly, congenital heart disease, and mental retardation. In Baller–Gerold syndrome, affected patients have craniosynostosis and radial/tibial upper-limb malformations (see Chapter 106) (Boudreaux et al., 1990).

Patients with the Apert syndrome, first described in 1906, have a shortened anterior–posterior diameter of the skull with a high, full forehead, flat occiput, flat facies, shallow orbits, hypotelorism, osseous and cutaneous syndactyly, and associated anomalies (Figures 10-3 and 10-4). Ten percent of patients have cardiovascular abnormalities, and approximately 10% have genitourinary anomalies, most commonly hydronephrosis and cryptorchidism (Cohen and Kreiborg, 1993b). One of the most characteristic findings of patients affected with Apert syndrome includes the complete digital fusion of the soft tissues of the digits 2, 3, and 4, which creates a mid-digital hand mass with a single common nail (see Figures 105-1 to 105-4).

ANTENATAL NATURAL HISTORY

The cranium develops as islands of bone within a fibrous membrane called the "ectomenix." The wedge-shaped proliferation of cells at the periphery is called the "osteogenic front." When osteogenic fronts come in close proximity to each other, a suture develops. The suture allows spatial separation of cranial bones during growth. The suture includes fibrous tissue defined radiographically by lucency and by proliferating osteogenic tissue on the periphery of the bone. The cranial sutures consist of five layers including two cambial and two periosteal layers separated by a middle vascular layer. The suture allows bone growth at sutural margins secondary to distant forces separating sutures (Van der Kolk and Beatty, 1994).

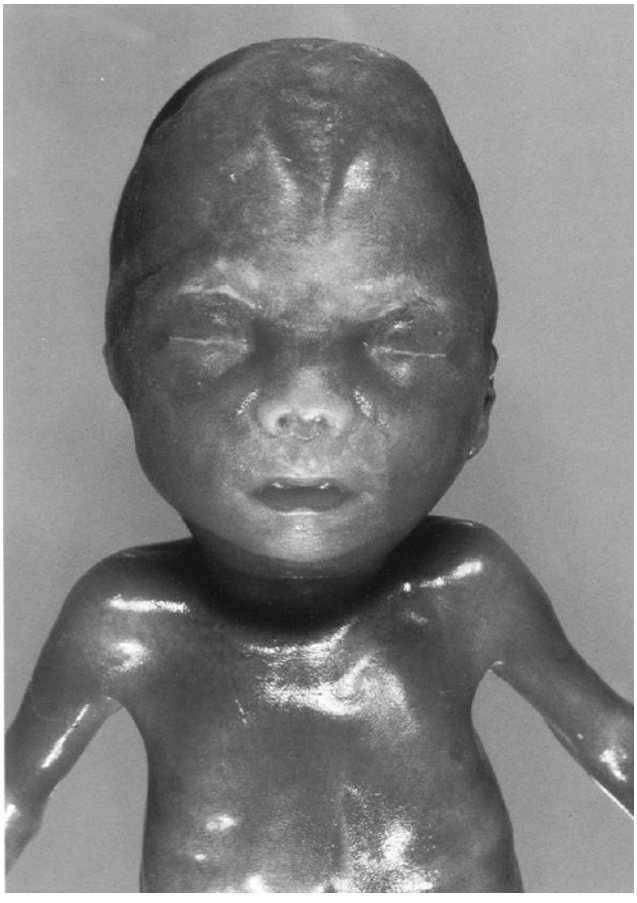

Figure 10-4 Fetus from Figure 10-3 after termination, demonstrating turricephaly and a wide open metopic suture. Prenatal sonograms and post-termination photographs of this fetus' extremities are shown in Figures 105-1 to 105-4.

The antenatal natural history for fetuses affected with craniosynostosis depends on whether the condition is isolated or syndromic. In general, fetuses with isolated craniosynostosis grow and develop normally. Fetuses with syndromic craniosynostosis are also generally normal, if not sometimes large for gestational age. There is no evidence that any of these syndromes are associated with increased lethality in utero.

MANAGEMENT OF PREGNANCY

One of the most important considerations in the management of pregnancy is to obtain a detailed family history. Both parents should be examined for the presence of facial asymmetry or for partial syndactyly of the fingers or toes. These findings are consistent with the mildest expression of some of the syndromic craniosynostoses. It is also important to remember that parents affected with one of the syndromic craniosynostoses may have had extensive plastic surgical repair and will therefore have a relatively normal appearance.

We recommend referral of the pregnant patient carrying a fetus with presumed craniosynostosis to a tertiary care

center capable of targeted sonographic examination of the fetus. It is particularly important to rule out the presence of associated hand and foot abnormalities as well as the more serious cardiovascular abnormalities that can be present in some of these syndromes. If there is a positive family history of isolated craniosynostosis, no further work-up is necessary. If, however, the family history is negative, we recommend prenatal karyotyping to rule out chromosomal abnormalities associated with craniosynostosis (Fryburg and Golden, 1993). Furthermore, in the setting of a negative family history, if additional sonographic findings suggest a syndromic diagnosis, it is important that the parents meet with a medical geneticist to discuss the implications of the potential diagnoses and perform molecular diagnosis. Many of the syndromic craniosynostoses are associated with normal intelligence; however, Apert syndrome is associated with a significant chance of developmental delay.

Fetal magnetic resonance imaging (MRI) has been used to confirm cranial abnormalities in a case of Apert syndrome (Boog et al., 1999). If the diagnosis is made before 24 weeks of gestation, parents can be given the option of terminating the pregnancy. If the diagnosis is made in the third trimester, we recommend that the delivery occur in a tertiary care center because of the possibility of associated feeding and breathing difficulties in the neonate. In addition, it will be important for a medical geneticist to examine the infant after birth to confirm the presumed clinical diagnosis and perform confirmatory molecular diagnosis testing. Fetuses with skull abnormalities suggesting a head circumference larger than normal may need to be delivered by cesarean section.

FETAL INTERVENTION

In utero correction of craniosynostosis is not recommended (Warren and Longaker, 2001).

TREATMENT OF THE NEWBORN

Infants with suspected craniosynostosis should have a detailed physical examination at birth. Some of the associated physical findings in the syndromic craniosynostosis are listed in Table 10-2. Anteroposterior and lateral views of the skull should be obtained. On radiography, the prematurely fused suture is either completely absent or represented by a line of increased density. In cases of coronal synostosis, the so-called harlequin appearance of the orbit is due to elevation of the ipsilateral sphenoid wing. Physical examination of the infant should be performed in consultation with a clinical geneticist to seek specific evidence of associated abnormalities. For example, 30% of infants affected with Apert syndrome have submucous cleft palate (Mulliken and Bruneteau, 1991). Furthermore, geneticists facilitate molecular testing to provide a definitive diagnosis. This is important even in the setting of isolated unilateral coronal craniosynostosis (Mulliken et al., 2004). In one study, mutations in *FGFR2,3* or *TWIST* were found in 8 of 47 patients studied with unilateral coronal craniosynostosis. Detection of a mutation was shown to influence the type of surgical repair (Mulliken et al., 2004).

Table 10-2

Differential Diagnosis of Craniosynostosis

Chromosome Abnormalities	
$5p^+$	
$7p^-$	
$13q^-$	
Single-Gene Disorders	**Pattern of Inheritance**
Apert syndrome	Autosomal dominant
Crouzon syndrome	Autosomal dominant
Pfeiffer syndrome	Autosomal dominant
Saethre–Chotzen syndrome	Autosomal dominant
Carpenter syndrome	Autosomal dominant
Jackson–Weiss syndrome	Autosomal dominant
Christian syndrome	Autosomal recessive
Summitt syndrome	Autosomal recessive
Baller–Gerold syndrome	Autosomal recessive
Gorlin–Chaudhry-Moss syndrome	Autosomal recessive
Teratogen	
Aminopterin	

For patients with suspected syndromic craniosynostosis, computed tomographic (CT) and MRI examinations are recommended to check for brain parenchymal abnormalities and for the presence of hydrocephalus.

Treatment of the affected newborn includes an assessment of four main functional areas: breathing, feeding, vision, and complications of increased intracranial pressure. In infants affected with syndromic craniosynostosis, the maxillary hypoplasia responsible for midface abnormalities reduces nasal and postnasal volume (Thompson et al., 1994). Foreshortening of the skull base, palatal arching, and choanal stenosis further compromise the upper airway. The hindbrain contents can herniate through the foramen magnum. Pediatricians should note the affected infant's respiratory rate and work of breathing, monitor oxygen saturation, and consider nasal stents or nasal prongs, or even tracheostomy to prevent airway obstruction. The role of continuous positive airway pressure (CPAP) is being investigated for affected infants. MRI of the trachea can also be considered.

The anatomic abnormalities that affect breathing also can affect feeding. Infants should be evaluated for the presence of cleft palate. Oropharyngeal coordination during sucking

and swallowing can be a major problem. A careful assessment should be made of feeding capabilities; feeding by gastrostomy tube can be considered.

One third of children with craniosynostosis have increased intracranial pressure. This is especially a problem in children who have multiple suture synostosis or syndromic synostosis (Thompson et al., 1994). Because intelligence quotient (IQ) and development can be affected, some authors recommend measurement of the intracranial pressure (Thompson et al., 1994). This helps to plan the timing of the surgical repair. Intracranial pressure can be measured by insertion of a subdural pressure transducer with pressure recordings made over a 24-hour period.

In patients with syndromic craniosynostosis who have proptosis, the globes are predisposed to infection, corneal ulceration, and recurrent prolapse of the orbital contacts. Excessive drying of the eyes may necessitate the use of artificial tears. Patients with severe proptosis are generally treated surgically.

SURGICAL TREATMENT

The primary objective of surgery is to allow adequate brain growth within the first 12 months of life. The secondary objective is to improve the patient's appearance. The optimal timing for surgical treatment of craniosynostosis is under debate. If evidence exists for symptomatic increased intracranial pressure (such as bulging fontanelles, or progressive optic atrophy), most surgeons would intervene as soon as possible (Warren and Longaker, 2001). In general, surgical repair consists of three phases: (1) suture release, cranial vault decompression, and upper orbital advancement at ages 6 to 12 months; (2) craniofacial surgery to correct midface abnormalities at ages 6 to 12 years; and (3) orthognathic surgery at ages 14 to 18 years (Warren and Longaker, 2001).

For patients who have isolated (simple) craniosynostosis, a single definitive operation performed during the first year of life produces excellent cosmetic results in 93% of affected patients (Whitaker et al., 1987; Thompson et al., 1994). For patients with scaphocephaly, a strip craniectomy is performed with a wide margin of excision. For patients with plagiocephaly and trigonocephaly, the frontal bones are removed and supraorbital ridges are adjusted via a bifrontal craniotomy (Thompson et al., 1994). Complications of surgery include bony infection, meningitis, aspiration pneumonia, and postoperative development of encephalocele (Whitaker et al., 1987).

For patients affected with syndromic craniosynostoses, a multidisciplinary assessment is recommended. The identification and control of elevated intracranial pressure is central to the planning of surgery. Most surgeons recommend an initial cranial vault expansion, followed by midface advancement to reduce maxillary hypoplasia. For patients affected with Apert syndrome, the surgery is typically staged. However, in Apert syndrome, only the coronal sutures are fused from the base upward; the sphenozygomatic, sphenotemporal, lambdoidal, and occipital mastoid sutures are all radiologically patent at birth. For individuals affected with Apert syndrome, the coronal sutures are released initially and frontal bone advancement occurs at 3 to 6 months of age (Mulliken and Bruneteau, 1991). The purpose of this initial surgery is to decompress the intracranial space, to protect proptotic globes, and to perform the initial construction of a normal-appearing supraorbital and frontal configuration. It is important for prospective parents to recognize that the syndromic craniosynostoses are more complicated than the isolated craniosynostoses. For most of the syndromes, initial decompression surgery is followed by plastic surgery in adolescence.

LONG-TERM OUTCOME

The long-term outcome depends on whether the craniosynostosis was simple or complex. In one study of 56 children with craniosynostosis, Noetzel et al. (1985) studied 27 patients with simple craniosynostosis. None of these patients had hydrocephalus on CT scan. Seventeen of 27 patients with simple craniosynostosis had average intelligence. An additional 6 had intelligence in the low average range, and 1 was developmentally delayed. This individual also had a history of perinatal depression. These authors noted that hydrocephalus occurred more frequently in complex craniosynostosis, specifically in affected patients with Pfeiffer and Crouzon syndromes. Of the 25 patients in the study who had complex or syndromic craniosynostosis, 19 had normal intelligence.

For most of the conditions associated with craniosynostosis, long-bone growth and pubertal development occur normally (Cohen and Kreiborg, 1993a). An additional complication of the complex craniosynostosis syndromes includes middle-ear infections (Kaplan et al., 1991). An unusual long-term complication of Apert syndrome is the presence of severe acne, which extends down to the forearm (Kaplan et al., 1991). This localized acne is now known to be due to a mutation in the fibroblast growth factor receptor 2 (*FGFR2*) gene (Munro and Wilkie, 1998). Patients with Apert syndrome also have excessive sweating.

GENETICS AND RECURRENCE RISK

All fetuses suspected of having craniosynostosis should have a detailed family history taken by a trained geneticist. Of 154 patients studied at John Hopkins Hospital, only 2.5% with isolated synostosis had a positive family history. In contrast, in patients affected with one of the syndromic craniosynostosis conditions, 50% had a positive family history (Van der Kolk and Beatty, 1994).

The first syndrome associated with craniosynostosis to be identified at the molecular level was a relatively rare form

of craniosynostosis known as the "Boston type." This condition is characterized by high penetrance and variable expression. Affected patients have a variety of phenotypes, including frontal orbital recession to pansynostosis to a cloverleaf skull deformity (Warman et al., 1993). Later that year Jabs et al. demonstrated that this condition was due to a substitution of histidine for a proline in the *MSX2* homeobox, which created a gain-of-function mutation. Overexpression of *MSX2* prevented osteoblast differentiation and mineralization of the extracellular matrix (Jabs et al., 1993).

The fibroblast growth factor receptor types 1, 2, and 3 genes are all involved in the molecular etiology of many of the conditions that cause craniosynostosis, specifically Apert, Crouzon, Jackson–Weiss, Pfeiffer, Muenke, and Beare–Stevenson syndromes (Li et al., 1994; Jabs et al., 1994; Gorry et al., 1995; Rutland et al., 1995; Wilkie, 2005). FGFRs are signal-transduction molecules that cross the cell membrane. All FGFRs share a similar structure in their molecular sequence, which consists of three extracellular immunoglobulin-like domains (IgI, IgII, and IgIII), a single-pass transmembrane segment, and a split tyrosine kinase domain (TK1/TK2) (Kan et al., 2002).

FGFR2 encodes a cell membrane receptor protein. Mutations in a single exon (IIIc) have been associated with three different phenotypes. The more severe phenotype associated with Apert syndrome has been mapped to exon IIIu. The mutation spectrum of Apert syndrome is suprisingly narrow. In a study of 118 unrelated patients with Apert syndrome, all had one of two specific cytosine-to-guanine transversions in the *FGFR2* gene on chromosome 10. Furthermore, in every case the mutation arose from the father (Moloney et al., 1996). The mutational spectrum of *FGFR2* is relatively narrow, with distinct mutations occurring in a limited number of exons (Kan et al., 2002). In a prospective study of 259 patients with craniosynostosis, the IgIIIa/IIIc region of the gene was shown to be a genuine mutation hotspot (Kan et al., 2002). Investigators have also shown that Pfeiffer syndrome is genetically heterogenous. It is caused by mutations in two different genes, the *FGFR1* gene, located on the short arm of chromosome 8, and *FGFR2* gene located on the long arm of chromosome 10 (Muenke et al., 1994; Schell et al., 1995). Muenke coronal craniosynostosis and a specific subtype of Crouzon syndrome with acanthosis nigricans are both caused by mutations in *FGFR3* (Vajo et al., 2000). In newly occurring cases in families, *FGFR3* mutations exclusively occur on the paternal copy of chromosome 4 and are associated with advanced paternal age (Rannan-Eliya et al., 2004).

The gene for Saethre–Chotzen syndrome has been mapped to 7p21 (Rose et al., 1994; van Herwerden et al., 1994). Saethre–Chotzen syndrome is caused by mutations in *TWIST*, a basic helix-loop-helix transcription factor (Howard et al., 1997). Drosophila embryos that lack the *TWIST* protein have a "twisted" appearance. Haploinsufficiency for this gene is the pathogenetic mechanism for this condition (Johnson et al., 1998). More than 35 mutations in *TWIST* have been described in individuals with Saethre–Chotzen syndrome (Paznekas et al., 1998). *TWIST* mutations are also the underlying basis for Baller–Gerold syndrome, which manifests as craniosynostosis and radial aplasia.

The known genes identified in the syndromic craniosynostoses are listed in Table 10-3. A summary of the

Table 10-3

Genes Involved in the Syndromic Craniosynostoses

Gene	Syndrome	Mode of Inheritance	Chromosomal Location
FGFR1	Pfeiffer (mild)	AD	8p11.2
FGFR2	Apert	AD	10q26
	Beare–Stevenson	AD	10q26
	Crouzon	AD	10q26
	Jackson–Weiss	AD	10q26
	Pfeiffer (severe)	AD	10q26
FGFR3	Muenke coronal craniosynostosis	AD	4p16.3
	Crouzon with acanthosis nigricans	AD	4p16.3
MSX2	Boston-type craniosynostosis	AD	5q34-q35
TWIST	Saethre–Chotzen	AD	7p21
	Baller–Gerold	AD	7p21

AD = autosomal dominant.

Table 10-4

Molecular Basis of Syndromic Craniosynostosis

Condition	Gene	Amino Acid Substitution
Craniosynostosis, Boston type	*MSX2*	Pro7His
Greig cephalopolysyndactyly	*GLI3*	—
Saethre–Chotzen syndrome	*TWIST*	Many
Crouzon syndrome	*FGFR2* Exon 9(B)	Tyr328Cys Gly338Arg Tyr340His Cys342Ser Cys342Arg Cys342Tyr Cys342Trp Ala344Ala Ala344Gly Ser347Cys Ser354Cys
	Exon 7(U)	Cys278Phe Deletion His, lle, Glu 287-289 Gln289Pro Trp290Arg
Pfeiffer syndrome	*FGFR1* Exon 5 *FGFR2* Exon 9(B)	Pro252Arg Cys342Arg Cys342Tyr Thr341Pro Asp321Ala Acceptor splice site
Jackson–Weiss syndrome	*FGFR2* Exon 9(B)	Ala344Gly Others?
Apert syndrome	*FGFR2* Exon 7(u)	Ser252Trp Pro253Arg Others?
Thanatophoric dysplasia, type II	*FGFR3*	Lys650Glu

molecular mutations discovered to date in the craniosynostosis syndromes is given in Table 10-4.

Adult individuals affected with one of the craniosynostosis syndromes should have DNA analysis to determine their specific mutation prior to contemplating pregnancy. If the underlying mutation responsible for their disorder is identified, prenatal diagnosis is available for them on fetal tissue obtained by chorionic villus sampling (CVS) or amniocentesis. The advantage of DNA testing is that the diagnosis is available earlier in gestation than by sonographic examination and it is more definitive. Adult individuals affected with one of the syndromic craniosynostoses will have a 25% or 50% risk of recurrence, depending on the specific syndrome. In theory, unaffected individuals with a prior affected child do not have an increased incidence of recurrence above the underlying background risk, although gonadal mosaicism is a small possibility. For patients with a negative family history, prenatal sonographic diagnosis in subsequent pregnancies is warranted to provide reassurance.

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11 CHAPTER Dandy–Walker Malformation and Variants

Key Points

- Dandy–Walker malformation refers to the combination of hypoplasia of the cerebellar vermis, cystic dilation of the fourth ventricle communicating with the cisterna magna, and increase in size of the posterior fossa.
- Related conditions include Dandy–Walker variant (varying hypoplasia of the inferior vermis without enlargement of fourth ventricle or cisterna magna), mega cisterna magna (enlarged cisterna magna in the setting of normal vermis), and Blake's pouch cyst (extension of the fourth ventricle into the cisterna magna, represented by septae within the cisterna magna).
- Some authors feel that there is no role in differentiating Dandy–Walker malformation and variant, as both can be associated with CNS and non-CNS malformations, aneuploidy, and adverse neurological outcome.
- False-positive diagnoses of Dandy–Walker malformation are possible, especially if noted before 18 weeks, or if the abnormality is confined to the cerebellar vermis alone.
- Following diagnosis, a detailed search for other CNS and non-CNS malformations is required, including prenatal MRI, and karyotype analysis.
- Other than multidisciplinary counseling, no other alterations to standard obstetric care are indicated.

CONDITION

The Dandy–Walker malformation is a nonspecific congenital brain malformation that results from a number of diverse causes. There are two principal features of the Dandy–Walker malformation: aplasia or hypoplasia of the cerebellar vermis and posterior fossa cysts that represent cystic dilatation of the fourth ventricle (Nyberg et al., 1988).

The first case of Dandy–Walker malformation was reported in 1887 (Murray et al., 1985). In 1914, Blackfan and Dandy described a hindbrain abnormality in a patient with cystic dilatation of the fourth ventricle, hypoplasia of the cerebellar vermis, separation of the cerebellar hemispheres, and absence of the lateral and median apertures of the fourth ventricle (cited in Chang et al., 1994). The term *Dandy–Walker malformation* was first used in 1954, combining case reports

of Blackfan and Dandy, and a subsequent report of Taggart and Walker (Chen and Chu, 1994).

The Dandy–Walker malformation originates before the 6th or 7th week of embryonic development (Russ et al., 1989). The malformation may occur in single-gene disorders, in chromosomal abnormalities, in environmentally induced malformation syndromes, or in conjunction with other multifactorial anomalies (Cornford and Twining, 1992).

The full Dandy–Walker malformation consists of complete vermian agenesis, cystic dilatation of the fourth ventricle that communicates with an enlarged cisterna magna, and an enlarged posterior cranial fossa. While obstructive hydrocephalus is nearly always an associated finding postnatally, it is usually not present prenatally (Niesen, 2002). It is unclear if such hydrocephalus is due to failure of the foramina of Lushka and Magendie to open, or to some other embryological disruption.

The full Dandy–Walker malformation is sometimes distinguished from the Dandy–Walker variant and mega cisterna magna (Chen and Chu, 1994). The Dandy–Walker variant consists of variable hypoplasia of the cerebellar vermis, without enlargement of the posterior fossa. There is usually a communication between the fourth ventricle and the cisterna magna. Ventricular dilatation may or may not be present and the cerebellar hemispheres are generally within normal limits (Estroff et al., 1992; Bromley et al., 1994). In mega cisterna magna (greater than 10 mm in anteroposterior dimension), an enlarged cisterna magna is present with a normal cerebellar vermis and fourth ventricle (Estroff et al., 1992). While many authors have tried to distinguish between Dandy–Walker malformation and its variant to better delineate the expected prognosis for the affected fetus, it is unclear how useful this is in clinical practice. In one series of 50 cases of Dandy–Walker malformation and 49 cases of Dandy–Walker variant, the incidence of additional CNS and non-CNS anomalies, and the incidence of karyotypic abnormalities, were similar in both groups (Ecker et al., 2000). Some authors feel that the term Dandy–Walker variant is imprecise and should not be used, and the preferred descriptive term "cerebellar hypoplasia" be used instead (Niesen, 2002). Others consider Dandy–Walker variant to be little more than a variant of normal (Patel and Barkovich, 2002).

A further normal anatomic entity, referred to as Blake's pouch cyst, is formed from the normal dorsal expansion of the fourth ventricle into the cisterna magna, and is detected prenatally by transverse lines, or septa, within the cisterna magna behind the cerebellar vermis (Robinson and Goldstein, 2006). This finding may be associated with development of symptoms such as headache and recurrent loss of consciousness (Calabro et al., 2000).

INCIDENCE

Dandy–Walker malformation occurs in at least 1 in 5000 liveborn infants (Parisi and Dobyns, 2003). In a series of postnatally ascertained Dandy–Walker malformation, it occurred in 12% of cases of congenital hydrocephalus and 2% to 4% of cases of childhood-onset hydrocephalus (Murray et al., 1985; Chen and Chu, 1994).

SONOGRAPHIC FINDINGS

A major consideration in the diagnosis of Dandy–Walker malformation is gestational age. Although Dandy–Walker malformation has been diagnosed in the first trimester (Achiron and Achiron, 1991; Gembruch et al., 1995; Nizard et al., 2005), a false-positive diagnosis can be made at gestational ages of less than 18 weeks. Bromley et al. (1994) prospectively evaluated 897 fetuses between 13 and 21 weeks of gestation to determine the normal development of the fetal cerebellum. A total of 147 fetuses were shown to have an open vermis at the time of initial scanning, of which 56% were open at 14 weeks of gestation, 23% were open at 15 weeks of gestation, and 6% remained open at 17 weeks of gestation. After 17.5 weeks of gestation, all fetuses were noted to have a closed vermis. These authors concluded that prenatal diagnosis of cerebellar malformations, in particular subtle findings such as the Dandy–Walker variant, should not be made at less than 18 weeks' gestation because development of the cerebellar vermis may be incomplete. True Dandy–Walker malformations are usually visible earlier in gestation, because the cerebellar hemispheres are hypoplastic and laterally displaced, and in addition, a cyst can be visualized (Figure 11-1).

The sonographic features of the Dandy–Walker malformation include a central cyst communicating with the fourth ventricle, agenesis or hypoplasia of the cerebellar vermis, and splaying of the cerebellar hemispheres with anterolateral displacement against the tentorium, thereby enlarging the posterior fossa (Russ et al., 1989). In a study of 15 prenatally

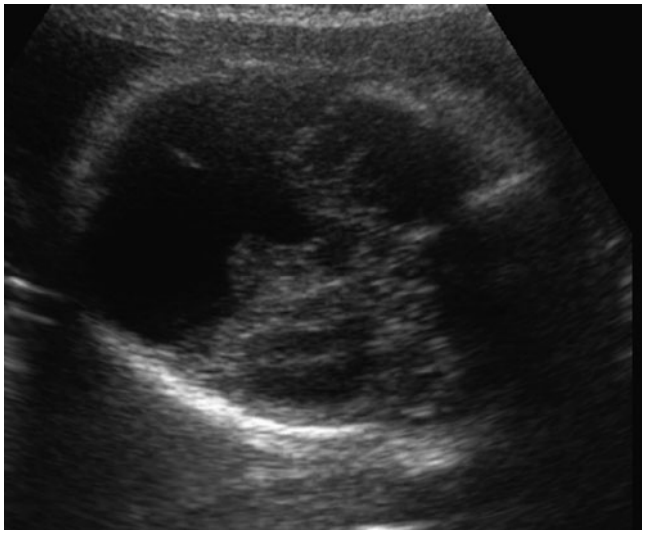

Figure 11-1 Transaxial sonogram of a fetal head demonstrating a posterior fossa cyst with cleft of the cerebellar vermis.

diagnosed cases of Dandy–Walker malformation, the anteroposterior diameter of the posterior fossa cyst was between 7 and 45 mm, with most being >10 mm (Russ et al., 1989). Macrocephaly was seen in 3 of 15 cases (20%), and there were additional brain anomalies in 68% of cases. Agenesis of the corpus callosum was seen in 7% to 17% of cases. In this study, extracranial anomalies were present in 60% of fetuses studied, including involvement of the cardiac, genitourinary, gastrointestinal, and skeletal systems. Of the 12 fetuses who had karyotyping, one-third were abnormal. Similar findings were noted by Nyberg et al. (1988), who reviewed seven proven cases of prenatally diagnosed Dandy–Walker malformation. Of the seven patients, five had hydrocephalus, four had multiple malformations, and two of these had abnormal karyotypes. These authors concluded that the presence of a Dandy–Walker malformation should prompt a careful search for concurrent abnormalities and consideration of a karyotype. In another study of 78 cases of prenatally diagnosed Dandy–Walker malformation, almost 20% had an associated karyotypic abnormality (Has et al., 2004).

Diagnostic criteria for Dandy–Walker variant are quite unclear, with some suggesting that this term should no longer be used as it does not appear to be predictive of outcome (Niesen, 2002; Patel and Barkovich, 2002). The sonographic criteria for the Dandy–Walker variant include partial or complete absence of the cerebellar vermis (Figure 11-2), with near normal-sized cerebellar hemispheres. The sonographic continuity between the fourth ventricle and the cisterna magna gives the appearance of a cleft (Estroff et al., 1992). In one study of 17 cases of Dandy–Walker variant, 4 fetuses also had ventriculomegaly and 3 had agenesis of the corpus callosum (Estroff et al., 1992). Almost half of the affected fetuses had other non-CNS abnormalities, including congenital heart disease, gastrointestinal malformations, renal malformations, and intrahepatic calcifications. Additionally, the presence of the Dandy–Walker variant was associated with a high incidence (29%) of abnormal karyotype (Estroff et al., 1992). In contrast, a recent study of 19 cases of Dandy–Walker variant, diagnosed strictly as isolated inferior vermian hypoplasia by prenatal MRI, demonstrated near normal outcome (Limperopoulos et al., 2006). This would underscore the importance of using strict prenatal diagnostic criteria, and perhaps using the term isolated inferior vermian hypoplasia for the select cases previously referred to as Dandy–Walker variant.

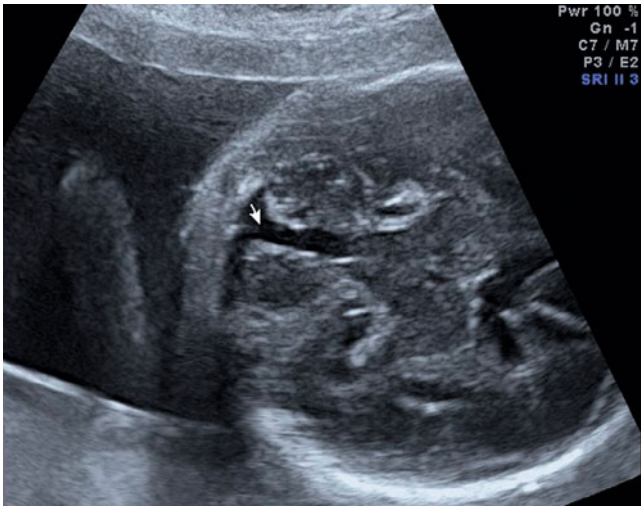

Figure 11-2 Transaxial sonogram demonstrating cleft of the cerebellar vermis and splaying of the cerebellar hemispheres.

The appearance of the cisterna magna has taken on increasing importance over recent years (Pretorius et al., 1992). The effacement of the cisterna magna gives the "banana sign" of the cerebellum seen in myelomeningocele (see Chapter 19 and Figure 19-2). A small cisterna magna implies an associated neural tube defect and a Chiari II malformation. In contrast, however, an enlarged cisterna magna can be associated with a Dandy–Walker cyst, cerebellar hypoplasia, and communicating hydrocephalus (Pretorius et al., 1992). Nyberg et al. (1991) studied 33 fetuses with the sonographic appearance of an enlarged cisterna magna. Of these 33 fetuses, 18 (55%) had underlying chromosomal abnormalities. Interestingly, the absence of hydrocephalus and milder enlargement correlated more strongly with the presence of an underlying chromosomal abnormality. The negative correlation between ventriculomegaly and chromosomal abnormality was also seen in another study (Chang et al., 1994). These authors tried to distinguish the prognosis based on the sonographic appearance of the fetal vermis. They reviewed sonographic findings in 65 fetuses with Dandy–Walker malformation. Of these, 37 had inferior vermian agenesis, or the milder form of the disorder, and 28 had complete vermian agenesis. Chromosomal abnormalities were seen in 23 of the 51 fetuses who were karyotyped (45%). Chromosomal abnormalities were less prevalent among fetuses with ventriculomegaly. Extracranial abnormalities were seen in 66% of fetuses with inferior vermian agenesis (Chang et al., 1994). In another series, chromosomal abnormalities were seen in 36% and 46% of cases of Dandy–Walker variant and Dandy–Walker malformation, respectively (Ecker et al., 2000).

DIFFERENTIAL DIAGNOSIS

Major considerations in the differential diagnosis include distinguishing between Dandy–Walker malformation, Dandy–Walker variant, enlarged cisterna magna, and Blake's pouch cyst, as well as the dorsal cyst seen in holoprosencephaly, and arachnoid cysts (see Chapter 8). The normal anteroposterior depth of the cisterna magna does not exceed 10 mm. The pathognomonic finding in Dandy–Walker malformation is a defect in the vermis through which the cyst communicates with fourth ventricle. The true Dandy–Walker cyst appears as a triangular midline fluid collection with symmetric splaying of the cerebellar hemispheres (see Figure 11-1) (Russ et al., 1989). Neither arachnoid cysts nor enlarged cisterna magna

Table 11-1

Conditions Associated with Dandy–Walker Malformation

Mendelian disorders
Joubert–Boltshauser syndrome
Walker–Warburg syndrome
Coffin–Siris syndrome
Fraser cryptophthalmos syndrome
Meckel–Gruber syndrome
Aicardi syndrome
Smith–Lemli–Opitz syndrome
Chromosome abnormalities
Trisomy 9/mosaic trisomy 9
Triploidy
45,X
49,XXX
6p.24–25 deletion
Duplication 5p,8p,8q,17q
Trisomy 13
Trisomy 18
Teratogens
Rubella
Cytomegalovirus
Toxoplasmosis
Coumadin
Alcohol
Isotretinoin
Maternal diabetes

is associated with vermian defects or other cerebellar or cerebral abnormalities. Retrocerebellar arachnoid cysts compress but do not communicate with the fourth ventricle. In general, arachnoid cysts are asymmetrically positioned in the posterior fossa and tend to be rounded rather than triangular. If the Dandy–Walker cyst herniates through the foramen magnum or a defect in the occiput, this may be mistaken for a primary encephalocele (Lee et al., 2005).

The dorsal cyst associated with alobar or semilobar holoprosencephaly can sometimes be confused with the Dandy–Walker malformation. However, in holoprosencephaly, the cyst is supratentorial and communicates directly with the single ventricle seen in this condition. In addition, a hallmark of the diagnosis of holoprosencephaly is the presence of fused or partially fused thalami (see Chapter 14) (Nyberg et al., 1988).

A list of the common conditions associated with Dandy–Walker malformation is given in Table 11-1. Of note are two Mendelian (single-gene) disorders that are commonly associated with Dandy–Walker malformation. In Joubert–Boltshauser syndrome, vermian agenesis is one of the criteria needed for diagnosis. Joubert–Boltshauser syndrome, an autosomal recessive disorder, consists of familial vermian agenesis, episodic hyperpnea, developmental delay, hypotonia, and abnormal eye movements (Keogan et al., 1994). In addition, Dandy–Walker malformation is seen in 53% cases of Walker–Warburg syndrome (Vohra et al., 1993). The Walker–Warburg syndrome consists of lissencephaly with cerebellar malformations, retinal malformations, and congenital muscular dystrophy. The Dandy–Walker malformation is seen in most cases of trisomy 9 or mosaic trisomy 9 (Bureau et al., 1993; McDuffie, 1994; Chen et al., 2002). Dandy–Walker malformation is now also included as one of the CNS malformations that support the diagnosis of Meckel–Gruber syndrome (Summers and Donnenfeld, 1995). For an exhaustive list of genetic disorders associated with Dandy–Walker malformation, refer to Chitayat et al. (1994).

The differential diagnosis for apparent defects of the cerebellar vermis must also include normality. False-positive diagnoses of Dandy–Walker malformation have been reported. In one series of 14 cases of prenatally diagnosed cases of Dandy–Walker malformation, subsequent autopsy confirmed this diagnosis in only 6 (43%) cases (Carroll et al., 2000).

ANTENATAL NATURAL HISTORY

The natural history for Dandy–Walker malformation in utero is not known. It appears that progressive changes usually occur slowly (Russ et al., 1989). Some degree of enlargement of the posterior fossa cyst and worsening hydrocephalus can be observed in utero, however.

Gestational age at diagnosis is important for predicting immediate pregnancy outcomes. In a study by Ulm et al. (1997), a comparison was performed of associated structural and chromosomal abnormalities in 14 fetuses with Dandy–Walker malformation diagnosed before 21 weeks and 14 fetuses diagnosed after 21 weeks. They concluded that fetuses diagnosed earlier in gestation had a worse prognosis.

It appears that the immediate prognosis for Dandy–Walker malformation is influenced by the presence of associated abnormalities. Of the nine fetuses with Dandy–Walker malformation in one report, three had multiple significant CNS and non-CNS abnormalities (Keogan et al., 1994). Fetuses with an isolated vermian hypoplasia all did well. Similarly, Cowles et al. (1993) described the presence of multiple associated CNS malformations in the Dandy–Walker malformation, including agenesis of the corpus callosum and occasional occipital encephaloceles. In their patient population, they observed extracranial malformations, including cleft lip and cleft palate, cardiac malformations, and urinary tract abnormalities. In Nyberg's study of seven prenatally diagnosed cases of Dandy–Walker malformation, there was high perinatal mortality, with five of the seven patients dying in the perinatal period (Nyberg et al., 1988).

MANAGEMENT OF PREGNANCY

When a suspected diagnosis of fetal Dandy–Walker malformation exists, the prospective parents should be referred to a center capable of a detailed anatomic survey of the fetus. There is a high incidence of associated CNS and extra-CNS malformations in this condition. Importantly, it is the presence of the additional sonographically detected anomalies that appear to adversely affect survival and prognosis for the infant and child with Dandy–Walker malformation. Summarizing many studies, the risk of associated intracranial anomalies appears to range from 25% to 70%, and the risk of additional intracranial anomalies appears to range from 20% to 60% (Chen and Chu, 1994). Between 20% and 50% of cases of Dandy–Walker malformation will have karyotypic abnormalities (Ecker et al., 2000; Has et al., 2004). Diagnosis of fetal karyotype is recommended, given the association between Dandy–Walker malformation and trisomies 9, 13, or 18, because of the confirmed association between enlarged cisterna magna and trisomy 18, and also because of the wide variety of chromosome abnormalities that have been reported with this brain malformation (Imataka et al., 2007).

There is an increased incidence of both mental retardation and perinatal mortality for fetuses and children with this condition. Therefore, the option of pregnancy termination should be made available to parents, if desired. In most cases, progressive increase in the size of the posterior fossa cyst, ventricular size, and cisterna magna dimensions occurs slowly. Rarely however, severe or rapidly increasing ventriculomegaly can necessitate aggressive obstetric intervention, possibly including elective preterm delivery (Russ et al., 1989). It is important to recognize that when Dandy–Walker malformation or variant occurs as an isolated finding, the prognosis is variable, and up to 50% of fetuses with this condition have been reported with a normal outcome. When the disorder is associated with an underlying Mendelian condition, such as one of those listed in Table 11-1, the prognosis is then distated by that specific disorder.

There are no specific indications for cesarean delivery in this condition. Similarly, delivery can occur in a community hospital; however, the prospective parents should be advised that the child will need subspecialty evaluation after birth.

FETAL INTERVENTION

There is no fetal intervention for Dandy–Walker malformation.

TREATMENT OF THE NEWBORN

The infant diagnosed prenatally with Dandy–Walker malformation or one of its variants should undergo a complete physical examination promptly at birth. The best imaging study for the posterior fossa is magnetic resonance imaging (MRI). We do not recommend obtaining a postnatal head ultrasound examination through the anterior fontanelle because of the high incidence of false-negative diagnoses. Parents should be counseled that hydrocephalus may not be present at birth, but will become apparent in 75% of survivors by 3 months of age (Estroff et al., 1992).

Both prenatal and postnatal consultation should be obtained with specialists in pediatric neurology, neurosurgery, and medical genetics. There is a high incidence of associated congenital anomalies, some of which may not be apparent on the antenatal scan. These are summarized in Table 11-2.

Interestingly, a strong association exists between the presence of large, aggressive facial hemangiomas and the Dandy–Walker malformation or similar posterior fossa abnormalities. In a postnatal study, seven of nine patients with unilateral facial hemangiomas had Dandy–Walker malformation (Reese et al., 1993). This has raised the question of a developmental-field abnormality as the cause of the Dandy–Walker malformation.

Table 11-2

Associated Abnormalities Seen in 148 Cases of Dandy–Walker Malformation

	Percent
Cranial	
Agenesis of corpus callosum	14.8
Abnormal gyral pattern	10.8
Occipital encephalocele	7.4
Aqueductal stenosis	3.3
Cardiac	
Ventriculoseptal defects	6.7
Patent ductus arteriosus	3.3
Atrial-septal defects	2.7
Pulmonary stenosis	2.0
Atrioventricular canal defect	2.0
Renal	
Obstructive uropathy	2.0
Polycystic kidneys	2.0
Abnormal uterus	2.0
Cryptorchidism	2.0
Face/hands	
Cleft lip/cleft palate	6.7
Dysmorphic face	5.4
Facial angioma	5.4
Syndactyly	2.7

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SURGICAL TREATMENT

Surgical treatment in the Dandy–Walker malformation consists mainly of placement of a ventriculoperitoneal shunt for cases of symptomatic hydrocephalus (Chen and Chu, 1994). More recent surgical practice has moved away from ventriculoperitoneal shunting to a choice of either surgical fenestration of the posterior fossa cyst membrane or ventriculocystoperitoneal shunting (Kumar et al., 2001). In one series of 42 cases of Dandy–Walker malformation managed surgically, only 2 patients required revision of a ventriculocystoperitoneal shunt or a cyst fenestration procedure (Kumar et al., 2001).

LONG-TERM OUTCOME

Review of the pediatric neurosurgical literature indicates a mortality rate of between 12% and 50%. However, in general, the postnatal diagnosis of children with Dandy–Walker malformation has a better prognosis than the prenatal diagnosis of fetuses with the same condition. In a study of 65 prenatally diagnosed cases of Dandy–Walker malformation, 22 resulted in liveborn infants (Chang et al., 1994). A total of nine (41%) of these died, seven of which deaths occurred during the first month of life and the remaining two within the first year. In another study, Russ et al. (1989) reviewed the outcome for 15 cases of prenatally diagnosed Dandy–Walker malformation. Excluding the elective terminations, there was an overall mortality of 55% in this group (6 of 11 liveborn infants). However, the coexisting structural and chromosomal abnormalities contributed to 83% of the postnatal deaths. In the six liveborn infants who died, three deaths occurred within 5 days of delivery, and three between 5 and 24 months of age. Overall, therefore there appears to be a liveborn mortality rate of between 30% and 70% when detected prenatally, but only between 10% and 25% when the diagnosis is made postnatally.

With regard to longer term morbidity, in a study of 26 patients with strictly diagnosed isolated Dandy–Walker malformation confirmed by MRI, the long-term prognosis was dependent on the state of the cerebellar vermis (Klein et al., 2003). In 21 patients with a vermis that retained its two fissures and three lobes, there were no additional brain malformations and all but two were functionally normal. However, in the five cases in which the vermis was highly dysplastic, all were severely mentally retarded. In Estroff's review of patients with the Dandy–Walker variant, of 11 survivors, 1 had trisomy 21 and another was severely handicapped (Estroff et al., 1992). Nine of the remaining 11 survivors were developing normally. However, six of these nine did not have any associated extracranial abnormalities. Reviewing the long-term prognosis for eight fetuses with the Dandy–Walker variant who had an isolated anomaly, six of eight (75%) were normal. One died and one was deaf and blind (Estroff et al., 1992). The functional outcome for survivors is variable, depending on the degree of disruption of the cerebellar vermis. An IQ of less than 80 has been documented in approxiamtely 50% of cases (Russ et al., 1989). It is important to realize that disruption of the cerebellum does not lead solely to motor and coordination dysfunction in survivors. Rather, it is now clear that the residual neurological impairment also includes developmental delay, including problems with language and social skills (Niesen, 2002). Even children with isolated inferior vermian hypoplasia (which has previously been referred to simply as Dandy–Walker variant) have overall developmental, functional, and behavioral profiles below the mean (Limperopoulos et al., 2006).

Thus, an appropriate summation of the available follow-up literature seems to indicate that prognosis is significantly better for fetuses with milder anomalies and if the Dandy–Walker malformation is isolated. The presence of additional abnormalities contributes significantly to an increased risk of mortality and developmental delay. However, the data on prognosis do not support the concept that Dandy–Walker variant has a completely normal outcome. This caveat underscores the limitations of trying to differentiate between Dandy–Walker malformation and variant (Ecker et al., 2000; Pilu et al., 2000).

GENETICS AND RECURRENCE RISK

The most important consideration in determining the recurrence risk for Dandy–Walker malformation is to determine whether the finding is associated with a Mendelian disorder, such as those listed in Table 11-1, or if a chromosomal abnormality is present. If chromosome studies have not been obtained antenatally, they should be obtained during the newborn period.

For isolated Dandy–Walker malformations, familial recurrences are infrequent but do occasionally occur (Obwegeser et al., 1994; Bragg et al., 2006). Ulm et al. (1999) described a family in which the first child and subsequent dizygotic twins were all affected with isolated Dandy–Walker malformation.

In a review of the genetics of Dandy–Walker malformation, Murray et al. (1985) performed a retrospective study of 21 autopsy-proven cases of Dandy–Walker malformation, together with a literature review of an additional 92 subjects. These authors noted the increased frequency of association of Dandy–Walker malformation with congenital heart disease, cleft lip and cleft palate, and neural tube defects. Of the 113 cases studied, 7 had recognizable single-gene disorders, including two cases of Meckel–Gruber syndrome, and one case each of arthrogryposis type 2B, Walker–Warburg syndrome, Ruvalcaba syndrome, Cornelia–De Lange syndrome, and congenital rubella. Excluding the known single-gene diagnoses, of the 106 remaining cases, 22 had other associated major malformations. These authors pooled information available on 44 siblings of the 106 index patients

and 54 siblings of 26 patients with Dandy–Walker malformation associated with hydrocephalus. They documented 1 additional case in 98 siblings, thus giving a 1% risk of recurrence.

These authors concluded that the Dandy–Walker malformation is a nonspecific CNS abnormality that can occur in single-gene disorders and chromosomal abnormalities (Murray et al., 1985). It can be environmentally induced, may exist as an isolated malformation, or may exist in conjunction with other abnormalities. They suggested the following information for genetic counseling: (1) When Dandy–Walker malformation occurs as part of a Mendelian disorder, the recurrence risks are those of the specific disorder. (2) When Dandy–Walker malformation is associated with a chromosomal abnormality, the recurrence risks include those of maternal age for trisomy, and those of the family, depending on whether there is a familial risk for an unbalanced chromosomal abnormality. (3) If the Dandy–Walker malformation is associated with other multifactorial abnormalities, such as cleft lip and palate or congenital heart defects, there is an additional 5% recurrence risk for those abnormalities. (4) If the Dandy–Walker malformation was isolated, there is an empiric recurrence risk of between 1% and 5% (Murray et al., 1985).

If the presence of an unbalanced karyotype has been documented in the fetus or newborn, parental chromosomes should be studied prior to judging recurrence risks. Prenatal diagnosis is available in subsequent pregnancies through the use of targeted ultrasound examination, ideally delayed until 18 weeks' gestation so as to avoid false-positive diagnoses. However, it remains possible to diagnose the full Dandy–Walker malformation by prenatal ultrasonography as early as 12 to 14 weeks' gestation.

In general, DNA diagnosis is not available for individuals with isolated Dandy–Walker malformation. Recently, however, in a group of seven patients with Dandy–Walker malformation and de novo interstitial deletion of chromosome 3q, a critical region associated with this anomaly was identified (Grinberg et al., 2004). This region encompasses two linked zinc finger genes, *ZIC1* and *ZIC4*. Mice created with a targeted heterozygous deletion of these two genes have a phenotype that closely resembles Dandy–Walker malformation.

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12 CHAPTER Encephalocele

Key Points

- Encephalocele is a rare defect of the cranial vault, which may contain meninges only, or also neural tissue.
- Most cases in Caucasian populations are occipital in location, while Southeast Asian populations are more commonly frontal.
- Causes include maternal diabetes, rubella, hypervitaminosis-A, isolated neural tube defect, amniotic-band syndrome, aneuploidy such as trisomies 13 and 18, and genetic syndromes such as Meckel–Gruber.
- Differential diagnosis includes cystic hygroma, cervical teratoma or hemangioma, or epidermal scalp cysts, while false-positive diagnoses have been made by mistaking clumps of fetal hair in the third trimester.
- Natural history and prognosis depends on the presence of associated malformations and presence of neural tissue within the meningeal sac.
- Pregnancy management includes prenatal MRI to confirm absence of neural tissue within the sac, and possible elective cesarean delivery if prognosis appears favorable.

CONDITION

Encephalocele refers to the herniation of cranial contents through a defect in the skull. This term includes both encephaloceles, which contain meninges and brain, as well as meningoceles, which consist of meninges and cerebrospinal fluid. Empty meningoceles are not as common as encephaloceles. Encephaloceles are subdivided according to their location: occipital and frontal. This distinction is important, as each of the conditions has a different prognosis based on their location. In occipital encephaloceles, the defect lies between the lambda and foramen magnum (Simpson et al., 1984). These encephaloceles are considered part of the spectrum of

neural tube defects. Sincipital or frontal encephaloceles are situated between the bregma and anterior margin of the ethmoid bone. The majority of these encephaloceles extend into the root of the nose, and they are not considered a form of neural tube defect, but rather are likely secondary to an environmental exposure. Occipital encephaloceles are considerably more common than frontal encephaloceles in populations of European descent, whereas frontal encephaloceles are much more common in populations from Southeast Asia.

The cause of encephalocele is unknown, but occipital encephaloceles are thought to be caused by failure of closure of the rostral neural pore. The majority of encephaloceles occur in the midline; however, they may also result from disruption of fetal-skull formation, such as in the amnion rupture sequence (Chervenak et al., 1984). Encephaloceles occur between 25 and 50 days of gestation for anterior defects and up to 60 days for posterior defects (Brown and Sheridan-Pereira, 1992).

INCIDENCE

In a recent review from New Zealand, encephaloceles were seen in one in 13,000 births (Monteith et al., 2005). In an earlier U.S. study extending more than 17 years, Wiswell et al. (1990) documented 112 cases of encephalocele in 763,364 livebirths, or 0.15 per 1000 livebirths. Of these infants with encephaloceles, 40% had associated congenital anomalies. Encephalocele is more often associated with extra-CNS malformations than anencephaly or spina bifida (Kalien et al., 1998). In an Australian study, the incidence of encephalocele was shown to be 0.08 per 1000 total births (David and Proudman, 1989). In Australians of European descent, the occipital location for the encephalocele is more common, whereas in patients of Southeast Asian extraction, the frontal location is more common (Richards, 1992). The United Kingdom, with its generally higher rate of all neural tube defects, has a higher incidence of encephalocele—between 0.3 and 0.6 per 1000 livebirths (Fleming et al., 1991).

Encephaloceles are associated with maternal rubella, diabetes, genetic syndromes (such as Meckel–Gruber), and amniotic bands. They have been produced experimentally with X-irradiation and hypervitaminosis A. In the Western world, 75% of encephaloceles are located in the occipital region (Chervenak et al., 1984). The frontoethmoidal encephalocele is more prevalent in Malaysia, Thailand, Indonesia, Burma, and parts of Russia. In Burma, a high prevalence of encephalocele has been noted among rural and peasant rice farmers (David and Proudman, 1989). There is no relationship between encephalocele and parental age.

SONOGRAPHIC FINDINGS

The sonographic appearance of encephalocele is diverse, depending on its contents. Encephaloceles can appear as a purely cystic mass, a solid mass with a gyral pattern continuous with the cranium, or a combined cystic and solid mass (Graham et al., 1982; Winter et al., 1993). A calvarial defect is usually identified. In most European studies, the encephalocele is present in the occipital region 75% of the time, in the frontal/sincipital region 15% of the time, and at the vertex 5% of the time. An encephalocele that is observed in an asymmetric or atypical location may be related to the amniotic-band syndrome or limb–body wall complex (Graham et al., 1982; Winter et al., 1993). Encephaloceles have been noted to have a unique "cyst within a cyst" (Figures 12-1A and 12-1B) or "target sign" appearance when the encephalocele is viewed from the en face position (Goldstein et al., 1991; Adetiloye et al., 1993).

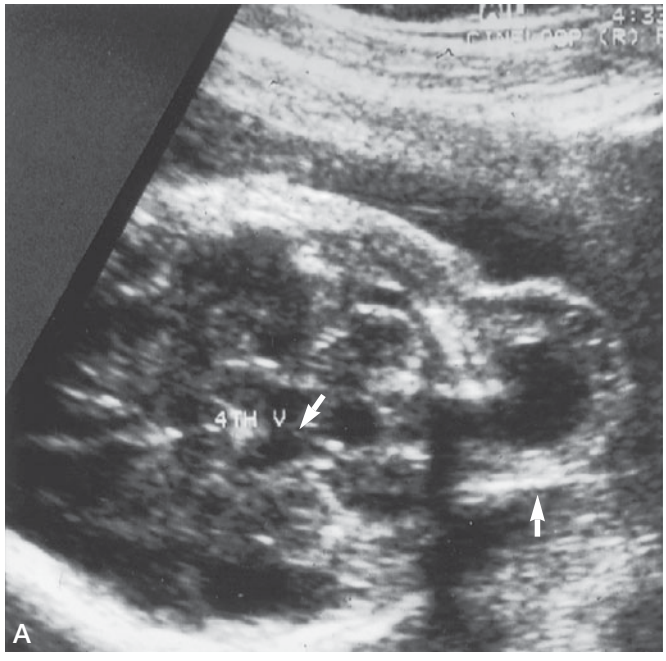
To diagnose an encephalocele sonographically, the following considerations should be taken into account:

- The mass should be seen attached to the fetal head or move with the fetal head.
- A bony defect should be revealed.
- Intracranial anatomic abnormalities should be detected, such as hydrocephalus.
- The spine should be examined to exclude associated spina bifida.
- The fetal kidneys should be examined, because of a high incidence of association with renal cystic disease (Meckel–Gruber syndrome).

In 7% to 15% of cases, neural tube defects are shown to be present in association with the encephalocele (Fleming et al., 1991). In addition, microcephaly is seen in 20% of cases. Other associated central nervous system (CNS) anomalies that may occur with encephalocele include agenesis of the corpus callosum, orofacial clefting, craniosynostosis, Dandy–Walker malformation, Arnold–Chiari malformation, hemifacial microsomia, Klippel–Feil anomaly, iniencephaly, and myelomeningocele (Cohen and Lemire, 1982).

In one study, Budorick et al. (1995) reviewed 26 cases of prenatally diagnosed encephalocele. Seventy-one percent of these cases were in the occipital location. Sixty-five percent of cases had associated major congenital anomalies. CNS features that were observed and helped with the diagnosis of encephalocele included visible skull defect (seen in 96% of cases), ventriculomegaly (23%), microcephaly (50%), beaked tectal plate (38%), and flattened occiput (38%).

In another study, Goldstein et al. (1991) reviewed the prenatal sonograms of encephaloceles in 15 fetuses. Of these, 13 were in the occipital location, 1 in the ethmoidal, and 1 frontoparietal. These authors could not accurately distinguish prenatally between meningocele and meningoencephalocele. They also noted an inward depression of the frontal bones (the lemon sign) in 33% of fetuses with encephalocele. Of the nine cases in which prenatal chromosome studies were performed, four (44%) were abnormal, including trisomy 13, trisomy 18, mosaic trisomy 20, and an unbalanced chromosome translocation. The outcome for the remaining 11 patients included 5 terminations of pregnancy, 2 stillbirths, and 4 neonatal deaths. Similarly, Wininger and Donnenfeld (1994) reviewed 15 cases of prenatally diagnosed encephalocele.



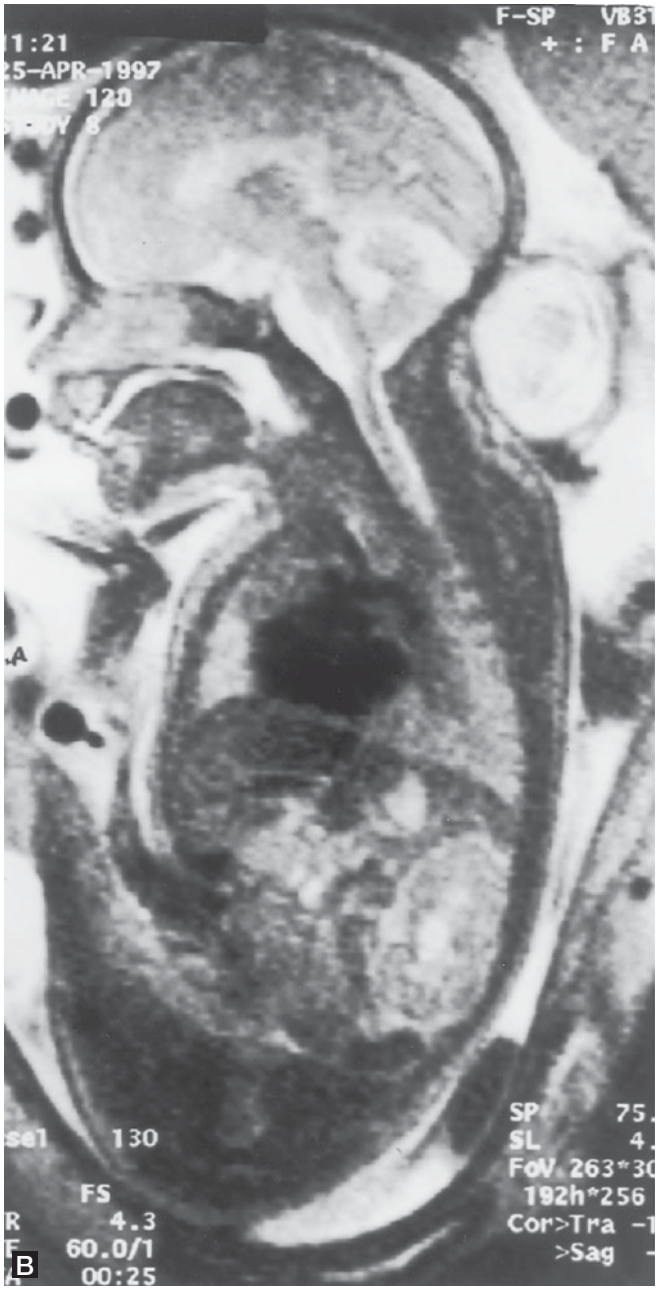


Figure 12-1 **A.** Transaxial sonogram demonstrating an occipital encephalocele with the appearance of a cyst within a cyst. The arrow indicates the location of the encephalocele. 4th v = the fourth ventricle. **B.** Sagittal half-Fourier single-shot turbo spin-echo sequence (HASTE) magnetic resonance image of the fetus with a posterior encephalocele shown in part (A). A small amount of brain tissue is seen within the sac. The remainder of the fetal brain appears normal except for the posterior aspect of the occipital lobe. (*Image courtesy of Dr. Deborah Levine.*)

These authors also demonstrated a high incidence of associated major anomalies (60% of cases). The mean gestational age at detection of these cases was 12 to 14 weeks. These authors identified three multifactorial disorders, two cases of chromosomal abnormalities, and two autosomal recessive syndromes.

DIFFERENTIAL DIAGNOSIS

Important considerations in the sonographic differential diagnosis of encephalocele include location of the extracranial mass (midline or lateral), contents of the mass (cystic or solid), and whether or not the anomaly is associated with an underlying cranial bony defect (Sherer et al., 1993). Encephaloceles are typically midline cystic structures that overlie or project through a defect in the calvarium. The diagnosis is helped by the identification of herniated brain tissue and associated hydrocephalus.

A major consideration in the differential diagnosis is cystic hygroma (Table 12-1). An occipital meningocele that contains only cerebrospinal fluid can be confused with a cystic hygroma. With cystic hygromas, however, the margins of the mass blend into the skin line, and a bony defect in the cranial vault should not be visible. Cystic hygromas frequently contain septations and there may be fewer CNS anomalies associated with cystic hygromas (see Chapters 31 and 32). In

Table 12-1

Differential Diagnosis Between Cystic Hygroma and Encephalocele

Sonographic Finding	Cystic Hygroma	Encephalocele
Bone defect in skull	Never	Always
Septae	Present and bilateral; often extend to neck	If present, only in midline; continuous with fetal brain
Contents of sac	Fluid only	Variable
Associated microcephaly	Rare	Common
Location	Posterolateral aspect of neck	Occipital, 70%; frontal, parietal, or nasofrontal, 30%

addition, other findings of hydrops, such as pleural effusions and ascites, are often found with cystic hygroma (Pearce et al., 1985; Goldstein et al., 1991). Encephaloceles can also be confused with cervical teratomas, which are solid or heterogeneous but have no demonstrable brain tissue. Hemangioma is an additional soft tissue mass that can be confused with encephalocele; they are heterogeneously echogenic, with no identifiable skull defects. They form an obtuse angle with the adjacent skull, as opposed to encephaloceles, which typically form an acute angle with the adjacent skull (Bronshtein et al., 1992; Winter et al., 1993). Sherer et al. (1993) described the case of a 27-week-old fetus with a right retroauricular mass thought to overlay a bony defect of the skull. This was initially diagnosed as an encephalocele, but it was later shown to be a subcutaneous hemangioma. Other considerations in the differential diagnosis include scalp edema (Winter et al., 1993), a clump of fetal hair (Noriega et al., 2001), epidermal scalp cyst (Shahabi and Busine, 1998), and branchial cleft cysts.

Once the encephalocele has been verified, a careful search must be made for associated anomalies. Encephaloceles are frequently associated with other anomalies, and the demonstration of such findings may help to make a syndromic diagnosis. A significant cause of encephaloceles is amniotic band or amniotic rupture (see Chapter 100). Encephaloceles due to amniotic bands tend to have irregular surfaces, and asymmetric placement.

A listing of the major syndromes of which encephalocele is a component is given in Table 12-2. The most common of these is Meckel–Gruber syndrome, an autosomal recessive condition that is characterized by the presence of an occipital encephalocele, polydactyly, polycystic kidneys, and multiple associated anomalies (Figures 12-2A and 12-2B). Meckel–Gruber syndrome should be suspected in fetuses with encephalocele and oligohydramnios, with four of five patients with oligohydramnios and encephalocele having this syndrome (Budorick et al., 1995). Encephalocele is found in association with several different chromosome abnormalities.

ANTENATAL NATURAL HISTORY

The presence of encephalocele is associated with an increased incidence of death in utero. An encephalocele is the predominant neural axis anomaly found in fetuses spontaneously aborted at less than 20 weeks' gestational age (Goldstein et al., 1991). The concept of antenatal evolution of encephalocele has also been documented. A report by Bronshtein and Zimmer (1991) documented by sonography the formation of a cephalocele in two stages. Initially, an occipital meningocele was detected by transvaginal scan at 13 weeks of gestation. By 19 weeks, brain tissue was visualized, and the diagnosis was changed to a meningoencephalocele, illustrating that the primary process was the formation of the meningocele, but that once an opening became present, brain tissue protruded into it at a later stage.

In the Budorick et al. (1995) study of 26 cases of prenatally diagnosed encephalocele, if more than 50% of the intracranial contents were exteriorized, postnatal survival was unlikely. In another study of 15 prenatally diagnosed cases, the long-term outcome was uniformly poor with only 3 of 14 fetuses with adequate follow-up being born alive (21%) (Goldstein et al., 1991). In a further review of 15 prenatally diagnosed encephaloceles, pregnancy outcome was also poor, with one fetus miscarrying at 23 weeks, and six terminations of pregnancy (Wininger and Donnenfeld, 1994). Of the eight liveborn infants, only five survived beyond the neonatal period, and all of the three for whom follow-up information was available had developmental delay.

Predictors of more favorable outcome in cases of prenatally diagnosed encephalocele include normal karyotype

Table 12-2

Syndromes in Which Encephalocele is a Major Component

Condition	Pattern of Inheritance	Associated Findings
Chemke syndrome	Autosomal recessive	Hydrocephalus, cerebellar dysgenesis, retinal dysplasia, corneal opacities, cataracts
Cryptophthalmos syndrome (Fraser)	Autosomal recessive	Skin of forehead covers one or both eyes; total/partial syndactyly of fingers or toes
Dyssegmental dwarfism	Autosomal recessive	Short tubular bones, bowing of extremities, vertebral anomalies, small thorax, cleft palate, micrognathia
Frontonasal dysplasia	Sporadic	Ocular hypertelorism, median cleft lip
Knobloch syndrome	Autosomal recessive	Retinal detachment, myopia, normal intelligence
Meckel–Gruber syndrome	Autosomal recessive	Polydactyly, polycystic kidneys, oligohydramnios, other CNS abnormalities
Amniotic band (rupture)	Sporadic	Limb amputations, facial clefts, thoracoabdominal wall defects, skull malformations
Roberts syndrome	Autosomal recessive	Short or absent limbs, facial cleft, hypertelorism, heart and kidney defects

and lack of associated CNS or other malformations. In such cases of isolated encephalocele prognosis may be favorable. In a series of 13 cases of isolated encephalocele, 6 cases in which neural tissue was present in the sac were terminated (Bannister et al., 2000). In the remaining seven cases with minimal or no neural tissue within the sac, one resulted in a stillbirth and the other six were liveborn with relatively normal outcome.

MANAGEMENT OF PREGNANCY

Fetuses in which encephalocele is suspected should be referred to a center capable of thorough anatomic study. Detailed sonography should be performed to verify the presence of the encephalocele and to search for associated anomalies. Because of the increased incidence of chromosomal abnormalities, a prenatal karyotype should be offered. Most encephaloceles are covered by skin, so typically there is no increase in the maternal serum α-fetoprotein level if second trimester biochemical screening is performed.

Once the encephalocele is diagnosed, further obstetrical management is dictated by the size of the defect, the gestational age at diagnosis, and the presence or absence of associated anomalies. A thorough discussion should be held with the prospective parents that describes the expected prognosis for the infant. Prognosis depends on

1. the presence and amount of brain in the herniated sac;
2. the presence or absence of hydrocephalus;
3. the presence or absence of microcephaly;
4. the presence or absence of other anomalies that suggest a syndromic diagnosis (Fleming et al., 1991).

Magnetic resonance imaging may help to better delineate fetal CNS anatomy (Figure 12-1B). Encephaloceles in the sincipital or frontal location have a better prognosis. This is probably because the defects are in general smaller, resulting in less herniation of neural tissue. Also, it appears that the loss of some areas of frontal cortex may produce fewer neurologic defects (Chervenak et al., 1984). Termination of pregnancy should be discussed with the parents. If parents want to continue the pregnancy, the opportunity to meet with a neurosurgeon, neonatologist, and medical geneticist should be provided.

The route of delivery is determined by fetal sonographic findings. If a large amount of neural tissue is observed in the sac, or if associated anomalies are present, minimizing maternal risk should be the primary consideration, and cesarean section probably has little role. Cesarean section may be considered when

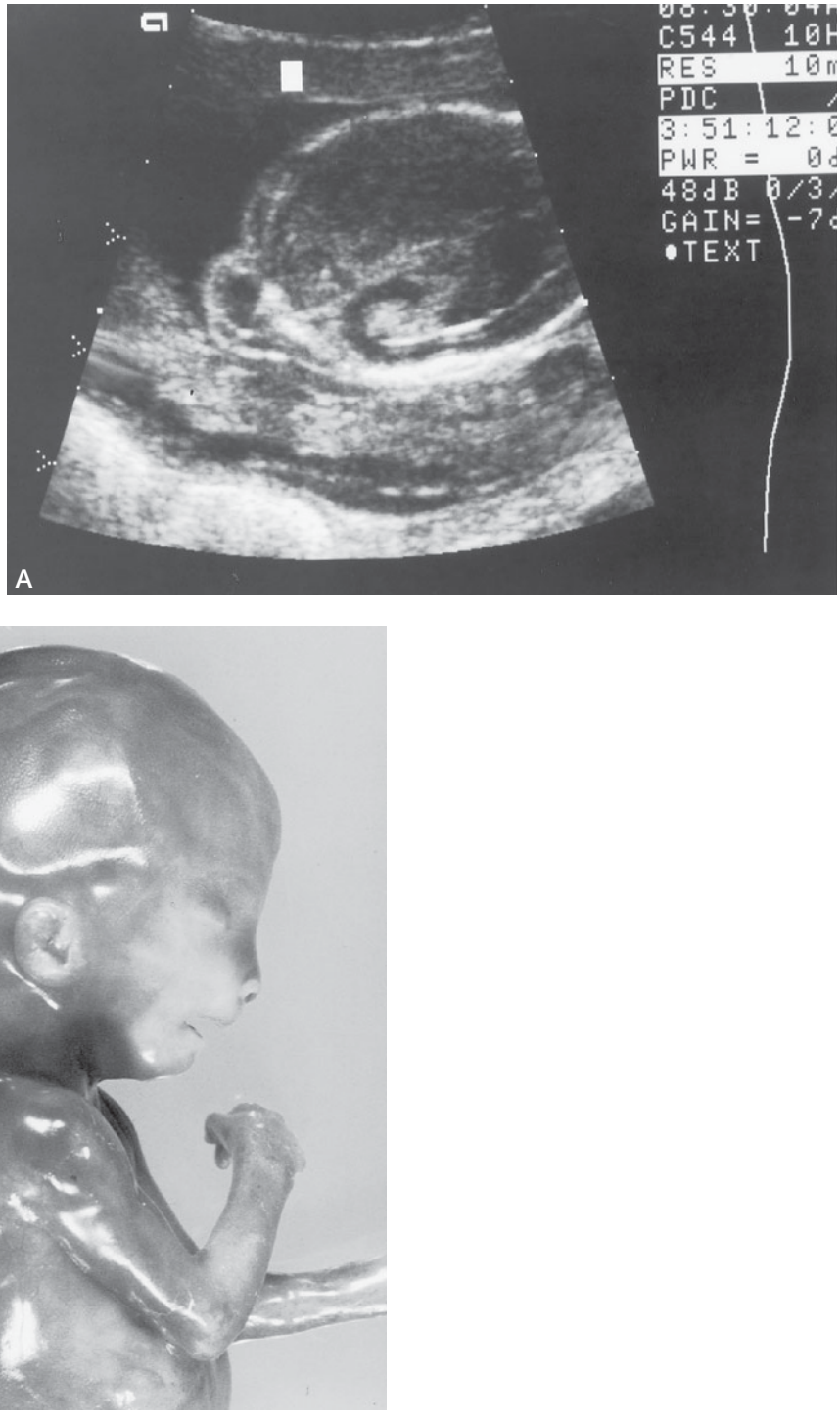


Figure 12-2 **A**. Transaxial sonogram of a fetal head demonstrating a small occipital encephalocele. This fetus has Meckel–Gruber syndrome. **B**. Corresponding autopsy photograph of the same fetus with an intact encephalocele. The fetus also has micrognathia. (*Photograph courtesy of Dr. Joseph Semple.*)

1. the encephalocele is large enough to cause cephalopelvic disproportion;
2. other obstetric considerations are present, such as a previous uterine surgery;
3. a coincidental viable twin is present;
4. the parents are aware of the risk of significant developmental defects in the infant but, after accepting these risks, still want full pediatric intervention (Chervenak et al., 1984; Chatterjee et al., 1985).

In situations in which parents wish full pediatric intervention, we recommend that the baby be delivered at a tertiary care center to facilitate coordination of services for the newborn.

FETAL INTERVENTION

There is no fetal intervention indicated for encephalocele.

TREATMENT OF THE NEWBORN

Treatment of the newborn with encephalocele depends to a large extent on the size and location of the lesion and whether or not associated anomalies are present. For large occipital encephaloceles, the long-term outcome is uniformly poor. Even if parents have decided not to terminate the pregnancy, they may decide that no aggressive intervention should be taken. Alternatively, certain parents may desire that everything be done for their newborn. Infants with encephalocele typically have an intact skin cover, and are usually microcephalic. A complete physical examination is indicated to rule out an associated syndrome (see Table 12-2). Consultation with a medical genetics specialist should be obtained, and with a pediatric neurosurgeon if the parents are considering surgery. In general, surgical treatment is performed as soon as possible, although few data exist that correlate timing of surgery with ultimate developmental outcome.

SURGICAL TREATMENT

The surgical challenges in cases of encephalocele include closing the anatomical defect in the cranial vault and achieving as near normal functional outcome as possible with minimal psychomotor defects (Habal, 1993). Surgical repair of encephalocele consists of opening and exploring the sac, excising malformed brain tissue, and closing the basal dural defect. Surgical repair is generally timed for 0 to 4 months of age (Date et al., 1993). Bony grafting is usually required in such situations to close the cranial defect (Bozinov et al., 2005). In cases of giant occipital encephaloceles with microcephaly secondary to massive brain herniation, the use of a fine mesh has been described to provide a rigid extracranial compartment for the encephalocele. Daily digital compression is performed and the mesh is gradually imbricated into the calvarium (Gallo, 1992).

Surgical considerations for frontal/sincipital encephaloceles are different because of the associated craniofacial deformities, and typically require multidisciplinary approach, including neurosurgery, ophthalmology, ENT, and plastic surgery (Barsani and Cecchi, 2006). In general, surgical treatment for frontal/sincipital encephaloceles include removal of the encephalocele, closure of the dura intracranially, followed by transcranial bone grafting, and correction of orbital hypertelorism or dystopia (David and Proudman, 1989). Hockley et al. (1990) described the following indications for urgent surgery: absence of skin cover, hemorrhage, airway obstruction, or impairment of vision. For most cases of frontal encephalocele, surgery is elective, with indications including protection of the brain; facilitation of nursing; prevention of infection; improvement of the airway, speech, and vision; or treatment of associated anomalies, such as hydrocephalus and hypertelorism.

LONG-TERM OUTCOME

The most important consideration in the long-term follow-up of a patient with encephalocele appears to be whether or not brain tissue is present in the extracranial sac. There is no question that the prognosis is much better for a fetus with a meningocele as opposed to a meningoencephalocele. In one report of 24 patients with surgically repaired encephalocele, follow-up information was available on 22 patients who survived (Date et al., 1993). In this study, one patient died from pneumonia at 8 months of age and another at 4 years. Of the 22 surviving patients, 14 had meningoceles. All of these surviving children were normal. Of the eight survivors with meningoencephalocele only two were normal, four were ambulatory and had mild to moderate retardation, and two were bedridden with marked retardation. These authors concluded that the presence of gross brain tissue in the sac was the most important prognostic factor (Date et al., 1993).

Similar results were seen by Simpson et al. (1984), who studied the outcome for 74 patients with encephaloceles. Of these infants, 17 had meningoceles; all did well, even if associated hydrocephalus developed. Of the 57 infants with meningoencephalocele, almost all did poorly despite surgical expansion of the cranial cavity or decompression of enlarged ventricles.

Docherty et al. (1991) described the outcome for 52 patients with occipital encephaloceles between 1971 and 1990. This study was limited, in that no information was given regarding whether the lesion was a meningocele or a meningoencephalocele. Hydrocephalus developed in 57% of patients, and over half of these required shunting. Twenty-three percent of patients died within the first year. Of the 23 survivors, 14 were normal and 9 were significantly handicapped, but this study was limited in that the underlying pathology of the lesion was not described. Based on the available literature, it seems reasonable to conclude that outcome for fetuses with meningocele is reasonably good, whereas outcome for fetuses with demonstrable brain tissue in the mass is uniformly poor. A more recent review of 31 cases of prenatally diagnosed encephalocele supported this view, with good long-term outcome for six of the seven cases of meningocele (Bannister et al., 2000).

GENETICS AND RECURRENCE RISK

An important consideration in the genetics of encephalocele is to determine whether the lesion is isolated. Rare families have been described in the literature with autosomal dominantly

inherited occipital encephalocele (Bassuk et al., 2004; Zhao et al., 2007). In one family there was clear documentation of 21 affected out of 113 members over five generations (Zhao et al., 2007). All affected individuals had normal or nearly normal neurologic function. Many nonisolated encephaloceles are associated with specific syndromes; in general, many of these are inherited as autosomal recessive conditions (see Table 12-2). It is therefore extremely important to determine whether the encephalocele has associated anomalies, making it consistent with a syndromic diagnosis, such as Meckel–Gruber syndrome.

An attempt should be made to study chromosomes either prenatally or postnatally. Previously reported chromosomal abnormalities that have been demonstrated in fetuses with encephaloceles include trisomies 13 and 18 and mosaic trisomy 20, as well as unbalanced translocations and inversions (Goldstein et al., 1991).

Although isolated encephalocele is not generally considered to have an increased risk of recurrence, parents can be offered early prenatal sonography in a subsequent pregnancy. Encephaloceles have been diagnosed as early as 12 weeks of gestation by transvaginal sonography (Cullen et al., 1990; Fleming et al., 1991). In a patient with a previous pregnancy affected by Meckel–Gruber syndrome, it is possible to diagnose encephalocele as early as 12 to 13 weeks in a subsequent pregnancy, thereby confirming the recurrence of the condition (Tanriverdi et al., 2002).

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13 CHAPTER

Exencephaly/Acrania

Key Points

- Rare fetal anomaly that is incompatible with survival.
- Bones of the cranial vault are absent but facial structures and skull base are preserved. Residual brain tissue is present and floats free in amniotic fluid.
- Likely to be the first trimester precursor to anencephaly. Now called fetal acrania–anencephaly sequence.
- Incidence is 3 per 10,000 second trimester pregnancies.
- Sonographic findings in the first trimester include: absent calcification of the cranial bones, lateral widening of the cerebral hemispheres (the "Mickey Mouse" sign), and echogenic amniotic fluid. Second trimester findings include free-floating disorganized brain tissue with preservation of the face.
- Often associated with omphalocele, amniotic band syndrome, limb–body wall complex, and pentalogy of Cantrell.
- Differential diagnosis includes acalvaria, massive meningoencephalocele, amniotic bands, limb–body wall complex, hypophosphatasia, and osteogenesis imperfecta type II.
- Condition is uniformly fatal postnatally.
- Recurrence risk depends on underlying etiology. If syndromic may have 25% to 50% recurrence risk. Otherwise, recurrence risk is 2% to 5%.
- Preconceptual folic acid (4 mg/day) is recommended for subsequent pregnancies.

CONDITION

Exencephaly is a rare fetal anomaly that is incompatible with extrauterine life. In exencephaly, the bones of the cranial vault are absent (acrania), but the facial structures and the base of the skull are preserved (Casellas et al., 1993). The terms exencephaly and acrania are used interchangeably in this chapter. Exencephaly is a precursor to anencephaly (the so-called fetal acrania-anencephaly sequence); it differs from anencephaly in that residual brain tissue is present and floating free in the amniotic fluid.

Exencephaly is frequently noted in animal teratogen studies. Human exencephaly appears to be confined to early gestation. Only rare reports exist of a third trimester diagnosis of an exencephalic fetus (Wilkins-Haug and Freedman, 1991). Anencephaly, however, is more common in humans than in animals. The greater prevalence of anencephaly in humans is attributed to a longer gestational period, which presents the opportunity for destruction of the free-floating brain matter.

Exencephaly is due to the failure of the anterior neuropore to close during the 4th week of embryonic development. The underlying defect is due to a failure in mesenchymal migration (Stagiannis et al., 1995). In pathologic studies, the exencephalic brain is noted to be covered by a highly vascular epithelial layer. In exencephaly, two relatively equivalent cerebral hemispheric remnants are present within a reddish mass of disorganized tissues, remnants of deep cerebral neural elements, blood vessels, fibrous tissues, and fluid-filled spaces (Hendricks et al., 1988). The remaining brain has been termed the "anencephalic area cerebrovasculosa." In exencephalic brain tissue, the gyri and sulci are shallow, flattened, and disorganized. All surfaces of the brain are highly vascular. The remaining central nervous system tissue is dysplastic, with little or no neuronal differentiation, and very little normal cortex (Hendricks et al., 1988).

INCIDENCE

Papp et al. (1986) reviewed cases of neural tube defect detected by maternal serum α-fetoprotein (AFP) screening. In 36,075 screened pregnancies, 10 cases of exencephaly were detected. This equals an incidence of 3 cases per 10,000 screened pregnancies. The same population had 14 cases of anencephaly per 10,000 screened pregnancies. In this report from Hungary, the mean age of the mothers of fetuses with exencephaly was 22 years. Of the 10 affected pregnancies detected, 9 were singletons and 1 was a twin gestation. In eight of the nine cases described, the maternal serum AFP levels were greater than 2.5 multiples of the median.

In experimental animals, there is an increased incidence of exencephaly in fetuses of female mice injected with clomiphene citrate prior to ovulation (Dziadek, 1993). In addition, hyperglycemia in mice induces exencephaly (Sadler, 1980). The phenomenon in mice is similar to the inhibition of neural tube closure seen in infants of mothers with diabetes.

SONOGRAPHIC FINDINGS

Exencephaly/acrania can be detected early and late in gestation. In the normal fetus, echogenic areas can be seen that correspond to calcification of the cranial bones at approximately 11 weeks. If calcification is absent at this point in gestation, exencephaly should be considered. Another finding can be lateral widening of the cerebral hemispheres with clear delineation of the interhemispheric fissure, the "Mickey Mouse" sign. Later in gestation, the most common finding in exencephalic fetuses is the presence of a large quantity of disorganized brain tissue that is not covered by the bones of the skull, with concomitant preservation of facial structures and bones at the base of the skull (Figure 13-1).

The first prenatal sonographic diagnosis of exencephaly was made at 39 weeks and described by Cox et al. in 1985. Subsequently, the gestational age at diagnosis has decreased considerably. Multiple case reports have contributed to the information available regarding sonographic diagnosis. In one report, in a routine sonographic examination performed at 29 weeks of gestation, the flat bones of the skull were noted to be absent with only a small part of the occipital bone present (meroacrania). Disorganized brain tissue was noted to be floating free in the amniotic cavity. In addition, no evidence of cerebral ventricles was seen, and the gyri were noted be extremely disorganized (Casellas et al., 1993).

Exencephaly is often associated with other major malformations, most commonly omphalocele, amniotic band syndrome, limb–body wall complex, and pentalogy of Cantrell.

First trimester diagnosis of exencephaly is possible (Nishi and Nakano, 1994; Bognoni et al., 1999). In a case diagnosed at 9 weeks, the following sonographic features were observed: the cranial pole was smaller than the chest, the cranial pole bulged dorsally, and the surface of the cranium was irregular (Becker et al., 2000). In another report at 10 weeks, a vaginal sonogram demonstrated absence of the calvarium, choroid, and echolucent areas normally seen in the brain at that point in gestation (Kennedy et al., 1990). In the affected fetus, the brain appeared echodense, with a pulsatile prominence in the area of the forebrain. Because of the concern regarding lack of cranial calcification, repeat sonography was performed at 14 weeks of gestation. At this later time, the cranium was noted to be absent above the occipital bones, a widened cervical spine was present, and fragments of neural tissue were seen attached but floating in the amniotic fluid in the process of degeneration (Kennedy et al., 1990).

More recently, Cafici and Sepulveda (2003) described an indirect sonographic sign of acrania/exencephaly, echogenic amniotic fluid. It is hypothesized that after 10 weeks

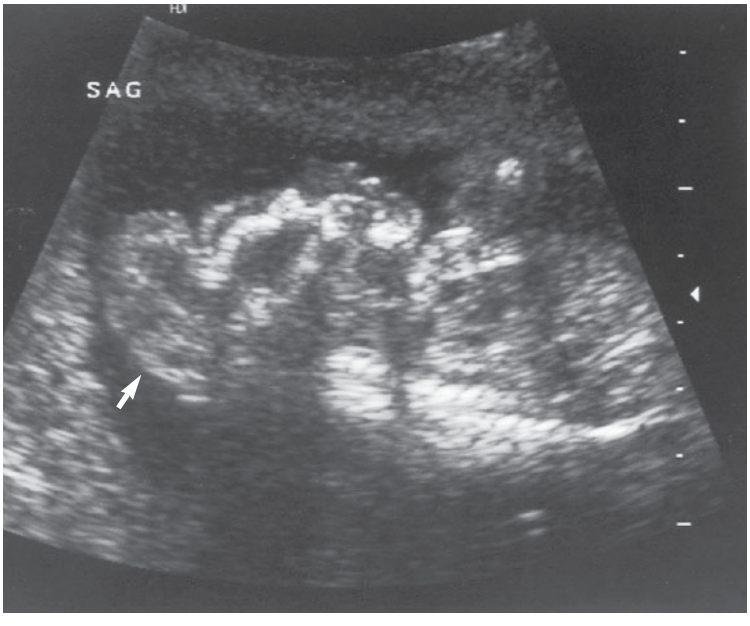

Figure 13-1 Sagittal view of a fetus demonstrating a large quantity of disorganized brain tissue not covered by skull bones (*arrow*).

of gestation, the exposed fetal brain rubs against the uterine wall. This mechanical trauma results in the exfoliation of blood and neural tissue into the amniotic fluid, which can be identified as echogenic free-floating particles.

Three-dimensional (3-D) scanning in the diagnosis of acrania–anencephaly sequence has also been described (Liu et al., 2005).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for exencephaly includes acrania, acalvaria, massive meningoencephalocele, amniotic bands or amniotic rupture, limb–body wall complex, and skeletal dysplasias. It is important to distinguish exencephaly from massive meningoencephalocele because the latter condition is not lethal. In massive meningoencephalocele, the cranial vault is always detected, and part of the brain is intracranial (Abu Musa et al., 1990). In meningoencephalocele, the exposed brain tissue appears more normal than in exencephaly, in which marked dysplasia and disorganized development of rudimentary brain tissue exists.

Acrania is a lethal malformation characterized by partial or complete absence of the calvarium and disorganized brain anatomy. It overlaps clinically with exencephaly. Acalvaria is a rare congenital anomaly in which the flat bones of the cranial vault, dura mater, and associated muscles are absent, but the skull base, facial bones, and intrancranial contents are present (Bianca et al., 2005). Acalvaria is potentially compatible with life.

In the amniotic band syndrome, rupture of the amnion leads to subsequent entanglement of fetal parts by fibrous mesodermic bands. This condition is suggested by the presence of asymmetric lesions in the brain, with associated defects of the spine, abdominal wall, and limbs (Hendricks et al., 1988; Abu Musa et al., 1990; Casellas et al., 1993; Cincore et al., 2003; Chen et al., 2004). In limb–body wall complex, exencephaly or encephalocele are associated with facial clefts, limb defects, and scoliosis. This condition is diagnosed by disruption of the body wall in association with multiple severe abnormalities (Pumberger et al., 2001; Luehr et al., 2002). Pentalogy of Cantrell (see Chapter 61) consists of a supraumbilical wall defect, defect of the lower sternum, deficiency of the anterior diaphragm, defect of the diaphragmatic pericardium, and the presence of intracardiac defects. In several reports, approximately 10% of patients with pentalogy of Cantrell have associated central nervous system malformations, including exencephaly (Hori et al., 1984; Denath et al., 1994; Bognoni et al., 1999). A final consideration in the differential diagnosis is the presence of a skeletal dysplasia. This can be suggested by lack of mineralization of skull bones, such as is seen in hypophosphatasia (see Chapter 98) and osteogenesis imperfecta type II (see Chapter 91). In the skeletal dysplasias, however, the intracranial anatomy is normal. Typical of the skeletal dysplasias are the abnormalities of the long bones, which include shortening or bowing.

ANTENATAL NATURAL HISTORY

Exencephaly is considered to be a precursor to anencephaly. In animals with short gestational periods, exencephaly is frequently observed. However, if the gestation is prolonged artificially, the exposed cerebral structures experience destruction, resulting in anencephaly (Casellas et al., 1993). Wood and Smith (1984) developed an experimental model for anencephaly by administering vitamin A to pregnant rats. The fetuses were noted to have exencephaly that spontaneously disintegrated and eventually became anencephaly. It is thought that the chemical and physical trauma to which the cerebral tissue (unprotected by its sheltering bone cover) is exposed determines its eventual destruction. In humans, destruction of exposed developing brain structures may be complete by 8 to 10 weeks of gestation (Abu Musa et al., 1990).

It has now been demonstrated in humans that a similar progression from exencephaly to anencephaly exists. Wilkins-Haug and Freedman (1991) described a case in which progression to anencephaly was demonstrated by multiple sonograms in a continuing pregnancy. In their case, a 16-week-old fetus was diagnosed with exencephaly. In the cranial area, a well-circumscribed tissue mass was demonstrated without sonographic evidence of cranial calcification. At 18 weeks of gestation, these findings were unchanged, and the parents elected to continue the pregnancy. Repeat sonography was performed at 24 weeks of gestation, when polyhydramnios was demonstrated, and the brain tissue appearance had changed significantly. The disorganized tissue mass was no longer well circumscribed, but was convoluted and floating free in the amniotic fluid cephalad to the frontal bones. At 29 weeks of gestation, the volume of the free-floating brain tissue had significantly decreased. Only a thin layer of tissue remained above the frontal bones. A female infant was delivered by spontaneous vaginal delivery at 30 weeks of gestation with Apgar scores of 1 and 0. The physical appearance of this infant was consistent with classic anencephaly. Physical examination of the cranial area revealed a minimal amount of erythematous, spongy tissue, without cranial or skin covering. This case demonstrates the destruction and disorganization of the developing brain that eventually results in the development of the anencephalic area cerebrovasculosa. A similar phenomenon has been described in another case report, in which selective feticide was performed in a twin pregnancy at 18 weeks of gestation. One twin was normal and the other affected with exencephaly (Papp et al., 1986). This case was followed by repeated sonograms for the healthy twin, and the exposed cerebral mass in the affected twin also regressed over time.

MANAGEMENT OF PREGNANCY

In a study of 3600 pregnant women in Taiwan who received first trimester serum and nuchal translucency screening for

Down syndrome, results were reviewed to determine if these tests could also diagnose acrania. Seven cases of exencephaly/acrania occurred, and all were detetected by nuchal translucency screening (Cheng et al., 2003) Five of the seven affected pregnancies underwent screening with free beta hCG and PAPP-A levels, and there were no differences between the affected and control pregnancies. However, fetuses with exencephaly are accurately detected with second trimester maternal serum screening (Driscoll and Professional Practice and Guidelines Committee of the American College of Medical Genetics, 2004). Maternal serum AFP, maternal serum human chorionic gonadotropin (hCG), and urinary β-core hCG levels are all elevated in this condition (Hayashi et al., 1994). Fetuses in which exencephaly is suspected should be referred to a center capable of detailed sonographic screening to confirm the diagnosis. Pregnancies in which amniocenteses have been performed also reveal extremely high levels of amniotic-fluid AFP (Papp et al., 1986). In addition, large numbers of actively phagocytic macrophages can be demonstrated in the amniotic fluid of fetuses with exencephaly (Papp et al., 1986). It is thought that the degeneration of the exposed neural tissue is potentiated by the macrophages, although it is not known whether these macrophages are fetal or maternal in origin.

Typically, exencephaly is not associated with chromosomal abnormalities, although one case reported deletion of the long arm of chromosome 13 (Lam et al., 1998). However, because of the severity of the defect, a chromosome analysis should be performed to permit accurate genetic counseling. Exencephaly is not compatible with postnatal life. Therefore, the parents should be given the option of termination of pregnancy if this condition is diagnosed before 24 weeks of gestation. Cesarean delivery should be considered for maternal indications.

FETAL INTERVENTION

There is no fetal intervention for exencephaly.

TREATMENT OF THE NEWBORN

Exencephaly is a lethal condition. There is no indication for resuscitation of the newborn.

SURGICAL TREATMENT

There is no surgical treatment for exencephaly.

LONG-TERM OUTCOME

Exencephaly is uniformly fatal.

GENETICS AND RECURRENCE RISK

Exencephaly may be one part of a multiple congenital anomaly syndrome that is inherited as a single-gene disorder. For example, exencephaly is part of the Roberts syndrome, which is inherited as an autosomal recessive condition and consists of limb-reduction anomalies, unilateral anophthalmia, and premature centromeric splitting on karyotype (Verloes et al., 1989). Exencephaly has also been reported to be associated with an autosomal dominant brachydactyly pedigree (Stagiannis et al., 1995). Exencephaly can also be an extreme manifestation of the Adams–Oliver syndrome, which is inherited as an autosomal dominant gene. This condition consists of congenital scalp defects and distal limb anomalies. Every attempt should be made to determine whether the exencephaly is isolated or part of a multiple malformation syndrome. If the fetus is terminated, an autopsy should be performed and chromosome analysis should be performed at the time of termination.

Exencephaly has been described in a product of a consanguineous (brother/sister) mating in which both parents had Waardenburg syndrome. This mating raised the question of homozygosity for a mutation in the *PAX3* gene. The *PAX3* gene is analogous to the mouse splotch gene. In splotch homozygotes, exencephaly develops in half of litters. This human mating possibly demonstrates the role of *PAX3* in neurulation, neural crest cell migration, and development of limb muscles in the human as well as the mouse (Aymé and Philip, 1995).

The recurrence risk for exencephaly depends on its underlying etiology. Cases that are associated with amnion rupture do not have an increased risk of recurrence. If a single-gene disorder is present, the recurrence risk will depend on whether it is autosomal recessive, autosomal dominant, or X-linked. Exencephaly is considered to be within the spectrum of neural tube defects, which have an increased risk of recurrence on the order to 2% to 5%. Preconceptual folic acid and sonographic examination are recommended in subsequent pregnancies.

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14 CHAPTER

Holoprosencephaly

Key Points

- A complex brain malformation characterized by the forebrain failing to cleave into two hemispheres, a process that is usually completed by 5 weeks.
- Four subtypes exist, listed in order of decreasing severity: alobar, semilobar, lobar, and middle hemispheric variant.
- Incidence is approximately 1 in 8000 second trimester pregnancies.
- Approximately 40% of cases have a chromosome abnormality. Of these 75% are due to trisomy 13.
- Maternal diabetes increases the risk of holoprosencephaly by 200-fold.
- Management of pregnancy should include fetal karyotype, DNA mutation testing, and consideration of fetal MRI. A detailed family history should be obtained.
- Mutations in eight different genes are associated with holoprosencephaly (*SHH*, *PTCH*, *SIX3*, *SL12*, *ZIC2*, *TGIF*, *TDGF1*, and *FAST1*).
- If chromosome abnormalities and craniofacial anomalies are absent, long-term survival is possible.

CONDITION

The term *holoprosencephaly* describes a spectrum of cerebral and facial malformations that result from absent or incomplete division of the embryonic forebrain, the prosencephalon. The abnormality occurs during the 3rd week of gestation (Müller and O'Rahilly, 1989). Two separate sets of terms are used to describe the facial and brain anomalies. DeMyer (1964) proposed a subclassification of holoprosencephaly based on the extent of sagittal division of the cerebral cortex, thalamus, and hypothalamus. In the most severe form, alobar holoprosencephaly, midline structures are absent and there is no division of the hemispheres. A single common ventricle is present and the thalami are fused. In semilobar holoprosencephaly, incomplete division of the forebrain results in partial separation of the hemispheres. In lobar holoprosencephaly, there is normal cortical division and two thalami, but abnormalities exist in the corpus callosum, septum pellucidum, or olfactory tract or bulbs. More recently, a fourth subtype of holoprosencephaly was described, known as the middle interhemispheric variant (MIH) (Simon et al., 2002; Pulitzer et al., 2004). In MIH, the posterior frontal and parietal lobes fail to separate, but the poles of the frontal and occipital lobes are well separated.

The facial abnormalities accompanying holoprosencephaly range from subtle to grotesque (Figure 14-1). In general, the more severe facial malformations are associated with alobar holoprosencephaly, but exceptions do occur (Table 14-1). The most severe facial malformation is cyclopia, a single or fused double eye and absent nasal structures (Figures 14-1A and 14-1B). A proboscis, a cylindrical protuberance, may also be present (Figure 14-1C). In ethmocephaly, the eyes are separate but closely placed (hypotelorism); a proboscis is present (Figure 14-1D). Ethmocephaly is the rarest of the facial malformations seen in holoprosencephaly. In cebocephaly, ocular hypotelorism is present along with a nasal structure that has a single nostril (Figure 14-1E). In the milder forms of holoprosencephaly, ocular hypotelorism, flat nose, and a median cleft lip occur (Figure 14-1F). *Arrhinencephaly* refers to the absence of the olfactory tracts and bulbs. Subtle, often missed forms of holoprosencephaly include mild hypotelorism, eye abnormalities (iris or retinal colobomas), mild midface hypoplasia, bifid uvula, and single central maxillary incisor tooth (Figure 14-1G).

INCIDENCE

The true incidence of holoprosencephaly is unknown, as presumably there is a high incidence of death in early embryonic life. In a study of 36,380 spontaneous abortions, Matsunaga and Shiota (1977) noted 150 embryos with holoprosencephaly. This equals a prevalence of 40 per 10,000. Using data from a population-based birth defects registry from California, Croen et al. (1996) identified 121 cases among a cohort of 1,035,386 livebirths and fetal deaths. This equaled a prevalence of 1.2 per 10,000 births. Of all cases, 41% (50 of 121) had a chromosomal abnormality, most commonly, trisomy 13. Among cases with normal chromosomes, increased risks are observed among Hispanic and Pakistani women

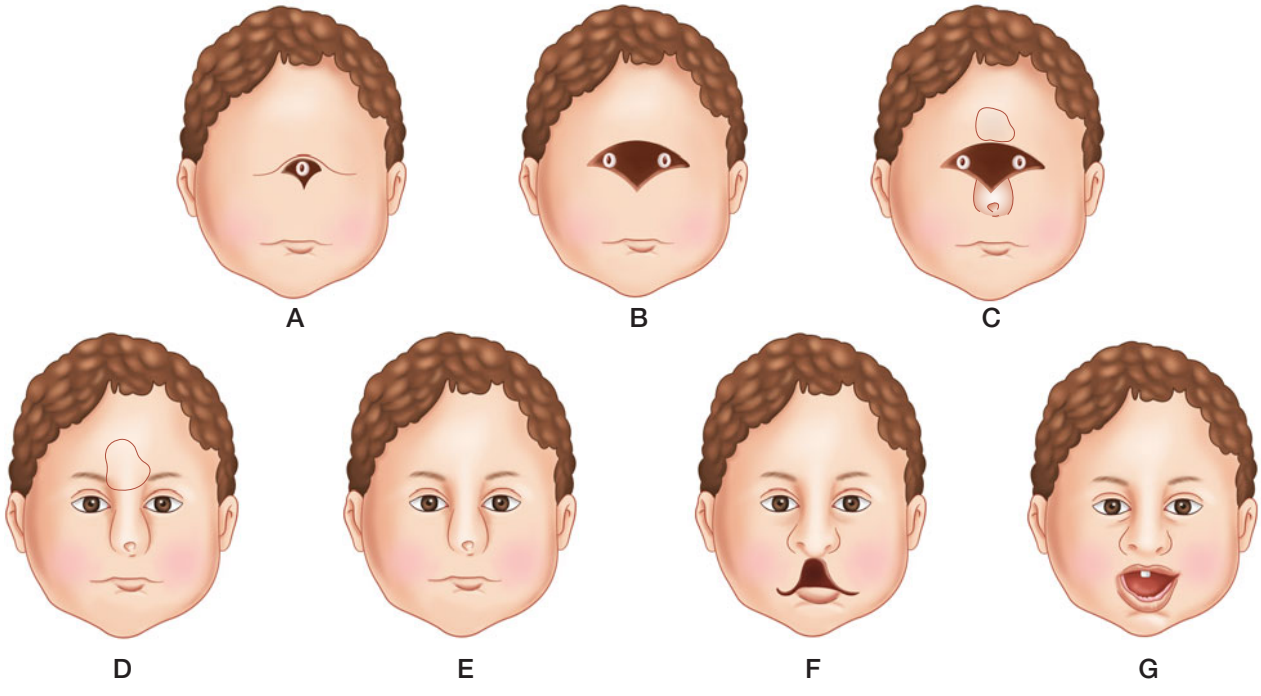

Figure 14-1 The spectrum of facial malformations that can accompany holoprosencephaly. **A** and **B** demonstrate cyclopia. **C** shows cyclopia with a proboscis. **D** shows ethmocephaly with a proboscis. **E** demonstrates cebocephaly with a single nostril. **F** shows mild holoprosencephaly with a midline cleft lip. **G** is the mildest form of holoprosencephaly with a single central incisor (see text for details).

Table 14-1

Post Delivery Assessment of a Fetus/Infant with Alobar Holoprosencephaly

Brain	Face	Clinical Findings
Alobar HP	Cyclopia	Median single or fused eyes; may have no eye; proboscis present or absent
Alobar HP	Ethmocephaly	Rarest facial type; severe ocular hypotelorism with proboscis
Generally alobar HP	Cebocephaly	Ocular hypotelorism and blind-ended, single nostril nose
Generally alobar HP	Median cleft lip	Ocular hypotelorism, flat nose, median cleft lip
Semilobar or lobar HP	Mild dysmorphism	Spectrum of milder abnormalities, including ocular hypotelorism, flattened midface and nose, unilateral or bilateral cleft lip, iris coloboma, single central incisor. Could also appear normal.

(Ong et al., 2007). There is an excess of female conceptuses in alobar (3:1), as opposed to lobar (1:1) holoprosencephaly (Cohen, 1989a). Prevalence is also increased in twins (Suslak et al., 1987). A more recent U.K. population-based survey included all cases in which the pregnancy was terminated after prenatal diagnosis (Bullen et al., 2001). The total prevalence (including terminations) was 1.2 cases per 10,000 registered births. The birth prevalence (affected livebirths and stillbirths at >24 weeks) was 0.49 cases per 10,000 births. Prenatal detection was 86% of cases with a program of routine second-trimester anatomic survey.

Maternal diabetes is the only confirmed human teratogen associated with holoprosencephaly; the incidence of holoprosencephaly among diabetics is increased 200-fold as compared with controls (Barr et al., 1983; Cohen and Shiota, 2002). Other postulated teratogens include ethanol (Jellinger et al., 1981; Ronen and Andrews, 1991; Cohen and Shiota, 2002), salicylate (Benawra et al., 1980), cytomegalovirus (Byrne et al., 1987), retinoic acid, and products of the cholesterol biosynthesis pathway (Cohen and Shiota, 2002).

SONOGRAPHIC FINDINGS

In most fetuses, a midline echo is normally generated by the reflection of sound waves from acoustic interfaces at the interhemispheric fissure. This echo is absent in alobar holoprosencephaly (Figure 14-2) (Pilu et al., 1987). In addition,

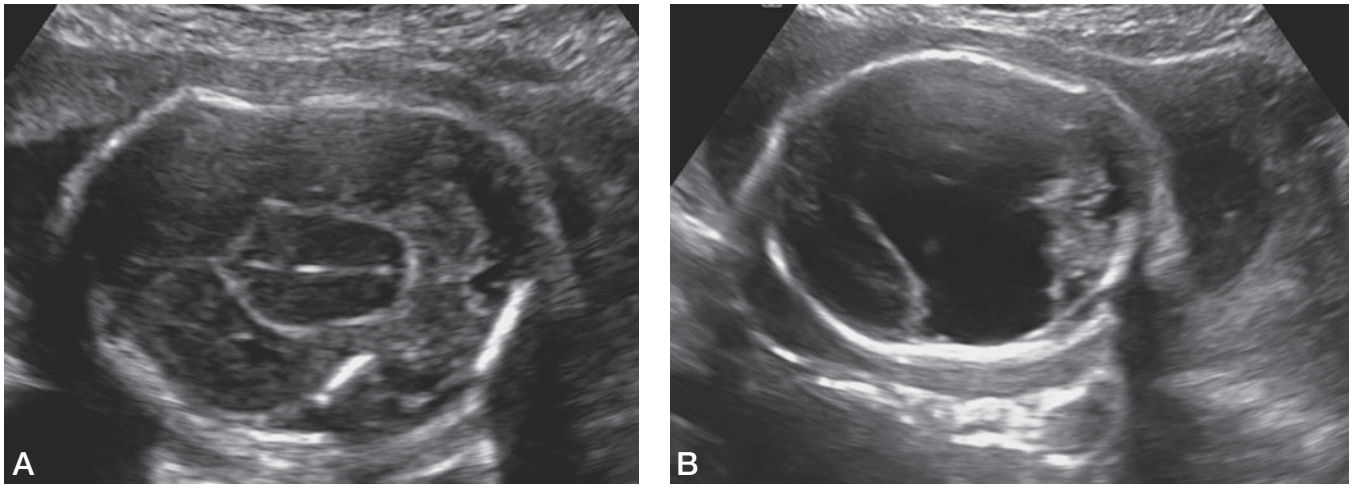

Figure 14-2 Prenatal sonographic image at 23 weeks from fetus with alobar holoprosencephaly. **A.** Axial view with fused thalami. **B.** Single communicating ventricle.

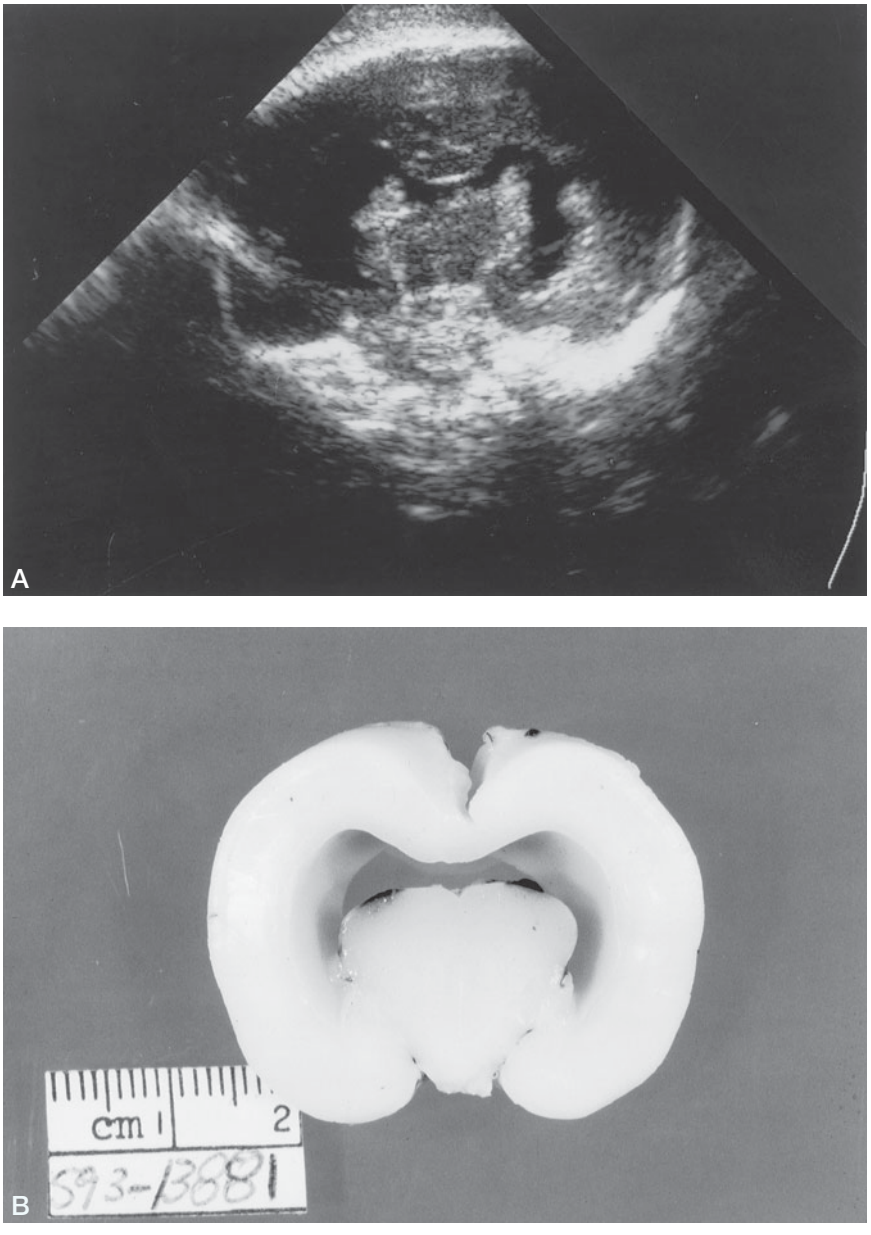

Figure 14-3 **A.** Coronal sonographic image demonstrating thalamic fusion. **B.** Corresponding pathologic specimen from a fetal brain, demonstrating a single ventricle and thalamic fusion. (*Photograph courtesy of Dr. Joseph Semple.*)

in the standard transverse view of the fetal head obtained during measurement of the biparietal diameter (BPD), ventriculomegaly may be noted. The extent of thalamic fusion is best evaluated on a coronal scan (Figure 14-3). When a large cystic abnormality of the fetal head is detected, evaluation of the midline structures of the fetal face is recommended. Greene et al. (1987) have described the use of two sonographic criteria for the diagnosis of holoprosencephaly: intracranial abnormalities and structural abnormalities of the face. In any case of suspected holoprosencephaly, the bony orbits should be visualized. Normal standards exist for the distance between orbits; this is important in the diagnosis of ocular hypotelorism (Mayden et al., 1982). Facial views will also demonstrate the presence of a proboscis. First trimester holoprosencephaly has been diagnosed by two and three-dimensional transvaginal sonography (Bronshtein and Wiener, 1991; Hamada et al., 1992; Stagiannis et al., 1995; Tongsong et al., 1999; Lai et al., 2000; Chen et al., 2005). The first trimester cross-sectional view of the fetal brain demonstrating both choroid plexuses (the so-called "butterfly sign") has been advocated as a screen for holoproscencephaly (Sepulveda et al., 2004).

Several studies have shown that extracranial abnormalities occur in approximately 50% of cases (Berry et al., 1990; McGahan et al., 1990). The most common anomalies are meningomyelocele, renal dysplasia, cardiac defects, and polydactyly.

DIFFERENTIAL DIAGNOSIS

The main considerations in the differential diagnosis of holoprosencephaly include hydrocephalus, midline cerebral defects, such as septo-optic dysplasia, hydranencephaly,

and porencephalic cysts. Holoprosencephaly may be distinguished from fetal hydrocephalus by demonstration of the absence of the midline echo and fusion of the thalami. Hydrocephalus due to aqueductal stenosis or an Arnold–Chiari malformation displays an intact falx cerebri, distinct and separate ventricles, and splayed thalami (Nyberg et al., 1987). In hydranencephaly, a thinned cerebral cortex may be noted. Finally, although both hydranencephaly and porencephalic cyst can demonstrate an absent or deviated falx, the thalami should be distinct with these diagnoses (Nyberg et al., 1987). Holoprosencephaly can occur as an isolated finding or in combination with other anomalies in a single-gene disorder, such as Smith–Lemli–Opitz syndrome (Peebles, 1998).

ANTENATAL NATURAL HISTORY

Holoprosencephaly is highly lethal during fetal life. It has been estimated that only 3% of holoprosencephalic conceptuses are liveborn (Cohen, 1989b). In a retrospective study, 40% of cases were associated with vaginal bleeding and were considered threatened miscarriages (Berry et al., 1990). The perinatal mortality rate is on the order of 89% (McGahan et al., 1990). It is important to recognize, however, there is a correlation between the severity of the condition and the outcome.

MANAGEMENT OF PREGNANCY

Holoprosencephaly is a profound fetal brain anomaly that cannot be altered or treated. Considerations for management of pregnancy include elective termination if the diagnosis is made earlier than 24 weeks, determining the cause of the holoprosencephaly, and planning the route of delivery. Because approximately 30% to 50% of fetuses with holoprosencephaly have chromosomal abnormalities, prenatal karyotype is strongly recommended. A chromosomal abnormality is more likely to be present if extrafacial abnormalities are detected on sonography (Berry et al., 1990; Bullen et al., 2001). Trisomy 13 accounts for ~75% of the chromosome abnormalities. A wide variety of other chromosomal abnormalities have also been described (Aronson et al., 1987; Gillerot et al., 1987; Münke, 1988, 1989; Urioste et al., 1988; Helmuth et al., 1989; Estabrooks et al., 1990; Isada et al., 1990; Lurie et al., 1990; Hamada et al., 1991; Hatziioannou et al., 1991; Kuchle et al., 1991; Petit et al., 1991; Van Allen et al., 1993).

If the karyotype is normal, we recommend sending amniocytes for commercial DNA mutation testing of the genes *SHH*, *TGIF*, *SIX3*, and *ZIC2* (see section "Genetics and Recurrence Risk").

Since familial recurrences of holoprosencephaly have been reported, a family history should be obtained to elicit information on family members with mental retardation, microcephaly, cleft lip and/or cleft palate, eye abnormalities, flattening of the midface, or the presence of a single central incisor (Figure 14-4) (Berry et al., 1984; Hattori et al., 1987). The mother should be asked whether she has a history of diabetes mellitus or was exposed to ethanol or salicylates. TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex) titers should be considered. Although sonography should adequately identify the presence of holoprosencephaly, fetal magnetic resonance imaging (MRI) has been reported as an alternative to improve antenatal definition of the central nervous system (CNS) anatomy (Horvath and Seeds, 1989; Toma et al., 1990; Pulitzer et al., 2004; Wong et al., 2005).

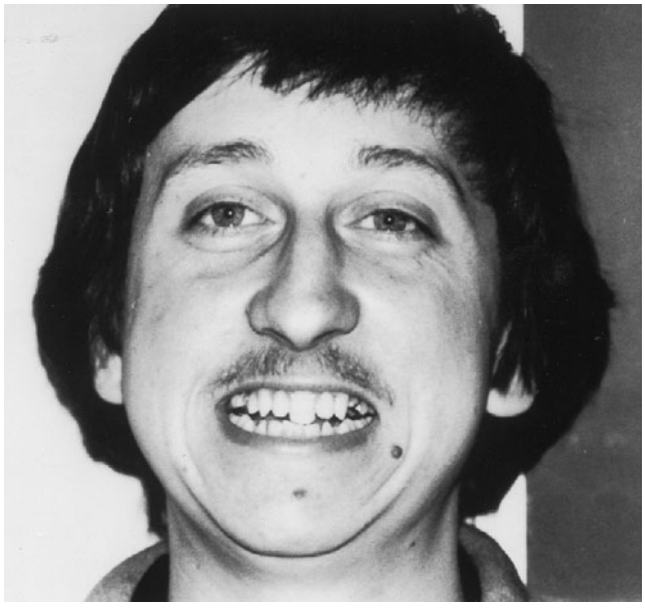

Figure 14-4 Adult with mild phenotypic features of holoprosencephaly, including a central incisor tooth and hypotelorism. These features may not be noticed in apparently normal individuals, yet they place the parent at high risk for offspring with more severe forms of holoprosencephaly. (*From Johnson VP. Holoprosencephaly: a developmental field defect.* Am J Med Genet. *1989;34:258-264.*)

Cesarean delivery may be considered for mild cases of holoprosencephaly. Occasionally, macrocephaly due to ventriculomegaly may prevent vaginal delivery. In nonviable cases of alobar holoprosencephaly, cephalocentesis may facilitate a nonoperative delivery. In a large study of 104 long-term surviviors with holoprosencephaly, the mean gestational age at birth was 38 weeks (Stashinko et al., 2004).

FETAL INTERVENTION

There is no fetal intervention for this condition.

TREATMENT OF THE NEWBORN

Infants with cyclopia, ethmocephaly, and cebocephaly do not survive the perinatal period. Given the expectations for severe

mental retardation in infants who survive with alobar holoprosencephaly, aggressive resuscitation, including mechanical ventilation, is contraindicated. In the delivery room, the infant should be warmed and dried. A thorough physical examination is recommended to document the presence of associated anomalies. If a karyotype was not obtained prenatally, it should be obtained at birth. Some infants will breathe and maintain their own temperature. Potential problems for the newborn include seizures, apnea, and feeding difficulties. If the parents are willing to take the infant home, they can be taught to feed the infant by gavage. Postnatal high-resolution MRI of the neonatal head may be helpful to further define anatomy and prognosis.

A common misperception is that children with holoprosencephaly do not survive past infancy (Hahn and Plawner, 2004). When chromosome abnormalities or severe craniofacial anomalies are present, this is true. However, infants with mild-to-moderate forms of holoprosencephaly will survive into childhood and adolescence.

LONG-TERM OUTCOME

There are increasing reports of long-term survivors with holoprosencephaly (Barr and Cohen, 1999; Hahn and Plawner, 2004; Stashinko et al., 2004) (Figure 14-5). Problems include mental retardation, seizures, feeding difficulties, endocrinopathies, such as diabetes insipidus, and abnormalities of tone and movement. Children with alobar holoprosencephaly are unable to walk, reach objects, or speak (Hahn and Plawner, 2004). In a study of 104 survivors with holoprosencephaly, only 4 of 30 individuals with semilobar holoprosencephaly had normal hand or arm function and only 2 could speak in sentences. In contrast, about half of the lobar holoprosencephaly patients could walk independently, use their upper extremities normally, and speak in sentences (Hahn and Plawner, 2004).

GENETICS AND RECURRENCE RISK

The various etiologies of holoprosencephaly are listed in Table 14-2. Holoprosencephaly due to sporadic, nonchromosomal, nonsyndromic reasons carries an empiric recurrence risk of 6% (Roach et al., 1975). In a 20-year review of cases from Western Scotland, Whiteford and Tolmie (1996) suggested that holoprosencephaly does not necessarily breed true, and that affected families had a 12% recurrence risk for serious neurologic disability. If a chromosomal abnormality is detected, the recurrence risk may be approximately 1% (in the case of trisomy 13 or 18) or higher (if a balanced translocation was found in a parent). In women with diabetes mellitus, the recurrence risk is 1% (Barr et al., 1983). A careful search must be made for relatives with the subtle findings of holoprosencephaly. The autosomal dominant form is notable for variation in the phenotype (see Figures 14-4 and 14-5 [Right]). Penetrance of the gene is on the order of 30% (Collins et al., 1993). In addition, DeMyer et al. (1963) described an autosomal recessive pattern of inheritance for holoprosencephaly.

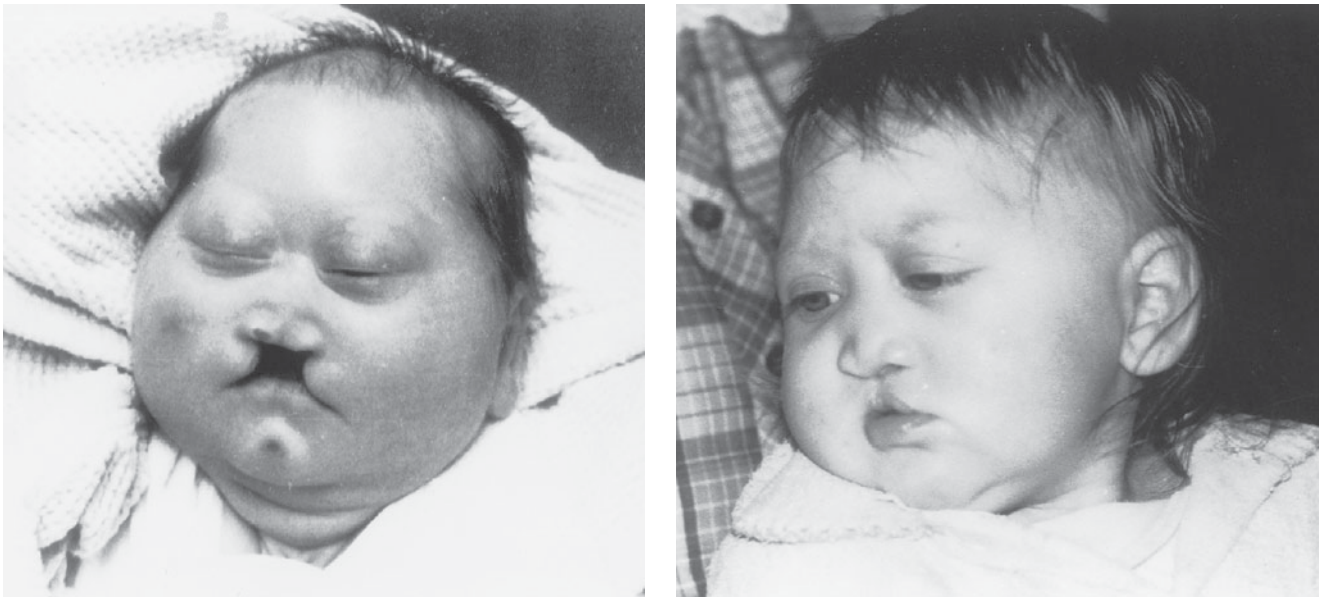

Figure 14-5 Postnatal photographs of surviving infants with milder forms of holoprosencephaly. (*Left*) Infant with severe hypotelorism, upslanting palpebral fissures, severe midface and nasal hypoplasia, and median cleft lip and palate. (*Right*) More mildly affected infant with midface hypoplasia, and a median cleft lip and palate that have been repaired. She is the daughter of the man shown in Figure 14-4. (*From Johnson VP. Holoprosencephaly: a developmental field defect.* Am J Med Genet. *1989;34:258-264.*)

Table 14-2

Etiologies of Holoprosencephaly

Categories	Factors
Genetic factors	Familial holoprosencephaly
Chromosomal abnormalities	Trisomy 13 Trisomy 18 Duplications, deletions, and rearrangements of multiple chromosomes
Monogenic syndromes	Pseudotrisomy 13 Pallister–Hall syndrome Meckel syndrome Velocardiofacial syndrome Smith–Lemli–Opitz syndrome
HPE gene mutations	*SHH* *PTCH* *TGIF* *TDGF1* *ZIC2* *SIX3* *GLI2* *FAST1*
Environmental exposures	Antiepileptic drugs Retinoic acid Alcohol Smoking Statin drugs Pregestational diabetes Cytomegalovirus infection Maternal hypocholesterolemia

Much progress has occurred in the molecular understanding of the development of holoprosencephaly (Münke et al., 1989). At least eight different human genes have been identified that are involved in the development of holoprosencephaly (Table 14-2) (Hahn and Plawner, 2004). Two of these genes (*SHH* and *PTCH*) are part of the sonic hedgehog signaling pathway, which regulates mental development in the forebrain and spinal cord (Hahn and Plawner, 2004). The human sonic hedgehog gene (*SHH*) has been shown to be the same as the holoprosencephaly 3 (*HPE 3*) gene located on chromosome 7q36 (Belloni et al., 1996; Roessler et al., 1996). In humans, loss of one *SHH* allele is sufficient to cause holoprosencephaly (Roessler et al., 1996, 1997). Results of a complete DNA analysis of the *SHH* gene in 344 unrelated cases of holoprosencephaly has identified 23 different mutations (Nanni et al., 1999). These include nonsense and missense mutations, deletions, and an insertion. No genotype–phenotype correlation is apparent based upon this mutational analysis. In autosomal dominant holoprosencephaly, mutations in *SHH* are the most commonly indentified genetic defect (Nanni et al., 1999). Furthermore, Smith–Lemli–Opitz syndrome, a recessively inherited disorder of cholesterol biosynthesis, is associated with holoprosencephaly. Low cholesterol levels lead to abnormal or incomplete modification of the *SHH* protein.

Genes that are involved in the nodal signaling pathway (important in neural patterning) are also involved in the pathogenesis of holoprosencephaly. These include transcriptional corepressor TG-interacting factor (*TGIF*), *TDGF1*, which encodes a membrane-associated protein, and *FAST1*. Other genes involved in the etiology of holoprosencephaly do not play a role in the above pathways. These include *SIX3*, the *HPE2* locus on human chromosome 2p21. This homeobox gene contains information that is essential for the development of the anterior neural plate and eye in humans (Wallis et al., 1999). *ZIC2*, a human homologue of the Drosophila odd-paired gene, maps to chromosome 13q32. Heterozygous mutations in *ZIC2* are the underlying cause of holoprosencephaly in approximately 3% to 4% of cases (Brown et al., 1998, 2001). Interestingly, patients with *ZIC2* mutations tend to have relatively normal faces (Brown et al., 2001). *GL12* mutations are associated with a distinctive phenotype that consists of abnormal anterior pituitary formation and panhypopituitarism, midface hypoplasia, with or without overt abnormalites of forebrain cleavage (Roessler et al., 2003). Table 14-3 summarizes our recommendations for postdelivery assessment of a fetus or infant with holoprosencephaly. Given the rapid progress in human genetic and developmental research, we recommend obtaining a skin biopsy or placental material to establish a fibroblast cell line for future DNA studies. Finally, in all cases of holoprosencephaly, it is essential to hold a follow-up meeting with the parents after delivery or termination to review all pathologic studies and to

Table 14-3

Postdelivery Assessment of a Fetus/Infant with Holoprosencephaly

Rule out chromosomal abnormality with high-resolution banding
Obtain a detailed family history
Examine the proband's family to rule out subtle abnormalities
Obtain an autopsy
Bank DNA for future genetic studies
Hold follow-up meeting to summarize results of above studies

summarize the understanding of the cause, genetics, and recurrence risk.

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15 CHAPTER

Hydranencephaly

Key Points

- Hydranencephaly is a rare condition in which the cerebral hemispheres are virtually absent.
- The typical case is that of an isolated finding without additional abnormalities.
- The diagnosis should be expected when a large cystic mass fills the cranial cavity and there is no recognizable cerebral cortex.
- The antenatal natural history is not well known but appears to represent an evolving intrauterine process secondary to a vascular insult.
- Correct diagnosis is important for the management of these cases. Vaginal delivery is optimal.
- The long-term outcomes associated with complete hydranencephaly are extremely poor.
- In most cases, there is no recurrence risk since hydranencephaly is most often associated with a destructive process rather than with a primary malformation.

CONDITION

Hydranencephaly describes a condition in which the cerebral hemispheres are virtually absent. The hemispheres are replaced by membranous sacs containing cerebrospinal fluid. The meninges and skull are intact. The cerebellum and brainstem are typically normal. The falx is usually present but may be partially or completely absent. Hydranencephaly is considered the most severe form of a spectrum of disorders that includes porencephalic cyst and schizencephaly. It is differentiated from extreme hydrocephalus by the lack of any identifiable cerebral cortex in hydranencephaly.

The most commonly accepted mechanism for the development of hydranencephaly is bilateral internal carotid artery occlusion resulting in cerebral infarction. Myers (1969) described the surgical ligation of the common carotid arteries and jugular veins of a rhesus monkey fetus at 84 to 86 days of gestation. On subsequent postmortem examination the fetal cranium was fully developed; however, the cerebral hemispheres were absent and replaced by thin membranous sacs filled with cerebrospinal fluid, while the brainstem and cerebellum were normal (Myers, 1969). Prenatal infections including toxoplasmosis (Altshuler, 1973; Plantaz et al., 1987), cytomegalovirus (Kubo et al., 1994), rubella (Deshmukh et al., 1993), and herpes simplex infections (Christie et al., 1986; Hutto et al., 1987) have also been associated with hydranencephaly. Hemorrhagic states such as familial factor XIII deficiency have also been reported (Takada et al., 1989).

The typical case of hydranencephaly is that of an isolated finding with no additional abnormalities. A variety of syndromes has been reported in association with hydranencephaly, including trisomy 13 (Dixon, 1988), agnathia malformation complex (Persutte et al., 1990), hypoplastic thumbs (Norman and Donnai, 1992), lethal multiple pterygium syndrome (Mbakop et al., 1986), and both renal aplastic dysplasia and polyvalvular developmental heart defect (Bendon et al., 1987). Four cases of hydranencephaly associated with severely dysplastic kidneys have also been reported (Gschwendtner et al., 1997). Hydranencephaly may occur in a surviving co-twin following single intrauterine fetal demise in a monochorionic pregnancy (Hahn et al., 2003). In addition, although this condition is usually sporadic, affected siblings (Hamby et al., 1950; Najafzadeh et al., 1982) and a set of affected twins have been reported (Regec and Bernstine, 1979). Hydranencephaly has also been reported in association with a primary congenital rhabdoid tumor of the brain (Velasco et al., 1993).

INCIDENCE

The reported incidence of hydranencephaly is between 1 in 4000 and 1 in 10,000 births (Romero et al., 1988). Hemihydranencephaly is an extremely rare condition and has been reported on six occasions (Muir, 1959; Warkany, 1971; Moser and Seljeskog, 1981; Suzuki et al., 1985; Ohtsuka, 1986; van Doornik and Hennekam, 1992).

SONOGRAPHIC FINDINGS

Hydranencephaly can be diagnosed in the first trimester and should be suspected when a large cystic mass fills the cranial cavity without recognizable cerebral cortex (Lin et al., 1992; Lam and Tang, 2000) (Figure 15-1). The lack of cerebral cortex differentiates the condition from severe hydrocephalus. The midbrain, basal ganglia, and posterior fossa are usually normal, and there is often a characteristic protrusion of the brainstem into the cystic mass (Romero et al., 1988). The falx is usually present but may be partially or completely absent. Macrocephaly may be present and is attributed to continuing production of cerebrospinal fluid by the choroid plexus (Raybaud, 1983; Greene et al., 1985). Polyhydramnios can be a common associated finding (Fleischer and Brown, 1977).

The sonographic appearance of hydranencephaly may sometimes be difficult, because visualization of a completely anechoic cystic mass is dependent on the timing of sonography in relation to the vascular insult. The diagnosis of hydranencephaly may not be clear when the infarction and hemorrhage are evolving. Recent hemorrhage appears echogenic, and as clot lyses it assumes the characteristic anechoic appearance of hydranencephaly (Greene et al., 1985; Edmondson et al., 1992). Serial sonography may therefore be

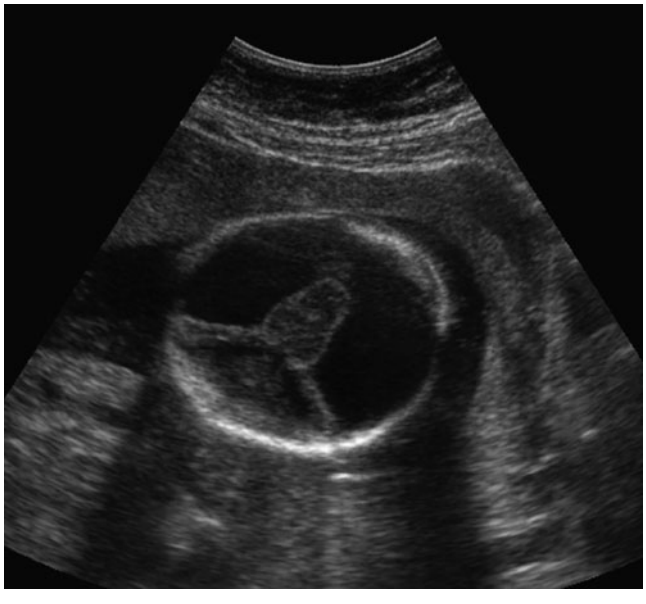

Figure 15-1 Prenatal sonographic image demonstrating the absence of cerebral cortex and presence of a large fluid-filled mass.

necessary to confirm the diagnosis, as hydranencephaly is an evolving process (Lam and Tang, 2000). Magnetic resonance imaging can be used to confirm the diagnosis (Byers et al., 2005).

DIFFERENTIAL DIAGNOSIS

The most common differential diagnoses that should be considered include extreme hydrocephalus, porencephaly, and lobar holoprosencephaly. When hydrocephalus is extreme the cerebral cortex may be very thin and closely applied to the cranium, thereby making it difficult to differentiate from cases of hydranencephaly with preserved falx. The presence of even minimal cerebral cortex indicates extreme hydrocephalus rather than hydranencephaly. In addition, hydranencephaly usually demonstrates a pronounced bulging of the brainstem into the cystic cavity, while in extreme hydrocephalus the presence of residual cortical matter prevents this characteristic appearance (Romero et al., 1988). Magnetic resonance imaging (MRI) has been reported as a complementary technique for the definitive intrauterine diagnosis of hydranencephaly (Vila-Coro and Dominguez, 1989; Byers et al., 2005).

Porencephaly may be differentiated from hydranencephaly by the asymmetric appearance of porencephalic cysts, although complete differentiation of the two conditions can be difficult because they may represent a continuum (Sanders et al., 1996). Features that help differentiate lobar holoprosencephaly from hydranencephaly include absence of the falx and midline structures, absence of the third ventricle, fusion of the thalami, and preservation of some cortical tissue in holoprosencephaly. Furthermore, facial anomalies and additional central nervous system anomalies are usually present with alobar holoprosencephaly. A list of the conditions that have been associated with hydranencephaly is given in Table 15-1.

ANTENATAL NATURAL HISTORY

Little is known about the antenatal natural history of hydranencephaly. In one reported case, the initial sonographic evaluation was normal at 18 weeks' gestation. Follow-up ultrasound examination at 25 weeks revealed sonographic evidence of hydranencephaly (Sanders, 1996). Other case reports document the intrauterine diagnosis of massive intracranial hemorrhage at 27 and 30 weeks of gestation, with subsequent development of hydranencephaly over a period of weeks (Greene et al., 1985; Edmondson et al., 1992). These findings confirm the theory that hydranencephaly represents an evolving intrauterine process that may be secondary to a profound vascular insult.

Table 15-1

Reported Associations with Hydranencephaly

Infections
Cytomegalovirus (Kubo et al., 1994)
Herpes simplex (Christie et al., 1986; Hutto et al., 1987)
Rubella (Deshmukh et al., 1993)
Toxoplasmosis (Altshuler, 1973; Plantaz et al., 1987)
Chromosomal abnormalities
Trisomy 13 (Dixon, 1988)
Neoplasms
Congenital rhabdoid tumor of the brain (Velasco et al., 1993)
Bleeding disorders
Factor XIII deficiency (Takada et al., 1989)
Syndromes associated with hydranencephaly
Agnathia malformation complex (Persutte et al., 1990)
Hypoplastic thumbs (Norman and Donnai, 1992)
Renal dysplasia (Bendon et al., 1987; Gschwendtner et al., 1997)
Polyvalvular heart defect (Bendon et al., 1987)
Lethal multiple pterygium syndrome (Mbakop et al., 1986)

MANAGEMENT OF PREGNANCY

An accurate prenatal diagnosis is necessary for appropriate management decisions. It is particularly important to make the distinction between hydranencephaly and extreme hydrocephalus. Patients should be counseled about the poor prognosis associated with this congenital anomaly, and termination should be offered. MRI is suggested (Vila-Coro and Dominguez, 1989). Serology and/or cultures for toxoplasmosis, cytomegalovirus, rubella, and herpes should also be performed. If there is any sonographic suspicion of other abnormalities, fetal karyotyping should be considered.

Serial ultrasound examinations are recommended to evaluate for the development of macrocephaly. Vaginal delivery is the preferred route of delivery due to the poor prognosis associated with hydranencephaly. Because macrocephaly is commonly associated with the disorder, cephalocentesis may be necessary to facilitate successful vaginal delivery (Greene et al., 1985). Cephalocentesis is performed by inserting an 18- or 20-gauge spinal needle into the fetal head under ultrasound guidance and aspirating cerebrospinal fluid. The fluid

removed is usually dark brown (Greene et al., 1985). If the fluid obtained is not dark brown, it should prompt analysis for protein concentration because in hydranencephaly a highly proteinaceous fluid is suggestive of an intracranial neoplasm (Velasco et al., 1993).

If there is any doubt about the diagnosis, delivery should be performed in a tertiary care setting where qualified subspecialists are available for resuscitation and syndrome diagnosis. If there is no doubt regarding the diagnosis, there is no advantage to delivery in a tertiary care setting. Fetal monitoring is not indicated. If fetal monitoring is performed and the results are not reassuring, cesarean delivery is not recommended.

FETAL INTERVENTION

No fetal interventions have been described following the prenatal diagnosis of hydranencephaly.

TREATMENT OF THE NEWBORN

The neonate with hydranencephaly usually presents with macrocephaly and frequent seizures, although the diagnosis may be delayed for several months because of relatively appropriate early behavior. In one series of 22 patients, the average age at diagnosis was 12 weeks, with a range of 1 day to 10.5 months (Herman et al., 1988). Common presenting symptoms include increasing head size, psychomotor retardation, and increasing spasticity. Most patients have ophthalmic abnormalities involving optic-nerve abnormalities, strabismus, and inferior displacement of the globe (the "setting sun" sign). Transillumination of the skull was the traditional method of postnatal diagnosis of hydranencephaly. However, transillumination of the skull may also be seen with extreme hydrocephalus. Computed tomographic (CT) scanning is helpful in distinguishing hydranencephaly from extreme hydrocephalus and may demonstrate maximal preservation of the frontal cortex and a normal cerebral vascular architecture in hydrocephalus (Herman et al., 1988). MRI is the most definitive imaging technique for the diagnosis of hydranencephaly (Hanigan and Aldrich, 1988).

Electrophysiologic studies, specifically electroencephalography (EEG) and visual evoked responses may also be helpful in distinguishing extreme hydrocephalus from hydranencephaly (Iinuma et al., 1989). The EEG in hydranencephaly is typically flat, and visual evoked potentials show no response. By contrast, in neonates with extreme hydrocephalus there is some EEG activity and normal visual evoked potentials (Herman et al., 1988; Iinuma et al., 1989). Auditory evoked potentials in hydranencephaly show an absent middle latency response, while somatic evoked potentials show an absent cortical response (Hanigan and Aldrich, 1988). If prenatal testing was not performed for cytomegalovirus, toxoplasmosis, rubella, and herpes infections, then appropriate serologic and microbiologic studies should be done during the newborn period.

SURGICAL TREATMENT

Unlike extreme hydrocephalus, shunting procedures are not indicated in hydranencephaly. Sutton et al. (1980) followed neonates with hydranencephaly with serial CT, EEG, and developmental evaluations for 4 to 23 months. No improvement was demonstrated in these five infants by radiologic or neurologic criteria despite aggressive surgical treatment and shunt placement. In contrast, five infants with extreme hydrocephalus treated during the same period improved dramatically after shunt placement (Sutton et al., 1980). In cases of unilateral hydranencephaly, shunting to prevent increasing compromise of the uninvolved side is indicated and has demonstrated favorable results (van Doornik and Hennekam, 1992). No other surgical interventions are recommended for hydranencephaly.

LONG-TERM OUTCOME

The outcome for children with complete hydranencephaly is universally poor. There is no specific treatment, and active medical intervention is not indicated. Almost half of infants with hydranencephaly die within 1 month, and fewer than 15% survive 1 year (Dixon, 1988). Nonetheless, it is important to counsel patients that prolonged survival can occur. In a series of 22 patients, 3 patients were alive at ages 9, 12, and 17 years, but all 3 required constant custodial care (Herman et al., 1988). Survival up to 19 and 20 years has been reported (McAbee et al., 2000; Covington et al., 2003).

In contrast, the prognosis for unilateral hydranencephaly is more favorable (Greco et al., 2001). In one study of the six patients with this disorder, four patients demonstrated mild developmental delay (van Doornik and Hennekam, 1992). No data were provided for one patient. Another patient had multiple congenital defects combined with hemihydranencephaly and severe retardation (van Doornik and Hennekam, 1992).

GENETICS AND RECURRENCE RISK

Hydranencephaly is usually the result of a destructive process in a previously normally formed brain rather than a primary malformation. There has been a reported association with trisomy 13 (Dixon, 1988). Therefore, for most cases there will be no recurrence risk. Familial cases are extremely rare,

and such families should be offered prenatal diagnosis with ultrasound examination in a subsequent pregnancy.

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16 CHAPTER Hydrocephalus

Key Points

- Hydrocephalus is usually due to obstruction of CSF flow, either within (noncommunicating hydrocephalus) or outside (communicating hydrocephalus) the ventricles.
- Ventriculomegaly simply refers to enlargement of intracranial ventricles. It can be associated with hydrocephalus or abnormal brain development.
- Ventriculomegaly is commonly defined as a measurement of 10 mm or greater in the posterior horns of the lateral ventricles noted on an axial brain scan, irrespective of gestational age.
- Approximately 40% of cases of ventriculomegaly have associated CNS or extra-CNS abnormalities, and 12% have an abnormal karyotype.
- Underlying causes include aqueductal stenosis, meningomyelocele, intrauterine infection (CMV, toxoplasmosis, syphilis), agenesis of corpus callosum, X-linked hydrocephalus syndromes, intracranial hemorrhage, Dandy–Walker malformation, and intracranial tumors.
- *L1CAM* gene mutations account for up to 25% of male cases of isolated congenital hydrocephalus.
- Recurrence risk, in the absence of a positive family history, or a known *L1CAM* mutation, is approximately 4%.

CONDITION

Hydrocephalus is a pathologic increase in intracranial cerebrospinal fluid (CSF) volume, whether intraparenchymal or extraparenchymal, independent of hydrostatic or barometric pressure (Raimondi, 1994). CSF is formed within the ventricular system—50% from the choroid plexus and 50% from the cerebral capillaries. The circulation of CSF is unidirectional (Vintzileos et al., 1983). It flows from the lateral ventricles through the foramen of Monro into the third ventricle. It then flows from the third ventricle to the aqueduct of Sylvius through the fourth ventricle into the spinal subarachnoid space (foramen of Magendie) or to the basal cisterns (foramen of Luschka) over the cerebral hemispheres. CSF is reabsorbed by arachnoid villi in venous sinuses. The flow of CSF is partially derived by arterial pulsations of the choroid plexus (Vintzileos et al., 1983).

Hydrocephalus may result from either fluid production that exceeds absorption or primary atrophy of the cerebral parenchyma. Most cases are due to mechanical obstruction to the flow of CSF at some level (DeLange, 1977). The site of obstruction may be inside the ventricular system (noncommunicating or internal hydrocephalus) or outside the ventricles (communicating or external hydrocephalus). Aqueductal stenosis comprises one-third of the cases of hydrocephalus in postnatal series; it is less common in prenatal studies. The aqueduct of Sylvius is the narrowest portion of the spaces through which the CSF flows, and aqueductal stenosis can be diagnosed following the finding of dilation of both lateral, and the third, ventricles (Raimondi, 1994; Davis, 2003).

Ventriculomegaly is a descriptive term of a pathologic process that has many causes. It may occur due to obstruction of CSF flow, or as a consequence of maldevelopment of the ventricle in anomalies such as agenesis of the corpus callosum (colpocephaly) or as an *ex vacuo* (destructive) phenomenon secondary to cerebral atrophy (Cardoza et al., 1988a). Ventriculomegaly is an indicator of underlying central nervous system (CNS) anomalies. It may also be the first sign of associated extra-CNS anomalies. The main causes of ventriculomegaly are aqueductal stenosis, Chiari II malformation (associated with meningomyelocele), Dandy–Walker malformation, agenesis of the corpus callosum, and fetal aneuploidy (D'Addario et al., 2007).

The hereditary nature of hydrocephalus was first appreciated by Bickers and Adams in 1949. It is now known that mutations in *L1CAM*, which result in a collection of X-linked conditions known as the L1 spectrum disorders, account for the majority of inherited cases of hydrocephalus (Zhang et al., 2006).

INCIDENCE

The incidence of isolated fetal ventriculomegaly is 0.5 to 1.5 per 1000 pregnancies. (Wilson et al., 1989; Wiswell et al., 1990; Davis, 2003). In a retrospective analysis of all liveborn and stillborn infants in U.S. Army hospitals between 1971 and 1987, 370 of 763,364 pregnancies had hydrocephalus (Wiswell et al., 1990). This equaled an incidence of 0.5 per 1000 total births, or 1 per 2063 total births. Of the infants with hydrocephalus, 37% had additional anomalies unrelated to the primary defect. No significant racial differences were seen, but an increased incidence of affected males was noted (64% male, 36% were female). A predominance of males is consistently observed in all studies of hydrocephalus due to the inherited X-linked forms of the abnormality.

SONOGRAPHIC FINDINGS

Hydrocephalus is generally easily diagnosed prenatally due to the striking sonographic appearance of enlarged ventricles (Figure 16-1). It is important to note that the fetal biparietal diameter may not necessarily be increased when the ventricles are dilated. The lateral ventricles can be visualized as early as 12 weeks of gestation. Early in the second trimester, the choroid plexus is very echogenic and large relative to the volume of the cerebral hemispheres, normally filling the entire lateral ventricle posterior to the foramen of Monro. This tends to obscure the lateral ventricular wall to which it is closely applied (Fadel, 1989). This, together with the hypoechoic brain mantle, may falsely be interpreted as dilated ventricles filled with CSF. In second trimester fetuses with hydrocephalus, the first recognizable abnormality is generally the relative shrinkage of the normally prominent choroid plexus. Additionally, the choroid plexus appears to hang away from the ventricular walls, an appearance that is referred to as "dangling choroid."

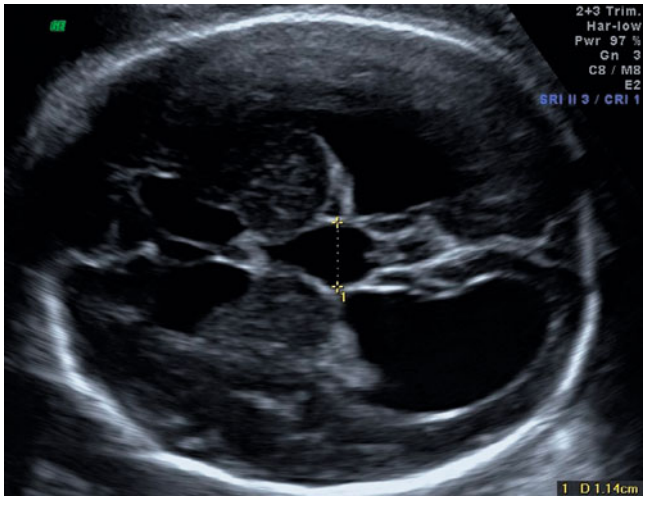

Figure 16-1 Axial sonographic image of a fetal head with communicating hydrocephalus. Third ventricle and lateral ventricles are markedly enlarged.

Several different methods have been proposed to quantitatively evaluate increased CSF. These methods include measurement of the ratio of the lateral ventricular width (LVW) to the hemispheric width (HW), (the LVW:HW ratio), or measurement of the ventricular atria. However, the LVW:HW ratio is not sensitive in early pregnancy. The first measurement of lateral ventricular dilation is the displacement of the medial wall of the lateral ventricle toward the midline, which will not change the LVW:HW ratio (Fadel, 1989). Furthermore, the echogenic outer lines originally thought to represent the lateral walls of the lateral ventricle in an axial scan of the fetal head have been shown by Hertzberg et al. (1987) to originate from deep cerebral veins. These reflections from small venous structures and deep fetal white matter may be displaced in the presence of hydrocephalus. The position of the fetal choroid plexus relative to the ventricular walls is dependent on gravity, and so the choroid angle (the angle between the long axis of the choroid plexus and the linear midline echo on a transverse axial sonogram through the body of the lateral ventricle), may be a useful indicator of ventricular size (Cardoza et al., 1988a). In normal-sized ventricles, this angle varies from 6 to 22 degrees, while in fetuses with ventriculomegaly the angle ranges from 29 to 90 degrees (Cardoza et al., 1988a). The choroid angle appears to increase with the severity of hydrocephalus.

The most common method for assessing ventricular size today is the atrial diameter measured on an axial sonogram through the fetal brain. In a study of 100 healthy fetuses between 14 and 38 weeks of gestation, the normal atrial diameter remained relatively constant throughout gestation despite growth of the surrounding brain (Cardoza et al., 1988b). These measurements were compared with 38 fetuses in whom ventriculomegaly had already been diagnosed. The mean diameter of the normal atrium was 7.6 $\pm$ 0.6 mm, and it was suggested that atrial diameters >10 mm, (greater than 4 SD above the mean), indicated the presence of ventriculomegaly. This measurement is quick to perform, is reproducible, and does not vary by gestational age (Cardoza et al., 1988b).

While an atrial diameter of >10 mm is considered abnormal, the term borderline ventriculomegaly is often used to refer to an atrial measurement of between 10 and 12 mm. Borderline ventriculomegaly is associated with an increased risk of CNS and non-CNS abnormalities, and suggests the need for a more detailed fetal anatomic examination. Several studies have substantiated this recommendation. Mahony et al. (1988) performed a prospective study of 20 fetuses with

apparently isolated borderline ventriculomegaly (defined as a 3- to 8-mm separation existing between the choroid plexus in the atrium of the lateral cerebral ventricle and the adjacent ventricular wall on an axial scan). Of the 20 fetuses identified, 8 had a normal outcome (40%). The remaining 12 fetuses had additional sonographic abnormalities. Of these 12, 4 had an uncertain prognosis and 8 died. In another study of 55 fetuses with borderline ventriculomegaly, 13 had isolated ventriculomegaly and 42 had associated abnormalities (Goldstein et al., 1990). Of 15 living children who could be identified, 9 (60%) were normal at 6 to 30 months of postnatal age, 3 (20%) were abnormal, and 3 (20%) were lost to follow-up. These authors concluded that borderline ventriculomegaly, when isolated, was associated with a better prognosis than more substantial ventriculomegaly. A literature review in 1993 found 109 cases of mild ventriculomegaly, 92 of which were isolated, and 11 of these had an abnormal karyotype (12%) (Achiron et al., 1993). In another retrospective study of 44 fetuses with borderline ventriculomegaly (10–12 mm), 17 fetuses (39%) had other sonographic abnormalities, 6 of which were in the CNS (Bromley et al., 1991). Of 36 liveborn neonates in this study, 26 were developmentally and clinically normal at 3 to 18 months of postnatal age, while 10 of the 36 were developmentally impaired, including 5 cases from apparently isolated borderline ventriculomegaly.

Unilateral hydrocephalus is extremely uncommon. This condition carries a better prognosis than bilateral hydrocephalus. Of eight reported prenatal cases, five were due to congenital absence or stenosis of the foramen of Monro, one was due to transient obstruction of CSF flow by an intracranial hematoma, one was due to holoprosencephaly, and one was due to unknown causes (Patten et al., 1991). It appears that unilateral hydrocephalus is not associated with the presence of extracranial anomalies, and such patients generally have required postnatal placement of a ventriculoperitoneal shunt (Patten et al., 1991; Anderson et al., 1993; Chari et al., 1993).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for hydrocephalus and ventriculomegaly includes aqueductal stenosis, meningomyelocele (Chiari II malformation), Dandy–Walker malformation, agenesis of the corpus callosum, aneuploidy, intrauterine infection (cytomegalovirus, toxoplasmosis, or syphilis), intracranial hemorrhage, CNS tumor, hydranencephaly, porencephaly, and holoprosencephaly. Meningomyelocele can be the underlying reason for hydrocephalus due to herniation of the cerebellum through the foramen magnum resulting in the Chiari II malformation. The fetal spine should therefore be carefully examined in multiple planes in all such cases (see Chapter 19).

In hydranencephaly, only remnants of the cortex remain, with fluid-filled sacs that are lined by leptomeninges replacing the rest of the brain (see Chapter 15). In porencephaly, the parenchyma of the brain contains one or more fluid-filled cavities (see Chapter 21). The Dandy–Walker malformation includes ventricular dilation (see Chapter 11). Demonstration of the absence of falx cerebri and fusion of the thalami can distinguish holoprosencephaly from other causes of hydrocephalus (see Chapter 14). Consideration should also be given to the possibility of underlying single-gene disorder.

One of the major concerns with the antenatal sonographic finding of hydrocephalus is the fact that ventriculomegaly is frequently associated with additional anomalies within and outside of the fetal brain. Associated intracranial anomalies (such as agenesis of the corpus callosum or the Dandy–Walker malformation) are present in at least one-third of cases. Extracranial abnormalities have been demonstrated in two-thirds of cases (Fadel, 1989). In another series of 61 cases of hydrocephalus, 51 fetuses (84%) had associated abnormalities, 34 of which were extracranial and 27 had multiple malformations (Nyberg et al., 1987). In this series, false-negative diagnoses were common, and included esophageal atresia, spinal abnormalities, lung hypoplasia, and cardiac defects. Of 61 fetuses, 41 ultimately died from associated conditions such as asphyxiating thoracic dystrophy (Jeune syndrome), Apert syndrome, in which hydrocephalus is considered a major associated malformation (Hyon et al., 1986), and the Walker–Warburg syndrome. This latter recessively inherited condition includes hydrocephalus, multiple CNS malformations, microophthalmia, severe mental retardation, congenital myopathy, and a limited life span (Crowe et al., 1986). Finally, inborn errors of metabolism, such as fumarase deficiency, can cause polyhydramnios and hydrocephalus in utero (Remes et al., 1992). In this condition, enlargement of the cerebral ventricles is due to cerebral atrophy, while the associated polyhydramnios is due to intrauterine hypotonia, causing poor swallowing.

ANTENATAL NATURAL HISTORY

In a review of 24 cases of fetal hydrocephalus, four fetuses underwent transabdominal or transvaginal cephalocentesis prenatally and intracranial pressures were measured. The results suggested that the fetal brain is subjected to extremely high intracranial pressures, resulting from a mixture of hydrocephalic pressure and intermittent uterine constriction (Oi et al., 1990). In another study of patients with fetal CNS defects who had cephalocentesis performed at the time of termination of pregnancy, intracranial CSF pressures and volumes were quite variable, with no correlation between the type of lesion and intracranial pressure observed (Simpson et al., 1988). It therefore does not appear that there is any value in measuring fetal intracranial pressure for predicting outcome.

Following the diagnosis of borderline ventriculomegaly, a significant number of fetuses will demonstrate spontaneous resolution of the ventricular enlargement and will have a normal outcome. In a study of 63 fetuses with

apparently isolated ventriculomegaly of 10 to 15 mm, 26 (41%) showed normalization of lateral ventricles, 27 (43%) remained stable, and only 10 (16%) demonstrated progressive enlargement (Parilla et al., 2006).

MANAGEMENT OF PREGNANCY

The finding of prenatal ventriculomegaly mandates referral to a center capable of targeted sonographic examination of the fetus due to the high incidence of associated CNS and extra-CNS anomalies. Prospective parents should be counseled regarding the diversity of conditions that can be associated with hydrocephalus (Pober et al., 1986). They should be counseled that ventriculomegaly is progressive in 2.5% to 4.5% of cases, and that the incidence of associated abnormalities varies from 54% to 84% (Rosseau et al., 1992). Serial sonograms should therefore be performed to determine whether the hydrocephalus is stable, progressive, or resolving.

The major factor that influences prognosis is the presence of associated abnormalities (Pober et al., 1986). Given the difficulty in excluding other CNS abnormalities, it would be reasonable to consider performance of a fetal magnetic resonance image (MRI) in cases of significant ventriculomegaly. In general, decisions about management options depend on the gestational age at the time of diagnosis and the presence and nature of associated abnormalities. Pregnancy termination may also be considered. Further recommended diagnostic studies include chromosome analysis, DNA analysis for *L1CAM* mutations, and an infectious work-up to rule out cytomegalovirus and toxoplasmosis. The most commonly associated chromosome abnormalities include trisomies 9, 13, and 18, as well as triploidy (Schrander-Stumpel and Fryns, 1998).

Mode of delivery should be individualized in all cases. In general, a cesarean delivery after demonstrating pulmonary maturity is recommended if the fetal head size is significantly enlarged (Figures 16-2 and 16-3). However, if ventriculomegaly is isolated, without significant head enlargement, vaginal delivery is also reasonable. If severe abnormalities incompatible with extrauterine life are present, such as thanatophoric dysplasia, cephalocentesis (removal of CSF from the ventricular system) to reduce head size to permit vaginal delivery can be considered.

FETAL INTERVENTION

In utero treatment, using shunts or repeated cephalocenteses, has been previously attempted for hydrocephalus to try to prevent progressive damage to the fetal brain caused by the chronically increased CSF pressure (Birnholz and Frigoletto, 1981; Clewell et al., 1982). Specific criteria for intrauterine therapy were established by the International Fetal Medicine and Surgery Society (IFMSS), including ventriculomegaly,

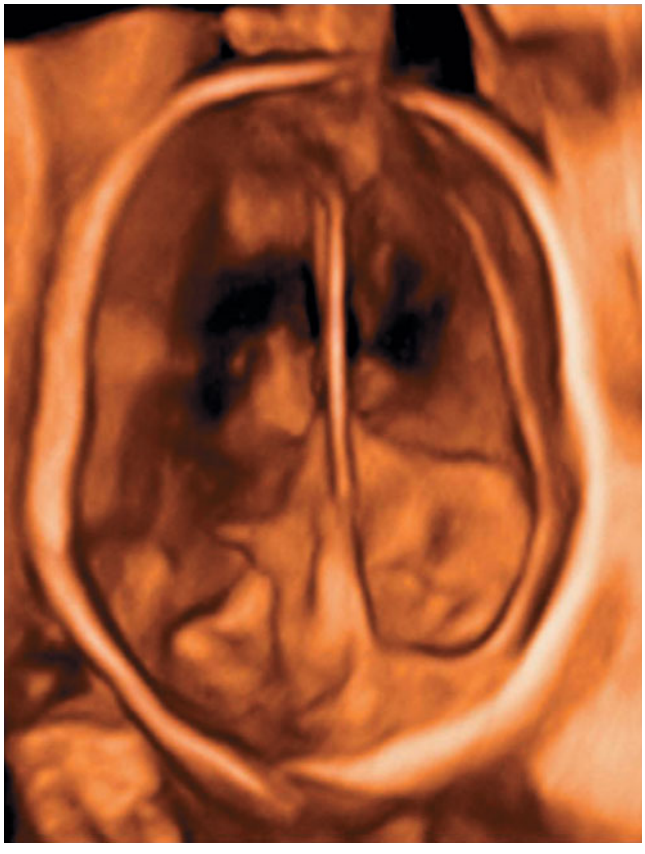

Figure 16-2 Axial 3D image showing marked bilateral ventriculomegaly.

and gestational age of less than 30 weeks. A registry was formed in 1982 under the auspices of the IFMSS (Manning et al., 1986; Drugan et al., 1989). This group analyzed the results of 39 antenatal procedures performed in the United States and 5 in Italy between 1982 and 1985. Of the 44 cases, 36 (82%) fetuses survived and 8 (19%) died in utero or during the perinatal period. Four of these deaths were related to the in utero procedure. Twenty-two of 36 survivors were left with varying neurologic and physical handicaps, with 48% being severely handicapped (Manning et al., 1986). Because of the high rate of procedure-related death and lack of significant improvement in outcome, such in utero treatment has been abandoned.

Hudgins et al. (1988) retrospectively reviewed the outcomes of 47 fetuses evaluated during a 4-year period in the fetal treatment program at the University of California at San Francisco. Twenty-five of these 47 fetuses with ventriculomegaly had severe associated abnormalities and were either electively terminated or died during the perinatal period. Of the remaining 22, 19 had stable ventriculomegaly, 2 had progressive ventriculomegaly, and 1 resolved in utero. Of the 19 postnatal long-term survivors, 13 (68%) were normal and 6 (32%) had moderate-to-severe developmental delay. Associated abnormalities were detected in 74% of fetuses, and there was a 20% false-negative rate of detection of associated abnormalities. These authors concluded that they were unable

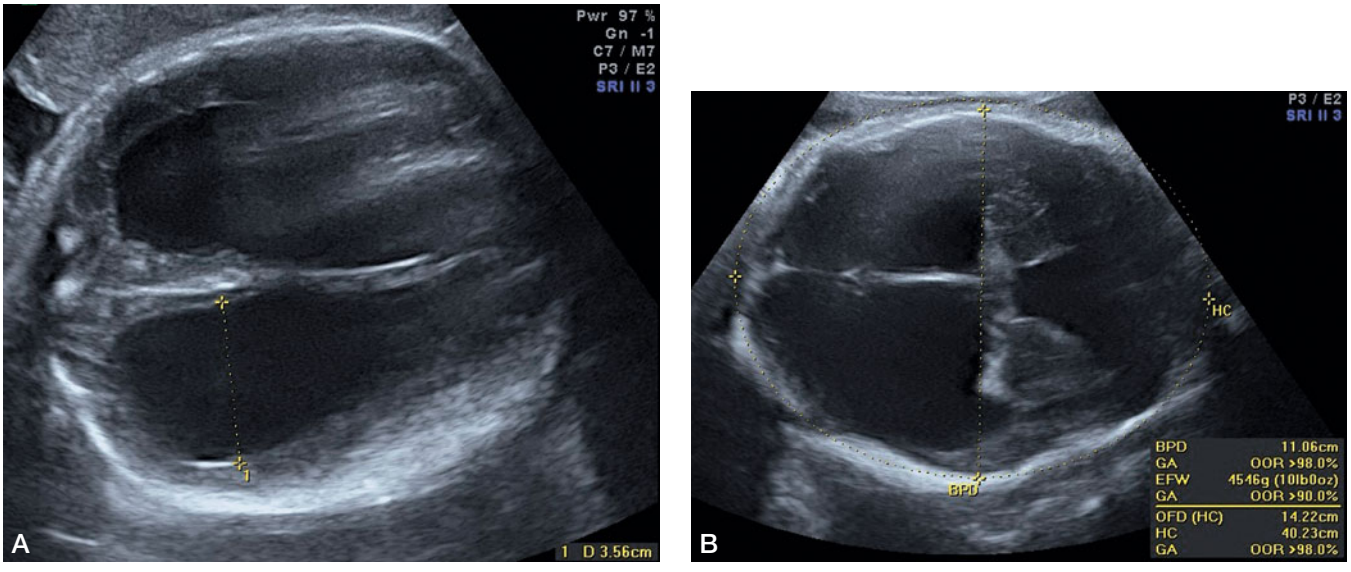

Figure 16-3 **A.** Aqueductal stenosis leading to marked hydrocephalus and **B.** macrocephaly at 36 weeks' of gestation.

to define a group of patients that would benefit from in utero shunting. In their series, only a 14% incidence of isolated, progressive ventriculomegaly was noted. While such fetuses with isolated, progressive ventriculomegaly are the most likely to benefit from in utero treatment, these fetuses represent such a small minority of the total population of fetuses with ventriculomegaly that in utero treatment is currently not recommended. Indeed, since 1985, a moratorium on fetal shunts for hydrocephalus had been agreed upon by members of the IFMSS (Davis, 2003). However, experimental approaches to more invasive fetal surgery for select cases of hydrocephalus are being investigated, such as hysterotomy and placement of a tunneled shunt from the fetal lateral ventricles to the skin at the fetal back (Davis, 2003).

Fetal intervention for hydrocephalus occurring secondary to meningomyelocele is discussed in Chapter 19.

TREATMENT OF THE NEWBORN

Infants who are delivered following a prenatal diagnosis of ventriculomegaly need a detailed physical examination (Figure 16-4). Consultation with a medical geneticist and a neurosurgeon is recommended. Postnatal diagnostic imaging of the CNS may include computed tomographic (CT) scan and magnetic resonance imaging (MRI). If a chromosome analysis was not performed prenatally, it should be performed during the newborn period. The major goals of treatment of the newborn are to determine an underlying cause for the hydrocephalus and to stabilize the infant for the placement of a ventriculoperitoneal shunt. Provided the newborn with significant hydrocephalus is not diagnosed with other abnormalities incompatible with life, the goal will usually be to arrange shunting in the first 4 days of life (Futagi et al., 2002).

If the infant has been found to have multiple associated abnormalities incompatible with survival, a detailed autopsy is recommended if death occurs during the neonatal period.

SURGICAL TREATMENT

The major treatment of hydrocephalus is the placement of a ventriculoperitoneal shunt. The shunt has a proximal portion, typically placed in the frontal horn of the lateral ventricle, together with a one-way valve that is placed extracranially. This then connects to the distal portion of the shunt, which is usually tunneled subcutaneously to the peritoneal cavity, although other rarer sites include the right atrium or the subclavian vein. High pressure between the intracranial portion and the intraperitoneal portion of the device results in flow out of the ventricular system.

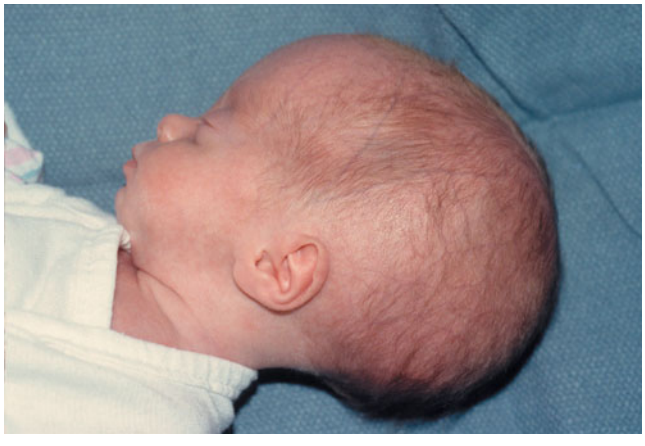

Figure 16-4 Postnatal photograph of a newborn infant diagnosed prenatally with hydrocephalus. Note enlarged head and prominent venous pattern on scalp.

Mortality related to this surgery is minimal. The major morbidities are associated with malfunction or blockage of the shunt and shunt infection. Unfortunately, such complications are extremely common, with 25% to 50% of all shunts requiring revision within the first 2 years of life (Liptak and McDonald, 1985).

LONG-TERM OUTCOME

The most important factor in the long-term outcome is the presence of associated abnormalities. In one study, Rosseau et al. (1992) reviewed follow-up data on 40 patients identified prenatally with hydrocephalus in a community-acquired series. Of these 40 patients, 3 were electively terminated and 37 delivered. Of the 37, 26 (70%) underwent the placement of a ventriculoperitoneal shunt. Ten of these 26 (38%) had satisfactory cognitive ability. Of the 11 patients who were not treated, reasons for nontreatment included misdiagnosis, resolution of hydrocephalus, or parental refusal. Multiple studies seem to indicate that approximately 40% to 50% of survivors have a normal IQ. The IQs are not proportional to brain expansion after the placement of the shunt. Degree of ventricular dilatation does not appear to be associated with long-term outcome (Hirsch, 1994). Similarly, the site of obstruction does not affect long-term intelligence.

In a study of 27 fetuses with isolated, borderline ventriculomegaly, 25 had a normal neurological outcome, 1 had petit mal seizures, and one was electively terminated (Lipitz et al., 1998). Approximately 10% of survivors have a seizure disorder (Hirsch, 1994). In a study of intelligence outcome in 44 children with shunted hydrocephalus, the site of obstruction, the number of shunt revisions, the number of postsurgical complications such as infection or hematoma, or the presence of seizures did not correlate with abnormalities in neuropsychologic functioning. Verbal intelligence was shown to be affected by the presence of motor deficits and the need for antiepileptic therapy. Nonverbal intelligence was affected by the presence of a brain malformation or the age at the time of shunt placement. In this study, if a shunt was placed later in life it indicated that the aqueductal stenosis developed slowly (Riva et al., 1994).

Futagi et al. (2002) reviewed 38 children who had surgical management of prenatally diagnosed hydrocephalus. Neurodevelopmental outcome was normal at a mean age of 7.4 years in only three patients, while one had borderline intelligence, seven had intellectual impairment, and 27 had significant motor impairment.

GENETICS AND RECURRENCE RISK

The major considerations in the genetics of hydrocephalus are related to the underlying cause. In a review of the causes of hydrocephalus in liveborn infants, Burton (1979) demonstrated that only 1.4% of siblings of 205 affected patients also had hydrocephalus. Specific subgroups were identified to be at high risk, including males with aqueductal stenosis. Classic X-linked recessive hydrocephalus, known as Bickers–Adams disease, or hereditary stenosis of the aqueduct of Sylvius (HSAS), has been mapped to chromosome Xq28 by linkage analysis (Willems et al., 1990). X-linked hydrocephalus is the most common of the inheritance patterns. In a fetus identified with hydrocephalus, a complete family history is essential. It is important to note that males affected with X-linked HSAS may be normocephalic and nondysmorphic, but they will have mental retardation (Kelley et al., 1988). Families with autosomal recessively inherited hydrocephalus have been described, but in general, consanguinity is also present (Zlotogora et al., 1994). Rare families with apparently dominantly inherited hydrocephalus have also been reported in the literature (Ferlini et al., 1995; Verhagen et al., 1998).

X-linked hydrocephalus comprises approximately 5% of all cases of hydrocephalus (Schrander-Stumpel and Fryns, 1998). These conditions are collectively known as L1 disease, and include HSAS (hydrocephalus due to aqueductal stenosis, mental retardation, clasped thumbs, and spastic paraparesis), MASA (mental retardation, aphasia, shuffling gate, and adducted thumbs), X-linked agenesis of the corpus callosum, and spastic paraparesis type 1 (SPG1) (Weller and Gärtner, 2001). MASA syndrome and SPG1 present with milder symptoms and have a longer life expectancy than HSAS. These four conditions are all caused by heterogeneous mutations in the gene encoding the neural cell adhesion molecule L1. L1 is involved in intracellular recognition and neuronal migration in the CNS (Jouet et al., 1995). A wide variation is observed in patients belonging to the same family, as well as in patients from different families.

L1 is a member of the immunoglobulin superfamily. Jouet et al. (1995) reviewed the 23 mutations described by that time in the L1 gene. Three mutations had been identified that affect different fibronectin domains and are critical for L1 function in brain development. More recently, over 140 different pathogenic mutations have been described in L1 (Finckh and Gal, 2000; Weller and Gärtner, 2001). Thus, heterogeneous mutations in the L1 gene form a clinical spectrum of disorders that can be recognized both prenatally and postnatally (Takechi et al., 1996). In one study, *L1CAM* mutations were identified in 22% (15/67) of cases of suspected L1 disease without a family history (Finckh and Gal, 2000). Therefore DNA testing is recommended for all affected male fetuses independent of family history. Families who have a history that suggests the presence of an X-linked disorder should have DNA collected to try to prospectively identify L1 gene mutations.

A family history should alert the health care provider to the potential presence of an X-linked disorder in the family. For families with no other family history and negative *L1CAM* mutation testing, the recurrence rate of hydrocephalus is 4%. This figure was ascertained from a prospective study performed of 251 pregnancies with couples with at least one

previous child with hydrocephalus (Váradi et al., 1988). Of 261 pregnancies, 15 had fetal CNS malformations including 12 cases of hydrocephalus and 3 cases of isolated neural tube defects.

Families in whom no genetic etiology can be identified should be offered detailed prenatal sonographic evaluation in a subsequent pregnancy due to the recurrence risk of 4%.

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17 CHAPTER

Intracranial Hemorrhage

Key Points

- Fetal intracranial hemorrhage is generally diagnosed in the late second trimester as an asymmetric echogenic mass within the ventricles, mostly associated with some degree of ventriculomegaly.
- Causes to be considered include drug use (warfarin, cocaine), alloimmune thrombocytopenia, coagulation disorders, or trauma.
- Grading of severity uses a similar scale to that for neonatal intraventricular hemorrhage (IVH), with prognosis being quite poor for most cases of Grades III or IV IVH.
- The only specific treatment relates to situations in which the underlying cause is alloimmune thrombocytopenia, where aggressive therapy with IVIG and steroids in subsequent pregnancies may minimize recurrence.

CONDITION

Fetal intracranial hemorrhage refers to bleeding that occurs antenatally from a blood vessel into the ventricles, subdural space, or parenchyma of the brain. Whereas neonatal hemorrhage is a relatively common occurrence, affecting 40% to 60% of infants delivered before 32 weeks of gestation, fetal intracranial hemorrhage is quite rare. Factors that may place the fetus at risk for intracranial hemorrhage include alterations in maternal blood pressure, a maternal seizure disorder, placental abruption, specific medication or substance exposure (such as warfarin or cocaine), severe abdominal trauma, hereditary coagulation disorders (Komlósi et al., 2005) or alloimmune platelet disorders (Kuhn et al., 1992; Sherer et al., 1998; Lynch et al., 2002). Coagulation disorders associated with fetal intracranial hemorrhage incude factor V Leiden (Komlósi et al., 2005), Factor X mutations (Herrmann et al., 2005), prothrombin G20210A mutation, protein C or S deficiency, antithrombin III deficiency, and antiphospholipid antibody syndrome (Lynch et al., 2002).

Three types of intracranial hemorrhages can occur: intraventricular (or periventricular), intraparenchymal, and subdural. Intraventricular or periventricular hemorrhages are the most common, emanating from small vessels within the subependymal germinal matrix before 33 weeks of gestation (McGahan et al., 1984). The pathogenesis of intraventricular hemorrhage (IVH) is related to fragility of the capillary bed of germinal matrix, a disproportionate amount of total cerebral blood flow to the periventricular area, and the lack of autoregulation of cerebral blood flow in the fetus or premature infant. IVH is the most common form of intracranial hemorrhage seen in the neonate and is categorized in severity on a four-point scale, with the most severe fourth grade including parenchymal involvement (Lynch et al., 2002).

Intraparenchymal hemorrhages may be identified as distinct echogenic areas within the cerebral tissue, with or without displacement of the underlying ventricular or outer surfaces of the brain. As these hemorrhages evolve, they become hypoechoic and flattened as the hematoma liquefies. Residual changes may include development of a

porencephalic cyst (see Chapter 21) or ventricular enlargement. Clots in the ventricular system are seen as bright echogenic areas that are similar to choroid plexus.

Subdural hematoma generally presents as fetal macrocephaly, with separation of the skull from the cerebral cortex. Hyperechoic and hypoechoic areas are identified, filling the space between the brain gyri and the skull. The presence of cerebral edema may cause acoustic enhancement of brain gyri. Catanzarite et al. (1995) have reported on the diagnosis of fetal subdural hemorrhage. They recommended imaging the fetal head in the axial or coronal plane at one level of the sylvian fissure. Normally the separation between the cortex and the inner table of the skull is less than 4 mm. Subdural bleeding can be seen as a collection of echodense material outlining the cortex and separating the sylvian fissure from the inner table of the skull. An additional report on fetal subdural hematoma came from Rottmensch et al. (1991), who identified enhanced echogenicity of the sulci as an indication of brain edema. These authors stated that brain function cannot be predicted sonographically except in the most severe cases.

In a retrospective study of pregnant women in whom a diagnosis of fetal intracranial hemorrhage was made, Achiron et al. (1993) identified five fetuses between 26 and 36 weeks of gestation at the time of diagnosis. Hyperechoic lesions were shown in the brain parenchyma and lateral ventricles in three of five fetuses. Transvaginal sonography permitted the enhanced visualization of ventriculomegaly in one fetus and periventricular leukomalacia in the second fetus. Of the five fetuses studied, two growth-restricted fetuses died after birth, and of the three survivors, two had normal long-term development. One infant developed hydrocephalus, suffered from neurodevelopmental retardation and eventually died at age 7 months (Achiron et al., 1993). In another series, Vergani et al. (1996) described their experience with six cases diagnosed at the University of Milan and 35 cases identified from the English literature. Of the 41 cases of fetal intracranial hemorrhage reviewed, 20 had isolated IVH, 13 had parenchymal hemorrhage, and eight had subdural or subarachnoid hemorrhage. These investigators devised a prognostic scoring system for IVH. A favorable outcome was seen in 50% (6 of 12) fetuses observed with Grade II IVH, but none of the fetuses with the equivalent of a Grade III IVH (blood filling the ventricles) had a favorable outcome.

INCIDENCE

In one study performed at a single institution, the University of Milan, six cases of antenatal intracranial hemorrhage were detected in 6651 fetuses studied. This suggests an incidence of almost one per 1000 fetuses (Vergani et al., 1996). An unusually high incidence of fetal subdural intracranial hemorrhage has been documented in Pacific Islanders who emigrate to New Zealand (Becroft and Gunn, 1989). The cause for this high incidence is unknown, but it suspected to be due to traditional forms of abdominal massage used to change fetal position in utero.

In one study, Sims et al. (1985) reviewed the clinical features and neuropathology of intracranial hemorrhage in 433 consecutive stillbirth autopsies. The authors identified 25 cases of periventricular or intraventricular hemorrhage or gliosis. Of the 25 cases, 10 had IVH alone, 5 had IVH plus an additional intraparenchymal hemorrhage, 5 had parenchymal hemorrhage only, and 5 had gliosis, indicating a remote neurologic injury. Other studies have shown that IVH is present in 6% of stillbirths at autopsy (Minkoff et al., 1985).

Immune thrombocytopenic purpura is the most common autoimmune disorder affecting pregnant women, with an incidence of 1 in 1000 to 1 in 10,000 pregnancies. Fewer than 1% of these women will have babies in whom an intracranial hemorrhage develops. In contrast, severe fetal thrombocytopenia commonly occurs with alloimmune thrombocytopenia, which develops as a result of maternal sensitization to fetal platelet antigens. This occurs in 1 in 2000 to 1 in 5000 pregnancies. Of these cases, approximately 10% to 30% are at risk for intracranial hemorrhage (Johnson et al., 1997; Bussel et al., 1988). This makes alloimmune thrombocytopenia the most common cause of severe thrombocytopenia in fetuses, and the most frequent cause of intracranial hemorrhage in term neonates (Bussel et al., 2005; Berkowitz et al., 2007).

SONOGRAPHIC FINDINGS

Sonographic diagnosis of fetal intracranial hemorrhage was first reported in 1982 in a woman with recurrent episodes of pancreatitis and a fetal death at 29 weeks of gestation (Kim and Elyaderani, 1982). Subsequently, the majority of reported antenatally detected cases of intracranial hemorrhage have occurred during the late second and third trimesters (Catanzarite et al., 1995; Elchalal et al., 2005).

Intracranial hemorrhage is identified as an echogenic area within the ventricles or brain parenchyma. Blood clots are usually echogenic (Figures 17-1 and 17-2) and evolve to characteristic echolucent cystic areas. The sonographic criteria for an intracranial hemorrhage include the presence of an echogenic mass, unilateral or bilateral ventriculomegaly with the presence of intraventricular echogenic foci, germinal matrix, echogenicity, or the presence of periventricular hypoechoic lesions (cysts). In approximately 50% of cases of IVH, sonographic findings will be bilateral (Elchalal et al., 2005).

The commonly used IVH classification system in neonatal imaging has been applied to prenatal sonographic findings, with some modifications (Elchalal et al., 2005). Grade I IVH refers to hemorrhage limited to the subependymal matrix; Grade II refers to no more than 50% filling of the ventricles and lateral ventricular enlargement of no more than 15 mm; Grade III involves more than 50% ventricular filling together with significant ventriculomegaly; Grade IV

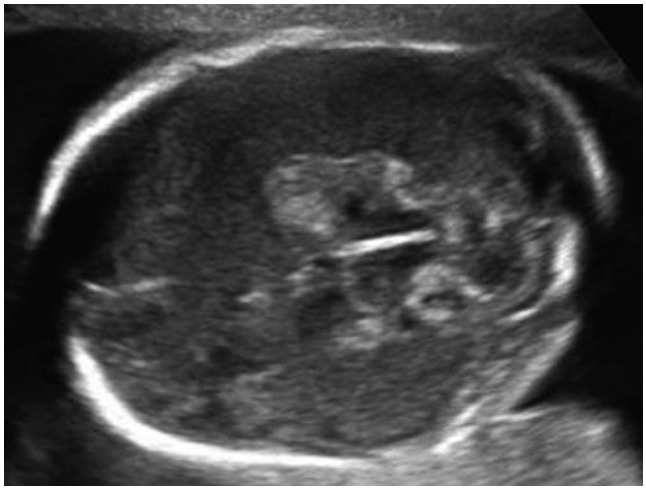

Figure 17-1 Axial sonographic image showing large echogenic area consistent with intracranial hemorrhage.

refers to intraventricular bleeding that also involves the periventricular parenchyma.

DIFFERENTIAL DIAGNOSIS

The major considerations in the differential diagnosis include identifying other potential causes of intraparenchymal or intraventricular masses, as well as identifying potential causes for hemorrhage. It is important to rule out the presence of a prominent choroid plexus. This may present as a densely echogenic mass within the ventricles, mimicking blood clot. The choroid plexus can occupy a large proportion of ventricular space, but this is a normal finding with an expected normal prognosis (Kim and Elyaderani, 1982). Other causes of an echogenic midbrain mass include intracranial neoplasm or infection. A case of malignant glioblastoma multiforme presenting with the appearance of significant intracranial hemorrhage in a 32-week fetus has been reported (Sell et al., 2006).

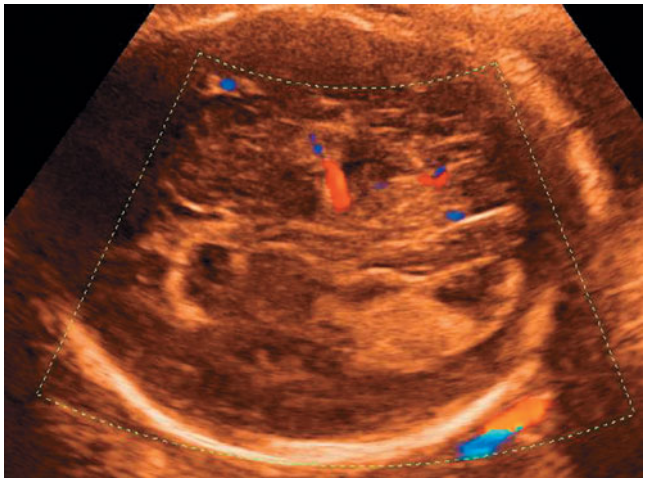

Figure 17-2 Axial sonographic image showing echogenic debris within lateral ventricles consistent with intraventricular hemorrhage.

Considerations in the differential diagnosis of the cause of hemorrhage include coagulation disorders, such as factor V Leiden (Komlósi et al., 2005), Factor X gene mutations (Herrmann et al., 2005), prothrombin G20210A mutation, protein C or S deficiency, antithrombin III deficiency, and antiphospholipid antibody syndrome (Lynch et al., 2002). Fetal thrombocytopenia due to maternal immune thrombocytopenia or maternal platelet antigen incompatibility should also be considered, with the latter being a much more likely cause of significant fetal thrombocytopenia and hemorrhage (Bussel et al., 2005; Berkowitz et al., 2007). Maternal TORCH infection and maternal medication or substance use are also causes of fetal intracranial hemorrhage.

ANTENATAL NATURAL HISTORY

Two main factors are implicated in the pathogenesis of neonatal intracranial hemorrhage, and the same factors are relevant for fetal intracranial hemorrhage: sudden changes in cerebral blood pressure, which cause subependymal hemorrhage in the fragile premature capillary bed of germinal matrix, and perinatal asphyxia, with its attendant hypoxia that tends to induce fluctuations in cerebral blood pressure, resulting in intracranial hemorrhage (Volpe, 1981). The pathogenesis of spontaneous intrauterine subdural hematoma remains less clear. It has been postulated that subdural hematoma may be due to the presence of intermittent aqueductal obstruction, which results in intermittent decompression. This can result in tearing of bridging veins and the development of subdural hematoma (Atluru and Kumar, 1987).

The natural history of intracranial hemorrhage can evolve from bleeding to clot formation to obstruction of spinal fluid drainage, which results in hydrocephalus, or the clot can destroy brain parenchyma and develop into a porencephalic cyst (see Chapter 21).

Porencephaly is defined as a fluid-filled cavity present within the cerebral hemispheres, which may or may not communicate with the spaces that contain cerebrospinal fluid (Eller and Kuller, 1995). A porencephalic cyst results from destruction of cerebral tissues secondary to trauma, infection, or hemorrhage (see Chapter 21). Type 1 porencephaly is a condition that is acquired during the third trimester, due to a destructive process. The area of destroyed cerebral parenchyma is replaced with cerebrospinal fluid. The germinal matrix is especially vulnerable to hypoxia and ischemia between 24 and 32 weeks of gestation due to the sparse supportive stroma, delicate vasculature, and increased metabolic activity of this area (Eller and Kuller, 1995).

Another complication in the evolution of fetal intracranial hemorrhage is hydranencephaly. Hydranencephaly is a congenital abnormality of the central nervous system marked

by absence of cerebral tissue, which can evolve following a subacute intraparenchymal hemorrhage (see Chapter 15). Edmondson et al. (1992) described a circumscribed hyperechoic mass that progressively became more sonolucent with increased fluid accumulation and resulted in loss of identifiable cerebral cortex over the left parietal and occipital lobes. Macrocephaly developed. The infant eventually died on day 4 of life. At autopsy, an organizing hematoma and extensive resorption of the underlying cortex were seen, leaving a fluid-filled cavity with a meningeal covering.

In a series of 33 cases of prenatally diagnosed intracranial hemorrhage, 16 were managed expectantly and 2 of these 16 (12%) resulted in spontaneous intrauterine demise (Elchalal et al., 2005).

MANAGEMENT OF PREGNANCY

The major consideration in the management of pregnancy is to determine the cause of the intracranial hemorrhage. The pregnant patient should be questioned regarding her medical history or the possibility of drug exposure. Maternal conditions associated with fetal intracranial hemorrhage include pancreatitis, preeclampsia, seizures, immune and alloimmune thrombocytopenia, and other disorders of coagulation. These include factor V Leiden, prothrombin G20210A mutation, protein C or S deficiency, antithrombin III deficiency, and antiphospholipid antibody syndrome (Lynch et al., 2002). Fetal conditions that have been reported to be associated with intracranial hemorrhage include factors V and X deficiency (Catanzarite et al., 1995). Alterations in maternal blood pressure, such as hypotension or hypertension associated with placental abruption or preeclampsia, can result in fetal intracranial hemorrhage.

An extensive history regarding the possibility of drug exposure should be obtained. For example, maternal exposure to warfarin has been associated with fetal subdural hemorrhage and evolution to hydrocephalus (Robinson et al., 1980; Ville et al., 1993). The pregnant patient who requires anticoagulation should be changed to heparin during pregnancy. In the normal second trimester fetus, vitamin K_2 is 20% of adult levels and vitamin K_1 is undetectable. Even in subtherapeutic doses, warfarin further reduces the bioavailability of vitamin K to the fetus (Ville et al., 1993). Also, maternal cholestasis and ingestion of cholestyramine can lead to vitamin K deficiency (Sadler et al., 1995). Furthermore, ingestion of aspirin has also been shown to result in fetal hemorrhage (Karlowicz and White, 1993). Salicylate competes with vitamin K at prosthetic group sites on enzymes that synthesize coagulant proteins. Cocaine has also been postulated to be important as a cause of fetal intrauterine hemorrhage because cocaine use leads to destructive lesions of the fetal brain, particularly cerebral infarction (Volpe, 1992). In another study, however, although maternal cocaine exposure was shown to lead to placental abruption, investigators did not find an association between prenatal cocaine use and fetal or neonatal intracranial hemorrhage (Dusick et al., 1993). Fetal trauma, such as in the traditional Polynesian maternal massage, can result in fetal subdural hemorrhage (Gunn et al., 1988).

The presence of a maternal seizure disorder can predispose to fetal intracranial hemorrhage. Neonates exposed to anticonvulsants in utero can have coagulation defects. Fetal anoxia that occurs during a maternal seizure may lead to redistribution of blood flow to the brain and to arterial hypertension (Minkoff et al., 1985). These authors recommended that the fetus of a patient with a seizure disorder who has seizures during pregnancy should be evaluated after the seizure for the presence of intracranial hemorrhage.

The fetus identified antenatally with an intracranial hemorrhage may have abnormal fetal heart rate patterns (Catanzarite et al., 1995), a nonreactive nonstress test, fetal tachycardia, or a positive oxytocin challenge test related to fetal anemia. No relationship, however, has been demonstrated between the umbilical and cerebral artery pulsatility index and severe intracranial hemorrhage (Scherjon et al., 1993).

Repeated sonography is indicated to monitor the evolution of the bleeding, to monitor for the development of hydrocephalus, porencephaly or hydranencephaly. Serial middle cerebral artery Doppler evaluation to check for significant fetal anemia is also recommended. Depending on the cause of the hemorrhage, the fetus may require transfusion with red cells, platelets, and intravenous γ-globulin (in the case of alloimmune thrombocytopenia). Some investigators have suggested daily nonstress tests and contraction stress tests, daily biophysical profiles, and weekly sonography until there is evidence of fetal lung maturity (Pretorius et al., 1986)

Aggressive antenatal management may be indicated for fetuses with alloimmune thrombocytopenia (AIT). Murphy and Bussel (2006) have suggested a regimen of intravenous γ-globulin (IVIG) with or without prednisolone from 20 weeks' gestation onward for patients with AIT at risk for fetal intracranial hemorrhage. Response to therapy can be guided by percutaneous cordocentesis and direct fetal platelet quantification (see Chapter 4). Patients can be categorized as high risk, in which a previous pregnancy has been complicated by fetal intracranial hemorrhage, or standard risk, in which AIT has been diagnosed but without an index case of intracranial hemorrhage. High-risk patients will likely do better with a more aggressive approach of IVIG combined with prednisolone from the second trimester onward, and with further treatment guided by fetal blood sampling. Such further treatment may also include serial fetal platelet transfusions in nonresponding cases. Standard-risk patients may be able to avoid fetal blood sampling, with its inherent morbidity, and may be managed with IVIG alone (Murphy and Bussel, 2006; Berkowitz et al., 2007). The rationale behind the efficacy of maternal IVIG administration is that it may either reduce maternal antibody production or transport across the placenta, or may delay the destruction of antibody-coated platelets in the fetal reticuloendothelial system.

The serologic diagnosis of AIT can be made by satisfying three requirements: demonstration of a platelet antigen incompatibility between the parents, demonstration of a

platelet antibody in maternal serum that binds paternal but not maternal platelets, and identification of an antibody as specific for platelet antigen incompatibility. When a prior sibling has had an antenatal intracranial hemorrhage due to AIT, the clinical manifestations are the same or worse in subsequent fetuses who carry the same antigen (Bussel et al., 1997; Murphy and Bussel, 2006). To prevent antenatal intracranial hemorrhage, treatment must be initiated as early as possible in the subsequent pregnancy.

Following the diagnosis of fetal intracranial hemorrhage it may also be useful to perform fetal MRI examination of the cranial anatomy. In certain cases, in which prenatal ultrasound examination has suggested a Grade II or Grade III IVH, fetal MRI may reveal additional information useful for predicting neurological prognosis (Elchalal et al., 2005).

We recommend that the fetus with an intracranial hemorrhage be delivered at a tertiary care center capable of resuscitation of the newborn infant. Cesarean delivery should be considered for fetuses known to have AIT (Burrows et al., 1988).

Aggressive management may or may not be indicated in the case of fetal subdural hematoma. In one report, a fetus with subdural hematoma was detected in utero at 32 weeks of gestation by the presence of multiple blood clots in the subdural space with secondary compression of brain tissue. Cordocentesis detected anemia in the fetus, who was treated aggressively with transfusion of packed red cells and platelets. Following transfusion, the nonstress test and biophysical profile improved, but delivery was delayed to reduce anticipated complications of prematurity. Nine days later, a second episode of intracerebral bleeding occurred, prompting delivery by emergency cesarean section. Despite the aggressive treatment, the infant died at 6 hours of age (Rottmensch et al., 1991).

FETAL INTERVENTION

No specific intervention is indicated for the fetus other than transfusion of intravenous γ-globulin and/or platelets in cases of AIT.

TREATMENT OF THE NEWBORN

Specific attention should be paid to evidence of increased intracranial pressure, by measurement of the head circumference and palpation of the sutures and fontanelles. The infant should also be specifically examined for the presence of petechiae or ecchymoses as evidence of coagulopathy. A blood count is indicated to determine whether the infant is anemic. Depending on the cause of the hemorrhage, postnatal transfusion with intravenous γ-globulin, packed red blood cells, or platelets lacking an incompatible antigen or steroid therapy in the case of AIT, may be indicated. A diagnostic work-up for AIT and viral sepsis should also be performed.

Postnatally, cranial anatomy should be assessed by computed tomography (CT) scan or magnetic resonance imaging (MRI). Specific consideration should be given to monitoring for the presence of posthemorrhagic hydrocephalus. Hydrocephalus develops as a consequence of acute obstruction to cerebrospinal fluid flow by a blood clot. If posthemorrhagic hydrocephalus is present, consultation with a neurosurgeon is appropriate.

SURGICAL TREATMENT

If posthemorrhagic hydrocephalus is present, the infant may need the placement of a ventriculoperitoneal shunt to drain cerebrospinal fluid.

LONG-TERM OUTCOME

In their review of 41 antenatally detected cases of intracranial hemorrhage, Vergani et al. (1996) documented that a poor outcome was present in 68% of fetuses. The outcome was directly related to the location and extent of the hemorrhage. A poor outcome was present in seven of eight (88%) fetuses with subdural or subarachnoid hemorrhage. Similarly, a poor outcome was present for 12 of 13 (92%) fetuses with parenchymal hemorrhage. A more favorable prognosis was present for fetuses with IVH, in which 9 of 20 cases (45%) had a poor outcome, but these were all observed in Grade II and III hemorrhages. Therefore, the presence of a Grade I IVH observed antenatally is generally associated with a favorable prognosis. In a series of 33 prenatally diagnosed cases of intracranial hemorrhage of 16 fetuses managed expectantly, a total of 8 neonates had moderate to severe neurological deficit at a mean age of 3 years (Elchalal et al., 2005).

All fetuses with intracranial hemorrhage are at an increased risk for the postnatal development of seizures and cerebral palsy (Scher et al., 1991). Similarly, the potential exists for the prenatal or postnatal development of hydrocephalus and neurodevelopmental delay.

The clinical course for fetuses diagnosed with AIT is more variable. The outcome ranges from benign resolution within 2 to 3 weeks after birth to an occasional fatal hemorrhage (Kuhn et al., 1992).

GENETICS AND RECURRENCE RISK

The genetic causes of intracranial hemorrhage include platelet incompatibility disorders and the hereditary coagulopathies.

Every attempt should be made to diagnose the underlying basis of the hemorrhage, as a number of the coagulopathies that involve protein or factor deficiencies are inherited in an autosomal dominant manner and are expected to have a 50% risk of recurrence. The exceptions are Factor X mutations, which are inherited as autosomal recessive conditions.

Ninety-eight percent of the population of fetuses with AIT are phospholipase A_1 (PLA1)-positive. The transmission of the gene for this platelet antigen is autosomal dominant (Morales and Stroup, 1985). Two percent of the population lacks this platelet antigen. The affected infant is generally diagnosed only after an initial hemorrhagic episode. The chance of recurrence depends on whether the father of the baby is homozygous, meaning that both of his chromosomes carry the gene for the platelet antigen. If the father is a homozygote, there is a 100% chance of having a subsequently affected child. However, if the father is heterozygous there is only a 50% chance that a subsequent child will inherit the chromosome carrying the gene for PLA1 (Kuhn et al., 1992). A review of the medical literature shows an overall 75% chance of having a subsequently affected child, but it is important to remember that the risk is either 50% or 100% for an individual couple.

For many of the inherited coagulopathies or platelet disorders, prenatal diagnosis is available on a DNA basis from chorionic villi or amniotic fluid cells, or by obtaining fetal blood at cordocentesis. Because of the relatively high recurrence risk for these conditions, careful sonographic monitoring in a subsequent pregnancy is indicated to monitor for the potential for fetal intracranial hemorrhage.

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Macrocephaly

18

CHAPTER

Key Points

- Macrocephaly is defined as a head circumference greater than three standard deviations (SDs) above the mean for age and sex.
- This disorder is rare, and the exact incidence is unknown.
- The antenatal natural history has not been elucidated.
- During the antepartum period, other causes of macrocephaly should be excluded such as hydrocephalus or intracranial space-occupying lesion.
- The diagnosis of macrocephaly should not alter prenatal care with regard to timing of delivery or mode of delivery.
- Long-term outcome regarding macrocephaly is sparse. The majority of cases appear to do well; however, it appears to be associated with an increased risk for autism. Unilateral macrocephaly seems to be associated with poor outcomes.
- The inheritance pattern of benign macrocephaly is autosomal dominant with incomplete penetrance with a male to female preponderance of 4:1. Differential diagnosis should include consideration of overgrowth syndromes, which may be due to single-gene disorders.

CONDITION

Macrocephaly is defined as a head circumference greater than 3 SD above the mean for age and sex. The terms *macroencephaly* and *megaloencephaly* have been used interchangeably with *macrocephaly*, which indicates an increased brain volume in the absence of hydrocephalus (Gooskens et al., 1988). It may be associated with subdural hematoma, other space-occupying lesions, an unduly thickened skull, or a large brain (Lorber and Priestley, 1981). Normal brains of adults usually weigh less than 1500 g. Weights above this are considered abnormal and macrocephalic. At birth the normal brain weighs approximately 370 g. Almost all cases of macrocephaly represent normal variants with a normal large brain (Lorber and Priestley, 1981).

The most common variety of this condition is benign familial macrocephaly, accounting for at least 50% of cases. It is usually associated with an autosomal dominant pattern of inheritance (DeMeyer, 1972). There is a male to female preponderance of 4:1 (Lorber and Priestley, 1981). Isolated sporadic macrocephaly without evidence of a familial disorder is less common (DeMeyer, 1972; Pettit et al., 1980). Macrocephaly may also be associated with generalized disorders of overgrowth, such as cerebral gigantism (Sotos syndrome),

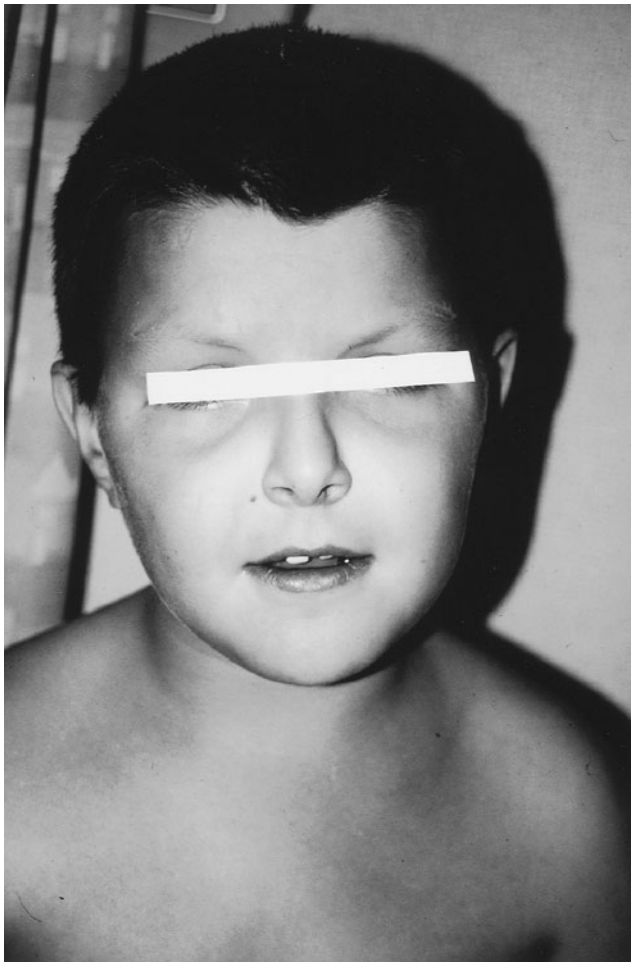

Figure 18-1 Nine-year-old boy who exhibits macrocephaly as part of an overgrowth syndrome. His head circumference is 4 SD above the mean. (*Photograph courtesy of Dr. Patricia Wheeler.*)

Beckwith–Wiedemann syndrome, Weaver syndrome, and achondroplasia (Ott and Robinson, 1969; Dodge et al., 1983) (see Chapter 124) (Figure 18-1).

Several neurocutaneous disorders are associated with macrocephaly. It is seen most consistently with multiple hemangiomatosis syndrome (Riley and Smith, 1960) and Bannayan–Riley–Ruvalcaba syndrome (Gorlin et al., 1992). Hypotonia associated with gross motor and developmental delay is also common (DiLiberti, 1992). In one series of 14 children with hypotonia and macrocephaly, 13 demonstrated evidence of lipid storage myopathy on muscle biopsy (DiLiberti, 1992). All 13 children had clinical examinations consistent with either benign familial macrocephaly or the Bannayan–Riley–Ruvalcaba syndrome. Although macrocephaly is generally a benign condition, in several series it has been associated with intellectual impairment. A syndrome of X-linked mental retardation associated with macrocephaly, coarse facies, hypertelorism, and macro-orchidism has been reported (Atkin et al., 1985). The affected males were moderately intellectually impaired, and there was some expression in heterozygotes. In another report, three sisters with moderate to severe intellectual impairment together with macrocephaly and distinctive facies were described, and it was suggested that this was either a dominant condition or the heterozygous expression of an X-linked entity (Fryns et al., 1988). In a subsequent report, a family with X-linked mental retardation was described in which the affected members had macrocephaly with heterozygous expression (Turner et al., 1994).

Unilateral macrocephaly is an unusual variant of macrocephaly, in which there is enlargement of only one cerebral hemisphere. It is due to abnormal neuronal cell migration in utero. It is usually associated with severe seizures during the neonatal period. The term *macrocephaly* is rather simplistic in such cases, as the anomaly is more typical of a hamartomatous malformation than a simple hypertrophy (Bignami et al., 1968; Townsend et al., 1975). Unilateral macrocephaly seems to be equally distributed between the right and left sides (King et al., 1985; Robain et al., 1988).

INCIDENCE

Macrocephaly is an unusual prenatal finding with an unknown incidence.

SONOGRAPHIC FINDINGS

Macrocephaly should be suspected in the presence of abnormally large head measurements (greater than 3 SD above the mean for gestational age), without evidence of hydrocephalus or intracranial masses. Sonography should confirm the absence of other fetal anomalies, particularly hydrocephalus, by the identification of a normal fetal lateral ventricle:hemisphere ratio. Magnetic resonance imaging (MRI) can be used as an adjunct to determine if the macrocephaly is isolated or complicated by other brain malformations (Parazzini et al., 2005).

Benign familial macrocephaly has rarely been diagnosed in utero. In one case report, the abnormally large head circumference was first noted at 32 weeks' gestation, at which time the biparietal diameter was consistent with a gestational age of 39 weeks (DeRosa et al., 1989). As the pregnancy progressed, the head size increased proportionately with other fetal biometric parameters.

Sonographic findings in unilateral macrocephaly include enlargement of one cerebral hemisphere, a shift of the midline structures, and mild ipsilateral ventriculomegaly (Sandri et al., 1991; Ramirez et al., 1994).

DIFFERENTIAL DIAGNOSIS

A family history and physical examination of the parents, including measurement of their head circumferences, may be helpful when the diagnosis of macrocephaly is considered

(DeRosa et al., 1989). Hydrocephalus, intracranial hemorrhage, and other intracranial masses (such as an intracranial tumor or vein of Galen aneurysm) should all be considered in the differential diagnosis. Syndromes associated with macrocephaly include Beckwith–Wiedemann syndrome, Gorlin syndrome (basal-cell-nevus syndrome), FG syndrome, Weaver syndrome, Sotos syndrome, and Bannayan–Riley–Ruvalcaba syndrome. Porencephaly, intracranial tumors, and other conditions associated with a shift of the midline echo should also be considered in the differential diagnosis of unilateral macrocephaly.

ANTENATAL NATURAL HISTORY

Little information is available for counseling the patient on the natural history of prenatally diagnosed macrocephaly. Counseling will depend on the etiology of the macrocephaly.

MANAGEMENT OF PREGNANCY

If the diagnosis of macrocephaly is suspected prenatally, a detailed sonographic examination is indicated to rule out other conditions associated with an enlarged fetal head, such as hydrocephalus or intracranial space-occupying lesions (Table 18-1). If no other abnormalities are identified, and no additional risk factors are present, there does not seem to be an indication for amniocentesis. A family history should be obtained, and a physical examination of the parents, including measurement of their head circumferences, should be performed to search for possible genetic syndromes associated with macrocephaly (DeRosa et al., 1989). Serial sonography is recommended to confirm the diagnosis and exclude other conditions that may become apparent later in gestation, such as short-limb skeletal dysplasias or hydrocephalus.

In one of the few case reports of prenatally diagnosed macrocephaly, a normal spontaneous vaginal delivery occurred in a patient with a maternal height of 4 ft 11 in and a weight of 211 lb (DeRosa et al., 1989). With regard to management of delivery, there does not seem to be a significant risk of macrosomia associated with the diagnosis of macrocephaly. In a series of 109 cases of macrocephaly, the mean birth weight in 95 full-term infants was normal (3462 g) (Lorber and Priestley, 1981). Only 13 children had birth weights above the 90th percentile (Lorber and Priestley, 1981). Head circumference at birth in 51 infants ranged from 32 to 40.5 cm, with a mean of 36.2 cm, as compared with a normal mean of 34.6 cm (Lorber and Priestley, 1981). A diagnosis of macrocephaly should not change the timing of delivery, and there is no indication for routine cesarean delivery unless other standard obstetric indications exist. It is not necessary for delivery to occur in a tertiary care setting.

Table 18-1

Conditions Associated with Macrocephaly

Benign familial macrocephaly
Sporadic macrocephaly
Neurofibromatosis
Cerebral gigantism (Sotos syndrome)
Achondroplasia
Osteogenesis imperfecta
Beckwith–Wiedemann syndrome
Neurocutaneous syndromes
Bannayan–Riley–Ruvalcaba syndrome
Weaver syndrome
Unilateral macrocephaly

FETAL INTERVENTION

No fetal intervention has been described for macrocephaly.

TREATMENT OF THE NEWBORN

Most cases of isolated macrocephaly do not give rise to difficulty in the delivery room. The clinical presentation varies from no apparent neurologic deficit in the majority of cases to severe seizures and mental retardation. It is interesting to note that idiopathic macrocephaly has been linked to an increased risk for autism (Bolton et al., 2001; Dementieva et al., 2005).

A thorough physical examination should be performed to search for phenotypic features of any of the genetic syndromes associated with macrocephaly. Measurement of the head circumference in children is a standard and essential part of the newborn clinical examination. Composite charts for head circumference from birth to 18 years are available, and a single head circumference measurement outside the range of normal should lead to further evaluation of the child (Nellhaus, 1968).

Other causes of macrocephaly, such as hydrocephalus, subdural hematoma, intracranial tumor, or other space-occupying lesions, must be ruled out as soon as possible.

Macrocephaly should be considered a diagnosis of exclusion following thorough clinical examination and imaging of the head. Cranial ultrasound examination is usually the first line for imaging of the neonatal head. Postnatal computed tomographic (CT) scanning or MRI is the more usual examination in older infants and children since the anterior fontanelle may not provide an adequate ultrasound scanning window. In some cases of autosomal dominant macrocephaly, histochemical examination of skeletal muscle biopsies for lipid storage myopathy may be useful in resolving clinical ambiguities (DiLiberti, 1992).

The clinical presentation of unilateral megaloencephaly is characterized by severe seizures in early infancy. Cranial asymmetry may be overlooked in the newborn if the skull is not examined carefully. CT imaging in such cases demonstrates enlargement of the hemisphere and displacement of the ventricles and the falx. MRI may be helpful in the radiologic evaluation of unilateral macrocephaly (Kalifa et al., 1987).

SURGICAL TREATMENT

No surgical treatment is required for benign, isolated macrocephaly.

LONG-TERM OUTCOME

The long-term prognosis for macrocephaly is not well known and depends on the etiology of the disorder. In a follow-up study of 109 children with macrocephaly, the rate of head growth was noted to be above normal in 80% of children during the first 4 months of life, and in a further 12% at 1 to 2 years of age (Lorber and Priestley, 1981). The majority of these children were neurologically normal. Ninety-six children were judged to be of normal intelligence, and of the remaining 13 children, 6 were judged to be in the normal-to-below average range. Seven children had significant intellectual impairment; 6 of these 7 children had normal CT examinations. Persistent muscular hypotonia was noted in 5 children, and 2 had seizures (Lorber and Priestley, 1981).

Nonetheless, it is interesting to note that macrocephaly appears to be associated with an increased risk for autism, and that macrocephaly is one of the most consistent physical findings in people with autism. In a case–control study of a cohort of boys born with macrocephaly, infantile macrocephaly was associated with an increased risk for autism (odds ratio 5.44, 95% CI 1.11–52.15; $p = 0.03$) (Bolton et al., 2001). Abnormal acceleration of head growth may be one of the reasons why these individuals are at risk for autism (Dementieva et al., 2005).

The prognosis for unilateral macrocephaly seems to be universally poor. In the reviews of this condition 8 of 16 children had died by 6 months of life and 7 more had died before 5 years of age (King et al., 1985; Robain et al., 1988). The remaining infant was 11 months of age at the time of reporting. In another series, all five children with unilateral macrocephaly were still alive at ages up to 9 years (Kalifa et al., 1987). The reason for better survival in this series may be improvements in anticonvulsant therapy.

GENETICS AND RECURRENCE RISK

The inheritance pattern of benign macrocephaly is autosomal dominant with incomplete penetrance (Asch and Myers, 1976; Lorber and Priestley, 1981; Cole and Hughes, 1991).

The high male:female ratio is puzzling for a condition with a well-defined autosomal dominant mode of inheritance. It is possible that boys are more likely to be referred for evaluation of hypotonia or weakness than girls (DiLiberti, 1992), but this is an unlikely explanation for the entire sex-ratio discordance. The recurrence risk for other causes of macrocephaly depends on the underlying syndrome diagnosed. Several of the conditions associated with generalized overgrowth, such as Sotos syndrome and Bannayan–Riley–Ruvalcaba syndrome, are due to known mutations in specific genes (*NSD1* and *PTEN*, respectively).

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19 CHAPTER Myelomeningocele

Key Points

- Open spinal cord defect that protrudes dorsally, is not covered by skin, and is associated with spinal-nerve paralysis.
- Current prevalence in the United States is still 0.5 to 1 case per 1000 pregnancies.
- Maternal risk factors include obesity, anticonvulsant medication, short interpregnancy interval, and genetic polymorphisms in various enzymes in the homocysteine methylation pathway.
- Sonographic findings include a small biparietal diameter, scalloping of the frontal bones, a compressed cerebellum, lateral ventriculomegaly, Chiari II abnormalities, splaying of dorsal vertebrae, and a dorsal sac.
- Karyotype should be performed, even in isolated neural tube defects.
- A prospective clinical trial comparing outcomes for open fetal surgery compared to standard postnatal surgery is in progress.
- Long-term outcome depends on the level of the spinal defect and the presence of associated anomalies.
- Morbidity has been significantly improved by interventricular shunting for hydrocephalus and clean intermittent bladder catheterization to reduce renal complications.
- Most neural tube defects are isolated and have a multifactorial inheritance pattern.

CONDITION

Myelomeningocele is an open spinal cord defect that protrudes dorsally, is not covered by skin, and is usually associated with spinal nerve paralysis. Technically, *spina bifida* refers to a cleft or opening in the vertebral body; this term is also used to collectively describe a group of disorders that involve the spinal cord. Lumbosacral lipomas are subcutaneous masses of fat in the lumbosacral region (Shurtleff and Lemire, 1995). Myelomeningoceles are malformations that result from

failure of the neural tube to fuse during early embryogenesis, between 25 and 28 days postovulation, when the anterior and posterior neuropores close. Skin-covered defects, such as lipomyelomeningocele, result from abnormalities in secondary neurulation and retrogressive differentiation that occurs between 28 and 56 days postovulation (Shurtleff and Lemire, 1995).

The first medical report of a myelomeningocele was made by a Dutch physician, Nicholas Tulp, who practiced between 1593 and 1674. He described a series of six cases of patients with spina bifida (Tulp, 1716).

"Open" neural tube defects are myelomeningoceles that are not covered by skin. Leakage of α-fetoprotein (AFP) from the cerebrospinal fluid (CSF) into the amniotic fluid results in an increased transport of AFP into the maternal circulation. Screening by maternal serum AFP analysis has resulted in an increased ability to detect these lesions prenatally.

Herniation of the spinal cord probably reduces intraspinal pressure. This allows the hindbrain to become downwardly displaced, resulting in the hindbrain herniation that is part of the Chiari type II malformation, which is seen almost exclusively in patients affected with myelodysplasia. It is characterized by caudal movement of the cerebellar vermis, brainstem, and fourth ventricle. The Chiari type II malformation is responsible for many of the early deaths in patients affected with myelodysplasia. Chiari, a professor of pathology in Prague, wrote two papers in 1891 and 1896 that described four types of pathologic changes occurring in 40 affected patients (Rauzzino and Oakes, 1995). These changes concerned the abnormal position of the cerebellum in relation to the foramen magnum. Arnold, in contrast, published a single case report in 1894 that described a single patient with myelodysplasia and other congenital anomalies (Rauzzino and Oakes, 1995).

INCIDENCE

The incidence and livebirth prevalence of myelomeningocele are correlated strongly with ethnic and geographic factors. The highest frequencies of neural tube defects are found in Great Britain, Ireland, Pakistan, Northern India, Egypt, and Arab countries. The lowest incidences are found in Finland, Japan, and Israel. Even in the United States, a geographic distribution of these defects occurs, with the frequency being the highest in the East and the South, and the lowest in the West (Harmon et al., 1995). There is an increased incidence of neural tube defects in Hispanics, especially if the mother was born in Mexico (Shaw et al., 1994).

The livebirth prevalence of infants with myelomeningocele has changed dramatically since the advent of widespread maternal serum screening for AFP. Before 1980, the livebirth prevalence of infants with neural tube defects was between 1.5 and 4.5 per 1000 livebirths. After 1980, this decreased to 0.74 to 2.5 per 1000 livebirths (Shurtleff and Lemire, 1995). In the United States, the current prevalence of neural tube defects is 0.5 to 1 per 1000 pregnancies (Shaer et al., 2007). The lowest incidence of neural tube defects is in African blacks, who have a livebirth prevalence of 1 per 10,000 (Shurtleff and Lemire, 1995). Because the screening tests detect anencephaly (see Chapter 7) as well as myelomeningocele, and many parents decide to terminate pregnancies affected with the uniformly fatal anencephaly, the incidence of myelomeningocele has increased as a percentage of all cases of neural tube defects (Rieder, 1994).

In a review of factors associated with neural tube defects in the NIH-sponsored Collaborative Perinatal Project that reviewed the pregnancies of 53,000 pregnant women, Myrianthopoulos and Melnick (1987) demonstrated that maternal diabetes mellitus, heart disease, lung disease, and use of diuretics, antihistamines, or sulfonamides were all associated with an increased risk of neural tube defects. In addition, women who had a short interval between the end of the previous pregnancy and the current pregnancy had an increased incidence of neural tube defects.

More recently, it has been shown that maternal use of the anticonvulsants valproic acid and carbamazepine, or the folic acid inhibitor aminopterin, is also associated with neural tube defects. Similarly, a maternal history of prepregnancy obesity or type II diabetes increases the chance of conceiving a child with neural tube defect (Shaw et al., 2000; Watkins et al., 2003). Neural tube defects are also associated with low socioeconomic status, a positive family history, and twinning. In general, females are affected more often than males (Källén et al., 1994).

Maternal polymorphisms or mutations in various enzymes in the homocysteine remethylation pathway confer an increased risk for fetal neural tube defects. The enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR) is important in the production of the circulating form of folic acid. Specific polymorphisms in the gene for MTHFR, such as maternal homozygosity for the 677T allele, or compound heterozygosity for the C677T/A1298C alleles, carry an increased risk (Peadar et al., 2004). Maternal variation in the gene for another enzyme, methionine synthase (MTRR) also carries an increased risk for affected fetuses when present in combination with an MTHFR polymorphism or low B12 levels (van der Linden et al., 2006).

The etiology of myelomeningocele is thought to be multifactorial in most cases; however, women who preconceptually take at least 400 μg of folate a day for 3 months have 70% to 80% reduction in risk of their fetuses having open neural tube defect (Centers for Disease Control and Prevention, 1992). The Center for Disease Control and Prevention estimated that the rates of open neural tube defects, both anencephaly and myelomeningocele, have fallen by 26% in the United States, compared to before 1998 when mandatory folate fortification of cereal grain products began (Matthews et al., 2002; Centers for Disease Control and Prevention, 2004).

SONOGRAPHIC FINDINGS

Prior to the mid-1980s, sonographic diagnosis of myelomeningocele relied on the meticulous scanning of the fetal vertebrae for abnormalities. Using this method, neural tube defects were missed. More recently, the prenatal sonographic diagnosis of myelomeningocele has been enhanced by the recognition of specific brain abnormalities that generally precede detection of the spinal lesion (Blumenfeld et al., 1993) (Table 19-1).

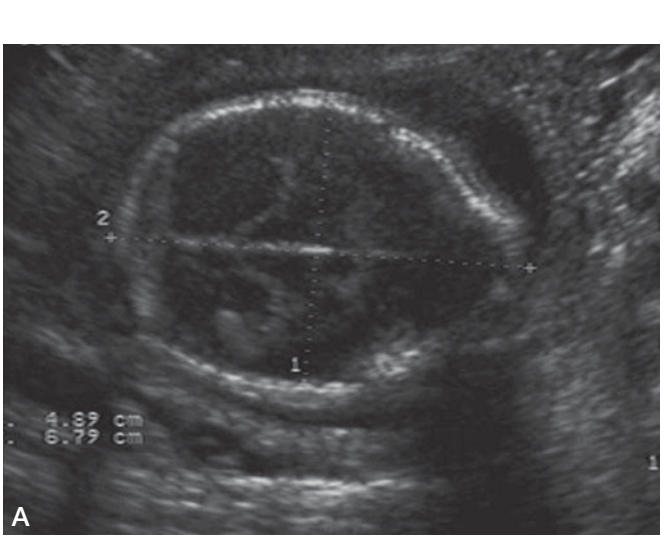
Intracranial Findings

The central nervous system (CNS) abnormalities described in neural tube defects include cerebral ventriculomegaly, microcephaly, abnormalities of the frontal bone, and obliteration of the cisterna magna with an apparently absent cerebellum or an abnormal concavity of the cerebellar hemispheres. These latter abnormalities have been referred to as the "fruit" findings, which include the lemon and the banana signs. The lemon sign (Figure 19-1) describes a concave or flattened frontal contour of the fetal calvarium rather than a normal convex frontal contour. The banana sign (Figure 19-2) describes the posterior convexity of the cerebellum within the posterior cranial fossa (Nicolaides et al., 1986). The lemon sign has been described in 1% of apparently normal fetuses, whereas the banana sign is not found in normal fetuses. The abnormal CNS sonographic findings are a consequence of the Arnold–Chiari malformation. In a prospective analysis, Campbell et al. (1987), who studied 436 fetuses at high risk for spina bifida, identified 26 fetuses with an open neural tube defect. Of the 26, 17 (62%) had a small biparietal diameter for gestational age, 9 (35%) had an abnormally small head circumference, and 100% had a positive lemon sign. In addition, 25 of 26 fetuses (96%) had a cerebellar abnormality. Of these, nine had an absent cerebellum, and 16 had a positive banana sign. Only one fetus in the study with an open neural tube defect had a normal cerebellum. These findings were further defined by Van den Hof et al. (1990), who demonstrated that

Table 19-1

Sonographic Abnormalities in Myelomeningocele

Intracranial Findings
Small biparietal diameter
Small head circumference
Lemon sign—scalloping of frontal bones
Banana sign—compressed cerebellum
Lateral ventriculomegaly
Chiari II abnormalities
Beaking of tectum
Hindbrain herniation—cerebellar vermis through foramen magnum
Elongation and kinking of medulla
Obliteration of cisterna magna
Spinal Findings
Splaying of dorsal vertebral elements
Meningocele sac
Myelomeningocele sac
Presence of placode on surface of sac
Neural elements bridging across the sac



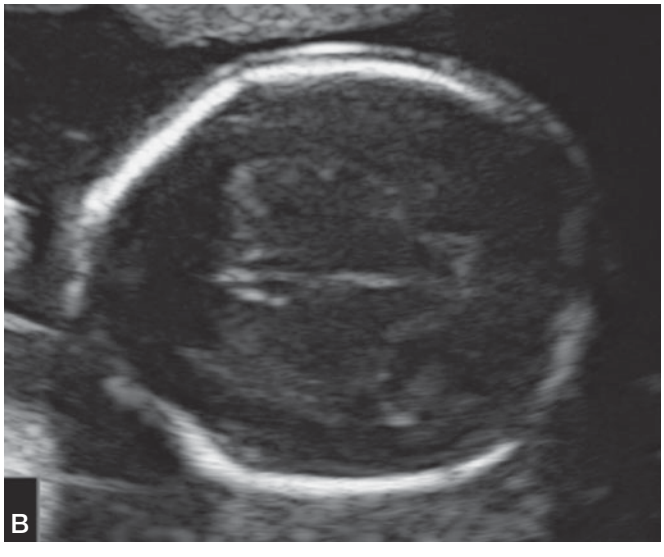


Figure 19-1 **A**. Transverse view of a fetal head demonstrating the "lemon sign" in a fetus with myelomeningocele. **B**. Similar sonographic presentation of an apparent lemon sign. This fetus, however, has craniosynostosis.

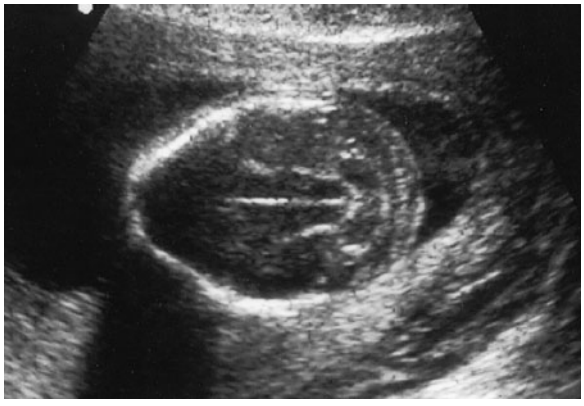


Figure 19-2 Suboccipital bregmatic view of a fetal head demonstrating the "banana sign," which derives from anterior curving of the cerebellar hemispheres with simultaneous obliteration of the cisterna magna.

the CNS abnormalities seen in myelomeningocele evolve with gestation. These authors studied 130 fetuses with open spina bifida and demonstrated a relationship between gestational age and the presence of the lemon and banana signs. A lemon sign was present in 98% of fetuses with open spina bifida at ≤24 weeks of gestation, although this finding was seen in only 13% of fetuses at >24 weeks. Cerebellar abnormalities were seen in 95% of fetuses at any stage of gestation, although the banana sign was more typical at <24 weeks, and apparent cerebellar absence was typical of fetuses at >24 weeks. Because the lemon sign is due to decreased intracranial pressure because of caudal herniation of the hindbrain contents, lack of the lemon sign may be due to skull maturation. Alternatively, the cerebroventriculomegaly that is very common in open spina bifida may compensate for the loss of the brain mass. This may displace the skull bones.

More recently, Ball et al. (1993) demonstrated that the lemon sign is not specific for myelomeningocele (Figure 19-1B). In this report of 23 cases of a positive lemon sign, 12 were associated with an open spina bifida, and 6 were seen in cases of encephalocele (see Chapter 12). An additional 5 fetuses did not have a neural tube defect, although they had a variety of other abnormalities, including thanatophoric dysplasia, cystic hygroma, and agenesis of the corpus callosum. An additional CNS finding associated with myelomeningocele was effacement of the cisterna magna, which was seen in 19 of 20 fetuses studied with myelomeningocele (Goldstein et al., 1989). In a review of 234 fetuses with open spina bifida diagnosed at <24 weeks of gestation, Watson et al. (1991) demonstrated that all but two fetuses had at least one of the cranial abnormalities described for affected fetuses. They also questioned whether there was a higher positive predictive value for open spina bifida when more than one sign was observed antenatally. These authors also cautioned that evaluation of motor function in the fetus was not predictive of future neuromuscular status.

A common accompanying intracranial finding in myelomeningocele (MMC) is lateral ventriculomegaly, in which the atrial measurements of the posterior horns exceed 1 cm. In the second trimester, the biparietal diameter and head circumference may be below the 5% for gestational age (Shaer et al., 2007). When MMC is diagnosed between 16 and 24 weeks, microcephaly has been observed in up to 69% of fetuses (Campbell et al., 1987; Thiagarajah et al., 1990). As pregnancy progresses, both biparietal diameter and head circumference tend to normalize in late second trimester. Hydrocephalus, present in 75% of cases, tends to progress slowly during the third trimester (Shaer et al., 2007).

Spinal Findings

As stated in Chapter 88, evaluation of the fetal spine depends on the visualization of the three ossification centers within the fetal vertebra. The centers of the neural arches should be parallel or converging. In the longitudinal plane, the spine should appear like a "railroad track," with gradual widening toward the fetal head and tapering toward the sacrum. However, the distal part of the spine may not be ossified in healthy fetuses at <22 weeks of gestation (Budorick et al., 1995). Spina bifida can be demonstrated in both the coronal and transverse planes. In the coronal plane, widening of the ossification centers in the neural arch interrupts the normal parallel configuration of the vertebral arches (Figure 19-3A). In the transverse plane, ossification centers in the neural arch either diverge or take on a U-shaped configuration (Figure 19-4). The presence of scoliosis or kyphosis is associated with neural tube defects (Figure 19-3B).

Kollias et al. (1992) assessed the sonographic accuracy of the estimation of spinal level involved in the MMC. Of 28 cases studied, sonographic and pathologic levels were in agreement in 18 (64%) and within one spinal level in 22 (79%).

Other sonographic findings that may suggest a MMC include a cystic meningeal sac, which may have a shimmering effect with fetal motion (Figure 19-5) (Budorick et al., 1995). The sonographer should also examine the fetus's lower extremities for the possibility of clubfeet.

With the presence of skin covering the neural tube defect, the lesion is considered to be a closed neural tube defect, such as lipomyelomeningocele, which has a different etiology. Closed neural tube defects are not usually associated with Arnold–Chiari II malformations and they have a much more favorable prognosis (Tortori-Donati et al., 2000; Ramin et al., 2002).

Magnetic Resonance Imaging

The adjunctive use of magnetic resonance imaging (MRI) of the fetus has provided additional and complementary information to ultrasound examination alone (Figure 19-6). The results of at least two studies suggest that fetal MRI is superior to ultrasound examination for prenatal diagnosis of the intracranial abnormalities associated with MMC (Dinh et al., 1990; Levine et al., 1999). In a comparison of sonography and MRI, both were equally accurate in assignment of MMC level

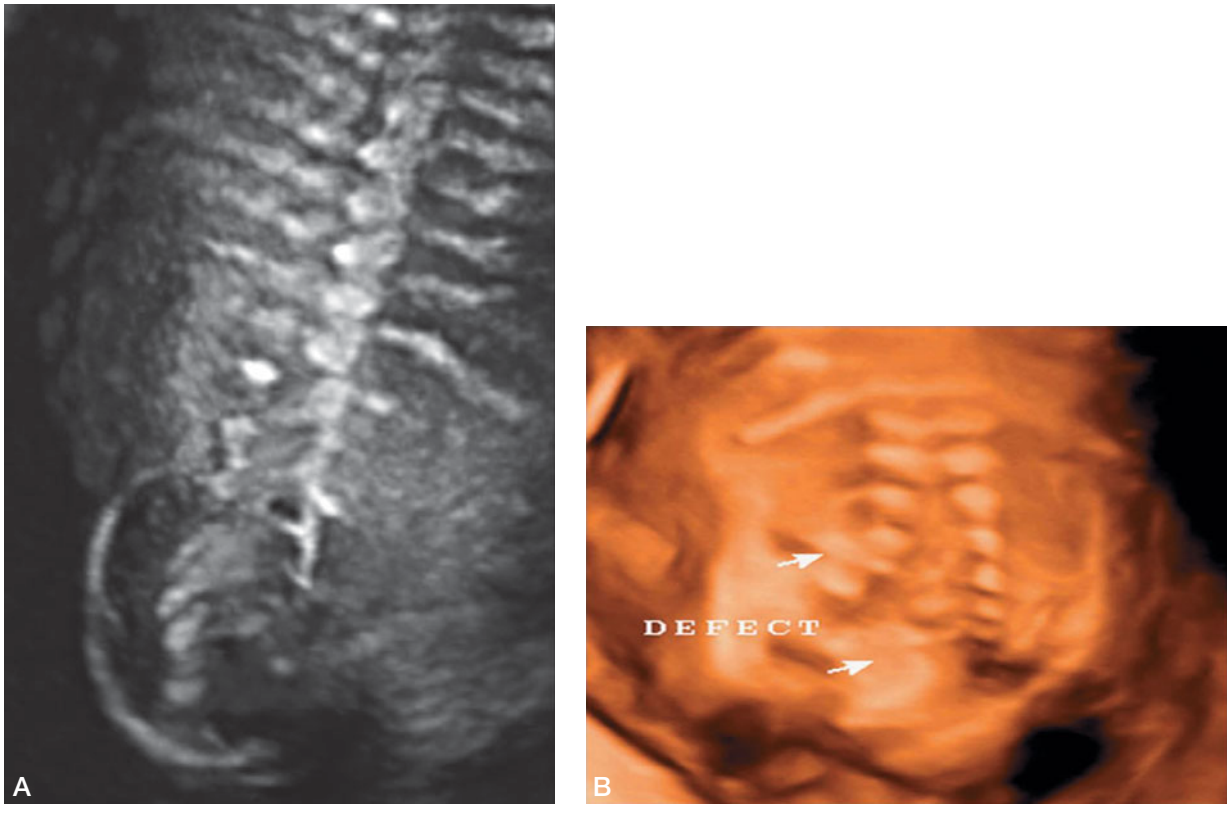


Figure 19-3 **A.** Ultrasound image in coronal plane demonstrating widened ossification centers of the neural arches which interrupt the normal parallel configuration. **B.** Three-dimensional reconstruction demonstrating scoliosis at the level of dysraphic defect.

(Aaronson et al., 2003). MRI may be a particularly helpful adjunct to ultrasound examination when there is a large maternal body habitus, oligohydramnios, low position of fetal head, or posterior position of fetal spine present (Glenn and Barkovich, 2006).

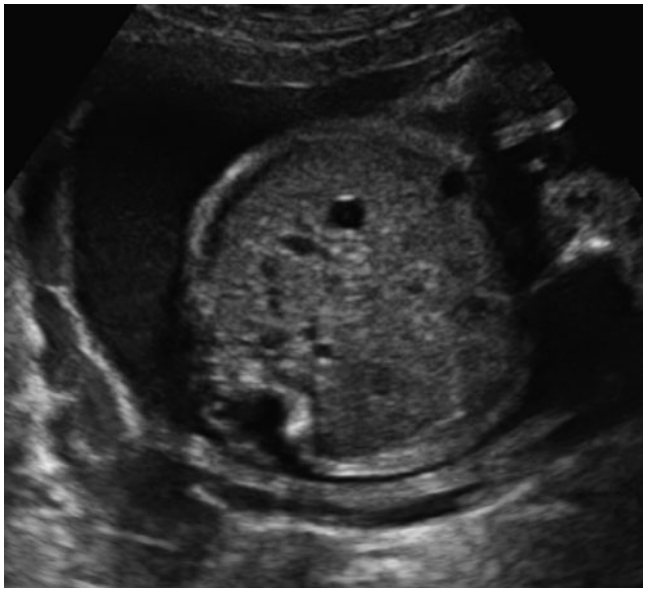


Figure 19-4 Transverse view of ossification centers in the neural arch with a U-shaped configuration.

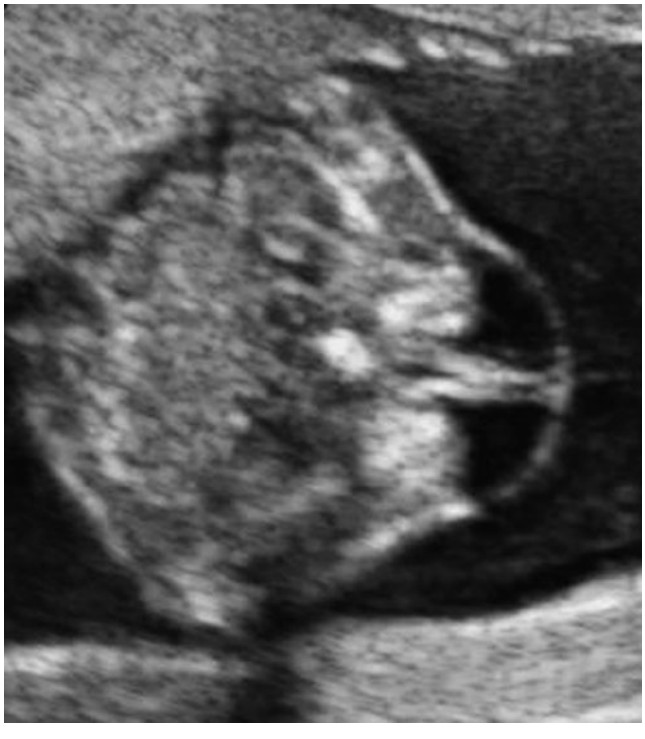


Figure 19-5 Transverse view through the sacrum of a fetus at 20 weeks with a large sacral sac.

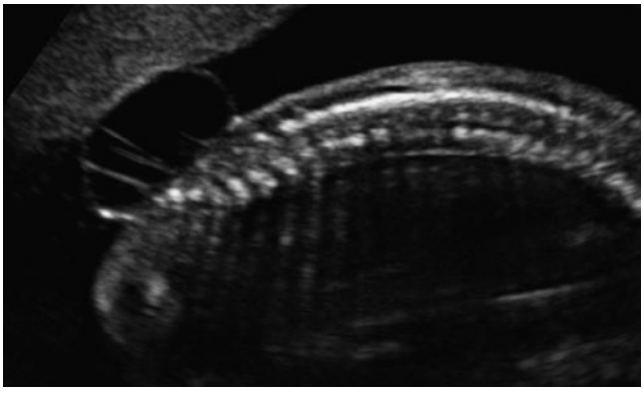


Figure 19-6 Prenatal MRI of a fetus at 28 weeks with a large L2-S2 meningomyelocele demonstrating a Chiari malformation with significant herniation of the cerebellum through the foramen magnum. (*Image courtesy of Dr. E. Twomey, Children's University Hospital, Temple Street, Dublin.*)

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for MMC includes isolated hemivertebrae (see Chapter 88). The lemon sign, as stated earlier, has also been seen in encephalocele (see Chapter 12), thanatophoric dysplasia (see Chapter 90), cystic hygroma (see Chapter 31), and craniosynostosis (see Chapter 10 and Figure 19-1B). The demonstration of a mass near the fetal sacrum should also suggest a possible diagnosis of sacrococcygeal teratoma (see Chapter 115). Sacrococcygeal teratomas are large cystic or solid masses arising from the coccyx. These masses may be associated with fetal hydrops or polyhydramnios. If the fetal sacral bones cannot be visualized, considerations in the differential diagnosis also include the caudal regression syndrome and sirenomelia (see Chapter 87).

ANTENATAL NATURAL HISTORY

With the presence of an open neural tube defect there is increased in utero lethality. For example, at 8 weeks of gestation, one fourth of all conceptuses with neural tube defects will be liveborn, one-fourth will be stillborn, and one half will spontaneously abort (Main and Mennuti, 1986).

Embryology

The formation of the neural tube begins at approximately day 19 with formation of the primitive streak. Epiblasts transform to ectoderm along the dorsal midline of the embryo. This gives rise to the neural plate, which then enfolds to form the neural groove. In the middle of the 4th week, neural folds on each side of the neural groove begin to fuse, thus forming the neural tube (Rieder, 1994). Current evidence suggests that there are two parallel processes that occur. At the level of the fifth somite, where the brain and spinal cord meet, the normal folds join in a zipperlike fashion that proceeds cranially and candally (Shaer et al., 2007). A second closure site appears in the forebrain; fusion also occurs at that site in two directions, and meets the zipper process proceeding from the hindbrain. In parallel, the zipper process moves to close the most rostral part of the forebrain. Lack of signaling between the neural tissue and overlying ectoderm and mesoderm may result in the bony defect that overlie the unfused sections of the neural tube (O'Rahily and Muller, 2002).

Open Neural Tube Defects

More than 80% of children with a neural tube defect can be detected by maternal serum AFP screening before birth (Brock and Sutcliffe, 1972). Although the determination of amniotic fluid acetylcholinesterase can be helpful, ultrasound examination is the method of choice for the diagnosis of neural tube defects. Direct visualization of the fetal spine can usually be accomplished by 16 weeks' gestation. Since the 1980s, the sonographic diagnosis of MMC has been enhanced by the introduction of high-resolution imaging tools and by recognition of specific brain abnormalities (Blumenfeld et al., 1993). First described by Arnold and Chiari at the end of the 19th century (Arnold, 1894; Chiari, 1895), the *Arnold–Chiari II malformation* is defined as the maldevelopment of a small posterior fossa and the herniation of the cerebellar vermis and brainstem (including the fourth ventricle) through an enlarged foramen magnum. Additionally, agenesis of the corpus callosum, enlargement of the massa intermedia, cortical heterotopia, and polymicrogyria can be seen. The origin of the Arnold–Chiari II malformation remains in dispute. The predominant hypothesis maintains that an imbalance of hydrodynamic forces occurs secondary to loss of CSF from the lesion (Padget, 1968; McLone and Knepper, 1989; Paek et al., 2000; Bouchard et al., 2003). An alternative theory interprets the hindbrain herniation as the consequence of a traction injury caused by cranial growth imbalance (Penfield and Coburn, 1938; Lichtenstein, 1942; Hoffman et al., 1975; McLone and Knepper, 1989). Overgrowth of the cerebellum and brainstem, along with a posterior fossa that is smaller than normal, leads to downward dislodgment of these structures, resulting in Arnold–Chiari II malformation (Barry et al., 1957). Despite the controversies about the origin of MMC-associated hindbrain herniation, these lesions are identifiable in the embryo from as early as 8 weeks of gestation and are established in the fetus by the 12th week.

Pathologic studies of human embryos and fetuses with MMC in earlier stages of gestation reveal an open neural tube but undamaged neural tissue with almost normal cytoarchitecture (Patten, 1953). This suggests that neural degeneration occurs at some point later in gestation (the "two-hit" hypothesis) (Ehlers et al., 1992; Hutchins et al., 1996). The first "hit" is the failure of neurulation early in gestation. The second "hit" is the spinal cord injury resulting from prolonged

exposure of the neural tissue to the intrauterine environment. In theory, this secondary event can be prevented if an adequate prenatal covering of the exposed neural tube can be provided. To have the best outcome, this repair must be fashioned before the onset of irreversible neural damage. There are several observations in human embryos, fetuses, and infants to support this premise (Neumann et al., 1994; Meuli et al., 1997).

In a pathologic examination of spinal cords of stillborn human fetuses with MMC (19–25 weeks of gestation), varying degrees of neural tissue loss at the site of the lesion were observed, but the dorsal and ventral horns were normal proximal to the defect (Hutchins et al., 1996). This group was among the first to suggest the two-hit hypothesis because they attributed these alterations to injuries occurring subsequent to the failure of primary neural tube formation. A study of 10 additional fetuses had similar findings (Meuli et al., 1997). Additional support exists for the two-hit hypothesis from in vitro studies. Drewek et al. (1997) reported that damage to open neural tissue appears to be progressive and results from exposure to toxic substances in the amniotic fluid during the third trimester.

Korenromp et al. (1986) observed that fetuses with MMC exhibited leg movement at 16 to 17 weeks. These investigators suggested that the affected fetuses did have good function at that point in gestation. No follow-up could be reported in this series because pregnancies were interrupted. Furthermore, Sival et al. (1997) compared the leg movements of 13 fetuses with MMC prenatally and postnatally. Only one of the 13 had abnormal leg movements before birth, but 11 demonstrated abnormal leg movements postnatally. Two possible explanations for this phenomenon exist. The prenatal leg movements could be secondary to spinal cord reflex rather than of cerebral origin, thus permitting motion without electrical impulses conducted through the damaged spinal cord tissue. In addition, leg movements early in pregnancy could result from cerebral function conducted through an exposed spinal cord that is not yet damaged. However, even extremely experienced sonographers find it difficult to distinguish between spontaneous and reflex-based fetal leg movements (Filly, 1994).

Most newborns with MMC show severe neurologic impairment of the lower extremities at birth, a finding suggesting that the neurologic injury may occur later in gestation or even at the time of delivery. It is remarkable that patients with lipomeningomyelocele (in which the neural tissue is covered and protected by skin) often have almost normal lower leg function and continence, despite a neurulation abnormality that is nearly identical to that present in newborns with open neural tube defects. These studies support direct injury to the protruding spinal cord as the primary cause of damage and loss of function (Hutchins et al., 1996; Meuli et al., 1997). As the pregnancy progresses, the volume of the amniotic fluid decreases, and this may result in more frequent contact of the exposed neural tissue with the uterine wall. Chick models of oligohydramnios, in which pressure necrosis of prominent areas of the body developed, support this hypothesis (Thévenet and Sengel, 1986).

Closed Neural Tube Defects

Clinically, closed neural tube defects should be differentiated from open neural tube defects because the embryogenesis appears to differ in most cases. In open defects, there is an essential failure during the primary neurulation, whereas closed neural tube defects appear to result from another form of disturbance during neural tube formation (McComb, 1996). With few exceptions, the structural malformations of closed neural tube defects are limited to the spinal cord and are not associated with the Arnold–Chiari II malformation or hydrocephalus. In contrast to open defects, newborns with a closed neural tube defect have no exposed neural tissue and do not leak CSF. Additionally, the prognosis of an infant affected by a closed defect is significantly better than one with an open neural tube defect. Generally, children born with closed defects have an intellectual function that is of the same distribution as the normal population, do not require CSF-diverting shunts, and have considerably fewer problems with lower extremity sensorimotor function and with bladder and bowel function (McComb, 1997). Because the clinical manifestations of closed defects can be undetected for days or even years, the origin of this group of neural tube defects is unidentified; no link to genetic, environmental, or dietary factors have been found. The major forms of closed neural tube defect are briefly described in the sections below.

Meningoceles are commonly located in the lumbosacral region in the vertebral arches. These lesions are often covered with skin, and the bony abnormality rarely involves more than two to three vertebrae. The meningocele sac consists of both arachnoid and dural meninges with CSF. Most meningoceles also contain neural elements. Meningoceles are an infrequent and heterogeneous group of cystic lesions. The accurate prevalence of meningocele is subject to debate, because meningoceles are often grouped with MMCs. Furthermore, their pathogenesis remains unknown. The neurologic outcome of affected newborns is normal, but surgical correction and resection of the herniated meninges are indicated (McComb and Chen, 1996).

Lipomatous malformations include all the closed neural-tube defects with excessive lipomatous tissue present within or attached to the spinal cord or filum terminale. These lesions are called lipomyelomeningocele, lipomyelocele, leptomyelolipoma, lumbosacral lipoma, or lipoma of the filum terminale. The origin of lipomatous closed neural tube defects is controversial. Two different theories have been advanced: (1) lipomas arise from cells originating from the somatic mesoderm and (2) lipomatous closed neural tube defects are a true malformation resulting from defective neurulation (Catala, 1997). Most affected infants have a good prognosis with nearly normal leg and urologic function.

Anencephaly and MMC are important contributors to fetal and infant mortality. All newborns affected by

anencephaly are stillborn or die shortly after birth, whereas children born with MMC usually survive. However, the risk of death with neural tube defects varies significantly worldwide, depending not only on the severity of the defect but also on such aspects as availability, use, and acceptance of medical and surgical intervention. For example, in some regions of northern China, nearly 100% (Moore et al., 1997); in the Netherlands, 35% (den Ouden et al., 1996); and in the United States, 10% (Shurtleff et al., 1994) of children affected by neural tube defects die.

MANAGEMENT OF PREGNANCY

MMC may be suspected either by abnormalities in maternal serum AFP screening or an abnormal sonographic examination. Once the MMC is suspected, the patient should be referred to a center capable of thorough anatomic diagnosis of the fetus. Confirmation of the MMC can be made by noting the presence of the cranial abnormalities discussed in the "Sonographic Findings" section. In addition, associated anomalies should be sought. Once the neural tube defect has been definitively identified, the parent should be offered the opportunity to obtain amniotic fluid for fetal karyotype analysis.

In a study of 77 fetuses retrospectively identified with isolated neural tube defects (Harmon et al., 1995), karyotype information was available in 43. The risk for chromosomal abnormalities based on the maternal age of this population was 0.3%. In the study group, however, 7 chromosomal abnormalities were discovered, an incidence of 16.3%. The difference between the expected occurrence of chromosomal abnormalities based on maternal age and the observed incidence of chromosomal abnormalities was highly significant. In the study, two cases of trisomy 18, three cases of triploidy, one case of a balanced Robertsonian translocation, and one Xq inversion were demonstrated. Subsequent studies have confirmed that between 2% and 16% of isolated neural tube defects occur in association with a chromosome abnormality or single-gene defect (Shaer et al., 2007). The most commonly associated aneuploidy in MMC is trisomy 18. We recommend obtaining a fetal karyotype because knowledge of the fetal cytogenetic status affects prognosis, management of the pregnancy, intervention, as well as recurrence risks.

Once the diagnosis of neural tube defect is confirmed, the parents should be offered the opportunity to discuss the long-term prognosis for a child with MMC with pediatric subspecialists. This is best performed in the context of a multidisciplinary team. We recommend that parents meet with a neonatologist, geneticist, pediatric neurologist, pediatric neurosurgeon, pediatric urologist, pediatric orthopedic surgeon, and if available, the physician coordinating the MMC clinic.

Long-term prognosis is related to the location of the MMC. In general, the lower the defect is on the fetus, the better the prognosis. If the diagnosis is made at <24 weeks of gestation, the parents should be offered the opportunity to terminate the pregnancy. Data from the statewide California AFP Screening Program suggest that families will act on information regarding neural tube defects. At <24 weeks of gestation, 80% of pregnant women will terminate the pregnancy when the defect is nonfatal, and 93% will terminate the pregnancy when the defect is fatal, such as anencephaly (Budorick et al., 1995).

If the diagnosis is made at >24 weeks of gestation, or if the parents elect to continue the pregnancy, the risks and benefits of elective cesarean section delivery prior to labor should be discussed. In 1991, Luthy et al. (1991) described their results of performing elective cesarean section without labor on fetuses with neural tube defects. They documented a lower risk of severe paralysis and on average, a motor function that was 3.3 spinal segments better than that expected on the basis of the anatomic level of the lesion when the affected children were 2 years of age. These authors suggested that unsplinted neural tissue and its blood supply were potentially traumatized by intrauterine pressures generated during labor. The study was subsequently criticized because it was not randomized. With additional observations, the most recent recommendations for delivery are the following (Shurtleff and Lemire, 1995): elective cesarean section is indicated when the fetus demonstrates movement of the knees and ankles and a MMC sac is observed protruding dorsally beyond the plane of the infant's back; cesarean section is contraindicated for fetuses with a known chromosomal abnormality, other congenital anomalies that significantly interfere with survival, or the absence of fetal knee or ankle movement; cesarean section has not been shown to be beneficial in primiparous women with a fetus already engaged in the breech position, fetuses with gibbous deformities, and fetuses with hypoplastic spinal cords.

FETAL INTERVENTION

The severity of complications observed in children with MMC prompted interest in the potential of in utero MMC repair to prevent these complications. The rationale for repair in utero is that the open neural tube defect allows exposure of the spinal cord to secondary injury from exposure to amniotic fluid, direct trauma or hydrostatic pressure (Adzick and Walsh, 2003). As described under "Antenatal Natural History," this has been referred to as the "two-hit hypothesis" (Hutchins et al., 1996).

Meuli-Simmen et al. (1995) used the latissimus dorsi muscle flap for fetal MMC repair in seven sheep fetuses with an artificially created lumbar MMC. Three fetuses survived the pregnancy. At term, the sheep survivors had healed cutaneous wounds and normal hind-limb function. These authors concluded that the latissimus dorsi flap is suitable for fetal surgery and provides efficient coverage of the lesion.

As a result of experimental work in animals, it is known that the neurologic deficits associated with open spina bifida

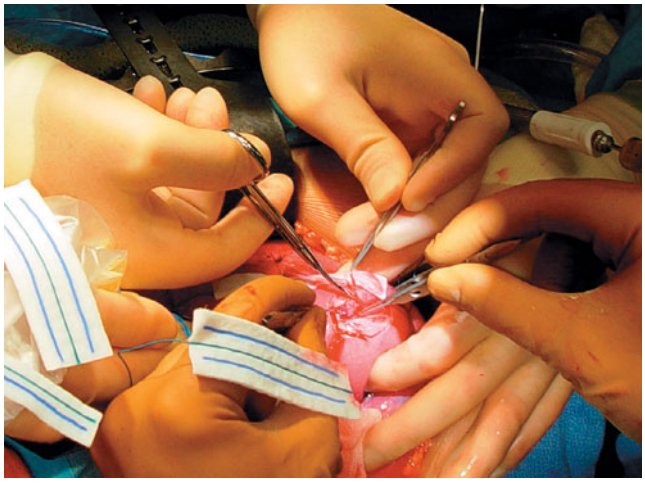


Figure 19-7 Intraoperative view of fetal surgical procedure performed at the Center for Fetal Diagnosis and Treatment at the Children's Hospital of Philadelphia prior to the start of the MOMS trial. The cystic component of the myelomeningocele is just being excised. The next steps in the procedure include closure of the dura to "neurulate" the plaquode and then mobilization of adjacent fascia to cover the repaired myelomeningocele. Lastly, extensive skin flaps are raised circumferentially to allow a skin closure of the top of the fascial closure.

are due partly to chronic mechanical injury and chemical trauma induced by exposure to amniotic fluid. These exposures progressively damage the unprotected fetal neural tissue during gestation. In fetal sheep, in utero repair of neural tube defects restored neurologic function by the time of birth (Meuli et al., 1997).

Fetal surgery to repair MMC is performed by maternal laparotomy and hysterotomy (Figure 19-7). The cystic membrane of the lesion is excised, the dura is closed over the placode and fascial layers are developed and closed over the defect. Lastly, skin flaps are developed laterally to complete closure of the defect (Adzick et al., 1998). Amniotic fluid is replaced with warmed lactated Ringer's solution. After repair, tocolysis was maintained with magnesium sulphate infusion, indomethacin rectal suppositories, and subcutaneous terbutaline.

The first attempt to repair by providing skin coverage for MMC was reported by Bruner et al. in 1997, using a maternal split thin skin graft endoscopically applied (Bruner et al., 1997). One patient died shortly after the surgery and the second patient showed no sign of improvement postnatally. Subsequently, the same group reported four patients who underwent open fetal surgical repair between 28 and 32 weeks' gestation with reversal of hindbrain herniation at birth (Tulipan and Bruner, 1998).

Similarly, the group at Children's Hospital of Philadelphia (CHOP) reported reversal of hindbrain herniation (Adzick et al., 1998). This was subsequently confirmed in a series of 10 patients undergoing MMC closure at 22 to 25 weeks' gestation (Sutton et al., 1999), in which 9 of 10 survived with reversal of hindbrain herniation. Four of the 9 later required ventriculoperitoneal shunting (Adzick and Walsh, 2003). Bruner et al. (1997) showed that 62% of 29 patients had reversal of hindbrain herniation when operated on between 24 and 30 weeks' gestation. Ventriculoperitoneal shunting was required in 17 of 29 (59%), but still compared favorably with historical controls in which 90% required ventriculoperitoneal shunting (Rintoul et al., 2002).

Prior to the start of the Management of Meningomyelocele (MOMS) trial, experience with open fetal surgical repair had been performed at CHOP, Vanderbilt, University of North Carolina, and the University of California at San Francisco, with a combined experience of approximately 160 patients. Findings suggested improved outcomes compared to historical controls. Sutton et al. reported that hindbrain herniation was uniformly reversed in the CHOP experience and only 43% required ventriculoperitoneal compared to an 84% rate observed in 297 historical controls (Sutton et al., 1999; Rintoul et al., 2002). Of note in this series of 50 patients were 3 deaths from preterm delivery at 25 weeks. The average gestational age at delivery was 34 4/7 weeks (Rintoul et al., 2002). While this study suggested a reduced need for ventriculoperitoneal shunting, it should be pointed out that the controls were historical and neurosurgical indications for shunting had become more conservative during this period. In addition, some infants undergoing fetal surgery for MMC merely experienced delayed time for ventriculoperitoneal shunting.

Danzer et al. (2007) have reported that open fetal surgery for MMC alters the fetal head growth. Repaired MMC fetuses have disproportionately small head circumference measurements while the lateral ventricles progressively enlarge (Van den Hof et al., 1990; Babcock et al., 1994; Bannister et al., 1998). In a series of 50 fetuses undergoing open fetal surgery to repair MMC, Danzer et al. (2007) found a significant increase in cortical index (head circumference/lateral ventricular diameter). Early neurodevelopmental evaluations at 2 years of age in the cohort of 51 MMC patients treated by open fetal surgery at CHOP reveal that 67% had cognitive language and personal-social skills in the normal range, 20% had mild delays, and 13% had significant delays (Johnson et al., 2006).

The lower extremity neuromotor evaluation following open fetal surgery for MMC suggests that 58% of patients had a better than predicted lower extremity function compared to infants with postnatally repaired MMC (Danzer et al., 2006; Carr, 2007). In this relatively early follow-up series (39 $\pm$ 15 months) of open fetal surgically repaired MMC, 21 children (52.5%) walked independently, 8 (20%) walked with braces, 7 (15.5%) ambulated with a walker, and 4 (10%) used a wheelchair. This was in contrast to less favorable outcomes in postnatally repaired MMCs in which only 1 child (6%) walked independently, 5 (29%) walked with braces, 10 (58.8%) ambulated with a walker, and 1 (6%) used a wheelchair (follow-up at 41.9 $\pm$ 16.6 months). This early assessment of lower extremity function may be misleading, as many children who had previously been able to ambulate with or without braces or walkers revert to a wheelchair at puberty due to increased weight and size that make ambulation very difficult.

Carr (2007) reported his experience with urodynamic evaluation of 22 patients who underwent fetal surgical repair of MMC at CHOP. In 13 of 22 patients he evaluated voiding spontaneously with 3 of 22 (13.6%) achieving volitional voiding. This compares favorably with expected 2% to 3% volitional voiding in postnatal MMC repair (Carr, 2006). The remainder of the 22 patients had either vesicoureteral reflex (10%), urinary tract infections (33%), or required vesicostomy (5%), or clean intermittent catheterization.

In order to address many of the questions raised by early outcomes of open fetal surgery in MMC, the NIH funded the MOMS trial. This prospective randomized trial will compare outcomes with open fetal surgery performed at 18 to 25 6/7 weeks' gestation with postnatal surgery. As of 2008, the recruitment to the trial has been slow, with only one half of the anticipated 200 patients enrolled. The primary outcome variables for this trial are the need for a ventriculoperitoneal shunt at 1 year of age and fetal or infant mortality. Additional information regarding the MOMS trial can be obtained at the website www.spinabifidamoms.com.

TREATMENT OF THE NEWBORN

The newborn infant with MMC should be handled in as sterile a manner as possible. The spinal lesion should be immediately covered with a nonadherent dressing moistened with warm physiologic Ringer's lactate or normal saline. A firm, protective ring of sterile dressings should be placed around the sac, and the sac itself should be covered with a nonadhesive dressing (Hahn, 1995; Shurtleff and Lemire, 1995). If the infant needs to be intubated, this should be performed in the prone or in the lateral recumbent position if possible. At all times, normothermia must be maintained.

An initial physical examination should be performed by the neonatologist and the pediatric neurologist or neurosurgeon to assess the functional level and the extent of the neurologic deficit (Figure 19-8). The sensory level can be determined by stimulating dermatomes with pinpricks.

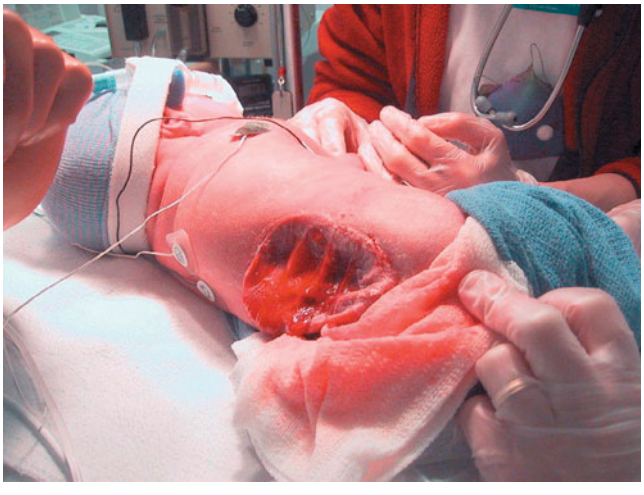


Figure 19-8 Appearance of a large thoracolumbar MMC at birth.

The spinal column should be examined for evidence of early scoliosis or kyphosis. Consideration should be given to performing a cranial computed tomographic (CT) and/or MRI scan so that the neurosurgeon can plan the postnatal surgical approach. The parents should be informed that if hydrocephalus is not present antenatally, it may develop after repair of the neural tube defect. Generally, if a shunt is necessary, it is placed before subsequent urologic or orthopedic repair.

The Arnold–Chiari type II malformation is present in 95% of patients with MMC. In 6% of affected patients, central ventilatory dysfunction may be present, as demonstrated by central apnea, stridor, respiratory distress, or aspiration. Bulbar involvement may result in vocal cord paralysis or dysphagia. Unfortunately, approximately half of all newborns with MMC have pneumographic abnormalities or abnormal responses to increasing CO_2 content in inspired air (Petersen et al., 1995). Therefore, standard tests of respiratory function are not useful to predict which infants will become symptomatic because of an Arnold–Chiari malformation.

SURGICAL TREATMENT

The earliest recorded surgical treatment of a child with spina bifida was performed in 1910 (Hahn, 1995). With the development of antibiotics, there was increased interest in treating this condition. It is currently recommended that surgical closure should occur within the first 24 to 72 hours of life to decrease morbidity and mortality as long as the sac is intact.

Exposure of neural tissue to trauma during birth potentially causes a shocklike state to the neural placode. The goals of operative repair include preserving all viable neural tissue, reconstituting a normal anatomic environment, and minimizing the chance of infection or preventing ascending infection of the neural axis (Hahn, 1995). During repair, the neurosurgeon must

1. identify the neural placode, intermediate epithelial layer, and the pia, arachnoid, and dura;
2. preserve neural tissues;
3. reconstitute a normal neural environment with reconstitution of the pia—arachnoidal, dural, fascial, and skin layers;
4. complete skin closure;
5. prevent leakage of CSF (Pang, 1995).

The operative mortality for MMC repair is near 0%. Currently, there is expected to be a 95% or higher survival rate for the first 2 years of life (Hahn, 1995).

Hydrocephalus develops in 80% of cases of MMC. This is often not apparent until the neural tube defect is repaired. It is not uncommon to require a shunt placement within a few days after neural tube defect repair.

Rintoul et al. (2002) performed a retrospective review of 297 patients born with MMC and described the natural history of ventricular shunting in MMC patients in relation to radiologic and functional criteria. Most closures (92%) and shunt placements (62%) were performed in the first week of life. The timing of shunt placement and the number of

shunt revisions were independent of the level of lesion. The incidence of shunting by functional level was 81%, which is consistent within the generally accepted range of 80% to 85% for an unselected spina bifida population (McLone, 1983; Caldarelli et al., 1996). The rate of ventricular shunting is significantly correlated to the anatomic level of the lesion (Rintoul et al., 2002). One hundred percent of the patients with thoracic-level lesions required postnatal shunting, compared with 88% of those with lumbar-level lesions and 68% of those with sacral-level lesions.

LONG-TERM OUTCOME

For those infants affected by MMC, the significant lifelong disabilities accompanying this malformation include paraplegia, hydrocephalus (Rintoul et al., 2002), pulmonary dysfunction (Sherman et al., 1997), sexual dysfunction, skeletal deformations and spinal deformities (Iborra et al., 1999), incontinence, and cognitive impairment (Tsai et al., 2002), with approximately 15% of them requiring some form of custodial care (McLone et al., 1985; McLone, 1998).

The long-term considerations for the infant and child with MMC include neuromuscular and urologic function, as well as prevention of orthopedic abnormalities. To stand erect, motor function is needed to at least the third lumbar level. To walk, the child must exhibit motor function from the fourth to the fifth lumbar level. To function sexually as an adult, a male must have motor function to at least the second to fourth sacral level.

The degree of handicap and survival rate depends on the level of spinal segments, the severity of the lesion, the treatment program, and the associated anomalies (Budorick et al., 1995). The lower the spinal level, the better the prognosis. Prediction of long-term IQ is impossible. Approximately one-fourth of patients have an IQ below 50, one-fourth of patients have an IQ above 100, and 50% of patients have a learning disability (Budorick et al., 1995).

Infants with MMC almost always have evidence of Chiari II malformation on MRI (Ruge et al., 1992). Despite aggressive postnatal intervention, nearly 14% of neonates with spina bifida do not survive past 5 years of age, with the mortality rising to 35% in those with symptoms of brainstem dysfunction secondary to the Chiari II malformation (Rauzzino and Oakes, 1995; Worley et al., 1996). Clinical symptoms include swallowing difficulty, apnea, and stridor. Strabismus, a nonlethal Chiari II complication, is found in as many as 61% of patients with MMC (Biglan, 1995). Furthermore, the hindbrain deformity leads to ventriculomegaly in most cases because of impaired circulation of CSF. Complications of ventriculomegaly probably lead to the impaired cognitive development seen in children with MMC (McLone and Naidich, 1989).

In recent years, there has been an increased appreciation of the long-term consequences of renal failure in adulthood (Zawin and Lebowitz, 1992). Therefore, urologic management is more aggressive and directed toward maintaining normal renal function (Stone, 1995). After the neural tube defect has been closed and a shunt has been placed, urodynamic studies are recommended. If the patient has high pressures due to bladder–sphincter dyssynergia, a voiding cystourethrogram (VCUG) can be performed to rule out vesicoureteric reflux. For many cases, anticholinergics or smooth muscle relaxants are recommended to alter the overreactivity of the abnormal detrusor. This treatment is meant to increase the capacity of the bladder. Prophylactic antibiotics are used to prevent urinary tract infection. Children are taught how to perform clean, intermittent bladder catheterization. This technique safely and effectively empties the bladder, preventing both upper tract deterioration and overflow incontinence (Zawin and Lebowitz, 1992). If frequent urinary tract infection is a problem, a vesicostomy can be performed, creating a fistula between the bladder and the abdominal wall. Eighty percent of children with neural tube defects achieve continence by intermittent catheterization and the use of anticholinergic medications.

Another potentially preventable complication of spina bifida is disease-associated latex sensitization (Cremer et al., 1998; Zsolt et al., 1999). Up to 43% of children with spina bifida are affected (Zsolt et al., 1999). However, it remains unclear whether this association is only a consequence of repeated exposure to latex-containing products (e.g., gloves or catheter material) (Chen et al., 1997) or is the result of a potential genetic contribution and alteration of the human leukocyte antigen phenotype (Rihs et al., 1998).

The presence of myelodysplasia can lead to musculoskeletal deformities. The goals of the orthopedic surgeon are to maintain mobile and pain-free joints, as well as to prevent decubitus ulcers in insensate limbs (Karol, 1995). The spine is at risk for the subsequent development of kyphosis and scoliosis. Significant spine deformities that require surgery develop in 10% of children with lesions at the thoracic level. Scoliosis is the most commonly encountered spinal deformity, which is treated by spinal fusion. Although patients with MMC can dislocate their hips, they are rarely surgically reduced. Contractures at the hip are surgically released to allow children to fit orthoses. External tibia rotation is commonly seen at the ankles. Sixty percent of children with MMC have clubfeet (see Chapter 107). This is treated differently for the child with MMC as compared with otherwise normal children. Neurologic clubfeet are more rigid than idiopathic clubfeet. The application of skin casts with stretching—the usual treatment for idiopathic clubfoot—can lead to skin breakdown for the child with MMC. Surgical treatment is generally recommended, but this should be delayed until the child is developmentally ready to stand.

Hunt (1990) and Hunt and Poulton (1995) described the long-term follow-up of 117 babies (50 boys, 67 girls) born between 1963 and 1971. All of these infants had surgical repair within the first 48 hours after birth. Of this cohort, 25 infants died within the first year of life, 15 died between ages 1 and 5 years, 8 died between ages 5 and 16 years, and 8 died between 16 and 25 years (Figure 19-9). The reports cover 69 survivors in 1990 and 61 survivors in 1995. Remarkably, 16 of the 56 deaths were from renal failure. In general,

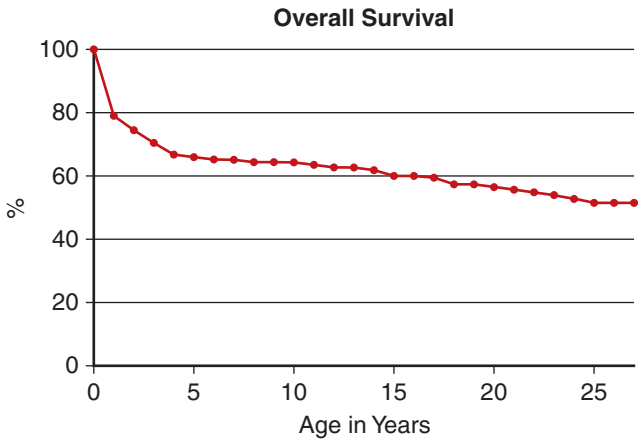


Figure 19-9 Overall survival for a cohort of 117 babies born with myelomeningocele between 1963 and 1971.

survival was lowest and disability greatest when the sensory level affected was above T11 (Figure 19-10). The survival was highest and disability the lowest when the sensory level was below L3 (Figure 19-11). Most severely affected cases had a poor renal prognosis due to neuropathic obstruction of bladder outflow. Of the survivors in 1990, 50% could walk for 50 yards or more and 50% were wheelchair-bound. Forty-seven of the 69 survivors had an IQ of >80, 12 had an IQ of between 60 and 79, and 10 had an IQ of <60. Approximately half of the young adults remained continent or managed their own incontinence. The other half needed help from other adults, and 43% of survivors used some sort of adult diaper or padding.

With regard to disability, 12% of patients walked normally and had a normal IQ. Fifty percent of patients could walk 50 yards and had normal intelligence. Twenty-five percent of patients had severe disability and could not walk or stand and had mental retardation. Twelve percent of patients had severe disability, blindness, and mental retardation, and needed help with transfers, dressing, and incontinence.

With regard to general health, one-third of patients had precocious puberty, one-third were overweight, and visual defects were common among these patients, including blindness in two of them. The presence of a history of ventriculitis, septicemia, or intracranial hemorrhage was associated with mental retardation, epilepsy, and blindness.

Sixteen of the 69 adult survivors were employed. Their occupations included light assembly work, clerical jobs, garage mechanic, gardener, and hairdresser. These authors concluded that most of the surviving young adults were badly handicapped. Thirty percent had mental retardation, as defined by an IQ of <80.

These authors stated that the sensory level to pinprick at birth was especially useful in the determination of long-term disability. When the sensory level was above T11, there was 50% survival to adult life. If the patient survived, there was a 50% chance of a normal IQ. Most of these patients had severe disability, with no prospect of walking or continence and only a 10% chance of being able to live independently. When the sensory level was between T11 and L3, there was a 55% chance of survival to adulthood. If the patient survived, there was a 70% chance of a normal IQ. Of this group of patients, 40% could walk, 15% were continent, and 45% were able to live independently. For the patients with a sensory level below L3, there was a 70% chance of survival to adulthood, and for the survivors there was an 80% chance of a normal IQ. Of these patients, 90% could walk and 45% were continent. Eighty-five percent of this group were able to live independently (Hunt, 1990; Hunt and Poulton, 1995).

In addition to the emotional impact on the family, the financial burden for family and community is enormous. In

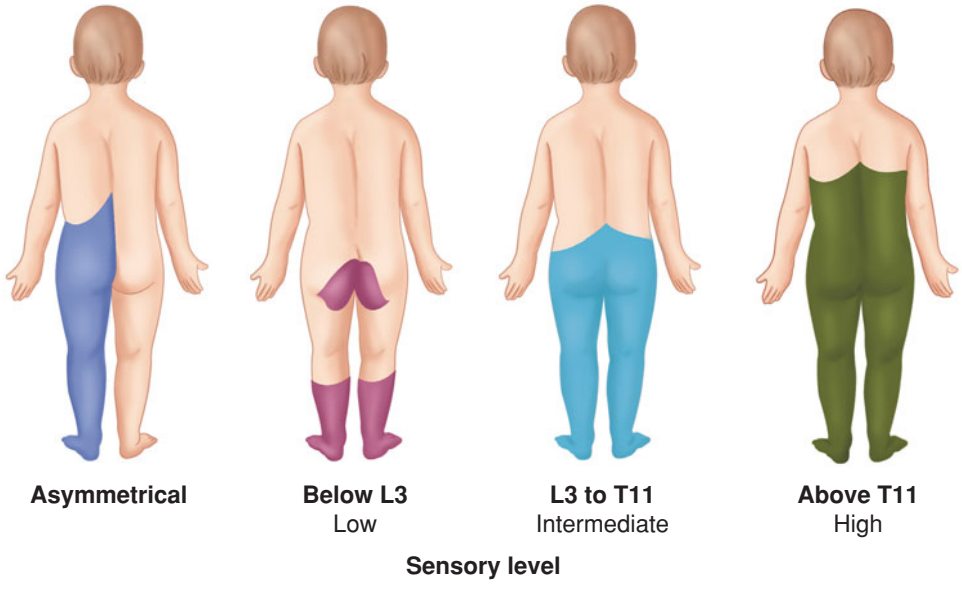


Figure 19-10 Illustration of sensory areas affected by the different anatomic locations of the neural tube defect. The hatch marks and coloration used in this figure relate to the data in Figure 19-11.

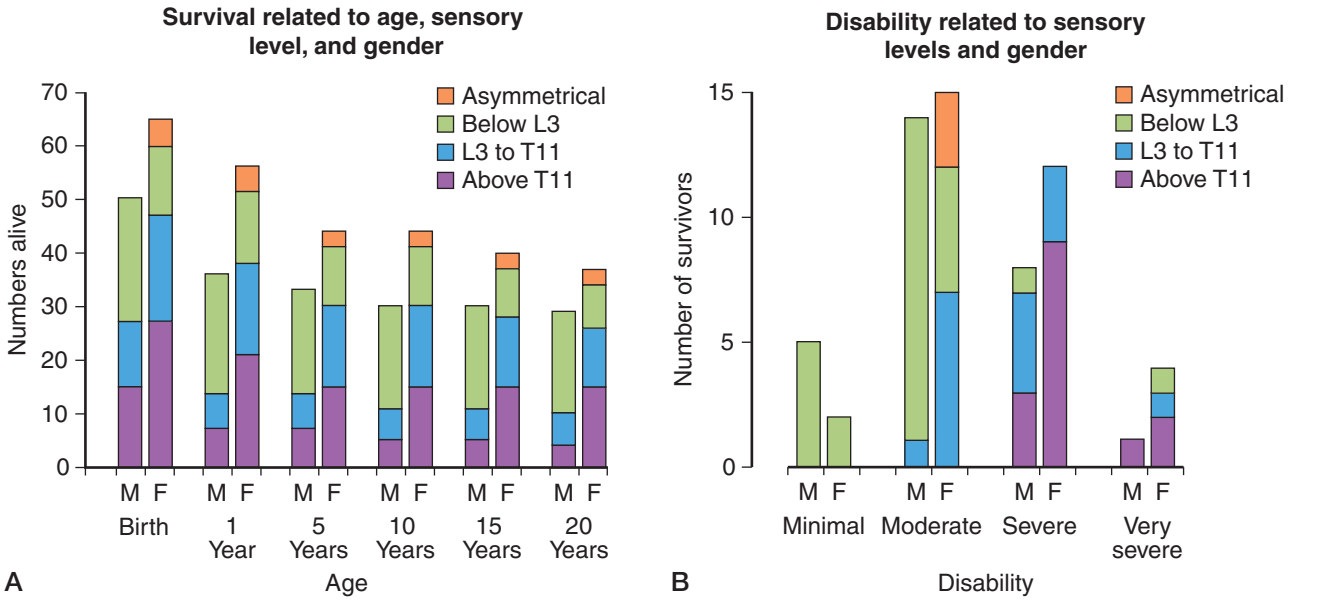


Figure 19-11 **A**. Long-term survival as a function of age, sensory level, and gender. **B**. Long-term disability as a function of age, sensory level, and gender.

the United States, the cost of care for infants with spina bifida in 1988 was almost 500 million dollars per year or $294,000 for each infant (Waitzman et al., 1996).

GENETICS AND RECURRENCE RISK

The vast majority of neural tube defects are isolated and multifactorial in origin (Main and Mennuti, 1986). In a landmark study, Holmes et al. (1976) classified 106 stillborn and liveborn infants with neural tube defects. They identified six different causes for the anomalies. This study consisted of a retrospective analysis of 79 autopsy cases and a prospective analysis of 27 liveborn infants. Of the 27 liveborn infants, 23 had an isolated neural tube defect, and of these 15 had anencephaly. Of the 79 retrospective cases, 67 were consistent with multifactorial inheritance. Five of the cases were consistent with a single-gene disorder, and all were thought to be due to Meckel–Gruber syndrome, an autosomal recessive condition. One case was clinically diagnosed as trisomy 13, although the definitive chromosome analysis was unavailable. One of the 79 was an infant of a mother with diabetics. Three cases were due to amniotic bands, and two cases were due to cloacal exstrophy. These authors suggested that the cause of neural tube defects was highly variable and that genetic counseling could not support a uniform 5% recurrence risk for all patients.

Main and Mennuti (1986) have suggested a recurrence risk of 1.5% to 3%, although with two affected siblings the recurrence risk increases to 5.7% in the United States and 12% in the United Kingdom (Main and Mennuti, 1986). For sisters of the mother who gives birth to an affected child with a neural tube defect, there is an increased risk. The presence of spina bifida occulta of a single vertebra in a parent does not increase the risk for a neural tube defect in the offspring.

Women who have already given birth to an affected infant with a neural tube defect should take 4 mg of folic acid daily at least 3 months prior to the next pregnancy (Wald et al., 1991). Several studies to date have demonstrated the preventive effect of folic acid supplementation prior to conception. These studies have been summarized by Rieder (1994). In one study, 11 cases of neural tube defects were observed in 1188 pregnancies supplemented with folic acid, or a prevalence of 0.9 per 100 livebirths. The patients not taking supplements had 54 cases of neural tube defects in 1286 livebirths, for a prevalence of 4 cases per 100. The mechanism by which folic acid mediates neural tube closure is unknown, although the preventive effect has been shown even in low-risk women (Milunsky, 1996). It is currently recommended that all women of childbearing age take at least 0.4 mg of folic acid every day (Wald et al., 1991; Baty et al., 1996).

Prenatal diagnosis of neural tube defects in a subsequent pregnancy can be performed by maternal serum AFP screening, amniotic fluid AFP screening, and prenatal sonographic examination.

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20 CHAPTER Microcephaly

Key Points

- Microcephaly is characterized by a smaller than normal head circumference. A head circumference measurement of 3 SD below the mean gives a clinically meaningful definition because it has been associated with mental retardation.
- Microcephaly has been associated with a number of genetic, infectious, and environmental exposures.
- Detailed ultrasound examination to exclude other anomalies is necessary.
- A careful history is needed when this diagnosis is suspected. Likewise, the head circumferences of the parents should be measured.
- Little information is known about the antenatal natural history of microcephaly, especially during the first and second trimesters.
- The diagnosis of microcephaly should not alter obstetric management.
- Newborns with microcephaly require an extensive work-up to determine the etiology of the condition.
- The long-term prognosis and recurrence risk for microcephaly is related to its underlying cause.

CONDITION

Microcephaly is characterized by a smaller-than-normal head circumference (Figures 20-1 and 20-2). The clinical significance of microcephaly is its association with a small brain—microencephaly. A difference of opinion exists as to whether the lower limit of a normal head circumference should be defined as 2 or 3 SD below the mean (Avery et al., 1972). When a head circumference of 2 SD below the mean is used to define microcephaly, the association with mental retardation is inconsistent. Using such a definition, 2.5% of the general population would be considered microcephalic, and therefore a large number of infants with normal intellectual function would be included (Martin, 1970; Sells, 1977). A head circumference measurement of 3 SD below the mean gives a more clinically meaningful definition of microcephaly, as the correlation of this measurement with mental retardation is stronger (Davies and Kirman, 1962; Warkany et al., 1981).

The most affected part of the brain in microcephaly is the forebrain, and there is frequently associated macrogyria, pachygyria, and basal ganglia atrophy (Davies and Kirman, 1962).

Microcephaly is caused by diverse genetic and environmental factors that disturb brain growth in prenatal and early postnatal life (Warkany et al., 1981). The proportion of cases of microcephaly due to genetic causes has been estimated at 20% to 33% (Van den Bosch, 1959; Cowie, 1987). However, much of the data on which such estimates are based relate to patients born before recent advances in syndrome diagnosis and genetics.

The classification of microcephaly has generally reflected a distinction between genetic and acquired causes (Table 20-1). The term *primary*, or *true*, *microcephaly* has been used when the condition is isolated and is due to an arrest of brain development. The term *secondary microcephaly* has been applied to acquired insults to the brain. Microcephaly may also be classified based on the presence or absence of associated malformations.

Determination of the precise cause of microcephaly is difficult. The diagnosis of isolated developmental microcephaly is usually one of exclusion, with other causes of microcephaly having been ruled out (Hunter, 1993).

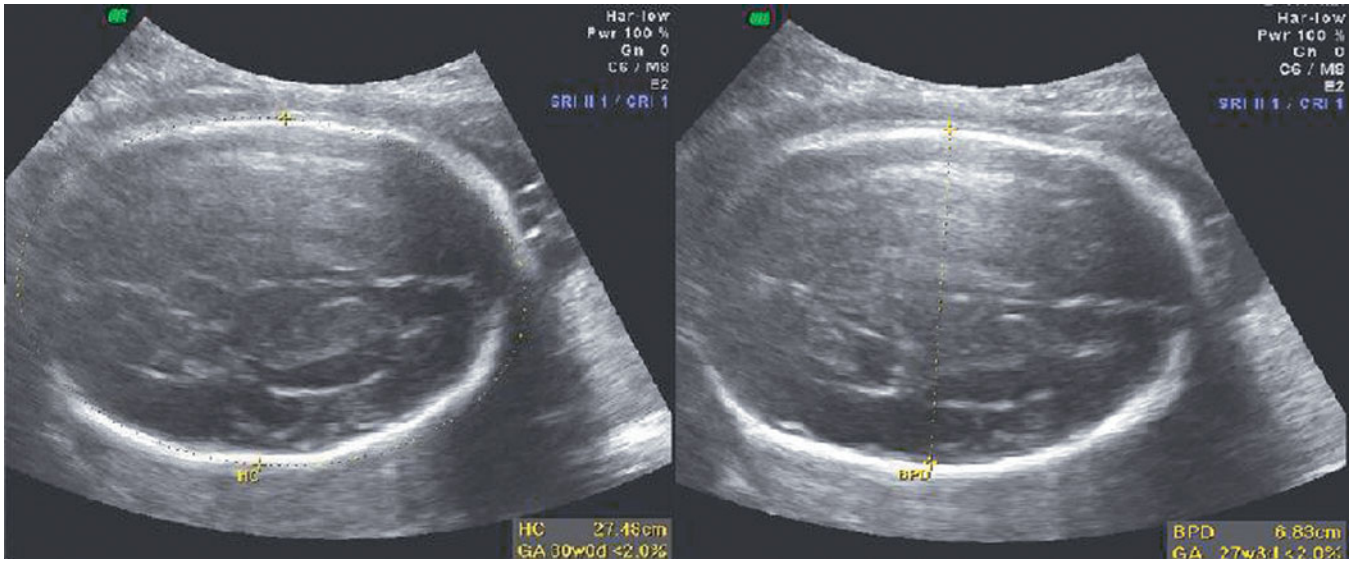

Figure 20-1 Axial image of fetal head showing biparietal diameter and head circumference measuring at less than the 2nd percentile for expected gestational age.

INCIDENCE

The overall incidence of microcephaly was 1.6 in 1000 livebirths in the U.S. Collaborative Perinatal Project, in which infants were observed throughout the first year of life. The incidence in whites was found to be 1.3 in 1000 livebirths and in blacks, 1.9 in 1000 livebirths (Myrianthopoulos and Chung, 1974). Estimates of the frequency of developmental microcephaly vary, depending on the population studied, ranging from 1 in 25,000 to 1 in 250,000 (Book et al., 1953; Van Den Bosch, 1959). The frequency of microcephaly from all causes in the Netherlands was estimated to be 1 in 93,000 (Van den Bosch, 1959). The variation in quoted incidence rates probably reflects different levels of ascertainment in different populations, as many studies do not include stillbirths or spontaneous losses.

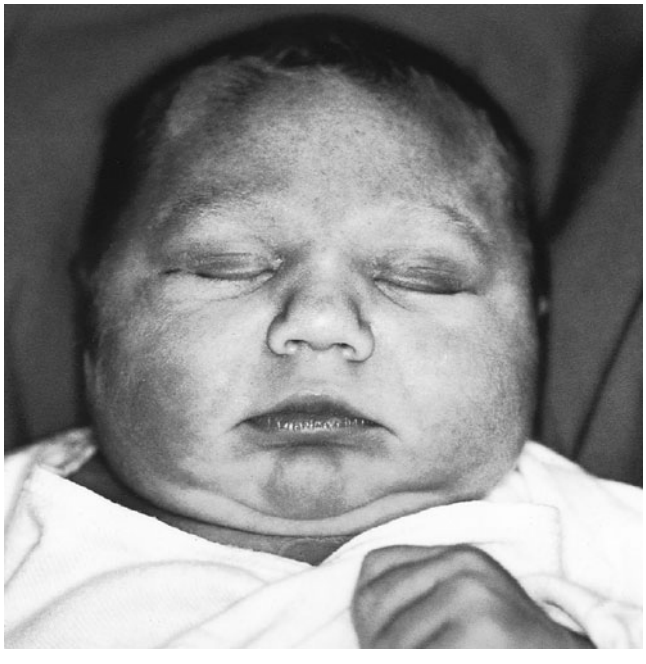

Figure 20-2 Newborn infant with severe microcephaly. The infant's length and weight were at 95%, but the head circumference was below 5%. The etiology for this infant's microcephaly, which was detected prenatally, is unknown (*Courtesy of John Foster.*)

SONOGRAPHIC FINDINGS

The diagnosis of microcephaly should be considered when the fetal head circumference is 3 SD below the mean for gestational age. A detailed fetal sonographic evaluation for associated anomalies should be performed in all cases of suspected microcephaly.

The use of head circumference rather than biparietal diameter (BPD) is more appropriate in the diagnosis of microcephaly. The BPD can be inaccurate if the fetus is breech and in conditions that cause intrauterine molding, such as oligohydramnios and multiple gestation. By contrast, the fetal head circumference should not be affected by molding. One series found that a BPD smaller than 3 SD below the mean was associated with a normal outcome in 44% of cases (Chervenak et al., 1984). This high incidence of falsely abnormal results was probably due to the inclusion of fetuses with simple intrauterine molding. In a later series of 24 fetuses with BPD values of more than 3 SD below the mean, only 4 proved to be microcephalic after birth, and 3 of these 4 fetuses had additional major malformations (Chervenak et al., 1987).

Table 20-1

Classification of Microcephaly by Etiology

Microcephaly with Associated Malformations		Microcephaly Without Associated Malformations
Genetic		Genetic
Chromosomal abnormalities		Primary microcephaly
Trisomy 21		Alpers syndrome
Trisomy 13		Paine syndrome
Trisomy 18		Inborn errors of metabolism
Trisomy 22		Disorders of folic acid metabolism
4p–		Hyperlysinemia
5p–		Methylmalonic acidemia
18p–		Phenylketonuria
18q–		
Single gene defects	Mode of inheritance	
Angelman syndrome	Deletion 15q	
Bloom syndrome	Autosomal recessive	
Borjeson–Forssman–Lehmann syndrome	Sex-linked recessive	
Cockayne syndrome	Autosomal recessive	
Coffin–Siris syndrome	Autosomal recessive	
DeLange syndrome	Autosomal dominant	
DeSanctis–Cacchione syndrome	Autosomal recessive	
Dubowitz syndrome	Autosomal recessive	
Fanconi pancytopenia	Autosomal recessive	
Focal dermal hypoplasia	X-linked dominant	
Incontinentia pigmenti	X-linked dominant	
Johanson–Blizzard syndrome	Autosomal recessive	
Langer–Giedion syndrome	Deletion 8q	
Lissencephaly syndrome	Autosomal recessive	
Meckel–Gruber syndrome	Autosomal recessive	
Menkes syndrome	Sex-linked recessive	
Roberts syndrome	Autosomal recessive	
Rubinstein–Taybi syndrome	Autosomal dominant/new mutation	
Seckel bird–headed dwarfism	Autosomal recessive	
Smith–Lemli–Opitz syndrome	Autosomal recessive	
Williams syndrome	Elastin mutation	
Environmental		Environmental
Prenatal exposure to infections		Prenatal exposure to radiation
Rubella syndrome		Fetal malnutrition
Cytomegalovirus disease		Perinatal trauma or hypoxia
Herpes virus		Postnatal infections
Toxoplasmosis		
Varicella zoster		
Prenatal exposure to drugs or chemicals		
Fetal alcohol syndrome		
Fetal hydantoin syndrome		
Vitamin A or vitamin A analog		
Aminopterin syndrome		
Cocaine exposure		
Methylmercury exposure		
Solvent exposure: toluene, gasoline		
Carbon monoxide poisoning		
Irradiation		
Maternal phenylketonuria		

Adapted from Ross JJ, Frias JL. Microcephaly. In: Vipken PJ, Bruyn AW, eds. Handbook of Clinical Neurology. Vol 30. *Amsterdam: Elsevier; 1977:507-524.*

Microcephaly may also be diagnosed based on an abnormal ratio of head circumference to femur length or of head circumference to abdominal circumference. Normograms for these ratios have been published (Romero et al., 1988). A diagnosis of microcephaly should be made with caution when using such normograms, because some causes of microcephaly may be associated with intrauterine growth restriction or abnormal long bone growth.

When microcephaly is present, the most affected part of the fetal brain is the forebrain. This has prompted investigators to evaluate the role of frontal-lobe measurements in the diagnosis of microcephaly. Ultrasonographic measurements of the frontal lobe and thalamic-frontal-lobe distance were below 2 SD in three cases of microcephaly diagnosed in utero and confirmed after birth (Goldstein et al., 1988). In two of the three cases, other conventional diagnostic measurements (BPD, occipitofrontal diameter, and head circumference) were also reduced. In one case in which the conventional parameters were equivocal, the authors found that additional measurements of the frontal lobe were diagnostic of microcephaly. Neonatal evaluation confirmed the diagnosis.

In a report on the prospective prenatal diagnosis of microcephaly in 21 pregnancies occurring in 15 families with a previously affected child with microcephaly, serial measurements of the fetal head, abdomen, and femur were made by ultrasound examination at intervals of approximately 4 weeks (Tolmie et al., 1987). Four fetuses with microcephaly were detected in the third trimester. One affected fetus was missed because no scans were performed after 24 weeks of gestation. The main reason for late diagnosis of affected fetuses was that the head growth did not slow appreciably until the third trimester (Tolmie et al., 1987). A diagnosis of microcephaly cannot be excluded by ultrasonography performed during the second trimester of pregnancy and a repeat third trimester ultrasound examination may result in better diagnosis and patient counseling (Malinger et al., 2002).

In addition, in cases of microcephaly, Doppler ultrasonography has been used during the second trimester to diagnose abnormal intracranial vascular anatomy (Pilu et al., 1998). It has been postulated that microcephaly in these cases was due to a reduced blood supply to the cerebral hemispheres.

DIFFERENTIAL DIAGNOSIS

If the microcephaly is isolated, the most likely consideration in the differential diagnosis is familial microcephaly. A detailed family history is imperative whenever a diagnosis of microcephaly is considered. The history should include a careful search for consanguinity and measurement of the head size of the parents and siblings. A maternal history of alcohol or other substance abuse, irradiation, use of medications (including phenytoin and isotretinoin), maternal disease, fever, and rash should be obtained.

If the microcephaly is seen in association with other anomalies, there is an extensive differential diagnosis that is beyond the scope of this chapter. McKusick's Online Catalog of Mendelian Inheritance in Man (OMIM), lists almost 500 entries for microcephaly (Abuelo, 2007).

ANTENATAL NATURAL HISTORY

Little information is available on the intrauterine natural history of microcephaly. In one series evaluating the presence of microcephaly prenatally, one affected fetus was missed following an ultrasound examination that was normal at 24 weeks (Tolmie et al., 1987). Microcephaly becomes more obvious in utero as gestation progresses. Because the prenatal diagnosis of microcephaly is rarely made before the third trimester of pregnancy, little is known about what occurs during the first and second trimesters.

MANAGEMENT OF PREGNANCY

A detailed sonographic examination is indicated to identify both intracranial and extracranial abnormalities associated with microcephaly. Karyotyping should be offered. A detailed background history should be obtained and should exclude consanguinity, prenatal infections (such as a febrile illness or a rash), prenatal exposure to drugs or chemicals (especially alcohol), and maternal phenylketonuria (PKU). If there is a history suggestive of maternal infection, maternal serology and polymerase chain reaction (PCR) studies of the amniotic fluid are indicated. Measurement of the head sizes of the parents and siblings may be helpful in determining whether this is a familial trait.

It is important to counsel parents about the difficulties encountered in the antenatal diagnosis of microcephaly (Schwarzler et al., 2003). It is often useful to counsel parents that definitive diagnosis in the newborn period may also be very difficult. Antenatal referral of the pregnant patient to a medical geneticist is recommended.

If there are other associated abnormalities, delivery should occur in a tertiary care center. Timing and mode of delivery should not be influenced by the presence of isolated microcephaly. If there are no other associated abnormalities it is reasonable to deliver the patient at a community hospital with appropriate postnatal subspecialty referral to medical genetics and pediatric neurology specialists.

FETAL INTERVENTION

No fetal intervention has been described following the prenatal diagnosis of microcephaly.

TREATMENT OF THE NEWBORN

Newborns with isolated microcephaly do not usually show evidence of neurologic deficits or seizures (Penrose, 1972; Volpe, 1987). This is in contrast to microcephaly due to other causes, such as chromosomal abnormalities or infection.

Neuroradiologic investigations may be useful in ruling out an underlying cause for microcephaly, such as hypoxic ischemic damage or neurologic injury due to the in utero death of a twin (Hughes and Miskin, 1986; Sherer et al., 1993). Postnatal imaging of the brain through the use of computed tomographic or magnetic resonance imaging is reasonable in most cases (Persutte et al., 1990). Serologic studies, such as TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes virus) titers, may be useful in ruling out antenatal infection.

Newborns with microcephaly should have a careful ophthalmologic examination, because the association of microcephaly and eye abnormalities is common. In one series, eye abnormalities were found in 23 of 40 cases with "true" microcephaly (Alzial et al., 1980). In a further series of 131 cases of microcephaly, eye abnormalities were present in 36% (Brandon et al., 1959). Eye abnormalities have been described in autosomal dominant microcephaly, autosomal recessive microcephaly, sex-linked microcephaly, and microcephaly secondary to maternal infection (Webster and Smith, 1977; Tenconi et al., 1983; Siber, 1984).

The postnatal onset of microcephaly potentially suggests an inborn error of metabolism, such as PKU, hyperlysinuria, or methylmalonic acidemia.

SURGICAL TREATMENT

No surgical intervention has been described for microcephaly.

LONG-TERM OUTCOME

The prognosis for microcephaly is related to its underlying cause. Microcephaly, when associated with other malformations or congenital infections, has a very poor prognosis, with minimal data available on long-term follow-up. Intellectual impairment in children with a head circumference 3 SD below the mean was more common in children with additional disorders (Dolk, 1991). Fifteen of 16 children with microcephaly and other disorders had mental retardation. Of 25 microcephalic children with no other disorders, only 25% had mental retardation (Dolk, 1991).

The predictive value of head size at 1 year of age for intelligence at 4 years of age was not strong in one series, with an IQ below 80 occurring in less than 50% of those with head circumference at least 2.5 SD below the mean (Nelson and Deutschberger, 1970). In another series of children who consistently had microcephaly (3 SD below the mean) on repeated measurements in infancy, 21 of 41 (51%) term infants had an IQ below 70 at 7 years of age (Dolk, 1991). Head circumference 2 SD below the mean was associated with an IQ below 70 in 11% of cases (Dolk, 1991).

GENETICS AND RECURRENCE RISK

The recurrence risk for microcephaly depends on the underlying cause. Both autosomal dominant and autosomal recessive patterns of inheritance for isolated microcephaly have been described. If the microcephaly is due to an aneuploidy, such as trisomy 18, the recurrence risk is approximately 1% in addition to the maternal age–related risk. If the microcephaly is due to a deletion or rearrangement in the chromosomes, parental karyotyping should be performed to rule out a balanced translocation, which would increase the recurrence risk. If microcephaly is secondary to drug exposure or infection, the recurrence risk is expected to be minimal in a subsequent pregnancy.

Empiric recurrence risks have been calculated for idiopathic severe microcephaly. Estimates of the recurrence risk for microcephaly with mental retardation in siblings are shown in Table 20-2. In one case series that reviewed the outcomes for 51 siblings of 21 patients identified with microcephaly and mental retardation, no cases of recurrence were noted in siblings (Bundey and Carter, 1974). The reason for this low recurrence risk is not known but may be that patients with isolated microcephaly were excluded from the study (Tolmie et al., 1987). In another series of 11 index cases with microcephaly and spasticity, three recurrences

Table 20-2

Recurrence Risks for Microcephaly with Mental Retardation

Reference	Recurrence Risk in Siblings (%)
Brandon et al. (1959)	6
Bundey and Carter (1974)	0
Bundey and Griffiths (1977)	13
Opitz et al. (1978)	20
Bartley and Hall (1978)	11
Herbst and Baird (1982)	5.9
Tolmie et al. (1987)	19

were found among 23 siblings (Bundey and Griffiths, 1977). In a population-based study from British Columbia that attempted total ascertainment, a 6% recurrence risk for microcephaly with mental retardation was noted (Herbst and Baird, 1982). It was not clear from this study whether microcephaly was defined as a head circumference of less than 2 or less than 3 SD below the mean. In a further series, a recurrence risk of 19% was reported from 29 cases of microcephaly in a referral genetic service for the west of Scotland (Tolmie et al., 1987).

A possible explanation for the higher risk of recurrence found in selected population studies (Bundey and Carter, 1974; Bartley and Hall, 1978; Tolmie et al., 1987) in comparison to other studies (Herbst and Baird, 1982) may be ascertainment bias. Nevertheless, these studies provide a useful source of information for prenatal diagnosis and counseling of parents with a diagnosis of fetal microcephaly.

Relatively recently, it has become appreciated that there is a new condition known as autosomal recessive primary microcephaly (MCPH) (Woods et al., 2005; Abuelo, 2007). This condition is characterized by congenital microcephaly, nonprogressive mild-to-moderate mental retardation, and an otherwise normal appearance. The brain is architecturally normal, but there is a significant reduction in the size of the cerebral cortex. At least four genes have been identified that are mutated in this disorder (Woods et al., 2005).

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21 CHAPTER Porencephaly

Key Points

- There are two main forms of porencephaly: (1) developmental porencephaly and (2) congenital encephaloclastic porencephaly. The first type represents primary failure of neuronal development and migration. The second type is more common and results from cortical destruction due to an external insult in an otherwise normal brain.
- Porencephaly can be diagnosed prenatally using sonography when fluid-filled spaces are noted in the fetal brain. MRI is a useful adjunct.
- A complete family history should be obtained to look for stroke, thrombosis, thromboembolism, and recurrent porencephaly.
- Work-up should include ruling out maternal cocaine and warfarin use, infection, hereditary thrombophilias, and increased bleeding.
- Long-term prognosis depends on the size and location of the lesions, and whether there is a hereditary thrombophilia or vasculopathy.
- The neonate should be evaluated after birth by a pediatric neurologist. Follow-up brain imaging is recommended.
- In most cases, an underlying cause for porencephaly is not identified. Most familial cases are due to underlying autosomal dominant mutations.

CONDITION

Porencephaly is a term that describes a fluid-filled cavity in open communication with the lateral ventricle (van der Knaap et al., 2006). The term *porencephaly* is often used interchangeably with *porencephalic cyst, schizencephaly, cystic brain degeneration*, and *congenital brain clefts.* Porencephaly was first described in 1859 as a cavity or cleft of the cerebral cortex (Heschl, 1859). These lesions may or may not communicate with the ventricular and subarachnoid systems. Two major subgroups are described: developmental porencephaly, which includes schizencephaly and congenital midline porencephaly and congenital encephaloclastic porencephaly (Hall, 2006).

Developmental porencephaly represents a primary failure of neuronal development and migration. Synonyms include *true porencephaly, schizencephaly*, and *congenital porencephaly.* Congenital midline porencephaly is a more recently described malformation, consisting of the triad of a midline parietal scalp anomaly (such as alopecia or cephalocele), hydrocephalus, and a midline intracranial cyst (Yokota and Matsukado, 1979; Vintzileos et al., 1987). While this malformation most likely represents a form of porencephaly, some authors consider it a variant of holoprosencephaly (Vintzileos et al., 1987).

In contrast, congenital encephaloclastic (disruptive) porencephaly results from cortical destruction due to an external insult in an otherwise normally developed brain. Synonyms include *pseudoporencephaly, false porencephaly*, and *cystic brain degeneration.* This destruction results in an intracerebral cystic cavity containing cerebrospinal fluid, and such a cyst may be single or multiple (Figure 21-1) (Hall, 2006). Congenital encephaloclastic porencephaly may have many different causes; of these, hemorrhagic infarction due to fetal venous congestion or occlusion is considered to be the most common (Dekaban, 1965; Cantu and LeMay, 1967; Nixon et al., 1974).

The known risk factors for acquired porencephaly are conditions that cause thrombophilia (such as Factor V Leiden and protein C deficiency), increased bleeding (perinatal alloimmune thrombocytopenia, von Willebrand disease), vasculopathy following in utero exposure to cocaine (Dominguez et al., 1991), infection with Coxsackie virus or cytomegalovirus (Tominaga et al., 1996; Chalhub et al., 1977),

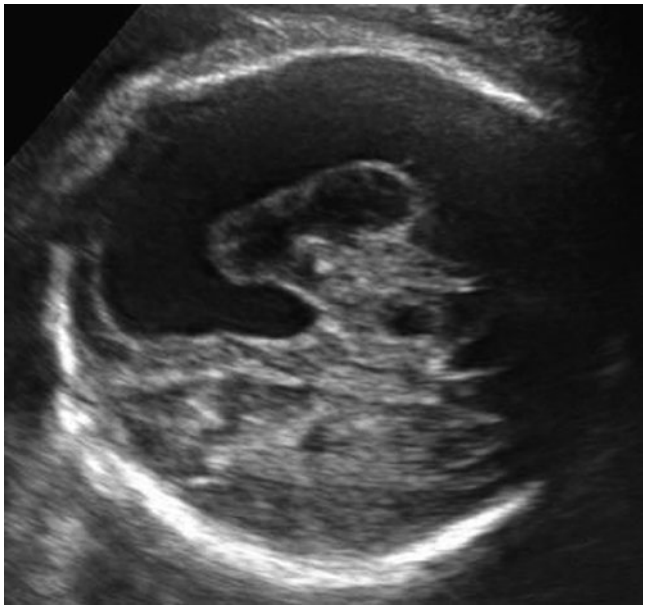

Figure 21-1 Axial image demonstrating a large porencephalic cyst with adjacent echogenic area suggestive of prior hemorrhage.

and trauma, resulting from ventricular puncture (Lorber and Grainger, 1963), amniocentesis (Eller and Kuller, 1994), or chorionic villus sampling (Sharma and Phadke, 1991) (Table 21-1). Familial porencephaly, consistent with both autosomal dominant and recessive patterns of inheritance, has also been reported (Berg et al., 1983; Sensi et al., 1990; Haverkamp et al., 1995). Mutations in the *COL4A1* gene are increasingly being recognized as an important cause of blood vessel rupture in the fetus (van der Knaap et al., 2006).

Table 21-1

Risk Factors for Encephaloclastic (Acquired) Porencephaly

Hereditary thrombophilias Factor V Leiden, protein C deficiency
Increased bleeding tendencies Maternal warfarin use, perinatal alloimmune thrombocytopenia, von Willebrand disease
Vasculopathy Maternal cocaine use, congenital infection
Trauma Amniocentesis, CVS
Familial *COL4A1* mutation

INCIDENCE

Porencephaly is an extremely rare condition with an unknown incidence.

SONOGRAPHIC FINDINGS

Porencephaly has been successfully diagnosed prenatally using both sonography and magnetic resonance imaging (Lithuania et al., 1989; Komarniski et al., 1990; Meizner and Elchalal, 1996; Levine et al., 1997; Pilu et al., 1997). The sonographic appearance is that of a fluid-filled space in the normal brain parenchyma. The cyst is more commonly unilateral but may be bilateral (Figures 21-1 and 21-2). When cysts are multiple they are frequently symmetric in appearance (Klingensmith and Cioffi-Ragan, 1986). Loss of cerebral tissue is often easily visible on coronal scans. Color Doppler sonography may be helpful in delineating a particular vascular abnormality associated with the cystic lesion (Suchet, 1994). Communication with the lateral ventricles or subarachnoid space is often visible. The ipsilateral ventricle is usually enlarged to compensate for the smaller brain mass. The diagnosis of porencephaly should be considered whenever marked asymmetric ventriculomegaly is found (Chervenak et al., 1983; Toma et al., 1990).

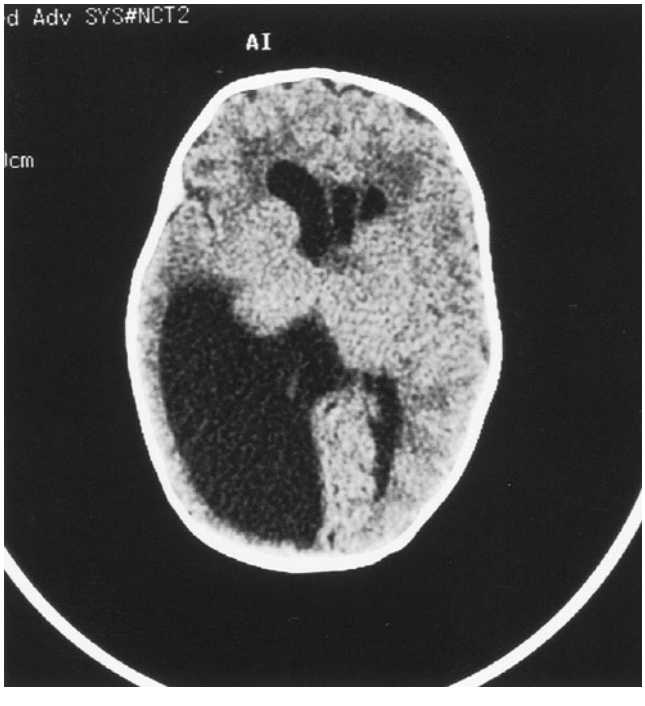

Figure 21-2 Postnatal CT scan taken in an infant noted antenatally to have an intracranial hemorrhage. The scan shows the evolution of the hemorrhage into a massive porencephalic cyst.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes other cystic brain lesions such as arachnoid cyst (see Chapter 8) and, more rarely, cystic tumors (Sauerbrei and Cooperberg, 1983). In one case of asymmetric hydrocephalus, the diagnosis of porencephaly was suspected but could not be confirmed with an ultrasound examination. Magnetic resonance imaging correctly identified the porencephalic cavity communicating with the lateral ventricle (Toma et al., 1990). If severe hydrocephalus is also present it must be distinguished from hydranencephaly. Hydranencephaly is considered to be an extreme form of encephaloclastic porencephaly.

ANTENATAL NATURAL HISTORY

In keeping with the vascular cause of many cases of porencephaly, in utero deterioration of porencephalic cystic masses has been documented (Klingensmith and Cioffi-Ragan, 1986). In this case, significant deterioration of cystic areas was noted between ultrasound examinations performed at 31 and at 36 weeks of gestation. In addition, the cystic deterioration corresponded to the distribution of the middle cerebral arteries (Klingensmith and Cioffi-Ragan, 1986). Other than this case report, little information is available to guide counseling of the patient with fetal porencephaly.

MANAGEMENT OF PREGNANCY

The pregnant woman should be asked if she has used either cocaine or warfarin. Serologic testing for cytomegalovirus, coxsackie virus, and toxoplasma should be considered. A complete family history should be obtained, with particular attention paid to occurrence of stroke, thromboembolism, and venous thromboses. If an autosomal dominant pattern of any of these conditions is established, the pregnant woman should be referred to a medical geneticist who can facilitate molecular testing for the hereditary thrombophilias and the hereditary vasculopathies. Because there are no reported associations with chromosomal disorders, amniocentesis for karyotyping is not indicated.

The prospective parents should be counseled that the prognosis depends on the location and size of the lesion. However, in almost all cases of true porencephaly, the neonatal outcome will be poor, with severe intellectual and neurologic sequelae (Romero et al., 1988). Neurologic sequelae can include spastic tetraplegia, blindness, and severe speech impediment. Fetal magnetic resonance imaging may be helpful in differentiating fetal intracranial cystic lesions (Levine et al., 1997). Consultation with a pediatric neurologist and a neonatalogist is recommended to discuss neonatal management. If diagnosed before 24 weeks of gestation, termination of pregnancy should be offered. Delivery at a tertiary care center is recommended. In cases of developmental porencephaly, vaginal delivery should be allowed in almost all cases because of the invariably poor neonatal outcome. In encephaloclastic porencephaly, particularly due to a known *COL4A1* mutation, cesarean section delivery should be offered to minimize birth trauma (Gould et al., 2005).

FETAL INTERVENTION

No fetal intervention has been described for this condition, and none is likely, as porencephaly appears as a result of the absence of cerebral tissue. Furthermore, if there is a vasculopathy present, intervention would in all likelihood cause additional damage.

TREATMENT OF THE NEWBORN

The infant should be evaluated promptly after birth by a pediatric neurologist. Imaging of the neonatal brain, using sonography and magnetic resonance imaging should be performed to aid in defining the extent of neurologic deficit. The initial signs and symptoms of porencephaly depend on the location of the defect and include seizures, varying degrees of developmental delay, visual and sensory deficits, and hydrocephalus. Porencephaly should be considered in any child with unexplained hemiparesis. The degree of impairment is variable, with some patients initially showing only mild to borderline impairment, while other infants are profoundly impaired (Nixon et al., 1974; Tardieu et al., 1981). No specific treatment is indicated, although appropriate medical therapy to control seizures is often needed.

SURGICAL TREATMENT

In some cases of porencephaly with associated hydrocephalus, there may be a role for surgical intervention to prevent further hydrocephalus-associated injury. This may be especially helpful in cases of a unilateral intracerebral cyst, resulting in a midline shift toward the contralateral side. Progression of impairment may therefore occur, unless a shunt is placed to collapse the cyst (Hall, 2006). In one series of nine children with progressive porencephaly, improvement was demonstrated following surgical placement of a ventriculoperitoneal shunt (Tardieu et al., 1981). The authors suggested shunts for any patient with progressive clinical signs of neurologic deterioration. They recommended shunts in patients less than 2 years of age in whom a large cyst is demonstrated, with hydrocephalus, macrocephaly, and developmental delay (Tardieu et al., 1981).

LONG-TERM OUTCOME

The long-term outcome for infants with porencephaly depends on the extent of the cystic destruction of cerebral tissue. Minimal data are available for accurate counseling. In most cases there is severe cerebral destruction, and the long-term outcome for such infants is extremely poor. A severe variety of postnatal encephaloclastic porencephaly has been described in 15 neonates with a birth weight of 600 to 1270 g and a gestational age at delivery of 24 to 32 weeks (Cross et al., 1992). Cerebral ultrasound examinations were characterized by irregular cystic lesions involving the periphery of the brain. Fourteen of the 15 infants died in the first 6 weeks of life, and 8 had clinical evidence of neurologic abnormality resulting in seizures. The only survivor had severe neurologic deficit at 12 months of age (Cross et al., 1992).

GENETICS AND RECURRENCE RISK

In many cases the underlying cause for porencephaly will not be identified. Prevention of porencephaly may be possible in cases of monochorionic twins with impending death of one fetus. In such cases, consideration of elective preterm delivery, or fetoscopic cord ligation of the abnormal twin, may prevent porencephaly, which may be caused by profound hypotension at the time of death of the twin (see Chapter 118).

Recently, there has been increasing appreciation of families that have an autosomal dominant form of porencephaly (van der Knaap et al., 2005; Breedveld et al., 2006). In the past, the dominant nature of the condition has been obscured because of individuals who appeared to lack expression of the phenotype. More recent studies, using MRI, demonstrate subtle CNS anomalies but no porencephaly, in individuals who are obligate carriers of dominant mutations. In parallel, in 2005, Gould et al. studied a mutant mouse that develops porencephaly. They showed that the perinatal cerebral hemorrhage was due to vascular defects resulting from a dominant mutation in the procollagen type IVa 1 gene (*CO14a1*). They subsequently went on to show in two human families with autosomal dominant porencephaly that there were mutations in the *COL4A1* gene. These findings have been validated in other studies (Breedveld et al., 2006; van der Knaap et al., 2006) and suggest that consideration of molecular testing is important if there is a positive family history.

Additional evidence to suggest the importance of autosomal dominant gene mutations that predispose to porencephaly comes from a German case–control study in which 76 porencephalic and 76 healthy infants were investigated for Factor V Leiden G1691A mutation, factor II G20210A variant, methylenetetrahydrofolate reductase (MTHFR) C677T variant, lipoprotein (a), proteins S and C, and antithrombin (Debus et al., 2004). Only the Factor V Leiden mutation, or a combination of two or three different risk factors was statistically significantly associated with porencephaly.

Families in which a *COL4A1* or Factor V Leiden (G1691A) mutation has been documented should be counseled that they potentially have a 50% incidence of recurrence. *COL4A1* mutations are associated with an increased incidence of strokes in the early adult years.

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22 CHAPTER Vein of Galen Aneurysm

Key Points

- The vein of Galen is a single, midline structure formed by the convergence of the two internal cerebral veins and the basal veins of Rosenthal posterior to the splenium of the corpus callosum; the vein courses posteriorly to empty into the straight sinus.
- Vein of Galen malformation, an extremely rare anomaly, is a complex arteriovenous malformation affecting the vein of Galen and the cerebral arteries.
- The size of the aneurysm determines its clinical presentation. A large aneurysm can result in as much as 50% to 60% of the cardiac output shunting through the lesion that may cause high-output congestive heart failure. This can present in utero as hydrops or as cardiac failure in early neonatal life.
- Cerebral parenchymal injury including cerebral infarction, periventricular leukomalacia, and hemorrhagic infarction can also be associated with this anomaly.
- Vein of Galen aneurysm may be suspected on antenatal ultrasound examination when a cystic or tubular mass is noted in the midline of the brain just above and behind the thalamus. Turbulent venous or arterial flow may be demonstrated using color Doppler within the draining vessel.
- Generalized cardiomegaly or right ventricular enlargement is commonly noted but should not be attributed to high-output cardiac failure until targeted fetal echocardiography has been performed.
- The differential diagnosis includes other midline cystic structures within the brain such as an arachnoid cyst or an interhemispheric cyst associated with agenesis of the corpus callosum.
- Because of the differences in the fetal and neonatal circulations, cardiac failure does not often occur until after birth.
- Serial antenatal ultrasound examinations should be performed to determine a change in size of the aneurysm and to monitor for hydrocephalus or congestive heart failure.
- Joint management with a pediatric cardiologist and pediatric neurosurgeon is suggested.
- The approach to therapy for a patient with a vein of Galen aneurysm will depend on the age of the patient, the clinical symptoms, and the angiographic architecture of the malformation.

LONG-TERM OUTCOME OF PRENATALLY DIAGNOSED VEIN OF GALEN ANEURYSM IS STILL NOT A WELL-KNOWN CONDITION

Vein of Galen aneurysm is also referred to as a varix of the vein of Galen or vein of Galen malformation. This anomaly is a complex arteriovenous malformation affecting the vein of Galen and the cerebral arteries. The vein of Galen is a single, midline structure formed by the convergence of the two internal cerebral veins and the basal veins of Rosenthal posterior to the splenium of the corpus callosum; the vein courses posteriorly to empty into the straight sinus. During embryologic development, cerebral arteries and veins cross in close proximity to each other; fistulous connections may exist because only a few cell layers separate these vessels (Padget, 1956). These fistulas persist because of an arteriovenous pressure gradient. The size and number of arteriovenous fistulous connections determine the eventual size of a vein of Galen aneurysm.

Aneurysm of the vein of Galen was first described in 1937 by Jaeger et al. (1937). The first precise anatomical definitions of these vascular malformations were described in 1960 (Litvak et al., 1960). Malformations of the vein of Galen most probably arise early in embryogenesis in the 20- to 40-mm fetus, when arteries and veins are still simple endothelial tubes (Padget, 1956). Following an anatomic analysis of 23 cases of vein of Galen aneurysm, it was concluded that the venous sac most probably represents persistence of the embryonic median prosencephalic vein of Markowski, not the vein of Galen per se (Raybaud et al., 1989). Even though there is plausible evidence that the aneurysmal sac is the persistent embryonic median prosencephalic vein of Markowski rather than the true vein of Galen, this author concluded that it was reasonable to retain the generally accepted nomenclature of *vein of Galen aneurysm*, but to restrict its use to cases in which the arteriovenous fistulas are within the wall of the venous sac. Vein of Galen aneurysms may be defined as direct arteriovenous fistulas situated between choroidal and/or quadrigeminal arteries and an overlying single median venous sac.

The size of the aneurysm of the vein of Galen determines its clinical presentation. When the aneurysm is large, as much as 50% to 60% of the cardiac output may be shunted through the lesion (Cumming, 1980). This arteriovenous shunt may result in high-output congestive heart failure, and these patients tend to present with hydrops in utero, or with cardiac failure in early neonatal life.

Other cases of vein of Galen aneurysm are not associated with cardiac failure and may not present until the first year of life. Hydrocephalus may also occur in association with a large vein of Galen aneurysm, although the cause is uncertain. Possible mechanisms for the development of hydrocephalus include compression of the sylvian aqueduct by the aneurysmal mass and defective cerebrospinal fluid resorption resulting from intracranial venous hypertension (Gold et al., 1964; Diebler et al., 1981).

Cerebral damage including cerebral infarction, periventricular leukomalacia, and hemorrhagic infarction may also occur in association with aneurysm of the vein of Galen (Norman and Becker, 1974). Suggested mechanisms by which such cerebral parenchymal injury may occur include

1. a steal-induced ischemic phenomenon from overlying abnormal vessels;
2. cerebral ischemia due to compromised perfusion from congestive heart failure;
3. hemorrhagic infarction from thrombosis of the dilated vein of Galen;
4. atrophy resulting from compression of adjacent structures by the aneurysm;
5. alteration of flow occurring as a result of surgical therapy (Gold et al., 1964; Norman and Becker, 1974).

Vein of Galen aneurysms have been classified into four subtypes according to the severity of the lesion and the age of the patient at the onset of symptoms (Amacher and Shillito, 1973). Four groups have been described:

1. Neonates with severe heart failure and cranial bruit.
2. Children with mild heart failure and cranial bruit.
3. Children younger than 1 year of age with cranial bruit and hydrocephalus.
4. Patients with headaches and syncope.

Thrombosed vein of Galen aneurysm may also represent a fifth subtype (Beltramello et al., 1991). Congestive heart failure does not seem to be a feature of thrombosed vein of Galen aneurysm, as it is possible that occlusion of the aneurysm by the thrombosis may protect patients from this complication. In all cases of vein of Galen aneurysm thrombosis described to date, the initial presenting symptoms were attributed to hydrocephalus (Beltramello et al., 1991). Twenty-one cases of vein of Galen aneurysm thrombosis have been reported in the literature (Beltramello et al., 1991). Of these, 12 cases were diagnosed in patients younger than 1 year of age, 4 in patients between 1 and 14 years of age, and 5 in adults. Neuroradiology findings in vein of Galen aneurysm thrombosis include intracranial calcifications in the region of the vein of Galen in 50% of cases and a midline spherical mass, shown by computed tomographic (CT) scanning, that does not fill angiographically (Beltramello et al., 1991).

INCIDENCE

The true incidence of vein of Galen aneurysm is unknown, but it is an extremely rare abnormality. One of the largest reported series has described 43 cases that had been referred for endovascular treatment, together with a review of 335 additional cases previously reported in the literature (Zerah et al., 1992). More recently, there have been more than 30 cases of prenatal aneurysm of the vein of Galen diagnosed through the use of ultrasound and pulsed Doppler examination

(Suma et al., 1991; Rodesch et al., 1994; Pilu et al., 1997; Has et al., 2003; Paternoster et al., 2003). The largest single prenatal experience described 18 cases of vein of Galen aneurysm diagnosed in the third trimester (Rodesch et al., 1994).

SONOGRAPHIC FINDINGS

The typical prenatal sonographic finding is that of a cystic or tubular mass in the midline of the brain just above and behind the thalamus (Figure 22-1). A draining vessel may be seen extending posteriorly in the direction of the straight sinus. Around this central cystic mass, heterogeneous cystic areas may be present that represent dilated blood vessels (Figure 22-2) (Comstock and Kirk, 1991). Turbulent venous or arterial flow may be demonstrated using color Doppler examination within the draining vessel (Figure 22-1) (Jeanty et al., 1990; Sepulveda et al., 1995). Occasionally, turbulent flow may be seen within the cystic mass even without the aid of Doppler sonography (Comstock and Kirk, 1991).

Magnetic resonance imaging (MRI) appears to be an important adjunctive tool in patients suspected to have vein of Galen aneurysm prenatally. MRI can be used to confirm the diagnosis and to demonstrate the anatomical structure of the anomaly (Kurihara et al., 2001) (Figure 22-3). Both MRI and 3D ultrasound may be useful because they allow a better understanding of the spatial orientation and the course of the vessels and they may help guide the postnatal management (Heling et al., 2000; Lee et al., 2000; Has et al., 2003)

Appearance of the cerebral ventricles is variable. Hydrocephalus may be seen prenatally and seems to be unrelated to the size of the aneurysmal dilatation (Comstock and Kirk, 1991). The antenatal appearance of the heart is also variable, but generalized cardiomegaly or right ventricular enlargement is commonly noted (Comstock and Kirk, 1991). Enlargement of the heart should not be ascribed simply to presumed high-output cardiac failure until targeted fetal echocardiography is performed. Coarctation of the aorta and transposition of the great vessels occur with increased frequency in infants with vein of Galen aneurysm (Figure 22-3) and may also be responsible for cardiomegaly (Warkany, 1971; Watson et al., 1976). Massive hydrops has been reported as early as 31 weeks of gestation (Hirsch et al., 1983; Reiter et al.,

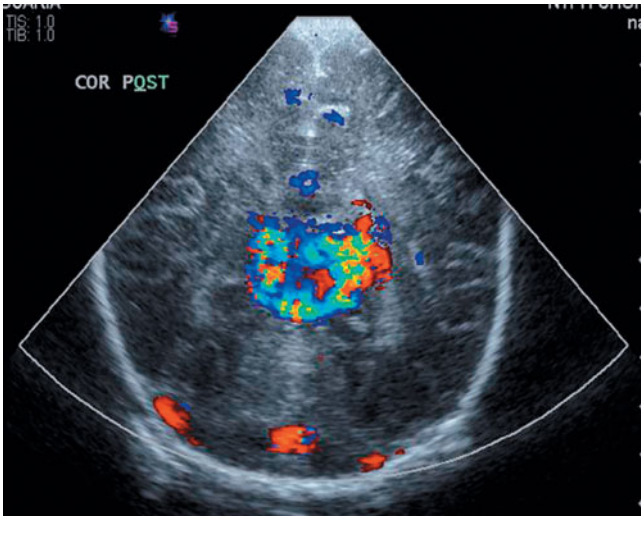

Figure 22-1 Prenatal sonographic image demonstrating midline cystic lesion suggestive of vein of Galen aneurysm in a 36-week fetus. Color Doppler demonstrates turbulent vascular flow.

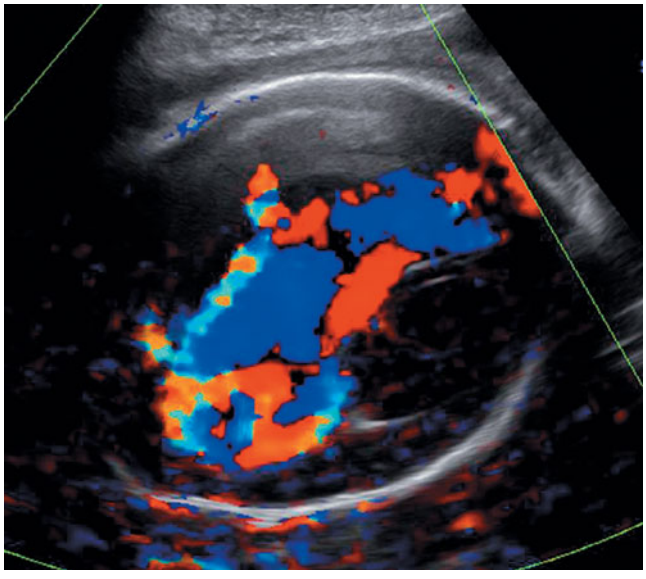

Figure 22-2 Doppler color flow studies demonstrating the presence of prominent convoluted vessels in a 33-week fetus with a large vein of Galen aneurysm.

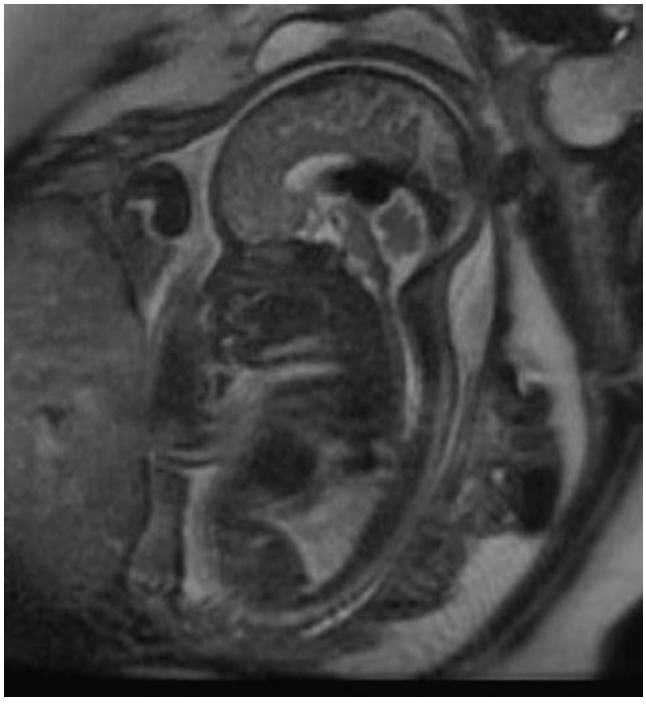

Figure 22-3 Magnetic resonance imaging of the same 36-week fetus demonstrates vein of Galen aneurysm in a sagittal plane.

1986). In addition, there have been autopsy reports of prenatal brain ischemia, periventricular leukomalacia, and cortical brain atrophy associated with vein of Galen aneurysm (Hirsch et al., 1983; Reiter et al., 1986; Baenziger et al., 1993).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of vein of Galen aneurysm includes other midline cystic masses within the brain, such as an arachnoid cyst or an interhemispheric cyst associated with agenesis of the corpus callosum. The major helpful diagnostic features of aneurysm of vein of Galen include the typical location of the cyst superior and posterior to the thalami and high-velocity blood flow within the cyst on Doppler examination (Figures 22-1 and 22-2). Neither an arachnoid cyst nor an interhemispheric cyst should demonstrate blood flow. A normal intracranial cystic structure, the quadrageminal cistern, may also mimic vein of Galen aneurysm in initial appearance, although in the case of a cistern, blood flow will not be demonstrable. The visualization of cardiomegaly or signs of congestive cardiac failure in utero add confirmatory evidence of an aneurysm of the vein of Galen. Prenatal MRI has been reported as a useful additional imaging tool in at least two cases in which vein of Galen aneurysm was suspected at prenatal ultrasonography (Yamashita et al., 1992; Martínez-Lage et al., 1993).

ANTENATAL NATURAL HISTORY

Because relatively few cases of prenatally diagnosed vein of Galen aneurysm have been reported in the literature, little is known about its antenatal natural history. The earliest prenatal diagnosis was made at 25 weeks of gestation, which was followed by an intrauterine fetal death at 28 weeks of gestation (Ballester et al., 1994). Most cases are not diagnosed until the third trimester, which limits the available knowledge on antenatal natural history (Suma et al., 1991; Rodesch et al., 1994).

The arteriovenous shunt develops in utero, but because of differences in the hemodynamics of the fetal and neonatal circulations, severe cardiac failure does not appear in most cases until after birth (Ciricillo et al., 1990). Fetal systemic vascular resistance is lower in the fetus because of the low placental resistance, and at birth, this resistance increases markedly as the placental circulation is removed. Following birth, low resistance remains within the cerebral arteriovenous fistula, which results in an abrupt increase in flow through the aneurysm and increased venous return to the right side of the heart. Pulmonary hypertension develops because of the resulting increase in pulmonary blood flow. Subsequently, right-to-left shunting at the atrial and ductal levels causes arterial hypoxemia. The increased diastolic flow to the aneurysm reduces coronary blood flow, which mainly occurs during diastole. Increased ventricular pressures also reduce subendocardial perfusion, which causes further myocardial ischemia and exacerbates cardiac failure. In the largest series of prenatally diagnosed vein of Galen aneurysms, there were no intrauterine fetal deaths, and the first clinical symptoms occurred in the newborn period in 94% of cases (Rodesch et al., 1994).

Although blood flow through a vascular malformation should be small in the fetus because of generally low systemic vascular resistance, there have also been reports of high-output cardiac failure occurring in utero with vein of Galen aneurysms (Hirsch et al., 1983; Reiter et al., 1986). These fetuses were hydropic as early as 31 weeks of gestation. At autopsy their brains exhibited periventricular leukomalacia and areas of diffuse microinfarction in both the gray and white matter. These autopsy findings were similar to the pathologic changes described in seven neonates with vein of Galen aneurysm (Norman and Becker, 1974). These observations demonstrate that in some cases irreversible brain ischemia may occur even before birth (Hirsch et al., 1983; Reiter et al., 1986).

MANAGEMENT OF PREGNANCY

Prenatal evaluation should include targeted sonography to exclude additional malformations, such as cerebral parenchyma destruction, as well as fetal echocardiography. Serial obstetric ultrasonography should be performed every 2 weeks to determine change in size of the aneurysm and to monitor for development of hydrocephalus or congestive cardiac failure. Karyotyping is not indicated. If there is any doubt about the diagnosis, prenatal MRI may help in making a definitive diagnosis of vein of Galen aneurysm (Martinez-Lage et al., 1993). In the unlikely event that the diagnosis is made before 24 weeks of gestation, termination should be offered because of the high perinatal mortality rate. However, most cases will present during the third trimester, thereby limiting options for parents (Suma et al., 1991; Rodesch et al., 1994). Subspecialty consultation with a pediatric cardiologist and a pediatric neurosurgeon is suggested because both the timing of neonatal surgical management and the prognosis will depend on the degree of cardiovascular involvement and the presence of parenchymal brain damage (Amacher and Shillito, 1973; Mickle et al., 1994).

Delivery should take place at a center where immediate neonatal consultation is available from subspecialists in pediatric neuroradiology, neurosurgery, and cardiology. No data are available regarding the optimal mode of delivery for fetuses with aneurysm of the vein of Galen (Doren et al., 1995). Elective delivery near term following confirmation of fetal lung maturity is reasonable. In one series, elective cesarean delivery was performed in many of the prenatally diagnosed cases (Suma et al., 1991). In another series of 18 cases of prenatally diagnosed vein of Galen aneurysm, there were 12 vaginal deliveries, five cesarean deliveries, and one induced abortion (Rodesch et al., 1994). If hydrocephalus and macrocephaly

are present, cesarean delivery is preferable. In the absence of associated hydrocephalus and macrocephaly, vaginal delivery with continuous intrapartum fetal heart rate monitoring is reasonable. Decreased intrapartum short- and long-term fetal heart rate variability in association with normal umbilical cord blood gas values was reported in one case in which an aneurysm of the vein of Galen was diagnosed in the neonatal period (Koh and Grundy, 1988).

FETAL INTERVENTION

There are no case reports of fetal intervention for vein of Galen aneurysm. Theoretically, if serial sonography demonstrates deteriorating cardiovascular status, early delivery might be an option to allow appropriate postnatal cardiovascular stabilization and neurosurgical treatment of the aneurysm.

TREATMENT OF THE NEWBORN

The clinical presentation of vein of Galen aneurysm depends on the age at which symptoms appear and on the amount of cardiovascular compromise that has been sustained (Amacher and Shillito, 1973; Diebler et al., 1981). The most severe presentation is in early neonatal life and consists of congestive heart failure and seizures. The possibility of an intracerebral arteriovenous fistula should be considered in any infant presenting with unexplained cardiac failure. In such cases, auscultation of the neonatal head for a cranial bruit may suggest the diagnosis, which can then be confirmed by cerebral ultrasound examination (O'Donnabhain and Duff, 1989). Death in the infant with vein of Galen aneurysm is usually caused by intractable cardiac failure associated with myocardial ischemia (McLeod et al., 1982), acute circulatory overload following ligation of a feeding vessel (Yasargil et al., 1976), or thrombosis of the aneurysm (Six et al., 1980).

The approach to therapy for the patient with a vein of Galen aneurysm depends on the age of the patient, the clinical symptoms, and the angiographic architecture of the malformation. Most patients diagnosed in utero will present with cardiac manifestations in early neonatal life (Suma et al., 1991; Rodesch et al., 1994). When vein of Galen aneurysm is suspected, confirmatory cerebral ultrasonography should be performed. Transcranial color Doppler ultrasound examination allows a rapid bedside diagnosis (Stockberger et al., 1993). Subsequent MRI with cerebral angiography will allow precise documentation of the abnormal vascular anatomy.

Pediatric cardiology consultation together with echocardiographic evaluation is important for assessing and treating associated congestive cardiac failure. In one series of prenatally diagnosed vein of Galen aneurysms, 12 of 16 newborns with cardiac symptoms were initially managed effectively with digitalization and diuretic therapy (Rodesch et al., 1994). Four of these infants died shortly after birth from acute heart failure or multiorgan failure with extensive brain damage. However, the majority of patients who are symptomatic at birth will require more aggressive intervention with either surgery or interventional radiology. Infants who are asymptomatic at birth should be treated expectantly, with follow-up radiologic imaging at 6 months of age. If the malformation persists, treatment is usually administered between 6 and 9 months of age.

SURGICAL TREATMENT

The first attempt at a direct neurosurgical approach for treatment of an infant with vein of Galen aneurysm was reported in 1947 (Osherwitz and Davidoff, 1947). Subsequently, another patient was successfully treated by clipping the posterior cerebral arteries feeding the malformation (Boldry and Miller, 1949). Open surgical intervention via craniotomy was the primary method of treatment of vein of Galen aneurysms until the early 1980s, although results were disappointing (Hoffman et al., 1982; Johnston et al., 1987). Subsequently, interventional neuroradiologic techniques have become the method of choice for treatment of these lesions. Initial imaging studies with CT scanning or MRI are suggested for patient selection before neurosurgical or radiologic intervention (Mickle and Quisling, 1994). Patients with severe multicystic encephalomalacia or other significant neurologic injury should not be considered candidates for aggressive therapy.

Most authors now agree that the main goal of therapy in the neonate with vein of Galen aneurysm and congestive heart failure is not complete occlusion of the aneurysm but improvement in cardiac function (Matjasko et al., 1988; Ciricillo et al., 1990; Horowitz et al., 1994).

Transvenous and transarterial embolization techniques have been increasingly described in the literature (Mickle and Quisling, 1986; Ciricillo et al., 1990; Lasjaunias et al., 1991). In the infant with congestive heart failure the initial procedure of choice appears to be endovascular, with a venous approach, either transfemoral or transtorcular (Horowitz et al., 1994; Mickle et al., 1994). The immediate goal is to increase resistance in the aneurysm to right ventricular output. The advantages of a transvenous approach over a transarterial approach include shorter anesthesia time and minimal contrast administration (Horowitz et al., 1994). The transvenous approach can be repeated as many times as needed and may be supplemented by transarterial embolizations. Endovascular coils are commonly used for venous embolizations (Horowitz et al., 1994). Another advantage of repeated embolizations with the transvenous approach is a graded thrombosis of the aneurysm, which may serve to minimize the risk of hemorrhage and neurologic injury (Horowitz et al., 1994).

Color and pulsed Doppler ultrasound examinations are useful in the evaluation of the success of interventional radiologic techniques. Pulsed Doppler analysis in the proximal descending aorta demonstrating diastolic retrograde velocity exceeding 20% to 25% of the systolic antegrade velocity

suggests that the aneurysm is still very large and that further interventional treatment is required (Ciricillo et al., 1990).

Survival statistics following interventional neuroradiologic techniques for the treatment of vein of Galen aneurysm appear to be substantially better than with open surgical procedures. In a review of experience with vein of Galen aneurysm at the University of California at San Francisco, five infants underwent craniotomy and clipping of feeding vessels between 1978 and 1983, and all died in the perioperative period (Ciricillo et al., 1990). Since 1983, at least eight neonates have been treated with interventional neuroradiologic embolization techniques; six survived (Ciricillo et al., 1990). In a more recent series of 11 cases, there was no infant mortality following therapy with embolization techniques (Friedman et al., 1993). Approximately 50% of neonates suffering from severe progressive cardiac failure can be expected to survive following such embolization techniques (Mickle and Quisling, 1994).

LONG-TERM OUTCOME

Little information is available on the long-term follow-up of prenatally diagnosed cases of vein of Galen aneurysm. In one series of 18 patients diagnosed prenatally, 13 infants survived the immediate neonatal period and 12 underwent embolization of the aneurysm (Rodesch et al., 1994). Total occlusion of the aneurysm was obtained in eight cases. Sixty-seven percent of the surviving newborns were neurologically normal when assessed with Denver Development Tests (Rodesch et al., 1994).

In another series of 22 patients with vein of Galen aneurysm treated with embolization techniques, there was a 50% mortality rate and a 37% incidence of severe mental retardation in survivors of procedures performed soon after the introduction of the technique (Friedman et al., 1993). For procedures performed after modification of the original technique, there was no mortality, and 6 of the 11 patients were functionally normal at 30 months of follow-up. Two patients had severe neurologic deficiency, and some developmental delay was observed in one other patient. The improvement in outcome results was attributed to earlier diagnosis, improvement in the microcatheters used for embolization, avoidance of overly aggressive neurosurgical procedures, and general improvements in neonatal care (Friedman et al., 1993). In addition, when vein of Galen aneurysm first presents in the older child, results of therapy are more favorable, with mortality rates as low as 20% (Hoffman et al., 1982).

Infants who require shunting for hydrocephalus with vein of Galen aneurysm appear to have a less favorable neurologic outcome (Zerah et al., 1992). For these infants, a significant difference in the clinical outcome was noted between the groups with shunting and those with no shunting (Zerah et al., 1992). Of the patients without shunts, 67% were free of any neurologic deficit or mental retardation, and fewer than 5% had significant mental retardation. In contrast, only 33% of the patients with a shunt had a favorable outcome, and significant mental retardation developed in more than 15% (Zerah et al., 1992). The authors' conclusion was that treatment of hydrocephalus in vein of Galen aneurysm can be achieved through obliteration of the malformation and that shunting should not be the preferred treatment for hydrocephalus in this condition.

The prognosis for patients with thrombosed vein of Galen aneurysm seems to be more favorable. The impact of treatment on outcome for thrombosed vein of Galen aneurysms is controversial. Some authors believe a clotted vein of Galen aneurysm may constitute a risk to the motor and mental development of the patient, whereas others feel that the thrombosed vein may shrink or fibrose without intervention and therefore may not be clinically significant (Six et al., 1980). In one case report of thrombosed vein of Galen aneurysm, spontaneous resolution of hydrocephalus occurred, and shunting was unnecessary (Six et al., 1980). In two other cases radiologic evidence of progressive shrinking of the clotted aneurysm to a residual inert calcification was demonstrated, without the need for therapeutic intervention (Beltramello et al., 1991).

GENETICS AND RECURRENCE RISK

There have been no reported cases of recurrent vein of Galen aneurysm. The inheritance pattern appears to be sporadic.

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Cleft Lip and Cleft Palate

23 CHAPTER

Key Points

- Overall incidence is 1 in 700 births. Marked ethnic and racial variation occurs in cleft lip with or without cleft palate.
- Seventy percent of cases are nonsyndromic, 30% are syndromic based on the presence of other anomalies and/or developmental delay.
- 2D sonographic detection rate of orofacial clefts is on the order of 65% to 73% of cases. 3D sonography allows better visualization of defects in the palate and MRI allows assessment of secondary palate.
- If a suspected orofacial cleft is diagnosed, referral should be made to a level II facility. Prenatal karyotype should be considered. There is a high rate of associated anomalies, particularly of the heart and central nervous system.
- Fetal treatment has been performed on animals.
- Long-term issues include midface hypoplasia, facial appearance, dental abnormalities, speech disorders, and hearing problems.
- More than 400 single-gene disorders are associated with cleft lip and palate. A family history should be obtained, and parents should be examined for subtle findings such as bifid uvula and missing teeth.
- At birth a thorough physical examination should be performed and a medical geneticist should be consulted. Many infants are treated by a multidisciplinary team that includes emphasis on feeding and adequate nutrition.

CONDITION

Cleft lip and palate are relatively common facial malformations that occur early in gestation. Although they are distinct anomalies, they frequently occur together (Seeds and Cefalo, 1983). In all cases of orofacial clefting, 60% to 75% involve cleft lip, with or without cleft palate, and 25% to 40% are isolated cleft palate (Figure 23-1). Most cases (80%) are unilateral, occurring twice as commonly on the left side as on the right (Gorlin et al., 1971; Seeds and Cefalo, 1983; Bronshtein et al., 1991). Isolated cleft palate is more frequently associated with other anomalies (Jones, 1988a).

Orofacial clefts derive from abnormalities in the migration and proliferation of facial mesenchyme, a neural crest cell derivative. Coalescence of facial mesenchyme results in the formation of the primary palate, which creates the initial separation between oral and nasal cavities, eventually creating part of the upper lip and anterior maxilla (Ross and Johnston, 1972). Cleft lip with or without cleft palate results from failure of the nasal and maxillary facial processes to fuse. Fusion of these processes may be affected by the amount of

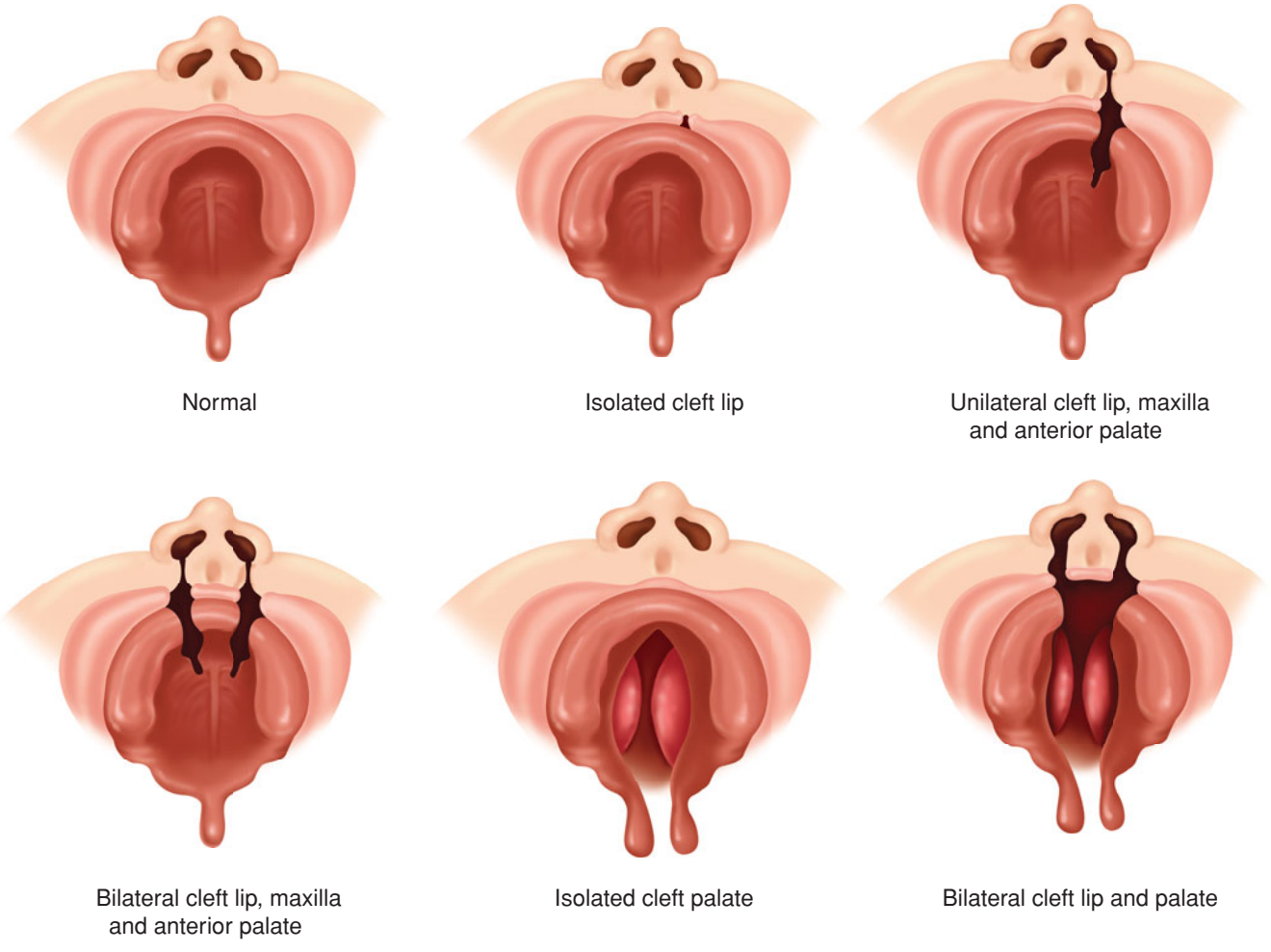

Figure 23-1 Schematic representation of the different types of malformations found in cases of orofacial clefting. The perspective is from the inside of the mouth looking upward toward the nose.

mesenchyme present, its rate of migration, and the distance over which this migration occurs (Lynch and Kimberling, 1981).

Fifty percent of cleft lip patients also have cleft palate, which is a secondary effect resulting from a defect in facial prominence fusion that precedes palate formation. Isolated cleft palate has a different pathophysiology than either cleft lip or cleft lip associated with cleft palate. It results from interference in any of the following processes that occur during normal closure of the palate:

1. The palatal shelves move from bilateral vertical positions lateral to each side of the tongue to horizontal positions overlying the tongue.
2. The tongue exerts resistance to the movement of the palatal shelves.
3. The tongue moves downward to below the palatal shelves.
4. The horizontal palatal shelves become flattened and extend their leading edges toward the midline.
5. The shelves meet in the midline and fuse. Their respective epithelia then dissolve at the point of contact (Lynch and Kimberling, 1981).

From the description above, it is apparent that the tongue plays a role in the etiology of cleft palate. Any factor that interferes with downward displacement of the tongue, tongue movement, or tongue pressure may interfere with palatal fusion.

INCIDENCE

The worldwide incidence of cleft lip with or without cleft palate is 1 in 700 births (Murray, 2002). Marked variation occurs in different racial and ethnic groups. Black infants have a lower incidence (1 in 2273 births), whereas the incidence among Japanese and Native Americans is higher (1 in 584 and 1 in 276, respectively) (Tretsven, 1963; Lynch and Kimberling, 1981). Isolated cleft palate occurs more rarely and does not vary in different ethnic backgrounds. Cleft lip and palate occur twice as often in males as in females (Bronshtein et al., 1991). In some studies, orofacial clefting has been shown to occur more commonly in fetuses whose mothers are of advanced age (Womersley and Stone, 1987; Shaw et al., 1991);

in a large population-based registry, however, no association between maternal age and cleft disorders was seen (Baird et al., 1994). Maternal smoking and alcohol use during pregnancy are thought to increase the incidence of clefts through gene-environment interactions (Eppley et al., 2005). Periconceptual multivitamin use, specifically folate supplementation, decreases the incidence of cleft palate (Werler et al., 1999, Eppley et al., 2005).

SONOGRAPHIC FINDINGS

Although fusion of the midline structures of the fetal face is complete by 7 weeks of gestation, the mandible and maxilla are not clearly visualized sonographically until week 10 (Cockell and Lees, 2000). Cleft lip and palate cannot be reliably diagnosed until 13 to 14 weeks by transabdominal sonography. The fetal palate is best observed in the axial plane and the fetal lips in the coronal views. Seeds and Cefalo (1983) were the first investigators to advocate a combination of frontal and coronal scanning of the midface (Figure 23-2). In 1984, Benacerraf et al. recommended routinely examining the face as part of a complete antenatal sonographic examination. They described a coronal view through fetal facial structures that encompassed both orbits, the maxilla, and the anterior portion of the mandible in one vertical plane. Sherer et al. (1991) described an oblique coronal facial view that was achieved by aiming the transducer beneath the fetal chin using the nares as a landmark. They sought echogenic evidence of an intact fissure created by the closed lips. The two advantages of this approach are that rarely was this view unobtainable due to position of the fetus and that the appearance of the philtrum was clearly defined. Using a combination of transverse, coronal, and profile views, Turner and Twining (1993) were able to define fetal facial structures in 95% to 97% of fetuses at 16 to 20 weeks of gestation.

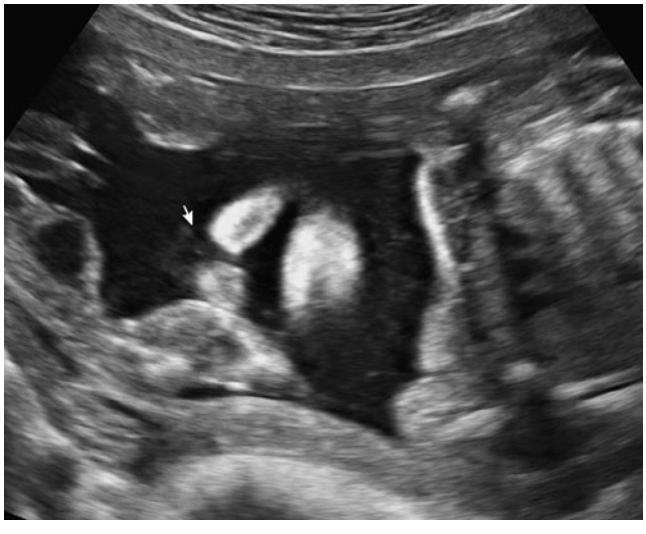

Figure 23-2 Coronal facial view of fetus at 23 weeks with a midline cleft lip. Arrow indicates the site of the cleft.

Bronshtein et al. (1994) described the use of transvaginal sonography to detect facial clefts in the early second trimester. In 14,988 examinations performed, 11 cases of orofacial clefts were detected. Of these, 10 were cases of cleft lip and palate and 1 was isolated cleft lip. All diagnoses were confirmed after termination of the pregnancy or at birth.

Despite these studies, sonographic diagnosis of facial clefts remains challenging. The overall detection rate is currently on the order of 65% (Cash et al., 2001) to 73% (Robinson et al., 2001). In general, cleft lip is easier to demonstrate than cleft palate. Bronshtein et al. (1991) advocated the use of the sagittal paramedian view to detect pseudoprognathism, a protrusion of the mandible relative to the maxilla. In bilateral cleft lip and palate, a paranasal echogenic mass may be present due to premaxillary protrusion of the prolabial structure that exists in this condition (Nyberg et al., 1992, 1993). Sherer et al. (1993) have advocated for the use of color Doppler imaging to demonstrate abnormal amniotic fluid flow across the fetal pharyngeal bone defect, although this technique has not gained widespread acceptance and is of uncertain value.

Because of the challenges associated with the 2D sonographic diagnosis of orofacial clefts, several authors advocate for a 3D approach (Figures 23-3A and 23-3B). One study examined the use of 3D sonographic visualization of fetal tooth buds as a means of improving antenatal characterization of fetal facial clefts (Ulm et al., 1999). In all 17 fetuses studied, it was possible to classify the clefts as either cleft lip alone or unilateral or bilateral cleft lip and palate. Lee et al. (2000) described a standardized 3D protocol that included multiplanar imaging of the upper lips and sequential axial views to evaluate the alveolar ridge contour and anterior tooth socket alignment.

More recently, 3D ultrasound has been used to evaluate the anatomy of the fetal palate from within the fetal head. Using this technique, a 3D volume of the fetal head is obtained and then a cut volume of tissue is removed from the back of the head. By rotating the remaining volume containing the anterior part of the face and head, the fetal palate can then be inspected from behind the face, revealing the interior of the mouth (Platt et al., 2006). Alveolar ridge disruption, or premaxillary protrusion (by multiplanar imaging or surface rendering) suggests the presence of bilateral cleft lip and palate. Additional advantages of 3D sonography include the fact that it allows assessment of the secondary (posterior) palate, it saves time, and that it is easier for prospective parents to visualize the defect (Rotten and Levaillant, 2004).

Fetal MRI is being increasingly used to evaluate structures that are difficult to identify by sonography alone. With MRI, the fetal nose and lips are best seen with coronal images. The secondary palate is best seen when amniotic fluid fills the mouth and outlines the tongue and palate (Smith et al., 2004). A major advantage of MRI appears to be that it allows a more accurate assessment of the secondary palate, which cannot be seen by 2D sonography (Ghi et al., 2003; Kazan-Tannus et al., 2005).

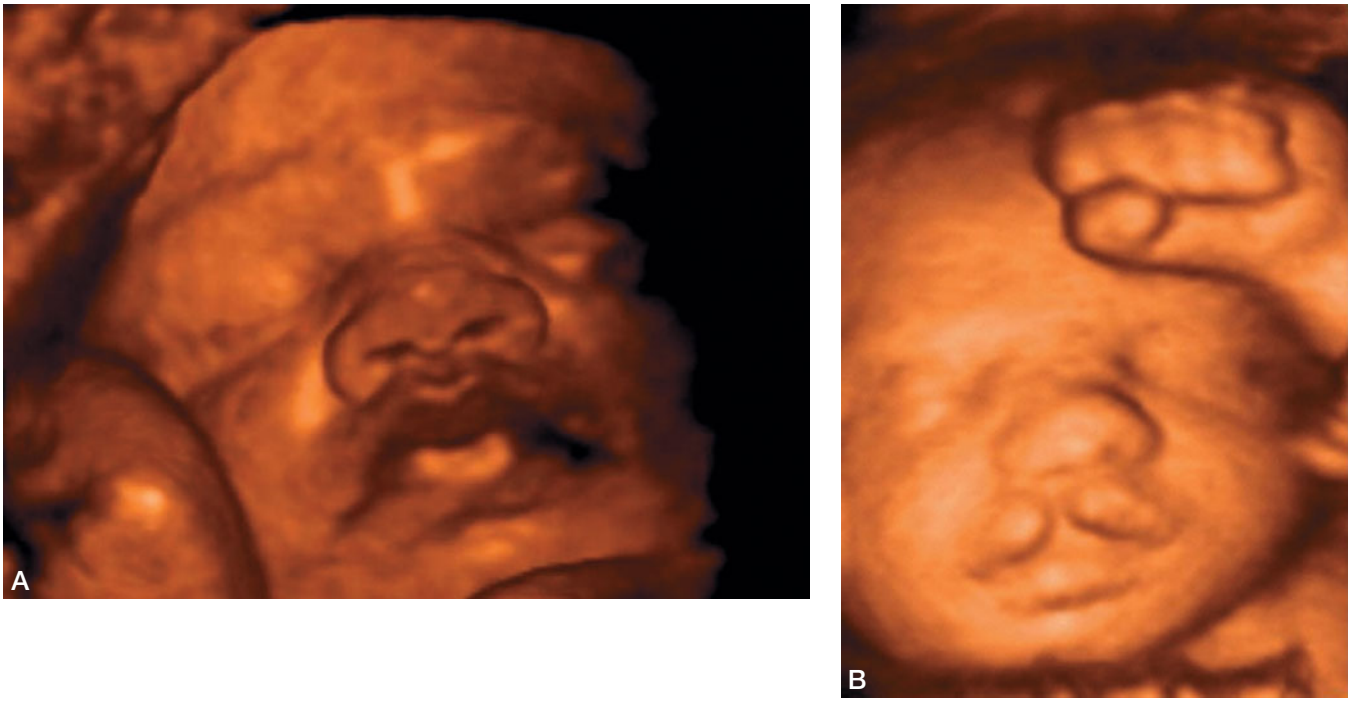

Figure 23-3 **A**. Three-dimensional ultrasound image of normal fetal face and lips. **B**. Three-dimensional ultrasound image of a fetus with a right unilateral cleft lip.

DIFFERENTIAL DIAGNOSIS

The most important consideration in the differential diagnosis of cleft lip is to distinguish between the normal vertical midline appearance of the philtrum and a pathologic median cleft lip. Although most cleft lips are left-sided and unilateral, a median cleft lip can be associated with syndromes such as orofacialdigital, type I, or frontonasal dysplasia. Consideration should also be given to detection of premaxillary agenesis, which is almost always associated with alobar holoprosencephaly (see Chapter 14).

When a paranasal echogenic mass is detected in cases of bilateral cleft lip and palate, the differential diagnosis includes hemangioma, anterior meningocele, teratoma, and enlarged tongue and proboscis (Nyberg et al., 1992). Of these conditions, only premaxillary protrusion associated with cleft lip and palate contains bone within the mass, resulting from anterior migration of maxillary and alveolar bones (Nyberg et al., 1992).

Once a cleft is identified, a diligent search should be made to detect associated anomalies. The finding of additional anomalies will significantly affect the differential diagnosis. More than 400 syndromes are associated with facial clefts (Shprintzen et al., 1985; Lidral and Murray, 2004). Common syndromes include Goldenhar (facioauriculovertebral dysplasia), Treacher–Collins (mandibulofacial dysostosis), Pierre–Robin, Stickler, DiGeorge, and Shprintzen (velocardiofacial) (Table 23-1). Additional anomalies seen in cases of Pierre–Robin sequence include micrognathia and polyhydramnios (Hsieh et al., 1999). Neurologic and myopathic conditions such as Stickler syndrome, can be associated with cleft palate. Syndromes that involve relatively broad faces, such as Crouzon and Waardenburg, are associated with an increased incidence of facial clefts.

ANTENATAL NATURAL HISTORY

Cleft lip and palate are seen more frequently in first trimester abortuses than in newborns. In one study of 3216 pregnancy losses, Kraus et al. (1963) demonstrated that 11.5% of fetuses spontaneously aborted at 8 weeks of gestation, 1.8% of abortuses at 6 to 19 weeks of gestation, and 0.16% of liveborn infants had orofacial clefts. Thus, fetuses with cleft lip and palate are at increased risk for intrauterine demise. The risk for fetal loss is related to the presence of associated anomalies, which were found in 61.7% of cases studied (Kraus et al., 1963).

In general, the antenatal detection of a facial cleft is more likely to be associated with other malformations than is the detection of a cleft at birth. In one study, Saltzman et al. (1986) described 12 cases of orofacial clefts diagnosed prenatally. Other malformations were detected in 10 (83%) of these fetuses. The chromosomes of 7 of these fetuses were studied prenatally or postnatally; 4 were abnormal due to trisomy 13 or 18. In a slightly larger study, Turner and Twining

Table 23-1

Common Syndromes Associated with Facial Clefts

Syndrome	Associated Findings
Goldenhar (facioauriculovertebral dysplasia)	Asymmetric facial hypoplasia, microtia, preauricular skin tags, hemivertebrae, cardiac defects
Pierre–Robin sequence	Micrognathia, U-shaped cleft of soft palate
Shprintzen (velocardiofacial syndrome)	Cardiac defects, hypotonia, growth restriction, chromosome 22q microdeletion; autosomal dominant
Stickler (hereditary arthro-ophthalmopathy)	Flat facies, micrognathia, hypotonia, myopia, scoliosis; autosomal dominant
Treacher–Collins (mandibulofacial dysostosis)	Malar and mandibular hypoplasia, downslanting palpebral fissures, ear malformations, absent lower eyelashes; autosomal dominant
Trisomy 13	Polydactyly, congenital heart disease, central nervous system abnormalities
Trisomy 18	Intrauterine growth restriction, congenital heart disease
Van der Woude (lip pit–cleft lip syndrome)	Lower lip pits, missing teeth; autosomal dominant

(1993) demonstrated additional anomalies in 88% of fetuses with facial clefts. Notable in this study were the large number of fetuses (9) with clefts and skeletal dysplasia. Benacerraf and Mulliken (1993) described a group of 32 fetuses at 16 to 40 weeks of gestation and over a 3.5-year period ascertained that 17 (53%) had associated anomalies. Five cases of trisomy 13 and 1 case of trisomy 18 were reported, giving a 35% rate of chromosomal aneuploidy in the setting of cleft with multiple anomalies. The associated malformations involved the central nervous system (11 cases), heart (9), kidneys (9), skeleton (10), and abdomen (2). Among the 15 fetuses without associated anomalies, 4 were terminated electively, 1 spontaneously aborted, 1 died from pulmonic stenosis and vertebral anomalies, and 9 survived and underwent successful postnatal surgical correction.

In postnatal studies, approximately 25% of infants with clefts have associated malformations (Kraus et al., 1963). Isolated cleft lip has the lowest frequency (range 7–45% of cases). The highest incidence of multiple and complex anomalies occurs with isolated cleft palate (range 13–72% of cases) (Gorlin et al., 1971; Shprintzen et al., 1985; Jones, 1988a; Ademiluyi et al., 1989). Shprintzen et al. (1985) described an extensive study of 1000 patients attending a craniofacial clinic, all of whom were seen by a clinical geneticist for a thorough dysmorphology examination. Associated anomalies were documented in 63.4% of patients. Craniofacial anomalies were most frequently represented, but short stature, microcephaly, and mental retardation (in 28% of cases) were also common findings.

MANAGEMENT OF PREGNANCY

The suspected diagnosis of orofacial cleft necessitates a thorough search for associated anomalies, ideally at a sonographic facility with experience in prenatal diagnosis of anatomic defects. Prenatal karyotyping should be considered in all cases following the diagnosis of orofacial clefing, but in particular if a facial cleft and additional anomalies are demonstrated. Orofacial clefting is seen in 75% of cases of trisomy 13 (particularly midline clefting), 15% of cases of trisomy 18, 1.5% of cases of trisomy 21, and as stated earlier, approximately 0.1% to 0.15% of chromosomally normal fetuses (Warkany, 1971). In a study of 263 fetuses and neonates with cleft lip +/− cleft palate performed by the Utah Birth Defect Network, 15 (5.7%) had aneuploidy (Walker et al., 2001). Aneuploidy was more likely to be present if there was bilateral cleft lip and palate. If a karyotype is performed, additional consideration should be given to fluorescence in situ hybridization (FISH) studies to rule out a microdeletion of chromosome 22 that is associated with DiGeorge and Shprintzen syndromes or molecular cytogenetic studies using array-CGH. Because the infant will require multiple operations postnatally, the

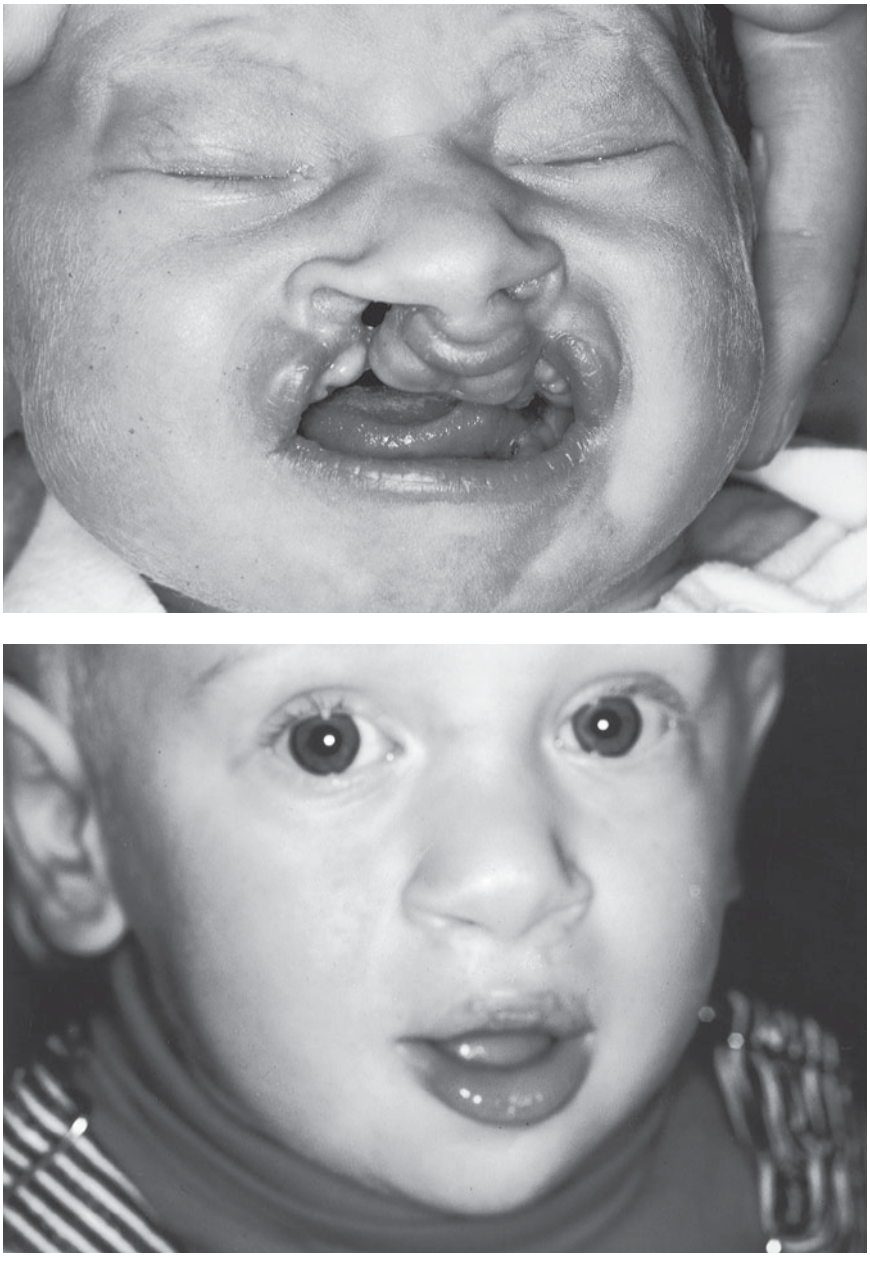

Figure 23-4 *Top*: Postnatal photograph of an infant who was diagnosed at 20 weeks of gestation with a bilateral cleft lip and palate. *Bottom*: Follow-up photograph of the same patient at 1 year of age following complete surgical repair. (*Courtesy of Dr. Michael Lewis.*)

presence of an abnormal karyotype may influence the parents' decisions regarding continuation of the pregnancy.

For the fetus with an apparently isolated cleft lip located lateral to the midline, the recommendations are less clear. There is no evidence in the medical literature of a case of unilateral isolated cleft lip diagnosed antenatally associated with an abnormal karyotype. On the other hand, even cleft lip has a significant rate of associated major anomalies in postnatal studies [7% in the Walker et al. (2001) study]. Thus, while the yield of cytogenetic abnormal results is likely to be extremely low, we recommend discussing with prospective parents the risk of the amniocentesis procedure versus the perceived benefits of knowing that the fetal chromosomes are normal.

Other than sonographic examination and karyotype, management of the pregnancy should continue in a routine manner. Fetuses with isolated cleft lip and palate can be delivered in a community hospital. Fetuses with multiple anomalies should be delivered in a setting where qualified subspecialists are available for newborn resuscitation, syndromic diagnosis, and therapy. We recommend that the prospective parents meet with a pediatric craniofacial surgeon soon after the antenatal diagnosis of facial cleft to discuss the steps involved in surgical treatment. Parents can then have the opportunity to observe the physical appearance of children with repaired facial clefts (Figure 23-4).

FETAL INTERVENTION

Because the fetal skin has unique scarless wound-healing properties, in utero repair of fetal facial clefts has been

proposed (Dado et al., 1990; Strauss and Davis, 1990; Longaker et al., 1991). It is well recognized that the characteristic facies following repair of cleft lip and palate, with midface retrusion and maxillary deficiency, are often the result of surgical scar formation that inhibits facial and maxillary growth. Because studies of mice and sheep have demonstrated that scarless cleft lip repair is possible antenatally, some have postulated that in the presence of normal functional maturity in the growing fetus, human facial appearance would be enhanced by the absence of scar and unimpaired facial growth.

To date, most research has focused on the use of animal models, such as the goat and sheep. The successful in utero repair of a teratogen-induced congenital cleft palate has been described in the goat (Weinzweig et al., 1999). In a sheep model, Papadopulos et al. (2005) have described the use of bone regenerating implants such as collagen lypophilisate, to fill in the maxillary alveolar defect created by cleft palate.

TREATMENT OF THE NEWBORN

Studies have shown that infants with clefting disorders have lower mean birth and placental weights than normal infants (Lilius and Nordstrom, 1992). The immediate concerns in treatment of the newborn infant with a cleft involve clearing of the airway and the ability to feed. Many hospitals have specialized feeding teams or individuals available with expertise in feeding infants with orofacial clefts. It is wise to involve these specialists early to help select a nipple and advise parents on feeding techniques. Breast feeding is possible but considerably more difficult than for the infant without a cleft palate. Infants with isolated cleft lip feed most easily and grow the most quickly. The mean weekly weight gain for all infants with clefts is 145 g, which is lower than the rate in normal infants (Jones, 1988b). This may be due to the nipple rubbing against the delicate nasal mucosa, which causes ulceration.

The infant with a cleft requires a thorough physical examination to look for associated anomalies that may have been missed on sonographic examination. If additional anomalies are detected, the infant should be referred to a medical geneticist. One author recommends consideration of an ophthalmologic evaluation during the first year of life in all infants with cleft palate because of the relatively high frequency of Stickler syndrome (Jones, 1988a). Severe myopia, glaucoma, and retinal detachment can develop in individuals affected with Stickler syndrome, but the disorder may be extremely difficult to diagnose during infancy. Chromosome analysis, including a FISH test to rule out microdeletion of chromosome 22, should be considered in all infants with cleft palate.

Subsequent treatment of the infant should occur in the setting of a cleft palate multidisciplinary team approach (NIH Consensus Panel, 1993). Hearing should be assessed as soon as possible. A plan should be made in conjunction with the primary pediatrician to ensure weekly assessment of nutritional intake and weight gain during the first month of life.

SURGICAL TREATMENT

The exact time of the first surgical repair depends on the anatomy of the malformation. For a unilateral complete cleft, a preliminary lip–nasal adhesion is often performed within the first month of life, followed by the more definitive repair at 4 to 6 months of age. For a unilateral or bilateral incomplete cleft, nose and lip correction can be performed any time within the first 6 months of life. For a bilateral complete cleft lip and palate, presurgical maxillary orthodontics may be indicated prior to surgical closure of the lip within the first few weeks (see Figure 23-3A). Bilateral cleft lip and nose correction and closure of the alveolar cleft are performed at 4 to 6 months (see Figure 23-3B) (NIH Consensus Panel, 1993). For lip repairs, the infant stays in the hospital for 1 day; for palate repairs, 2 days. In otherwise healthy infants, there is virtually no mortality associated with these procedures (Dado et al., 1990).

Surgical closure of the hard and soft palate is usually complete by 1 year of age. The goal of palate surgery is to restore normal function. Generally, speech results are excellent in 75% to 85% of children, with no need for further surgical procedures. In the small percentage of children in whom velopharyngeal insufficiency persists, secondary surgical procedures can be performed at 3 to 7 years of age, bringing the percentage of children with normal speech to 90% to 95%.

LONG-TERM OUTCOME

The salient long-term issues for a child with cleft lip and palate include midface hypoplasia, appearance (and related psychologic problems), dental abnormalities, speech disorders, and hearing problems (Felix-Schollaart et al., 1992). Cleft palate has also been shown to be associated with olfactory deficits, more often in boys than in girls (Richman et al., 1988). Children with cleft lip and palate are prone to multiple progressive problems as they grow. As many as 25% to 35% have speech abnormalities requiring secondary palate surgery and speech therapy. All children with cleft palate require speech evaluation, and some will need therapy. Speech and language evaluations are recommended at least annually until 4 years of age (NIH Consensus Panel, 1993). In addition, there are secondary defects that result from the surgical corrective procedures. In patients with unilateral cleft lip and palate, a secondary nasal deformity from a depressed alar base and tip and deviation of the septum can exist. Bilateral cleft lip–cleft palate deformity predisposes to bilateral widening of the alar base and a short columella. Scarring from surgical repair results in midface growth deficiency, with maxillary retrusion and relative mandibular prognathism (Hallock, 1985).

Infants with cleft lip and palate have hearing abnormalities that begin surprisingly early in postnatal life. They require frequent and ongoing audiologic surveillance (NIH Consensus Panel, 1993). In one study of 23 infants younger than 1 year of age, only 2 had normal hearing at age 6 months (Hélias et al., 1988). Of the 19 infants affected by hearing abnormalities, evidence of conduction deafness was documented by abnormal brainstem auditory-evoked responses. Fifteen infants had chronic otitis media with effusion, presumably due to the fact that the eustachian tube is smaller in patients with cleft palate. Obstruction of the eustachian tube is related to the inability of the tensor veli palatine muscle to dilate the eustachian tube actively during swallowing (Hélias et al., 1988). Early myringotomy with placement of bilateral tympanotomy tubes improved hearing acuity and consonant articulation in patients with cleft palate (Hubbard et al., 1985; Grant et al., 1988).

Common dental anomalies include missing, extra, or malpositioned teeth. In infants with cleft lip and palate, deciduous tooth formation and eruption is normal, but permanent dentition may be delayed (Poyry and Ranta, 1986; Poyry et al., 1989). Almost all children with cleft palate defects will require fixed orthodontic appliances (braces) on their permanent teeth. During the period of mixed dentition, removable or fixed appliances may be necessary for expansion and alignment of the incisors (Asher-McDade and Shaw, 1990).

Regular psychologic screening, preferably by an expert in craniofacial disorders, is also recommended to assess the child's cognitive development, behavior, and self-image (NIH Consensus Panel, 1993).

GENETICS AND RECURRENCE RISK

Cleft lip and palate are classified as isolated (nonsydromic) (70% of cases) or syndromic (30% of cases), based on the presence of other anomalies and/or developmental delay. The Online Mendelian Inheritance in Man (OMIM) catalog lists more that 400 single-gene causes of cleft lip and/or palate (Lidral and Murray, 2004) (see Table 23-2). It is therefore important to rule out a syndromic diagnosis before discussing the risk of recurrence. A complete family history should indicate other cases occurring within the same pedigree.

When counseling families regarding recurrence risk, it is important to examine parents for the so-called microforms of cleft palate, including a bifid uvula, submucous cleft of the soft palate, hypodontia, and linear-lip indentations. This latter finding is characteristic of Van der Woude syndrome, a dominantly inherited disorder in which there is a high penetrance of cleft lip and palate but no extrafacial associated anomalies. The incidence of Van der Woude syndrome is 1 in 33,600 livebirths (Sander et al., 1995). The finding of lip pits in a parent and an affected infant with a cleft disorder strongly suggests Van der Woude syndrome and a 50% risk of

Table 23-2

Major Genes Involved in Syndromic Cleft Lip and Palate

Gene	Syndrome	Inheritance Pattern	Chromosomal Location
PTCH1	Basal cell nevus (Gorlin Goltz)	Autosomal dominant	9q22
MID1	Opitz	X-linked	Xp22
MSX1	Cleft lip/palate and oligodontia	Autosomal dominant	4p16
PVRL1	Margarita Island cleft lip/palate and ectodermal dysplasia (CLPED1)	Autosomal recessive	11q23
P63	Ectrodactyly-ectodermal dysplasia, cleft (EEC)	Autosomal dominant	3q28
IRF6	Van der Woude	Autosomal dominant	1q32
TBX22	Cleft palate and ankyloglossia	X-linked	Xq21
FGFR1	Hypogonadotropic hypogonadism, anosmia, and cleft (Kallmann)	Autosomal recessive	8p11
COL2A1	Stickler	Autosomal dominant	12q13

Table 23-3

Empirical Recurrence Risk Figures for Orofacial Clefts

			Cleft Lip and Palate (%)	Cleft Palate Alone (%)
Normal parents	Number of affected children	Number of normal children		
	1	0	4.0	3.5
	1	1	4.0	3.0
	2	0	14.0	13.0
One parent affected	Number of affected children	Number of normal children		
	0	0	4.0	3.5
	1	0	12.0	10.0
	1	1	10.0	9.0
	2	0	25.0	24.0
Both parents affected	Number of affected children	Number of normal children		
	0	0	35.0	25.0
	1	0	45.0	40.0
	1	1	40.0	35.0
	2	0	50.0	45.0

Modified, with permission, from Cohen MM Jr. Craniofacial disorders. In: Emery AE, Rimoin DL, eds. Principles and Practice of Medical Genetics. *New York: Churchill Livingstone; 1983:593-595.*

recurrence. Mutations in the interferon responsive factor 6 (*IRF6*) gene are the underlying basis for Van der Woude syndrome (Kondo et al., 2002). Knowledge of the disease-causing mutation makes DNA-based prenatal diagnosis for the condition available. Embryoscopy has also been used to diagnose cleft lip as early as 11 weeks of gestation in a fetus at risk for Van der Woude syndrome (Dommergues et al., 1995).

If the parents have a negative physical examination and family history, the empiric risk for a second affected child is 4% (Lynch and Kimberling, 1981; Tenconi et al., 1988). Table 23-3 summarizes empiric recurrence risks for several clinical scenarios.

Nonsyndromic cleft lip with or without cleft palate is a complex trait that is determined by multiple loci that interact and are affected by environmental exposures. Point mutations in *FOXE1*, *GLI2*, *JAG2*, *LHX8*, *MSX1*, *MSX2*, *SATB2*, *SKI*, *SPRY2*, and *TBX10* are additional rare causes of isolated clefts (Stainer and Moore, 2004; Vieira et al., 2005). The results of direct sequencing of *MSX1* suggest that point mutations in this gene may be responsible for as many as 2% of nonsyndromic clefts.

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Hemifacial Microsomia

24 CHAPTER

Key Points

- Second most common facial anomaly after cleft lip and palate.
- Characteristic findings include hypoplasia of malar, maxillary, and/or mandibular regions of the face with associated anomalies of the ears and vertebrae.
- Incidence is as high as 1 in 3,000-5,000 livebirths if mild cases are included.
- Associated with eye, ear, vertebral, cardiac, renal, and urinary anomalies.
- Karyotype is indicated.
- Deliver infant in tertiary care center if polyhydramnios is present.
- Perform complete audiologic evaluation on all infants postnatally.
- Rule out syndromic causes.

CONDITION

Hemifacial microsomia is the second most common facial anomaly after cleft lip and palate. It is a predominantly unilateral malformation of craniofacial structures that originally develop from the first and second branchial arches. The characteristic findings of hemifacial microsomia include hypoplasia of the malar, maxillary, and/or mandibular regions of the face with associated abnormalities of the ears and vertebrae (Burck, 1983). The term *hemifacial microsomia* was first used by Gorlin and Pindborg (1964), who described a condition consisting of unilateral microtia, macrostomia, and failure of formation of the mandibular ramus and condyle. Since then, hemifacial microsomia has been considered one phenotypic manifestation of a group of disorders that affect the face, ears, eyes, vertebrae, heart, and kidneys. This spectrum of disorders has been called "oculoauriculovertebral dysplasia," although this is technically incorrect because the term *dysplasia* refers to abnormalities of cellular differentiation. An association between hemifacial microsomia, auricular malformations, and specific malformations of the eye known as epibulbar dermoids was first recognized by Goldenhar in 1952 (Heffez and Doku, 1984). Although the name *Goldenhar syndrome* is widely used, the use of the word *syndrome* is also incorrect because there is no known unique cause for this phenotype.

At present, hemifacial microsomia is considered to be part of a complex developmental field defect known as the oculoauriculovertebral (OAV) anomaly. There is no agreement on the minimal diagnostic criteria and the phenotypic spectrum for this condition (Rollnick, 1988). It is not known whether OAV anomaly represents one entity with variability in the phenotype or whether there are several different entities with similar phenotypes. Causal heterogeneity for this group of conditions has been described (Rollnick, 1988). However, any fetus identified with asymmetry of the facial structures or hemifacial microsomia should be considered to be at risk for associated eye, ear, vertebral, cardiac, and renal malformations.

INCIDENCE

The incidence of hemifacial microsomia varies considerably according to the minimal diagnostic criteria used to define the condition. When the most mildly affected individuals are included, the incidence is on the order of 1 in 3000 to 1 in 5000 livebirths (Benacerraf and Frigoletto, 1988). When only the most severely affected patients are included, the incidence was on the order of 1 in 45,000 livebirths in one study performed in Northern Ireland (Morrison et al., 1992). Approximately two-thirds of cases of hemifacial microsomia

are unilateral (Singer et al., 1994). When unilateral, the right side is more commonly involved (Poon et al., 2003). When the condition is bilateral, one side is more severely affected than the other (Heffez and Doku, 1984). In one report of 294 patients affected with the oculoauriculovertebral anomaly, a male to female ratio of 2:1 was observed (Rollnick et al., 1987). In the same study, 78% of affected individuals were white. In this study, 154 patients (52%) had no other congenital anomaly in addition to the anomalies required for diagnosis, which consisted of microtia, mandibular hypoplasia, anomalies of the cervical spine, and/or anomalies of the eye, including epibulbar dermoids or lipodermoids. Of the remaining patients, 51 (18%) had one additional anomaly and 89 (30%) had two or more additional anomalies (Rollnick et al., 1987).

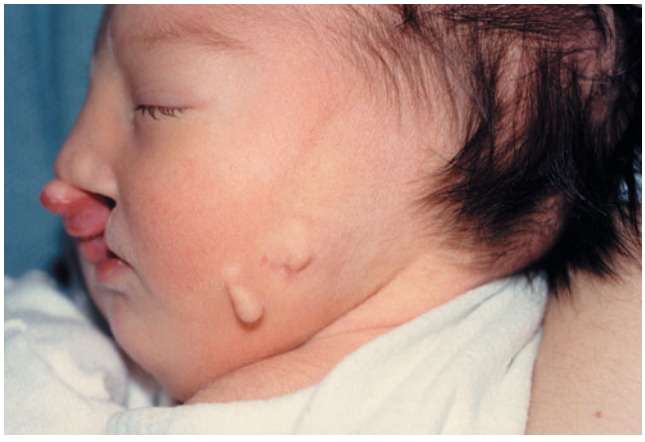

Figure 24-1 Postnatal photograph of a newborn who was noted antenatally to have hemifacial microsomia and a bilateral cleft lip and palate. Note the lack of ear development but the presence of two small ear tags.

SONOGRAPHIC FINDINGS

Relatively few reports of prenatal sonographic diagnosis of hemifacial microsomia have been described. In 1986, Tamas et al. described a fetus with polyhydramnios, unilateral anophthalmia, and a malformed, low-set ipsilateral ear. This was followed by a report in 1988 from Benacerraf and Frigoletto, who described a fetus at 29 weeks of gestation with moderate polyhydramnios, an abnormal fetal facial profile with micrognathia, a right kidney hydronephrosis and hydroureter, an enlarged echogenic left lung, a ventriculoseptal cardiac defect, and a two-vessel umbilical cord. Prenatally, a cystic adenomatoid malformation of the lung was suspected, but this was refuted postnatally when it was found that the right lung was absent and the left lung was hyperexpanded. The infant died during the newborn period. Physical examination at birth revealed a right-sided mandibular hypoplasia, an abnormal right ear, and vertebral anomalies that were not appreciated antenatally. Goldenhar syndrome was diagnosed postnatally (Benacerraf and Frigoletto, 1988).

Potential sonographic findings in cases of hemifacial microsomia or OAV anomaly might include polyhydramnios due to impaired fetal swallowing. This is likely to be the result of either unilateral mandibular hypoplasia or micrognathia due to hypoplasia of the condyle and ramus, which has been documented in 60% of infants affected with these conditions (Heffez and Doku, 1984). Some infants with OAV anomaly have intrauterine growth restriction (Kobrynski et al., 1993). In one fetus with Goldenhar syndrome, a lipoma of the corpus callosum, which presented as a hyperechoic midline structure, was described (Jeanty et al., 1991). In another case, the prenatal sonographic diagnosis of OAV anomaly at 15 weeks' gestation was suggested by the presence of a maxillary cleft in association with unilateral microophthamia (DeCatte et al., 1996). More recently, Goldenhar syndrome was diagnosed in a fetus at 24 weeks due to marked hemifacial microsomia and ipsilateral cerebellar hemisphere hypoplasia (Martinelli et al., 2004).

In any fetus in whom facial asymmetry is suspected, an attempt should be made to sonographically examine the fetal ears, because microtia or other ear abnormalities are frequently seen in association with the mandibular hypoplasia (Figure 24-1). The spine should be observed closely, as skeletal anomalies are the most common associated malformations (due to hemivertebrae and scoliosis) (Poon et al., 2003). The prevalence of associated congenital heart disease in infants with OAV anomaly is increased (Kumar et al., 1993; Poon et al., 2003). Two-thirds of these cases are either tetralogy of Fallot or a ventriculoseptal defect. In one study, 19% (6 of 32) of patients with OAV anomaly had congenital heart disease. The cardiac lesions in this study were varied and more complex than previously reported, including double outlet ventricle, pulmonary atresia with ventriculoseptal defect, and total anomalous pulmonary venous return. Five of the six cases were conotruncal malformations. Pulmonary and renal anomalies were noted to be more common in the patients with congenital heart disease. Morrison et al. (1992) also reported that 8 of their 25 patients with OAV anomaly had congenital heart disease. In fetuses with hemifacial microsomia, the presence of congenital heart disease is an important prognostic factor because of the very high neonatal mortality rate when congenital heart disease exists. In Morrison et al.'s study (1992), six of eight infants died before 2 years of age, and in Kumar et al.'s study (1993), four of six infants died during the newborn period.

A high incidence of urinary tract abnormalities has also been demonstrated in infants with OAV anomaly. Of 20 infants with OAV anomaly, 14 were demonstrated to have a variety of renal and urinary anomalies, including ectopic or fused kidneys, renal agenesis, vesicoureteral reflux, ureteropelvic obstruction, ureteral duplication, and multicystic kidneys (Ritchey et al., 1994). Therefore, any fetus identified with hemifacial microsomia should undergo a detailed

sonographic study with particular attention paid to the ears, heart, vertebrae, and kidneys.

Hemifacial microsomia, initially detected by prenatal sonography, has also been demonstrated by magnetic resonance imaging at 20 weeks of gestation (Hattori et al., 2005).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes conditions that are considered to be part of the phenotypic spectrum of hemifacial microsomia and OAV anomaly, as well as other syndromes that include hemifacial microsomia as one component. The differential diagnosis of hemifacial microsomia variants includes microtia, hemifacial microsomia, Goldenhar syndrome, OAV dysplasia, and otomandibular dysostosis. The minimal criteria for these conditions are given in Table 24-1. Other conditions associated with the hemifacial microsomia phenotype include branchio-oto-renal syndrome, a dominantly inherited disorder that consists of hemifacial microsomia, preauricular and branchial sinuses and kidney anomalies; Townes–Brocks syndrome, another dominantly inherited disorder that consists of hemifacial microsomia and anal and digital anomalies; and hemifacial microsomia/radial limb defects, which include the additional finding of triphalangeal thumbs. There have been other case reports of hemifacial microsomia in association with other, more severe anomalies (Dodinval, 1979; Rollnick, 1988).

Table 24-1

Minimal Criteria for Diagnosis of Hemifacial Microsomia Variants

Diagnosis	Minimal Criteria
Microtia	Isolated microtia
Hemifacial microsomia	Unilateral microtia Small and/or malformed mandible Anomalies of cervical spine
Goldenhar syndrome	Unilateral microtia Small and/or malformed mandible Epibulbar dermoids and/or lipodermoids
Oculoauriculo-vertebral dysplasia	Unilateral microtia Small and/or malformed mandible Epibulbar dermoids and/or lipodermoids Anomalies of the cervical spine

From Rollnick BR, Kaye CI. Hemifacial microsomia and variants: pedigree data. Am J Med Genet. *1983;15:233-253.*

ANTENATAL NATURAL HISTORY

Little is known about the antenatal natural history for fetuses with hemifacial microsomia. More information is available regarding its pathogenesis. Experiments performed in animals have suggested that abnormalities of blood flow to the first and second branchial arches may produce malformations similar to those found in hemifacial microsomia and its variants (Poswillo, 1974). Poswillo showed that the presence of an expanding hematoma in the region of the ear and jaw produced a branchial arch abnormality that destroyed the differentiating tissues in that region. Additional studies using triazene in the pregnant rat or thalidomide in the pregnant monkey produced hemorrhage and formation of a hematoma in the anatomic distribution of the stapedial artery. A clinical correlation in humans has been documented by Robinson et al. (1987), who described three unrelated children with unilateral craniofacial defects. Abnormal carotid artery blood flow studies were documented in two of the three patients described. This group hypothesized that the craniofacial defects were the result of an in utero vascular accident, most likely due to interruption of blood flow to structures supplied by the stapedial artery. Interestingly, these patients also had unilateral cerebral atrophy. In one patient, a decreased right carotid pulse was documented. This patient also had colonic stenosis, which has also been postulated to be the result of an in utero vascular compromise.

A large-scale epidemiologic study of 230 children with hemifacial microsomia and 678 controls was performed to identify whether vasoactive exposures or vascular events during early pregnancy affected the incidence of this malformation (Werler et al., 2004). An increased risk of hemifacial microsomia was associated with vasoactive medication use (such as pseudoephedrine and phenylpropanolamine), multiple gestation, diabetes, and second trimester vaginal bleeding. These findings appeared to collectively support the hypothesis that vascular disruption is one etiology for hemifacial microsomia.

While the vascular theory for the pathogenesis of hemifacial microsomia and OAV anomaly explains the abnormalities of the facial features, it does not explain some of the associated findings, including epibulbar dermoids and other eye malformations and congenital heart disease. These associated abnormalities could be explained by an abnormality in the interaction of neural crest cell derivatives with branchial arch mesenchyme. This could be the result of exposure to a teratogen such as retinoic acid (Lammer et al., 1985). Abnormalities of cranial neural crest cell derivatives also affect conotruncal development of the heart and the anterior chamber of the eye. Teratogens that are known to cause anomalies of the first and second branchial arches in humans and animals

are primidone, thalidomide, and maternal diabetes (Rollnick, 1988). Another theory regarding the cause of hemifacial microsomia is that this condition is the result of a local deficit of oxygen or a brief, total hypoxic insult to the embryo, resulting in decreased oxygen for tissue formation.

MANAGEMENT OF PREGNANCY

When a fetus is identified with hemifacial microsomia, a detailed sonographic survey should be performed to examine the fetus for the aforementioned associated anomalies, including microtia, micrognathia, vertebral malformations (most commonly hemivertebrae), congenital heart disease (especially conotruncal defects), and renal abnormalities. An attempt should be made to examine the parents for subtle manifestations of OAV anomaly, such as preauricular tags or fistulae, small or abnormally shaped ears, narrow external auditory canals, or micrognathia. Isolated microtia is considered to be a minimal expression of OAV anomaly (Llano-Rivas et al., 1999). The parents should be asked if there is any history of hearing deficit in the family. If hemifacial microsomia is demonstrated in the fetus, consideration should be given to obtaining a fetal karyotype. Many chromosomal abnormalities have been described in association with facial asymmetry and the OAV anomaly (Table 24-2) (Rollnick, 1988). In addition, complete or mosaic trisomy 22 should be considered. This can be diagnosed using fluorescence in situ hybridization studies (Kobrynski et al., 1993). Knowledge of the fetal karyotype will certainly help in establishing a prognosis for the infant and in guiding further treatment. There is no indication for cesarean delivery other than for standard obstetric reasons. We recommend that these infants be delivered in a tertiary care center if polyhydramnios is present, suggesting micrognathia, which indicates the potential for airway compromise at birth. Most infants with OAV anomaly can be delivered in a community hospital, but should receive multispecialty evaluation, including a clinical genetics examination shortly after birth.

Table 24-2

Chromosome Abnormalities Associated with OAV Anomaly

Chromosome 5p deletion
Monosomy 6q
Mosaic trisomy 7
Duplication of 7q and 8q
Mosaic trisomy 9
Chromosome 18q deletion
Trisomy 18
Recombinant chromosome 18
Ring chromosome 21
Deletion chromosome 22q 13.31
47,XXY
49,XXXXY

From Rollnick BR. Oculoauriculovertebral anomaly: variability and causal heterogeneity. Am J Med Genet Suppl. *1988;4:41-53.*

FETAL INTERVENTION

There are no fetal interventions indicated for hemifacial microsomia.

TREATMENT OF THE NEWBORN

The overall goal in the treatment of the newborn with hemifacial microsomia is to determine whether the anatomic defects are localized to the head or whether there are associated anomalies that will influence long-term health. The most important aspect of newborn treatment is a detailed physical examination, with specific attention to the ears, documenting the presence of auricular or preauricular appendages, blind-ending preauricular fistula, abnormalities in ear size or shape, presence of epibulbar dermoids or lipomas, colobomas (notching) of the upper eyelid, hemivertebrae, congenital heart disease, and renal anomalies (Thomas, 1980). If the vertebrae were not adequately visualized antenatally, we recommend obtaining a postnatal radiograph of the vertebrae to look for malformations of the spine. In addition, we recommend obtaining a postnatal echocardiogram, because of the relatively high incidence of congenital heart lesions. It is especially important to document cardiac anatomy, because of the relatively high postnatal mortality for infants identified with hemifacial microsomia and congenital heart disease (Morrison et al., 1992; Kumar et al., 1993). In addition, because of the high incidence of genitourinary malformations in infants with the OAV anomaly, we recommend that a screening ultrasound examination be performed in the neonatal period to identify significant urologic abnormalities before functional consequences ensue (Ritchey et al., 1994).

In one study, conductive hearing loss was observed in 85% of patients (Rahbar et al., 2001). However, there was no correlation between the severity of the dysmorphic features and the degree or type of hearing loss. A complete audiologic evaluation should be performed on every infant with hemifacial microsomia.

SURGICAL TREATMENT

The goals of surgical treatment include improving facial symmetry, stimulating further facial growth, correcting maxillary deficiency, providing a growth center in the temporomandibular joint, improving chewing, allowing for early soft tissue expansion, and minimizing psychologic trauma associated with an asymmetric facial appearance (Heffez and Doku, 1984). The surgical treatment depends on the severity of the mandibular hypoplasia. Mandibular hypoplasia has been classified according to its severity. Grade 1 is a small but normal temporomandibular joint and ramus; Grade 2 is an abnormal but functional temporomandibular joint and ramus; and Grade 3 is an absent temporomandibular joint and ramus. With increasing severity of the bony abnormalities, there is more severe hypoplasia of the associated facial and lingual muscles, which exaggerates the asymmetry of the facial appearance. In addition, there is generally a correlation between severity of the microtia and the mandibular anomalies. The mandibular deformity is surgically corrected in two or more stages. The first operation generally is performed when the child is between 5 and 12 years of age and can cooperate with the required postoperative orthodontic therapy. For severely affected patients who have an absent mandibular ramus, an augmentation procedure is performed using costochondral bone grafts (Heffez and Doku, 1984). A second operation is generally required during the teenage years, after the majority of facial growth has occurred.

LONG-TERM OUTCOME

For patients with hemifacial microsomia or the OAV anomaly, the long-term health outcome is good. More than 90% of these patients have normal intelligence. Except for those who have severe conotruncal cardiac defects, the general health and life expectancy of these patients are excellent. Long-term problems, however, are hearing abnormalities and facial nerve weakness.

GENETICS AND RECURRENCE RISK

The cause of hemifacial microsomia and OAV anomaly is heterogeneous. The majority of patients with hemifacial microsomia occur sporadically within a family. A scarcity of reports of concordance of the defects in monozygotic or dizygotic twins supports this interpretation of the genetics (Setzer et al., 1981; Burck, 1983; Boles et al., 1987). However, there have been multiple reports of autosomal dominant inheritance with variable expression of the phenotype (Burck, 1983; Singer et al., 1994). There also have been multiple case reports of this finding with two affected siblings and unaffected parents, suggesting autosomal recessive inheritance (Rollnick, 1988). As previously mentioned, many chromosomal abnormalities have been associated with hemifacial microsomia. Therefore, if a chromosome study was not obtained prenatally, it should be obtained during the newborn period. Rollnick and Kaye (1983) described 97 individuals affected with hemifacial microsomia. Of these, 44 (45%) had relatives with either ear anomalies, mandibular hypoplasia, or early onset hearing loss. The most frequent malformations included preauricular skin tags. In this study, 8% of first degree relatives had at least a minor manifestation of hemifacial microsomia.

When counseling the family for recurrence of hemifacial microsomia, a syndrome must be ruled out. If a medical geneticist suggests a diagnosis of Townes–Brocks syndrome, DNA should be studied for the presence of a mutation in the *SALL1* gene (Keegan et al., 2001). In addition, the physician must examine the parents and siblings and obtain a complete family history. If the family history is negative and the parental physical examination is negative for the milder forms of hemifacial microsomia, the recurrence risk is 2% to 3% (Burck, 1983; Rollnick and Kaye, 1983).

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25 CHAPTER Hypertelorism

Key Points

- Defined as an increased distance between inner and outer canthi.
- Prenatal sonographic measurements are obtained from either the outer-to-outer or inner-to-inner bony orbital margins.
- Unknown incidence but rare.
- Main concern is its association with median facial and/or brain defects as well as syndromes.
- Offer karyotype and FISH analysis for 22q11.2 deletion (associated with autosomal dominant form of Opitz syndrome).
- Prognosis depends on severity of associated anomalies and/or if a syndrome is present.
- DNA analysis is available for a number of the single-gene disorders associated with hypertelorism.

CONDITION

Hypertelorism is a condition in which a larger-than-average distance exists between the orbits. The distances between the medial canthi and pupils are also increased (Kirkham et al., 1975). The term was first used by Greig in 1924, who described hypertelorism as a "great breadth between the eyes." The orbits represent a bridge between the face and the cranium. Seven different bones are required to form the orbit (frontal, zygomatic, sphenoid, ethmoidal, maxillary, lacrimal, and palatine) (Dollfus and Verloes, 2004).

Ocular hypertelorism is defined as an increased distance between the medial orbital walls. This can be demonstrated either radiographically or clinically by an increased interpupillary distance. If the interpupillary distance is greater than 2 SD above the mean for the patient's age, hypertelorism is said to exist (Brodsky et al., 1990). More recently, it has been recommended that the diagnosis of hypertelorism be made

radiographically by interorbital measurements. The difficulty with using intercanthal distance to define hypertelorism is that soft tissue changes of the face can increase the intercanthal distance without affecting the interorbital distance (Trout et al., 1994). Telecanthus is an increased distance between the inner canthi. This can either be primary, defined as an increase in soft tissue with normal interpupillary and interbony distance, or secondary, which is really orbital hypertelorism, with an increased interbony or interpupillary distance (Murphy and Laskin, 1990). The major concern regarding the fetal finding of hypertelorism is its association with median facial and brain defects, such as encephalocele, facial cleft, and craniosynostosis.

INCIDENCE

Hypertelorism is rare. Its exact incidence is unknown. Hypertelorism may occur as an isolated condition or in association with other anomalies.

SONOGRAPHIC FINDINGS

Imaging of the fetal orbits and measurements of the interorbital distance are not routinely performed in most centers that offer targeted fetal sonographic studies. Measurement of the fetal interorbital distance is not included in either the American Institute of Ultrasound in Medicine (AIUM) or American College of Obstetrics and Gynecology (ACOG) guidelines for obstetrical sonography (American College of Obstetrics and Gynecology, 2008). Fetal orbital measurements should be performed in any pregnant woman known to have had a previously affected child with a condition associated with hypertelorism, such as Waardenburg, Opitz or Noonan syndromes. Detection of fetal hypertelorism in any structural survey should alert the sonographer to the possibility of other anomalies.

In 1985, de Elejalde and de Elejalde studied 1108 pregnant women and measured the interorbital distances in fetuses between 7 and 38 weeks of gestation. They derived normal growth percentiles for the intermalar and interethmoidal distances for fetuses between 10 and 40 weeks of gestation. The intermalar and interethmoidal distances were comparable to the postnatal measurements of inner and outer canthal distances. In 1982, Mayden et al. described fetal inner and outer orbital diameter measurements in 180 normal pregnancies. The outer orbital diameter was demonstrated to be closely related to the biparietal diameter. Fetal orbits were identified in three different head positions, including occipitotransverse, occipitoposterior, and occipitoanterior. Twelve years after this report, the validity of this nomogram was tested in a high-risk antenatal population by another group of investigators, who obtained inner and outer orbital measurements from 422 fetuses between 12 and 37 weeks of gestation (Trout et al., 1994). This group identified three cases of hypertelorism, with inner orbital measurements above the 95th percentile for gestational age and outer orbital distances within the normal limits but near the 95th percentile for gestational age. In the three cases of hypertelorism identified, all fetuses had serious associated abnormalities, including cleft palate, diaphragmatic hernia, imperforate anus, porencephaly, encephalocele, and truncus arteriosus. The three fetuses with hypertelorism were all diagnosed between 20 and 33 weeks of gestation. These investigators recommended routine measurement of the interorbital distance at the level of the thalamus at the same time that the conventional biparietal diameter measurement was taken. They measured outer orbital diameter from outer-to-outer bony margins of the orbit, whereas the inner orbital diameter was measured from inner-to-inner bony margin of the orbits. The bony orbits were seen reliably from 12 weeks of gestation onward. These investigators stressed that it was the inner orbital diameter measurement that was most clearly associated with postnatal hypertelorism. The three affected fetuses described in this study had inner orbital diameter measurements that were more than 2 SD from the mean for gestational age, whereas the outer orbital diameter measurements were borderline high.

In another report of 1600 fetuses screened by transvaginal sonography at 12 to 18 weeks of gestation, 8 ocular abnormalities were found, but no cases of hypertelorism were described (Bronshtein et al., 1991). To date, there have been no reports of fetal hypertelorism in the first trimester.

In one case report, a fetus at 20 weeks of gestation was diagnosed with Opitz syndrome (Hogdall et al., 1989). This syndrome consists primarily of hypertelorism and hypospadias, with either X-linked or autosomal dominant patterns of inheritance. In this report, the fetus was described as an "at-risk" member of a large kindred affected with the autosomal dominant form of Opitz syndrome. At 18 weeks of gestation, a prenatal sonogram was within normal limits. At that time, the outer orbital measurement was 30 mm (the normal mean for gestational age is 29 mm; range, 24–33 mm). The inner orbital measurement was 15 mm (mean for gestational age, 11 mm; range, 8–15 mm). At 20 weeks, the study was repeated and a small phallus with hypospadias was noted. In addition, the outer orbital measurement was 36 mm (mean for gestational age, 33 mm; range, 28–37 mm) (Figure 25-1). The inner orbital measurement was 17 mm (mean for gestational age, 13 mm; range, 10–16 mm). Because of the provisional diagnosis of an affected fetus with Opitz syndrome, the pregnancy was terminated. Perinatal autopsy studies revealed widely separated eyes and an enlarged fourth ventricle, as well as hypospadias, and imperforate anus. Thus, the fetus was confirmed as affected. This study also reinforced the findings of Trout et al. (1994), who determined that the inner orbital measurement is the more sensitive indicator of hypertelorism.

More recently, three-dimensional (3D) ultrasound imaging has been used to improve visualization of the fetal face. This has been especially helpful in the diagnosis of frontonasal dysplasia (Sleurs et al., 2004) and Binder syndrome (Cook et al., 2000).

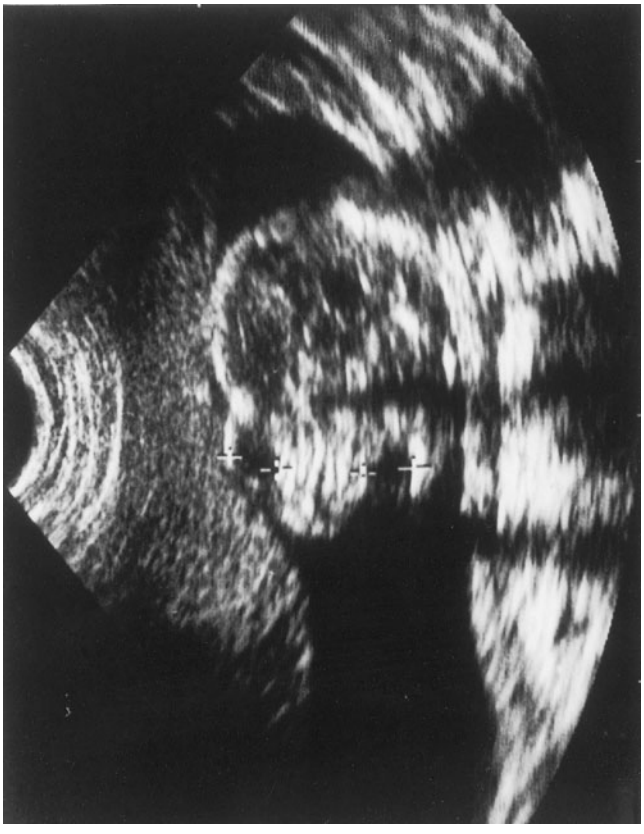

Figure 25-1 Prenatal sonographic image of a fetus at 20 weeks of gestation with Opitz BBB syndrome. Lateral view of orbits demonstrating increased distance between inner aspects of the globes. *(From Hogdall C, Siegel-Bartelt J, Toi A, Ritchie S. Prenatal diagnosis of Opitz (BBB) syndrome in the second trimester by ultrasound detection of hypospadias and hypertelorism.* Prenat Diagn. *1989;9:783-793. Copyright 1989 John Wiley & Sons, Inc. Reprinted, by permission, of John Wiley & Sons, Ltd.)*

DIFFERENTIAL DIAGNOSIS

Hypertelorism occurs in more than 550 disorders (Dollfus and Verloes, 2004). Hypertelorism is strongly associated with other abnormalities, especially of the frontal part of the brain, such as encephalocele and dacrocystocele. A number of conditions are associated with hypertelorism, and these are summarized in Table 25-1. Most significantly, these consist of chromosomal abnormalities, single-gene disorders, developmental abnormalities of the skull, such as craniosynostosis, and midface abnormalities such as frontonasal dysplasia.

Table 25-1

Conditions Associated with Hypertelorism

Chromosomal abnormalities
- 45,X (Chrousos et al., 1984)
- 22q11.2 deletion (Fryburg et al., 1996)
- Trisomy 9p (Centerwall and Beatty-DeSana, 1975)
- Interstitial deletion of chromosome 1 (Sarda et al., 1992)
- Interstitial deletion of chromosome 13 (Dean et al., 1991)
- Interstitial deletion of chromosome 17 (Park et al., 1992)

Single-gene disorders
- Aarskog syndrome
- Apert syndrome
- Coffin–Lowry syndrome
- Crouzon syndrome
- LEOPARD syndrome (*PTPN11*)
- Noonan syndrome (*PTPN11*)
- Opitz syndrome, autosomal dominant
- Opitz syndrome, X-linked (*MID1*)
- Robinow syndrome
- Waardenburg syndrome, type 1 (*PAX3*)
- Waardenburg syndrome, type 2 (*MITF*)

Developmental abnormalities
- Anterior cephalocele
- Craniosynostosis
- Dacrocystocele
- Frontal, ethmoidal, sphenoidal meningoencephalocele
- Frontonasal dysplasia
- Median cleft face
- Megaloencephaly

Rare syndromes
- Sclerocornea, hypertelorism, syndactyly, ambiguous genitalia (Martinez-Frias et al., 1994)
- Diaphragmatic hernia, exomphalos, absent corpus callosum, hypertelorism, myopia, deafness (Donnai and Barrow, 1993)
- Hypertelorism, hypospadias, Tetralogy of Fallot (Farag and Teebi, 1990)
- Hypertelorism, downslanting palpebral fissures, malar hypoplasia, low-set ears, joint and scrotal abnormalities (Seaver and Cassidy, 1991)

ANTENATAL NATURAL HISTORY

Ocular hypertelorism occurs by three pathogenic mechanisms: (1) early ossification of lesser wings of the sphenoid bone, fixing orbits in the fetal position; (2) failure of development of the nasal capsule, which allows the primitive brain to protrude into space normally occupied by the nasal capsule, as in frontal encephalocele; (3) a disturbance in the development of the skull base due to craniosynostosis or midfacial malformations (Cohen et al., 1995).

The antenatal natural history depends on the underlying condition responsible for the hypertelorism. For example,

there is a higher-than-normal rate of miscarriage in fetuses affected with Opitz syndrome (Patton et al., 1986). The natural history for isolated fetal hypertelorism is unknown.

Hypertelorism has occurred as the result of first trimester fetal trauma. In one report, two fetuses were described who were exposed to dilation and curettage during the first trimester of pregnancy (Holmes, 1995). The cause of hypertelorism was hypothesized to be the result of exposure to marked and acute mechanical forces on the fetal circulatory system. This resulted in shear stress with release of vasoactive modulators and potentially resulted in the multiple congenital abnormalities described in these two fetuses.

MANAGEMENT OF PREGNANCY

When fetal orbital hypertelorism is documented, a detailed anatomic survey should be performed to look for associated malformations, especially in the central nervous system. Strongly associated findings include anterior cephalocele; clefts of the face, lip, palate, and nose; megaloencephaly; and craniosynostosis. Because multiple chromosomal abnormalities have been documented in association with fetal hypertelorism, a karyotype should be offered. An association between the autosomal dominant form of Opitz syndrome and microdeletion of chromosome 22q11.2 has been demonstrated (Fryburg et al., 1996; Lacassie and Arriaza, 1996). Both parents should have their inner and outer canthal distances measured and compared with normal standards for adults (Figure 25-2). If the fetal hypertelorism is apparently isolated, there is no indication for a change in the standard management of pregnancy. If, however, the orbital hypertelorism is found to be associated with a severe brain defect, the parents should be counseled regarding the grim prognosis for this condition. Termination of pregnancy can be discussed if the abnormality is found before 24 weeks of gestation.

Families at risk for the single-gene disorders listed in Table 25-1 should have fetal orbital measurements taken during serial sonographic studies. In one study, hypertelorism was considered as a marker of brain involvement in neurofibromatosis. In this report, 11 patients with neurofibromatosis were described who had hypertelorism. All the patients had severe central nervous system abnormalities. In an additional 23 patients with neurofibromatosis but no hypertelorism, no central nervous system abnormalities were demonstrated, despite extensive skin involvement (Westerhof et al., 1984). Although this finding has not been validated prenatally, it would be of interest to routinely measure orbital distances in fetuses at risk for neurofibromatosis, and to correlate those distances with neurologic abnormalities observed postnatally.

FETAL INTERVENTION

There are no fetal interventions recommended for hypertelorism.

Figure 25-2 The mother of the fetus in Figure 25-1 also had hypertelorism. (*From Hogdall C, Siegel-Bartelt J, Toi A, Ritchie S. Prenatal diagnosis of Optiz (BBB) syndrome in the second trimester by ultrasound detection of hypospadias and hypertelorism.* Prenat Diagn. *1989;9:783-793. Copyright 1989 John Wiley & Sons, Inc. Reprinted, by permission, of John Wiley & Sons, Ltd.*)

TREATMENT OF THE NEWBORN

The infant with isolated hypertelorism should have a detailed physical examination, including postnatal measurements of the inner and outer canthal distances. If a fetal chromosomal analysis was not obtained antenatally, it should be obtained in the immediate postnatal period. In addition, consultation with a medical geneticist is recommended. Consideration should be given to postnatal assessment of the affected infant's intracranial anatomy by computed tomographic (CT) scan or magnetic resonance imaging (MRI). In the absence of documentation of cerebral abnormalities, or in the setting of a family with isolated hypertelorism as a physical trait, the infant affected with isolated hypertelorism should require only routine newborn care.

Infants with hypertelorism and hypospadias should be considered to be at risk for Opitz syndrome (Figure 25-3) (Cappa et al., 1987). Infants with Opitz syndrome have a 30% chance of having laryngotracheal or esophageal clefts. These infants are at high risk for stridor, wheezing, and choking upon feeding. Infants who are clinically diagnosed with

Figure 25-3 A 14-month-old boy with hypertelorism and hypospadias, who was given a clinical diagnosis of Opitz G/BBB syndrome. He had a chromosome deletion of 22q11.2. (*From Fryburg JS, Lin KY, Golden WL. Chromosome 22q11.2 deletion in a boy with Opitz (G/BBB) syndrome*. Am J Med Genet. *1996;62:274-275. Copyright ©1996 John Wiley & Sons, Inc. Reprinted, by permission, of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.*)

this condition should have a barium swallow examination and endoscopy to rule out the presence of these clefts. Many affected infants require tracheostomy, feeding gastrostomy, or a Nissen fundoplication.

SURGICAL TREATMENT

Surgical treatment is not indicated during the newborn period or during very early childhood. Surgical treatment should be contemplated only after evaluation by a craniofacial team. The surgical treatment for hypertelorism was first described by Tessier (1974). This treatment involves mobilization of the orbits and their contents to the midline to achieve normal separation between the orbits (Ortiz-Monasterio et al., 1990). In Tessier's description of the surgical technique for hypertelorism, it was demonstrated that:

1. extensive areas of the craniofacial skeleton could be completely devascularized and repositioned and still survive;
2. the orbits could be circumferentially mobilized and repositioned without affecting the patient's vision;
3. intracranial and extracranial surgery could be combined to treat serious deformities of physical appearance (Tessier, 1974; Whitaker and Vander Kolk, 1988).

Plastic surgery for hypertelorism is generally not performed before 24 months of age because of the small size of the facial structures and the position of the tooth buds in the maxilla (Whitaker and Vander Kolk, 1988). In one report, however, McCarthy et al. (1990) described surgical treatment of hypertelorism as safe, desirable, and effective even in a child less than 5 years of age.

LONG-TERM OUTCOME

The long-term outcome for a child with isolated hypertelorism is good. If the hypertelorism is associated with severe cerebral abnormalities, the prognosis will depend on the extent of the severity of the associated anomalies. Many of the single-gene disorders that have been described in association with hypertelorism (Table 25-1) do involve mental retardation or mild developmental disabilities. The reader is referred to Chapter 10 for further information on disorders such as Apert and Crouzon syndromes, which include hypertelorism and craniosynostosis as physical findings.

GENETICS AND RECURRENCE RISK

The genetics of hypertelorism will depend on the underlying cause for this finding. If a chromosomal abnormality such as an interstitial deletion or partial trisomy is detected, parental chromosomes must be studied. Further genetic counseling will depend on whether the parents are shown to be carriers of a balanced translocation. Ten percent of cases of Turner syndrome (45,X) have hypertelorism (Chrousos et al., 1984). The recurrence risk for Turner syndrome is not considered to be increased above background, and it is independent of maternal age.

A number of single-gene disorders are associated with hypertelorism. Opitz syndrome is a multiple congenital anomaly disorder that primarily affects midline structures and presents with hypertelorism, hypospadias, laryngotracheoesophageal defects, the central nervous system (particularly vermis hypoplasia or agenesis), and the heart (De Falco et al., 2003; Pinson et al., 2004). Interestingly, Opitz syndrome is genetically heterogeneous, meaning that at least two different genes are known to cause an essentially identical phenotype. In the autosomal dominant form there is an unknown gene that maps to chromosome 22q11.2 and can be detected using the DiGeorge syndrome FISH probes. Another form is X-linked, and is caused by mutations in the gene *MID1*. *MID1* encodes a protein containing a RING, B-box-coiled-coil motif that belongs to the tripartite motif (TRIM)

gene family (De Falco et al., 2003). Clinical testing for *MID1* mutations is available.

Noonan syndrome is an autosomal dominant syndrome characterized by hypertelorism, short stature, and heart defects. Mutations in the gene *PTPN11*, located on chromosome 12q24, are thought to be the molecular etiology for this condition. A related but much rarer dominant disorder, LEOPARD syndrome (*L*entigines, *E*KG abnormalities, *O*cular hypertelorism, *P*ulmonary stenosis, *A*bnormal genitalia, *R*etardation of growth, *D*eafness) is also caused by mutations in *PTPN11* (Legius et al., 2002). Waardenburg syndrome, another autosomal dominant disorder, is characterized by dystopia canthorum, which is lateral displacement of the inner canthi and lacrimal puncta (Dollfus and Verloes, 2004). Clinically, affected individuals present with variable deafness, a white patch of hair, and eye color that differs between the two eyes (iridal heterochromia).

Waardenburg syndrome (WS) is also genetically heterogeneous. WS type 1 is caused by mutations in *PAX3*, the paired-box 3 gene. WS type 2 is caused by mutations in *MITF*, the microphthalmia-associated transcription factor gene.

In the infant with hypertelorism, every attempt should be made to make a definitive diagnosis, either clinically or by molecular analysis. This will permit accurate estimates of recurrence risk and counseling, as many of the conditions associated with hypertelorism described in Table 25-1 are inherited as autosomal dominant traits. If one of the parents is diagnosed retrospectively as having a single-gene disorder, such as Noonan syndrome, the parents can be counseled about the 50% recurrence risk in future children.

If a gene mutation has been identified as part of a syndrome associated with hypertelorism, prenatal diagnosis in subsequent pregnancies can be performed by DNA analysis. Otherwise, prenatal diagnosis in future pregnancies can be made by sonographic measurement of the fetal orbits.

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26 CHAPTER Hypotelorism

Key Points

- Defined as a decreased distance between the medial aspects of the orbital walls.
- Incidence is approximately 1 in 1220 livebirths.
- Main concern is its strong association with brain anomalies (especially holoprosencephaly).
- A fetal karyotype should be offered due to its association with aneuploidy, most commonly trisomy 13.

CONDITION

The term *hypotelorism* was used as early as 1960 to indicate a decrease in interorbital distance (Judisch et al., 1984). *Ocular hypotelorism* is defined as a decreased distance between the eyes or pupils, whereas *orbital hypotelorism* is defined as a shortened distance between the medial aspects of the orbital walls, with reduced inner and outer canthal distances (Converse et al., 1975; Judisch et al., 1984). The major concern regarding the finding of fetal hypotelorism is its association with midline craniofacial defects and major cerebral anomalies.

Orbital hypotelorism results from developmental abnormalities of the telencephalon, which is a derivative of the forebrain. It is strongly associated with holoprosencephaly (see Chapter 14) (Converse et al., 1975; Achiron et al., 1995). Frequently, hypotelorism is more obvious radiographically or sonographically than clinically. In one study, the normal range of interorbital distances was documented in anteroposterior facial radiographs obtained in 250 normal children. The mean values ranged from 15 mm in infancy to 23 mm at 12 years of age. The interorbital distance was found to be narrower for girls than for boys. The interorbital distance normally remains small until 18 months of age, when distance gradually increases in both sexes. Interorbital growth levels off in females at age 13 years, but in males this distance continues to increase until 21 years of age (Converse et al., 1975). Interorbital distances are closely related to ethnic background. Individuals who trace their ancestry to Eskimos or Mongolians may have hypotelorism as a normal genetic variation (Awan, 1977).

INCIDENCE

Hypotelorism is uncommon. Most references list the incidence of hypotelorism as unknown, but one reference documented hypotelorism in 1 in 1220 deliveries in Taiwan (a frequency of 0.08% livebirths) (Kuo et al., 1990).

SONOGRAPHIC FINDINGS

Imaging of the fetal orbits and measurements of the interorbital distance are not routine in most centers that provide antenatal sonography. Measurement of the interorbital distance is not included in the American Institute of Ultrasound

in Medicine (AIUM) or American College of Obstetrics and Gynecology (ACOG) guidelines for obstetrical sonography (American College of Obstetrics and Gynecology, 2008). Fetal orbital measurements should be taken in any pregnant woman with a previously affected child, or in the setting of a facial cleft, or with a central nervous system malformation such as hydrocephalus or holoprosencephaly. When orbital hypotelorism is discovered, the finding should be taken seriously, because of its strong association with cerebral abnormalities (Trout et al., 1994). In 1982, Jeanty and colleagues determined the ocular diameter, interocular distances, and binocular distances in a group of fetuses. They proposed the use of inner and outer canthal distances as an indication of fetal growth. In another study of 1108 pregnant women, the interorbital distances were analyzed in fetuses between 7 and 38 weeks of gestation. A chart consisting of normal growth percentiles for the intermalar and interethmoidal distances was created for fetuses between 10 and 40 weeks of gestation (de Elejalde and de Elejalde, 1985). These investigators thought that the intermalar and interethmoidal distances were comparable to postnatal measurements of inner and outer canthal distances. In 1982, Mayden and colleagues constructed a nomogram from measurements of fetal inner and outer orbital diameters obtained in 180 normal pregnancies. These investigators demonstrated that the outer orbital diameter was closely related to the biparietal diameter. After constructing this nomogram, they studied an additional 463 fetuses considered to be at high risk for anomalies. They diagnosed three cases of hypotelorism with fetal orbital measurements below the 95% confidence limits. In two of these three fetuses, hypotelorism was confirmed postnatally, and the other was lost to follow-up. This nomogram was also used to examine six fetuses at risk for ocular abnormalities due to prior affected children in the family. In all six cases, normal antenatal measurements were predicted and correlated with normal neonatal interocular distances (Mayden et al., 1982). Twelve years after this report, the validity of this nomogram was tested in a high-risk antenatal population. These later investigators obtained inner and outer canthal measurements of 422 fetuses studied prospectively at gestational ages of 12 to 37 weeks (Trout et al., 1994). Six cases of hypotelorism and two cases of cyclopia were identified. For all of these affected fetuses, both the inner and outer canthal measurements fell clearly more than 2 SD below the mean. Most cases had measurements that were 3 or 4 SD below the mean and were very clearly abnormal. In all the cases of hypotelorism, there were associated intracranial or extracranial abnormalities, including holoprosencephaly, encephalocele, cleft palate, cardiac anomalies, imperforate anus, congenital diaphragmatic hernia, and digital anomalies. These investigators recommended measurement of the interorbital distance at the level of the thalamus at the same time that the biparietal diameter was measured (Figure 26-1). They stated that bony orbits were seen reliably in transabdominal scans from 12 weeks of gestation and later.

Other investigators recommend a coronal view of the fetus to demonstrate both orbits, the maxilla, and the anterior portion of the mandible in a vertical plane. They recommend moving the transducer posteriorly to image both bony orbits (Meizner et al., 1987). In one case report, a fetus at 38 weeks of gestation was demonstrated to have hypotelorism in association with microphthalmia, microcephaly, and alobar holoprosencephaly (Kuo et al., 1990). These investigators stressed the importance of using measurements based on normal standards for the patient's specific ethnic group, which in this case was Chinese.

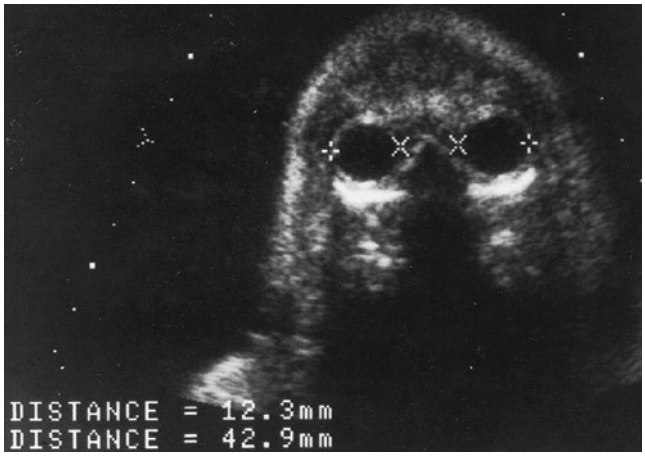

Figure 26-1 Antenatal sonogram demonstrating the presence of hypotelorism. The Xs mark the inner orbital measurement (12.3 mm) and the +s mark the outer orbital measurement (42.9 mm). Both of these measurements are abnormal for gestational age. (*Photograph courtesy of Dr. Marjorie C. Treadwell.*)

Transvaginal sonography has also been used to detect fetal ocular abnormalities. In one report of 1600 cases screened at 12 to 18 weeks of gestation, 8 cases of ocular abnormalities were seen (Bronshtein et al., 1991). There were associated defects of the central nervous system in 5 of the 8. These authors recommended that the optimal section in a transvaginal scan consists of a transverse image of the fetal skull at the orbital plane. They also recommended an oblique tangential section from the nasal bridge, which can also detect hypoechogenic circles lateral to the nose in the anterior part of the orbits representing the fetal lens. Using this approach, Bronshtein et al. (1991) were able to detect the fetal eyes within the orbits in 40% of cases at 11 weeks of gestation and 100% of cases at 12 weeks of gestation. A more recent report summarized normal binocular and intraocular distances for fetuses scanned transvaginally between 11 and 16 weeks of gestation (Rosati and Guariglia, 2003).

DIFFERENTIAL DIAGNOSIS

Fetal hypotelorism is strongly associated with abnormalities of the brain, specifically telencephalon derivatives, including the spectrum of malformations seen in holoprosencephaly (see Chapter 14) (Wong et al., 1999). Other associated conditions include arrhinencephaly, cebocephaly, ethmocephaly,

otocephaly, and cyclopia (Lin et al., 1998). Many chromosomal abnormalities are associated with orbital hypotelorism. The most common is trisomy 13 (Rosati and Guariglia, 2003) but trisomy 20p, partial trisomy 15p, trisomy 21, chromosome 5p deletion, and trisomy 4 mosaicism (Gentile et al., 2005) have also been reported. In one study, three of six fetuses with orbital hypotelorism had chromosomal abnormalities including trisomy 13, ring 21, and chromosome 7 short arm deletion (Trout et al., 1994). Hypotelorism is also associated with abnormalities of head shape, including microcephaly and trigonocephaly. Syndromes associated with hypotelorism include Meckel–Gruber, Williams, Coffin–Siris, Langer–Giedion, oculodentodigital dysplasia, nasal maxillary dysostosis (Binder syndrome), and craniosynostosis-medial aplasia (Jeanty et al., 1982; Judisch et al., 1984). Hypotelorism occurs in more than 60 syndromes (Dollfus and Verloes, 2004). It can be the result of an underlying skull or central nervous system malformation.

ANTENATAL NATURAL HISTORY

The antenatal natural history depends on the underlying condition responsible for the hypotelorism. The natural history for isolated fetal hypotelorism is unknown.

MANAGEMENT OF PREGNANCY

When orbital hypotelorism is documented, a detailed anatomic survey should be performed to look for associated malformations, particularly in the central nervous system. Holoprosencephaly should be ruled out. In addition, because of the multiple chromosomal abnormalities seen in association with hypotelorism, a fetal karyotype should be offered. Both parents should have their inner and outer canthal distances measured and compared with normal standards for adults. If the hypotelorism is apparently isolated, there is no indication for a change in the standard management of pregnancy. If the orbital hypotelorism is found to be associated with holoprosencephaly, the parents should be counseled regarding the poor prognosis for this condition. Termination of pregnancy should be discussed if the abnormality is found before 24 weeks of gestation.

FETAL INTERVENTION

There are no fetal interventions for hypotelorism.

TREATMENT OF THE NEWBORN

The infant with isolated hypotelorism should have a detailed physical examination, including postnatal measurements of the inner and outer canthal distances. If a chromosomal analysis was not obtained antenatally, it should be obtained during the postnatal period. In addition, consultation with a medical geneticist is recommended. Consideration should be given to postnatal assessment of the infant's intracranial anatomy by computed tomographic (CT) scan or magnetic resonance imaging (MRI). In the absence of documentation of cerebral abnormalities, the infant with isolated hypotelorism should require only routine newborn care.

SURGICAL TREATMENT

Surgical treatment is not indicated during the newborn period or during early childhood. For the patient who has isolated severe orbital hypotelorism resulting from a mass effect, such as a frontoethmoidal encephalocele, plastic surgery is possible later in life. In one report, severe orbital hypotelorism was successfully corrected surgically in a 15-year-old girl (Cavina et al., 1999).

LONG-TERM OUTCOME

The long-term outcome for a child with isolated hypotelorism is expected to be good. If the hypotelorism is associated with severe cerebral abnormalities, prognosis will depend on the severity of the associated anomalies.

GENETICS AND RECURRENCE RISK

The genetics of hypotelorism will depend on the underlying cause for this finding. If a chromosomal deletion or partial trisomy is detected, parental chromosomes should be studied. Further genetic counseling will depend on whether the parents are shown to be carriers of a balanced translocation. If the underlying diagnosis is trisomy 13, the parents should be counseled that there is a recurrence risk of 1% in addition to the maternal age–related risk. Hypotelorism has been reported as an isolated trait inherited as an autosomal dominant in a three-generation pedigree (Judisch et al., 1984). In this family, intelligence was completely normal. If parental measurements are consistent with a familial trait of hypotelorism, the parents can be counseled about the 50% recurrence risk. At present, no specific gene has been identified for isolated hypotelorism. However, multiple genes have been identified that cause hypotelorism as a result of holoprosencephaly, including sonic hedgehog (*SHH*), sine oculis homeobox (*SIX3*), TG interacting factor (*TGIF*), and zinc finger protein of cerebellum (*Z1C2*) (Dollfus and Verloes, 2004).

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27 Macroglossia

CHAPTER

Key Points

- Defined as "true" and "relative." In "true" macroglossia histologic abnormalities are present. In "relative" macroglossia, the tongue is normal but appears large due to jaw underdevelopment or oropharyngeal hypotonia.
- Incidence is 1/11,000 to 1/25,000 livebirths.
- Differential diagnosis includes overgrowth syndromes, trisomy 21, congenital hypothyroidism, inborn errors of metabolism, lymphatic and vascular malformations, and tumors.
- A karyotype is indicated to rule out trisomy 21.
- Prevent airway obstruction at birth.
- Partial glossectomy in childhood is curative.
- Recurrence risks depend on underlying etiology.

CONDITION

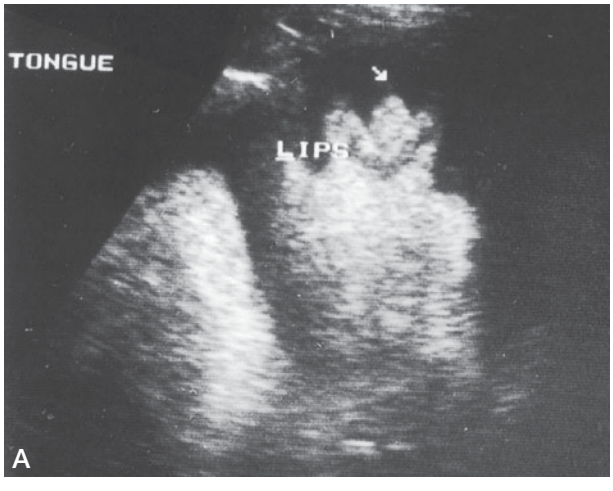
In children, *macroglossia* is defined as a resting tongue that protrudes beyond the teeth or the alveolar ridge (Weiss and White, 1990;Weissman et al., 1995). The antenatal diagnosis of macroglossia is somewhat subjective. In the neonate, the tongue grows faster than the other oral structures; it is not limited by the presence of teeth. At rest, some normal neonates may exhibit apparent enlargement of the tongue and protrusion through the lips. For the majority of these newborns, however, the tongue recedes into place with normal anatomic growth of the mouth (Myer et al., 1986). The first scientific report of macroglossia occurred in 1854, when Virchow and Uber described a lingual lymphatic malformation that arose

from dilation of lymphatic spaces in the tongue (Vogel et al., 1986).

Vogel et al. (1986) have defined two types of macroglossia: "true" and "relative." *True macroglossia* means that histologic abnormalities of the tongue are present that correlate with the clinical findings of tongue enlargement. Examples of such findings include vascular malformations, muscular hypoplasia, tumor infiltrate, or the presence of abnormal elements within the tongue, including edema, inflammation, or storage material. In Beckwith–Wiedemann syndrome, the histology of the tongue is normal, and the macroglossia is due to hyperplasia of the muscle fibers. In lymphangioma, histologic analysis reveals numerous endothelial-lined cystic spaces that contain lymphatic fluid, erythrocytes, and lymphocytes in a thin stroma of connective tissue. The striated muscle in the tongue subsequently atrophies where compression has occurred from dilated lymphatics (Rice and Carson, 1985). *Relative macroglossia* means that there is apparent tongue enlargement, but no histologic changes within the tongue are demonstrated. An example of relative macroglossia is in trisomy 21, in which the tongue is normal but appears large due to mandibular or maxillary underdevelopment or generalized oropharyngeal hypotonia.

INCIDENCE

Macroglossia is a rare fetal finding (Weissman et al., 1995). To our knowledge, there are no published reports of the true incidence of macroglossia presenting in utero. An estimate of the incidence of macroglossia may be calculated indirectly from the incidences of three common conditions that are associated with macroglossia—Beckwith–Wiedemann syndrome, congenital hypothyroidism, and trisomy 21. The incidence of Beckwith–Wiedemann syndrome is 1 in 13,500 births (Patterson et al., 1988). Approximately 82% to 99% of infants with Beckwith–Wiedemann syndrome have macroglossia (McManamny and Barnett, 1985; Elliott and Maher, 1994). Taking the more conservative estimate of macroglossia



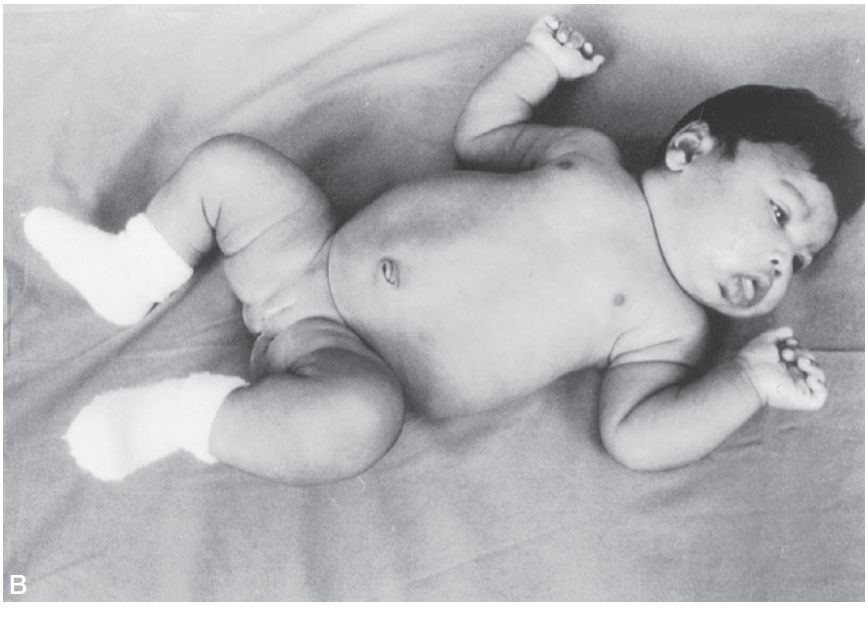


Figure 27-1 **A**. Prenatal sagittal scan performed at 34 weeks of gestation, demonstrating a large tongue that protrudes beyond the fetal lips. **B**. Postnatal photograph of same individual at 2 months of age. The macrosomia, macroglossia, and lax abdominal musculature were consistent with a diagnosis of Beckwith–Wiedemann syndrome. (*From Viljoen DL, Jaquire Z, Woods DL. Prenatal diagnosis in autosomal dominant Beckwith–Wiedemann syndrome.* Prenat Diagn. *1991;11:167-175. Copyright 1991 John Wiley & Sons Ltd. Reprinted, by permission, of John Wiley & Sons Ltd.*)

in Beckwith–Wiedemann syndrome (82%), this would give an approximate incidence of 1 in 16,000 livebirths with macroglossia due to Beckwith–Wiedemann syndrome. Overall, trisomy 21 occurs in 1 in 1000 livebirths. Approximately 8.9% of fetuses with trisomy 21 have macroglossia (Weissman et al., 1995). This would give a livebirth incidence of macroglossia due to trisomy 21 of 1 in 11,000. Congenital hypothyroidism occurs in 1 in 5,000 livebirths (Kourides et al., 1984). Approximately 20% of newborns with hypothyroidism have macroglossia (Grant et al., 1992). This would equal a livebirth incidence of 1 in 25,000 livebirths with hypothyroidism and macroglossia. Summation of these studies gives a range of 1 in 11,000 to 1 in 25,000 livebirths presenting with macroglossia as a symptom.

SONOGRAPHIC FINDINGS

The tongue can be successfully imaged by an inferior coronal view of the fetal face. The tongue can also be visualized by the sagittal profile face view, if the tongue is extending from the mouth (Figure 27-1A) (Weissman et al., 1995). Fetuses with macroglossia have a large protruding tongue (Figure 27-2A). In normal fetuses, the growth of the tongue is linear between 13 and 18 weeks of gestation (Bronshtein et al., 1998). Although nomograms have been published for both first and second trimester fetal tongue size (Achiron et al., 1997; Bronshtein et al., 1998), the diagnosis is usually subjective. Additional sonographic findings include polyhydramnios due to impairment in fetal swallowing. Considerations in the further assessment of fetuses with macroglossia include a detailed search for associated anomalies. Specifically, it is important to rule out fetal goiter (Kourides et al., 1984). A large for gestational age fetus with polyhydramnios might also suggest maternal diabetes, or one of the overgrowth syndromes (see Chapter 124). A macrosomic fetus with macroglossia and other findings, such as omphalocele, increased abdominal circumference, adrenal gland cyst, nephromegaly, and cardiovascular abnormalities, is most likely to have Beckwith–Wiedemann syndrome (Cohen, 2005). Table 27-1 summarizes the prenatal ultrasonographic findings in six cases of Beckwith–Wiedemann syndrome. Macrosomia due to Beckwith–Wiedemann syndrome is a constant finding and can be diagnosed between 16 and 22 weeks of gestation (Viljoen et al., 1991). Prenatal diagnosis of Beckwith–Wiedemann syndrome has been reported at 19 weeks of gestation (Winter et al., 1986), 28 weeks of gestation (Wieacker et al., 1989), and 30 weeks of gestation (Cobellis et al., 1988). Prenatal sonographic diagnosis is not always conclusive for this condition. Even in the setting of a positive family history and multiple prenatal sonograms, the diagnosis was missed in a fetus who presented with severe hydronephrosis, cardiomegaly, and hepatomegaly in utero (Nowotny et al., 1994). Furthermore, there is clinical overlap between Beckwith–Wiedemann syndrome and an X-linked overgrowth syndrome, Simpson Golabi Behmel syndrome (DeBaun et al., 2001).

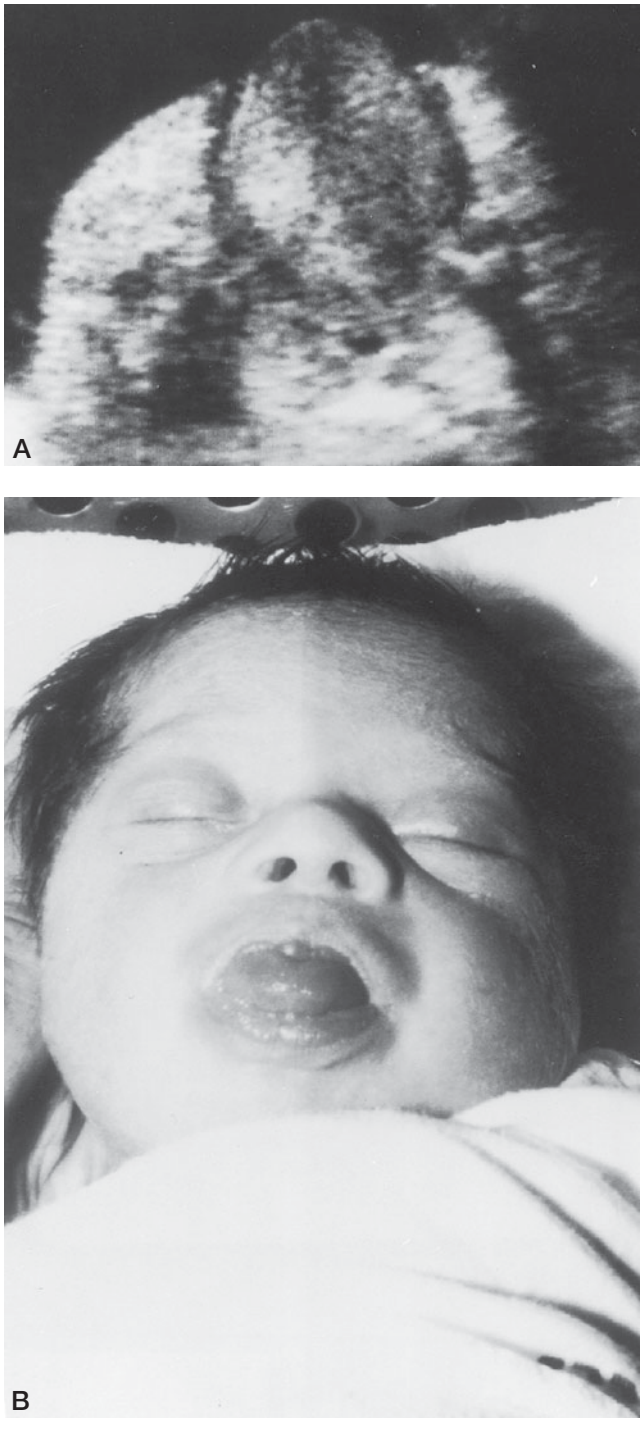


Figure 27-2 **A**. Axial scan through the floor of the fetal mouth, performed at 22 weeks of gestation, demonstrating a large tongue that extends outside of the mouth. This was the only abnormal finding. **B**. Postnatal photograph of same infant during the neonatal period, showing an enlarged tongue. The karyotype revealed trisomy 21. (*From Weissman A, Mashiach S, Achiron R. Macroglossia: prenatal ultrasonographic diagnosis and proposed management.* Prenat Diagn. *1995;15:66-69. Copyright 1995 John Wiley & Sons Ltd. Reprinted, by permission, of John Wiley & Sons Ltd.*)

Table 27-1

Ultrasonographic and Clinical Findings in Six Fetuses with Beckwith–Wiedemann Syndrome

Clinical Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Total
Family history of BWS	Sporadic	Affected sibling	Affected sibling	Affected sibling	Affected sibling	Mother has BWS	5/6
Ultrasound feature (wga*)							
Diagnosis suspected	20	20	18	16	18	22	—
Hydramnios	+(20)	—	+	+	+	Mild (22)	5/6
Macroglossia	—	—	—	—	—	(34)	1/6
Macrosomia	+(20)	+	+	+	+(18)	+(34)	6/6
Renal hyperplasia	+(20)	—	—	—	—	+(22)	2/6
Adrenal hyperplasia	—	—	—	—	—	—	1/6
Omphalocele	+	+	+	+	+(18–19)	—	5/6
Abdominal circumference	—	—	—	—	+(19)	+(22)	2/6
Hepatomegaly	—	—	—	—	—	+(29)	1/6
Termination of pregnancy	—	—	+(19)	—	+(21)	—	2/6
Birth weight (g)	4285	4600	—	5100	—	5300	

**wga = Gestational age in weeks. (From Viljoen et al., 1991.)*

An additional important consideration in fetal sonographic assessment of macroglossia is the possibility of lingual lymphatic malformations, often seen in association with other lymphatic malformations, such as cystic hygroma. Prenatal sonographic assessment should also specifically exclude abnormalities associated with trisomy 21, such as shortening of the long bones, an increased nuchal fold, cardiovascular defects, widening of the space between the first and second toes, and renal pyelectasis.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of conditions associated with macroglossia is given in Table 27-2. The most important considerations in the differential diagnosis include the overgrowth syndromes, such as Beckwith–Wiedemann (Figure 27-1B) and Simpson-Golabi-Behmel, trisomy 21 (Figure 27-2B), congenital hypothyroidism, lingual lymphatic malformations, tumor/epignathus (Figures 27-3A and 27-3B), and hemangiomas/vascular malformations. Prior to the recognition of Beckwith–Wiedemann syndrome in 1963, lymphangioma was the most common cause of macroglossia presenting during the newborn period. Sixty percent of lymphangiomas that involve the tongue present at birth (Rice and Carson, 1985). Lingual lymphatic malformations are the most common vascular abnormalities of the tongue and are frequently localized to the anterior two-thirds of the tongue. Inborn errors of metabolism that can be associated with macroglossia include Hunter, Hurler, Maroteaux–Lamy, and Sanfilippo syndromes, as well as Pompe (glycogen storage disease, type II) I-cell disease, and GM_1

Table 27-2

Differential Diagnosis of Conditions Associated with Micrognathia

- Chromosome abnormalities
  - Trisomy 21
  - Pallister–Killian syndrome (mosaic trisomy 12p)
- Inborn error of metabolism
  - Congenital hypothyroidism
  - Hurler syndrome
  - I-cell disease
  - GM_1 gangliosidosis
  - Pompe disease
  - Farber's lipogranulomatosis
- Overgrowth syndromes
  - Beckwith–Wiedemann syndrome
  - Simpson-Golabi-Behmel syndrome
  - Maternal diabetes
- Anatomic abnormalities
  - Lymphangioma
  - Hemangioma
  - Epignathus
  - Teratoma

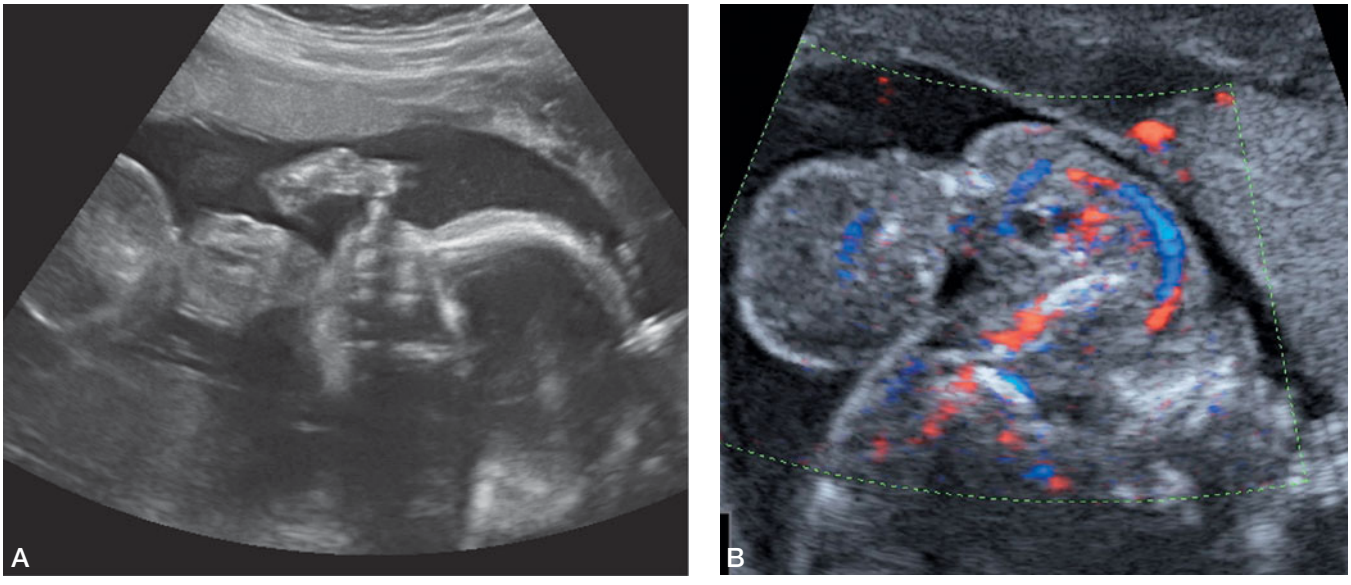


Figure 27-3 **A**. Sagittal view of a fetus at 19 weeks showing a teratoma protruding from the tip of the tongue into the amniotic cavity. **B**. Transverse view of the same fetus showing vascular supply through the tongue mass.

gangliosidosis. Of these, the disorders that can present during the newborn period are Hurler, I-cell, GM_1 gangliosidosis, and possibly Pompe. Patients with I-cell disease are typically growth-restricted and have abnormal neurologic signs. Farber's lipogranulomatosis, in its most severe form, can also present during the neonatal period. These infants will have the classic triad of subcutaneous nodules, hoarseness, and joint involvement.

ANTENATAL NATURAL HISTORY

The antenatal natural history of macroglossia is unremarkable. As an isolated finding, there is no evidence for in utero lethality due to the presence of macroglossia. However, macroglossia due to trisomy 21 does have an increased risk for pregnancy loss. As stated earlier, there can be polyhydramnios associated with macroglossia due to impairment of swallowing.

MANAGEMENT OF PREGNANCY

When macroglossia is documented in utero, a detailed fetal sonographic anatomical evaluation is indicated to look for associated anomalies. It is important to rule out the anomalies associated with Beckwith–Wiedemann syndrome, such as omphalocele, macrosomia, and nephromegaly. It is also important to rule out trisomy 21. Nicolaides et al. (1992, 1993) described a series of 13 fetuses with macroglossia. In 10, a chromosomal abnormality was found, and 9 of the 10 had trisomy 21. None of these patients had isolated macroglossia; additional anomalies were always documented. However, Weissman et al. (1995) have described a case of isolated macroglossia due to trisomy 21 (see Figure 27-2). Given the fact that macroglossia is a relatively rare finding, we recommend obtaining a chromosomal analysis on the fetus with macroglossia. This is important for two reasons: one is to rule out trisomy 21 or mosaic trisomy 12p as the cause of the macroglossia. The other consideration is that in some cases of Beckwith–Wiedemann syndrome, there are abnormalities seen in chromosome 11p15.

If hypothyroidism is suspected in the fetus, particularly in the presence of a goiter, it has been recommended to obtain amniotic fluid thyroid-stimulating hormone (TSH) levels to confirm the diagnosis. According to Kourides et al. (1984), the normal TSH levels in amniotic fluid at 26 and 38 weeks of gestation are 0.44 ± 0.21 μU per milliliter and 0.27 ± 0.15 μU per milliliter, respectively. The fetus reported by Kourides et al. had markedly elevated TSH values of 2.4 and 2.9 μU per milliliter at 26 and 38 weeks. These authors advocate the early diagnosis of hypothyroidism to permit treatment of the infant on day 1 of life. Although newborn screening for hypothyroidism is routine in most states, the diagnosis is not usually communicated to the pediatrician until 2 to 3 weeks after birth. Thus, the infant does not generally receive treatment until approximately 3 to 4 weeks of age. If hypothyroidism is prenatally diagnosed, treatment can begin immediately after birth and reduce symptoms. If the macroglossia is due to Beckwith–Wiedemann syndrome, the fetus may be large for gestational age, and cesarean delivery may be necessary because of dystocia.

FETAL INTERVENTION

There are no fetal interventions indicated for macroglossia.

TREATMENT OF THE NEWBORN

The immediate considerations in treatment of the newborn with macroglossia include preventing airway obstruction, monitoring for difficulties in feeding and swallowing, and monitoring for hypoglycemia if a clinical diagnosis of Beckwith–Wiedemann syndrome is suspected. Physical examination should confirm the macroglossia. During the newborn period this will be notable for the tongue protruding through the lips. Palpation of the tongue is generally unremarkable and unrevealing. The diagnosis of Beckwith–Wiedemann syndrome is important to make because of the increased rate of infant mortality associated with this condition. Babies with Beckwith–Wiedemann syndrome are at risk for severe neonatal hypoglycemia, seizures, and congestive heart failure (Viljoen et al., 1991).

The most common neonatal findings in infants with Simpson-Golabi-Behmel syndrome are a birth weight and length >95% for age, macroglossia, coarse facial features, extramammary nipple, and genitourinary anomalies (DeBaun et al., 2001).

As mentioned earlier, in infants with trisomy 21, the tongue is not actually enlarged. In a radiographic study of the tongue of several patients with Down syndrome, Ardran et al. (1972) demonstrated that the problem in Down syndrome was due to large lingual tonsils, which narrowed the airway. They hypothesized that the gaping mouth of the patient with Down syndrome related to the need to provide an airway. The major problems in Down syndrome relate to oropharyngeal hypotonia and midface underdevelopment. The tongue protrusion present during the first year of life in infants with trisomy 21 tends to disappear with improved muscular tone as the patients grow older. Limbrock et al. (1991) advocate the use of a palatal plate to stimulate oral muscular tone to improve spontaneous tongue positioning, drooling, and the open-mouthed posture seen in infants and children with trisomy 21.

If no prenatal studies have been obtained, the physical examination is the most important component of the assessment of the newborn with macroglossia. If physical findings suggest Down syndrome, a chromosomal analysis should be performed. If physical findings suggest Beckwith–Wiedemann syndrome, a chromosomal study should also be performed to look for abnormalities of 11p15 (Slavotinek et al., 1997). Special efforts should be made to verify the results of newborn screening thyroid function tests. In the absence of any other diagnosis, consideration should be given to the diagnosis of inborn errors of metabolism. Urine for mucopolysaccharides, oligosaccharides, and sialyloligosaccharides will identify most metabolic diseases. Pompe (glycogen storage disease, type II) would not be identified by the urine tests, but the clinical findings of cardiomyopathy and significant hypotonia should suggest the diagnosis. Similarly, the clinical findings present in Farber lipogranulomatosis should help in diagnosis, although the assay for acid ceramidase in leukocytes, fibroblasts, and amniocytes will be definitive.

SURGICAL TREATMENT

Many infants with macroglossia will have spontaneous resolution of the problem due to normal growth of the oropharynx, mandible, and maxilla. The major treatment for this condition is a partial glossectomy early in life to restore adequate breathing and swallowing, and to leave a tongue capable of normal speech, taste sensation, and further orofacial development (Rice and Carson, 1985). Most surgeons recommend operative intervention by 6 months of age to prevent dental abnormalities such as prognathism and malocclusion. McManamny and Barnett (1985), who are strong advocates for partial glossectomy, state that macroglossia is unsightly, predisposes to drooling, and gives a false impression of mental retardation. Macroglossia affects dentition and prevents orthodontic treatment until the tongue is reduced. Macroglossia also affects the pronunciation of consonants, thereby impairing clarity of speech.

The goals of surgery include preservation of normal taste sensation, restoration of normal size and shape of the tongue for proper articulation after incision, and correction of a dental arch deformity and malocclusion of the teeth by later orthodontics (Gupta, 1971). Surgical methods include an anterior V-shaped wedge resection, a bilateral marginal resection, a U-shaped resection with the open end facing posteriorly, and a combined transoral–transcervical approach for an extremely large lesion (Myer et al., 1986; Wang et al., 2003). Partial glossectomy is curative, and postoperatively there is no recurrence. In occasional cases in which the initial resection is inadequate, a second procedure is performed to remove more of the tongue. For most patients, however, the treatment is completely curative and these lesions heal well. Even in cases of Beckwith–Wiedemann syndrome, there is no evidence that the muscular hyperplasia causes the tongue to increase in size after surgery.

LONG-TERM OUTCOME

Patients with macroglossia need to be followed for evidence of chronic alveolar hypoventilation, which has been documented in patients with Beckwith–Wiedemann syndrome and has been noted to cause a secondary reversible pulmonary hypertension syndrome (Smith et al., 1982). If there is a suggestion of airway obstruction, patients should be monitored closely for evidence of hypoventilation with intermittent blood gas evaluation. In rare cases, tracheostomy has been recommended. Symptomatic macroglossia can lead to noisy breathing, difficulty with chewing and swallowing, drooling, slurred speech, an open bite deformity, a dry cracked tongue, and ulceration and secondary infection of the tongue (Vogel et al., 1986). In patients who are diagnosed with either Beckwith–Wiedemann or Simpson-Golabi-Behmel syndrome, close follow-up for development of embryonal tumors is warranted (Schneid et al., 1997; DeBaun et al., 2001).

These include frequent postnatal sonographic studies to assess for Wilms tumor, hepatoblastoma, and nephroblastoma (McManamny and Barnett, 1985).

In a long-term follow-up of 13 children with Beckwith–Wiedemann syndrome ascertained by congenital macroglossia, Hunter and Allanson (1994) described normalization of the craniofacial appearance by adolescence, leaving little clue as to the original diagnosis. None of the patients described in this series had mental retardation.

GENETICS AND RECURRENCE RISK

Isolated macroglossia has been described as a familial trait inherited as an autosomal dominant manner in two unrelated families (Reynoso et al., 1986). Recurrence risks for trisomy 21 are described more fully in Chapter 131. Beckwith–Wiedemann syndrome is a complex and genetically heterogeneous condition. Most cases are chromosomally normal. The gene has been localized to chromosome 11p15 by linkage analysis in the 15% of families that appear to have a familial transmission of this condition (Slavotinek et al., 1997). Chromosomal analysis is recommended in cases of Beckwith–Wiedemann syndrome to rule out duplications or abnormalities of chromosome 11p15, although this is only found in 1% to 2% of cases (Rump et al., 2005). Although most cases of Beckwith–Wiedemann syndrome are sporadic, recessive and multifactorial inheritance has also been suggested (Viljoen et al., 1991). Overexpression of insulinlike growth factor 2 (*IGF2*), the gene involved in Beckwith–Wiedemann syndrome, is maternally imprinted and functions as a growth factor and tumor suppressor (Weksberg et al., 1993). In 28% of parents who carry informative DNA polymorphisms, uniparental disomy has been demonstrated (Slatter et al., 1994). In all the cases studied by Slatter et al., there was paternal uniparental disomy present as a mosaic cell line. Therefore, there is good evidence in sporadic cases that uniparental disomy of chromosome 11 occurs as a postzygotic event. In families in which this is demonstrated, there should theoretically be no recurrence risk. In parents who have an affected infant with Beckwith–Wiedemann syndrome, a family history should be obtained to rule out dominant patterns of inheritance.

Germline mutations in the cyclin-dependent kinase inhibitor gene *CDKN1C* (p57KIP2) are found in approximately 40% of familial cases of Beckwith–Wiedemann syndrome (Rump et al., 2005). A higher frequency of omphalocele has been shown in the cases associated with *CDKN1C* mutations (Lam et al., 1999).

Simpson Golabi Behmel syndrome is an X-linked condition that arises as a result of deletions or point mutations in the *glypican-3* gene at Xq26 (DeBaun et al., 2001).

Macroglossia due to inborn errors of metabolism is inherited in a pattern consistent with a single-gene defect. Recurrence risk is related to the underlying disorder, whether it is an autosomal recessive or X-linked condition.

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28 CHAPTER Micrognathia and Agnathia

Key Points

- Facial malformation characterized by mandibular hypoplasia and a small receding chin that fails to maintain the tongue in a forward position.
- Incidence is 1 in 1600 fetuses.
- Very high incidence of associated anomalies.
- Differential diagnosis includes Pierre Robin, Stickler, Treacher Collins, and Nager syndromes.
- Fetal karyotype, including FISH studies for DiGeorge syndrome, is indicated.
- DNA studies may be indicated if a syndrome is suspected.
- Delivery should occur in a tertiary center due to the potential for neonatal airway problems.

CONDITION

Micrognathia is a facial malformation characterized by mandibular hypoplasia and a small, receding chin that fails to maintain the tongue in a forward position (Figure 28-1).

Early in embryonic development, the mandible grows slowly. Between 4 and 8 weeks of gestation, the developing tongue remains in the nasal cavity, between the palatine shelves, and a physiologic micrognathia is present. Around the 8th week of gestation, the mandible grows rapidly, and the tongue is normally pulled downward and forward. This allows the palatine shelves to come together to form the secondary palate. At this point in gestation, the mandible extends beyond the maxilla, but continued growth of the maxilla once again produces a relative micrognathia in the fourth and fifth months of gestation. The mandible continues to grow during the third trimester. If the compensatory growth of the mandible is incomplete at birth, a relative micrognathia can exist (Hawkins and Simpson, 1974).

Micrognathia may result from environmental or genetic factors. For example, sharp flexion of the fetal neck in utero results in continuous pressure of the chin against the sternum, which impedes mandibular growth (Hawkins and Simpson, 1974). Micrognathia is also one component of many chromosomal and genetic syndromes (see "Differential Diagnosis").

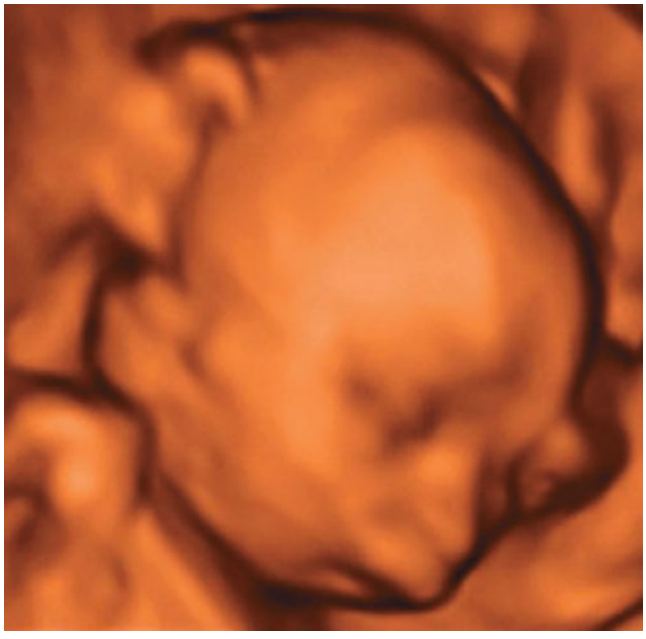

Figure 28-1 Three-dimensional image demonstrating micrognathia.

Micrognathia is commonly thought of as one component of the Pierre Robin syndrome. This clinical triad consists of micrognathia, upper airway obstruction, and a U-shaped cleft palate. The name derives from a 1923 report by Pierre Robin, a French stomatologist, who described the association between newborn micrognathia and upper airway obstruction caused by glossoptosis (posterior displacement of the tongue). The symptoms associated with this "syndrome" are primarily due to an underlying mandibular abnormality (Figure 28-1). During fetal life, when the mandible is hypoplastic, the tongue cannot descend normally into the oral cavity at 7 to 11 weeks of gestation. If the tongue does not descend, it will remain pressed against the base of the cranium. This will then interfere with fusion of the medially growing palatal shelf and ultimately result in a cleft palate (Shprintzen, 1988).

Normal mandibular growth may depend on the presence of mandibular movement during intrauterine development. In one study, Sherer et al. (1995) examined the correlation between lack of mandibular movement, manifested by the absence of fetal swallowing and the development of subsequent micrognathia. For more than a 4-year period, these investigators studied 28 fetuses with polyhydramnios, defined as an amniotic fluid volume of >20 cm^3. The study group consisted of 14 fetuses studied sonographically with absent mandibular movement and a nonvisualized stomach. These findings were interpreted as being consistent with absent fetal swallowing. The control group consisted of 14 fetuses with polyhydramnios but who had sonographic evidence of swallowing. In the study group, 2 fetuses were stillborn. Of the 12 liveborn infants, 11 died in the neonatal period between 1 hour and 7 days of life. All the fetuses in the study group had micrognathia confirmed at birth, whereas none of the fetuses in the control group had micrognathia. These authors concluded that lack of fetal swallowing movements were likely to be important in the development of micrognathia. In this study, four major groups of underlying anomalies were identified in cases of absent fetal swallowing:

1. Complete absence of any fetal movements (fetal hypokinesia/akinesia sequence).
2. Major central nervous system abnormalities with neurologic impairment of the swallowing mechanism.
3. Abnormal karyotype.
4. Isolated absent swallowing due to Moebius sequence (sixth and seventh cranial nerve palsy) (Sherer et al., 1995).

The most severe form of micrognathia is agnathia—total or virtual absence of the mandible. This extremely rare and lethal anomaly also known as otocephaly, is the result of a developmental field defect thought to be secondary to an insult to developing neural crest cell derivatives (Persutte et al., 1990). Prenatal sonographic diagnosis has been reported for this condition (Persutte et al., 1990) (Figures 28-2A and 28-2B).

INCIDENCE

The incidence of mild-to-moderate micrognathia in the general population is unknown. In a high-risk referral center, 56 cases of micrognathia were identified in 2086 fetuses (2.6%) studied in a tertiary sonographic unit for more than 8 years (Nicolaides et al., 1993). More recently, the incidence of micrognathia in a single center was estimated to be 1 in 1600 fetuses (Vettraino et al., 2003).

SONOGRAPHIC FINDINGS

The first prenatal diagnosis of micrognathia was made in a patient deemed to be at risk for Pierre Robin syndrome because the parents already had an affected child. At 23 weeks of gestation, the facial structures were studied and considered to be within normal limits. The same patient returned at 35 weeks of gestation, when polyhydramnios and a striking micrognathia were demonstrated. This report indicated that significant fetal mandibular growth occurs during the third trimester (Pilu et al., 1986). In a later study of 2086 high-risk fetuses, severe micrognathia was diagnosed by the presence of a prominent upper lip and a small chin in 56 cases (Nicolaides et al., 1993). Significantly, all cases with micrognathia in this study had additional malformations or evidence of intrauterine growth restriction. A review of 20 prenatally diagnosed cases of Pierre Robin sequence noted a high incidence of associated polyhydramnios (60% of cases) and cleft palate (45% of cases) (Hsich et al., 1999). Micrognathia has been diagnosed in the first trimester (Teoh and Meagher, 2003).

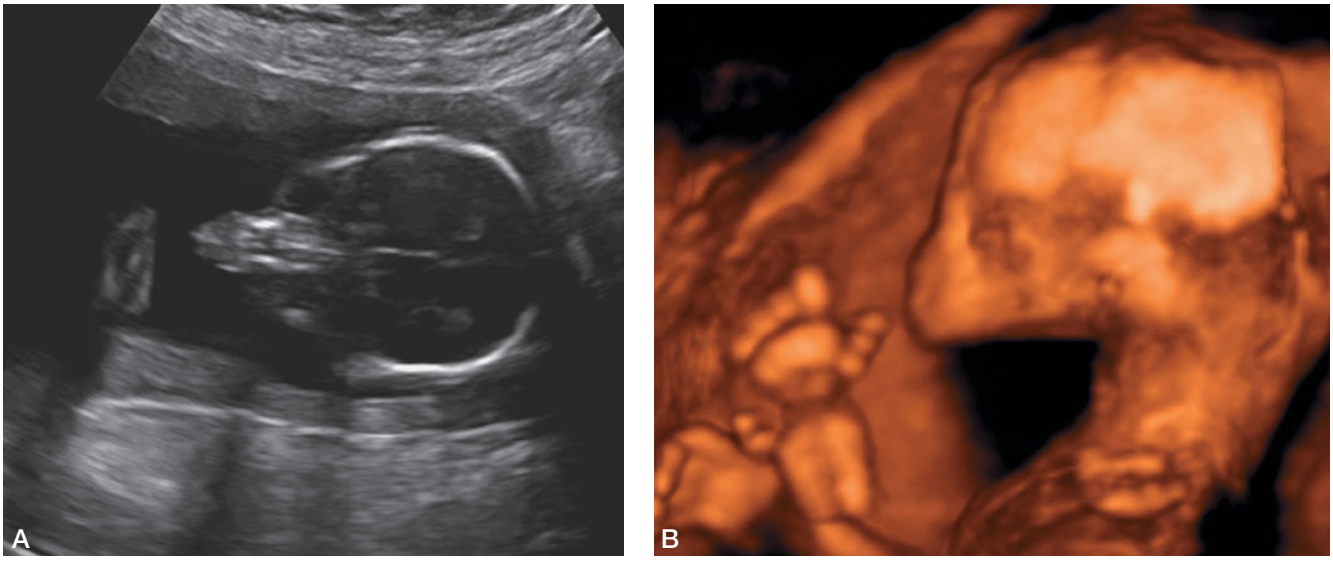

Figure 28-2 Fetus with agnathia. **A**. Two-dimensional oblique transverse view of fetal face demonstrating severe hypoplasia of maxillary structures. **B**. Three-dimensional image of same fetus showing the absence of lower facial structures. Due to the craniofacial abnormality the ears cannot migrate upward from the fetal neck. (*Photograph courtesy of Prenatal Diagnosis Center, Women and Infant's Hospital.*)

All reports of sonographic studies performed on fetuses with micrognathia stress the extremely high incidence of associated anomalies and the grim prognosis for this finding. Bromley and Benacerraf (1994) described their experience with 20 fetuses diagnosed with micrognathia between 15 weeks of gestation and full term. Thirteen of these fetuses had polyhydramnios (a 70% incidence). These authors hypothesized that the polyhydramnios was due to difficulty in fetal swallowing. These authors recommended a full sonographic evaluation of the fetal face, which optimally includes a midsagittal profile, coronal sections of the lower face, and axial evaluation of the orbital area. In this report, micrognathia was subjectively defined as an unusually small mandible with a receding chin demonstrated on the midsagittal view of the fetal face (Figure 28-3). The fetal mandible was not measured.

Several reports have attempted to establish sonographic nomograms of fetal mandibular length in relationship to gestational age (Otto and Platt, 1991; Paladini et al., 1999). To provide objective evidence of micrognathia, Chitty et al. (1993) created a growth chart for mandibular length in 184 normal fetuses between 12 and 27 weeks of gestation. The fetal mandible was measured from the proximal end of the ramus at its insertion site into the temporomandibular joint to its distal end where it meets the cartilaginous symphysis mentis. The measurement was made in a plane that visualized one ramus of the jaw. The ultrasound beam was placed at a right angle to the plane of the mandible. A single measurement was recorded. Normal values obtained in this study are given in Table 28-1. At more than 28 weeks of gestation, it became difficult to identify and define fetal facial landmarks. This was due to change in fetal positioning and adjacent bony structure shadowing. These authors, as well as others, stated that accurate and reliable measurements of the mandible were not possible in the third trimester. In another study, fetal mandibular measurements were obtained in a scan plane parallel to the mandible that included the fetal hypopharynx. In this report of 204 women with uncomplicated pregnancies and reliable gestational dating, the anterior, posterior, and transverse fetal jaw measurements were shown to increase with gestational age (Watson and Katz, 1993).

Paladini et al. (1999) also showed that mandibular growth correlated linearly with gestational age and biparietal diameter. This group developed the jaw index

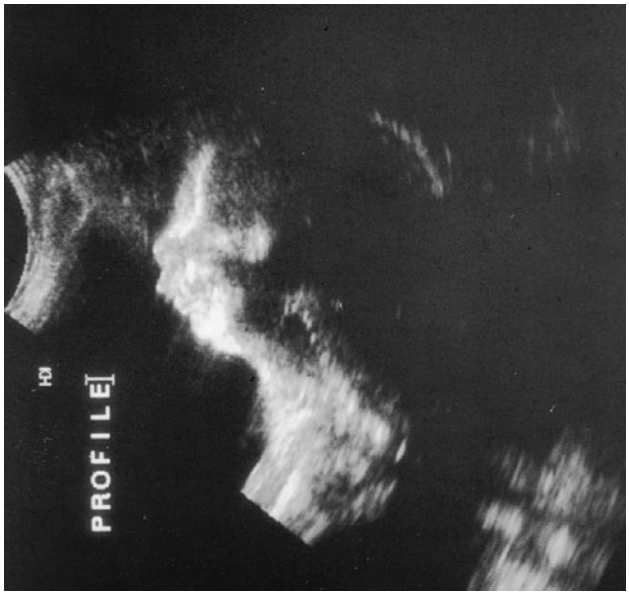

Figure 28-3 Severe fetal micrognathia demonstrated in sagittal view obtained at 29 weeks of gestation.

Table 28-1

Mean Fetal Mandibular Measurement

Gestation (wk)	25th Percentile (mm)	50th Percentile (mm)	97.5th Percentile (mm)
12	6.3	8.0	9.7
13	8.2	10.2	12.3
14	10.0	12.4	14.7
15	11.7	14.4	17.2
16	13.4	16.4	19.5
17	15.0	18.4	21.8
18	16.5	20.2	24.0
19	18.0	22.1	26.2
20	19.4	23.9	28.3
21	20.8	25.6	30.4
22	22.2	27.3	32.4
23	23.5	28.9	34.4
24	24.8	30.6	36.4
25	26.0	32.2	38.3
26	27.3	33.7	40.2
27	28.4	35.2	42.1
28	29.6	36.7	43.9

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(anteroposterior mandibular diameter/BPD × 100) to objectively diagnose micrognathia. In a population of 198 fetuses with malformations, they compared the jaw index to subjective assessment of micrognathia. The jaw index had a 100% sensitivity and a 98.1% specificity in diagnosing micrognathia at a cutoff level of less than 23, which was better than the 73% sensitivity when using a subjective approach. More recently 3D ultrasound imaging has been recommended, as it provides a true midline sagittal view of the fetal face (Lee et al., 2002).

Fetal micrognathia is highly associated with the presence of additional structural abnormalities, including intrauterine growth restriction, skeletal dysplasias, congenital heart disease, and polyhydramnios. A diagnosis of isolated micrognathia is unlikely. Vettraino et al. (2003) performed a retrospective review of outcome for 15 fetuses diagnosed with "isolated" micrognathia; 14 of 15 had additional anomalies, including 11 cases of cleft palate, and 3 cases of syndromes or associations.

DIFFERENTIAL DIAGNOSIS

Micrognathia is diagnosed either subjectively or objectively, by comparing individual fetal jaw measurements with the nomograms for fetal mandible measurements as a function of gestational age. The differential diagnosis must include conditions that are known to be associated with micrognathia. These are summarized in Table 28-2, and include chromosomal abnormalities, neuromuscular abnormalities,

Table 28-2

Conditions Associated with Micrognathia

Chromosomal abnormalities
- Trisomy 18
- Triploidy
- Trisomy 13
- Trisomy 9
- Trisomy 8

Neuromuscular abnormalities
- Pena–Shokeir syndrome
- Fetal akinesia/hypokinesia syndrome
- Arthrogryposis multiplex congenita

Single-gene disorders
- Familial trait (autosomal dominant)
- Stickler syndrome (autosomal dominant)
- Treacher Collins syndrome (autosomal dominant)
- Diastrophic dysplasia (autosomal recessive)
- Campomelic dysplasia (autosomal recessive)
- Saethre Chotzen syndrome (autosomal recessive)
- Nager acrofacial dysostosis (autosomal dominant)
- Multiple pterygium syndrome (autosomal recessive)
- Thrombocytopenia–absent radius syndrome (autosomal recessive)

Other syndromes
- Congenital ichthyosis
- Beckwith–Wiedemann

Teratogen
- Isotretinoin exposure

single gene (Mendelian) disorders, other syndromes, and teratogen exposure. Stickler syndrome, an autosomal dominant disorder consisting of micrognathia, myopia, epiphyseal dysplasia, juvenile arthropathy, cleft palate, mild sensorineural hearing loss, and airway obstruction, is frequently missed during the newborn period. In a retrospective review of patients with micrognathia and symptoms consistent with the Robin malformation, Shprintzen (1988) found a very high incidence of Stickler syndrome. Most of these cases were diagnosed later in childhood. Treacher Collins syndrome, a dominantly inherited disorder consisting of micrognathia, small ears, downslanting palpebral fissures, malar hypoplasia, lower eyelid coloboma, and abnormal hair growth, has been diagnosed prenatally by noting the presence of a hypoplastic mandible, absent ears, and severe polyhydramnios (Crane and Beaver, 1986; Meizner et al., 1991; Cohen et al., 1995). Similarly, Nager syndrome (acrofacial dysostosis), a dominantly inherited disorder that consists of mandibulofacial abnormalities and shortened upper extremities, has also been diagnosed by prenatal sonography via the demonstration of markedly hypoplastic mandible, malformed external ear, poorly ossified long bones of the arm, and polyhydramnios (Benson et al., 1988; Paladini et al., 2003).

ANTENATAL NATURAL HISTORY

Fetal micrognathia is frequently associated with severe underlying abnormalities (Figure 28-4). At least three separate studies suggest that increased lethality is associated with this malformation. In a study by Turner and Twining (1993) of 3200 fetuses scanned at a single institution, 9 were identified with micrognathia. The underlying diagnosis for these 9 fetuses included 3 cases of trisomy 18, 4 cases of skeletal dysplasias (including short rib-polydactyly, 2 cases of campomelic dysplasia, and 1 case of diastrophic dysplasia), 1 case of Roberts syndrome, and 1 case of multiple anomalies. Nicolaides et al. (1993) described their experience with 56 cases of fetal micrognathia. Thirty-seven (66%) of these had abnormal chromosomes. Surprisingly, the prognosis was equally poor for the 19 fetuses with normal chromosomes. Of the 19, 10 were terminated electively, 4 had died during the neonatal period, and 5 died in utero. Only 1 infant was born alive. Most of the fetuses affected with micrognathia had associated abnormalities, including ventriculomegaly (8 cases), hydronephrosis (9 cases), and diaphragmatic hernia (2 cases). In the study performed by Bromley and Benacerraf (1994), 80% of fetuses with micrognathia (16 of 20) did not survive postnatally. Of these, 6 were terminated electively and 10 died in utero or during the immediate neonatal period. After reviewing the autopsy diagnoses on the products of conception these authors concluded that at least four of the six cases in the electively terminated fetuses would definitely have been lethal had the pregnancy continued to term.

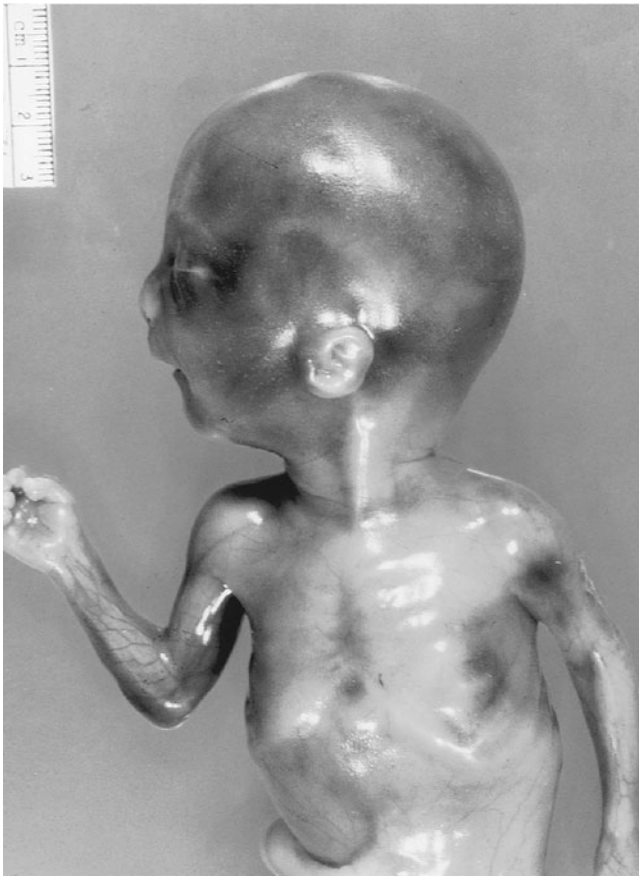

Figure 28-4 Milder micrognathia demonstrated in a fetus terminated at 19 weeks of gestation due to multiple anomalies detected sonographically. (*Photograph courtesy of Dr. Joseph Semple.*)

MANAGEMENT OF PREGNANCY

An attempt should be made to examine both parents, because a significant number of mild-to-moderate cases of micrognathia are inherited as familial traits. A family history should be obtained to seek specific evidence of other cases of micrognathia (especially family members affected with Stickler syndrome), or exposure to drugs such as isotretinoin. Following a diagnosis of micrognathia, a targeted fetal anatomy scan should be performed, with particular attention paid to the diagnosis of cardiac or skeletal defects. Fetal magnetic resonance imaging may provide additional information regarding the fetal face (Robson and Barnewolt, 2004). It is recommended that the fetal ears be examined to rule out Treacher Collins syndrome or oculoauriculovertebral dysplasia (Goldenhar syndrome) (see Chapter 24) (Bromley and Benacerraf, 1994).

When micrognathia is diagnosed, fetal karyotyping is indicated, and consideration should be given to ruling out the 22q11 microdeletion associated with DiGeorge syndrome by fluorescent in situ hybridization analysis (see Chapter 139).

In an 8-year survey of 2086 high-risk fetuses, 56 were shown to have micrognathia (Nicolaides et al., 1993). Of these 56 affected fetuses, 37 (66%) had chromosomal abnormalities. These karyotypes included 21 cases of trisomy 18, 9 cases of triploidy, and 3 cases of trisomy 13, but no cases of trisomy 21. Similar results were reported by Bromley and Benacerraf (1994), who demonstrated that 5 of 20 (25%) with micrognathia had an abnormal karyotype. Of the 5, 3 had trisomy 18, 1 had trisomy 13, and 1 had trisomy 9. Conversely, in sonographic studies of 83 fetuses with a known diagnosis of trisomy 18 and 42 fetuses with triploidy, micrognathia was detected in only 21 (25%) and 9 (21%), respectively. Therefore, only the most severe jaw defects are demonstrable by prenatal sonography in aneuploid fetuses (Nicolaides et al., 1993).

In the setting of a known family history of Stickler syndrome, DNA diagnosis for mutations in *COL2A1*, *COL11A1*, or *COL 11A2* may be indicated. Furthermore, if the fetal face suggests Treacher Collins syndrome, mutations in the *TCOF1* gene may be diagnostic.

If a fetus is diagnosed with micrognathia and an additional anomaly, the parents should be counseled regarding the expected poor prognosis for the fetus. Agnathia is uniformly fatal at birth. Termination of pregnancy can be offered if the fetus is at less than 24 weeks of gestation.

Infants with micrognathia need to delivered in a tertiary care center because the micrognathia can cause severe respiratory distress and the anatomy of the jaw makes orotracheal intubation difficult. Neonatologists and pediatric anesthesiologists should be available to resuscitate an infant expected to have micrognathia (Figure 28-5). The ex utero intrapartum treatment (EXIT) procedure has been described to allow airway management of a newborn with dysgnathia complex (Baker et al., 2004). Cesarean delivery is not necessary other than for standard obstetric indications.

FETAL INTERVENTION

There are no fetal interventions for micrognathia.

TREATMENT OF THE NEWBORN

Infants with micrognathia are at serious risk for airway obstruction because the anterior attachment of the tongue is displaced posteriorly, so the tongue tends to fall back into the pharynx. The tongue can therefore act as a ball–valve mechanism in the pharynx. These infants are at serious risk for regurgitation and aspiration due to difficulties in breathing and feeding simultaneously. Most patients can maintain an adequate airway as long as they are awake and actively moving their tongue. When they fall asleep, however, the tongue musculature relaxes and the airway can become obstructed. Relief of obstruction can be achieved by pulling the tongue forward or by placing the patient in the prone position (Hawkins and Simpson, 1974). Any infant with micrognathia should be admitted to a special care nursery and observed by pulse oximetry. The propensity for respiratory obstruction can then be monitored while the infant is under supervision in the prone position.

Affected infants also have difficulty with oral feedings (Vettraino et al., 2003). Feedings should be offered with a soft nipple in an almost upright position. In some centers, these infants are offered a nasopharyngeal positive-pressure tube with nasogastric feedings to promote weight gain and maintain patency of the airway. If the infant appears to be stable and pulse oximetry is normal, conservative (nonoperative) treatment is best.

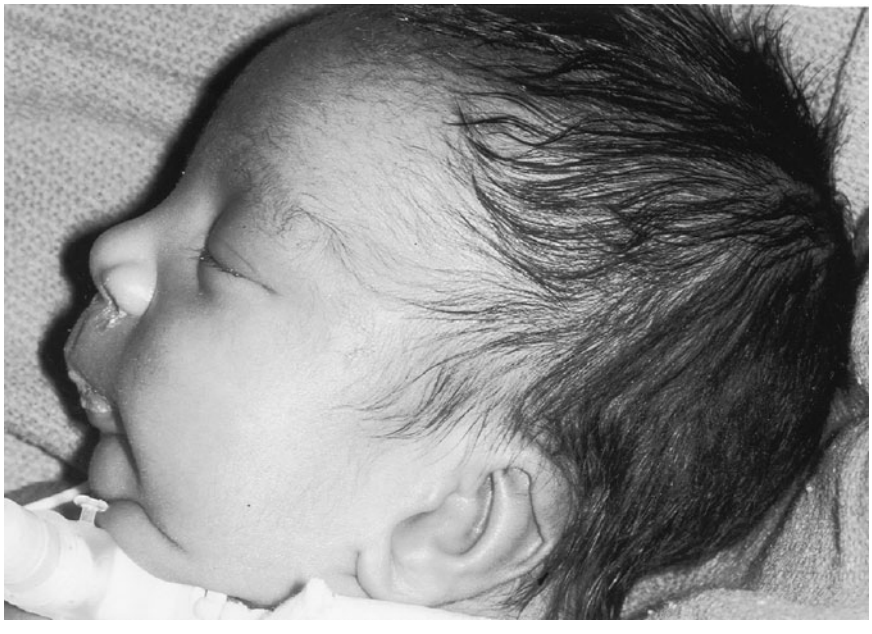

Figure 28-5 Infant depicted in Figure 28-3, who was delivered after a full-term gestation. He required immediate placement of a tracheostomy tube in the delivery room due to the inability to orally intubate him.

Infants with micrognathia should be closely examined for the presence of associated anomalies. If present, consultation with a medical geneticist is indicated. If a syndrome is under consideration, blood or skin fibroblasts should be obtained as a source of DNA for mutation analysis.

SURGICAL TREATMENT

There are multiple options for surgical treatment, including glossopexy (anchoring of the tongue to the mandible and lower lip) and tracheostomy. Most infants are given an initial trial of conservative management, but if multiple pneumonias develop, consideration should be given to performing tracheostomy to maintain the airway. Monroe and Ogo (1972) described their experience with 65 infants with micrognathia. Of these, nine had a tracheostomy tube placed for an average of 19.2 months. Two of these nine infants died. There was a very high incidence of associated abnormalities. They described the case histories of an additional seven patients who did not have a tracheostomy tube placed. These authors concluded that five of the deaths could have been prevented by performing tracheostomy. If the infant is failing to thrive because of difficulties with swallowing, gastrostomy tube placement may be considered to allow improved nutrition.

LONG-TERM OUTCOME

Monroe and Ogo (1972) reviewed records of 65 patients with micrognathia treated at the Children's Memorial Hospital in Chicago between the years 1950 and 1969. Eight deaths occurred in this group of patients. All were due to aspiration with or without pneumonia. Of the 65 patients, 51 (78%) failed to thrive. In addition, there was a high incidence of associated anomalies (56% of patients). These included congenital heart disease (14 patients), ear abnormalities (7), clubfoot (4), congenital hip dislocation (3), and syndactyly (3). Of the long-term survivors in the Bromley and Benacerraf (1994) study, one had Treacher Collins syndrome, one had Pierre Robin malformation, one had intrauterine growth restriction but is now normal, and one had multiple congenital anomalies but survived postsurgical repair.

The long-term outcome for many infants with micrognathia will depend on the extent and severity of the associated malformations. For the infant with isolated micrognathia, the potential for mandibular growth means that symptoms will potentially disappear over the first few years of life. If any long term concerns exist due to the child's physical appearance, orthodontic therapy and jaw advancement can be offered during adolescence (Kennett and Curran, 1973).

GENETICS AND RECURRENCE RISK

The recurrence risk for the syndromes listed in Table 28-2 with a known pattern of inheritance will be 25% or 50%, depending on whether the syndrome is autosomal recessive or dominant, respectively. Both parents should be examined, as it is possible that one of them has an undiagnosed syndrome. The recurrence risk for a fetal chromosomal abnormality will be 1%, or the age-related maternal risk, whichever is higher.

A few reports suggest that a single gene exists that predisposes to micrognathia or related orofacial defects. In one report, 10 of 65 patients with micrognathia had at least one family member with cleft palate (Monroe and Ogo, 1972). In another case report of a consanguineous Middle Eastern family (in which the parents were first cousins), three children with polyhydramnios and micrognathia were noted. This family apparently had an autosomal recessive gene that predisposed them to lethal micrognathia. All three fetuses affected by this condition died during the newborn period because of hyaline membrane disease and asphyxia. Amniography performed during pregnancy in affected infants showed that no contrast material was swallowed into the fetal intestinal tract (Berant et al., 1978).

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Microphthalmia/ Anophthalmia

29 CHAPTER

Key Points

- Microphthalmia, anophthalmia, and coloboma represent a spectrum of developmental anomalies of the eye known as MAC.
- Prevalence is 1 in 10,000 births. Approximately 10% of affected children have a chromosome abnormality. There may be an increased incidence of MAC in mothers older than age 40 and in multiple gestation.
- Nomograms exist for normal fetal eye measurements at 12 to 37 weeks' gestation. Refer for targeted fetal anatomical evaluation because of high likelihood of associated anomalies.
- Strongly associated with chromosome abnormalities and single-gene disorders.
- Karyotype is indicated. If bilateral anophthalmia is present, consider DNA testing for *SOX2* mutations.
- Refer for consultation with medical geneticist and pediatric ophthalmologist.
- Progress depends on severity of eye defects and presence of associated anomalies. Recurrence risk depends on syndromic diagnosis.
- Many developmental gene mutations are being identified as underlying basis of MAC.

CONDITION

Microphthalmia is one stage in a spectrum of developmental abnormalities that affect the eye, with coloboma at the milder end and anophthalmia at the severe end. Collectively the eye defect is known as MAC (microphthalmia, anophthalmia, coloboma). Although microphthalmia and anophthalmia can present as isolated findings, they are more commonly appreciated as part of syndromes involving multiple malformations (Bronshtein et al., 1991). Both are associated with abnormalities of the central nervous system.

Warburg (1993) proposed a phenotypic classification of microphthalmia that consists of three groups: genetic (monogenic and chromosomal), prenatally acquired (teratologic agents and intrauterine deformations), and associations. Genetic disorders commonly result in malformations of the eye, whereas prenatally acquired insults result in disruption or deformation of an initially normal eye.

The eye derives from three embryologic germ layers. Neuroectoderm gives rise to the optic vesicle; neural crest cells are responsible for migration to the anterior chamber of the developing eye. Ectoderm is responsible for the formation of the lens placode. Neuroectodermal and mesodermal

Table 29-1

Spectrum of Conditions Included in Microphthalmia

Total microphthalmia
Congenital cystic eye
Apparent anophthalmia
Simple microphthalmia
Microphthalmia with intraocular malformations (complex microphthalmia)
Congenital cataract
Anterior chamber malformation
Colobomata
Uveal
Optic nerve
Cystic
Multiple ocular malformations
Partial microphthalmia
Anterior segment
Posterior segment

cells participate in the closure of the optic fissure. The variety of cells and tissue types involved explains variability of phenotypic abnormalities of the eye (see Table 29-1) (Warburg, 1993). The embryonic optic fissure is formed from invagination along the inferior aspect of the optic cup and optic stalk at the 5- to-8-mm stage of gestation. This fissure allows the ingress of the hyaloid artery and egress of retinal axons through the optic nerve. In the normal eye, the embryonic optic fissure closes at 33 to 44 days after conception. If the fissure fails to fuse, a defect in the neuroectodermal and uveal tissues will be produced, forming a coloboma. The coloboma is a layer of sclera lined by maldeveloped neuroectoderm (Leatherbarrow et al., 1990). Colobomas of the uvea are frequently associated with microphthalmia and microcornea. Congenital cystic eye is a malformation that results from failure of invagination of the optic vesicle. Cysts frequently develop from proliferation of neuroectodermal tissue at the edge of the persistently open embryonic fissure. The optic cup originates from localized evagination of forebrain. The optic cup is the supporting framework for further optic development. Thus, conditions that result in abnormalities of the forebrain also potentially affect the optic cup (Weiss et al., 1989).

Microphthalmia is a deformity that results from arrest of ocular growth and development. The eye is considered microphthalmic at birth if its greatest diameter is smaller than 15 mm. The normal newborn eye has a diameter of 16 to 19 mm (Price et al., 1986). Anophthalmia results from a failure in development or early involution of the primary optic vesicle during the 2nd or 3rd week of gestation. In degenerative anophthalmia, the optic tract and vesicles develop normally initially, but subsequently undergo degeneration and result in severe microphthalmia. Because the lens depends on the optic vesicle for its differentiation, it is usually absent. In anophthalmia, the non-neuroectodermal structures are usually normally formed. Thus, the orbits, eyelids, cilia, lacrimal apparatus, conjunctiva, and extraocular muscles are usually normal (Figure 29-1).

INCIDENCE

A national birth registry in the United Kingdom noted a prevalence of either anophthalmia or microphthalmia of 1.0 per 10,000 births (Busby et al., 1998). Thirty-four percent

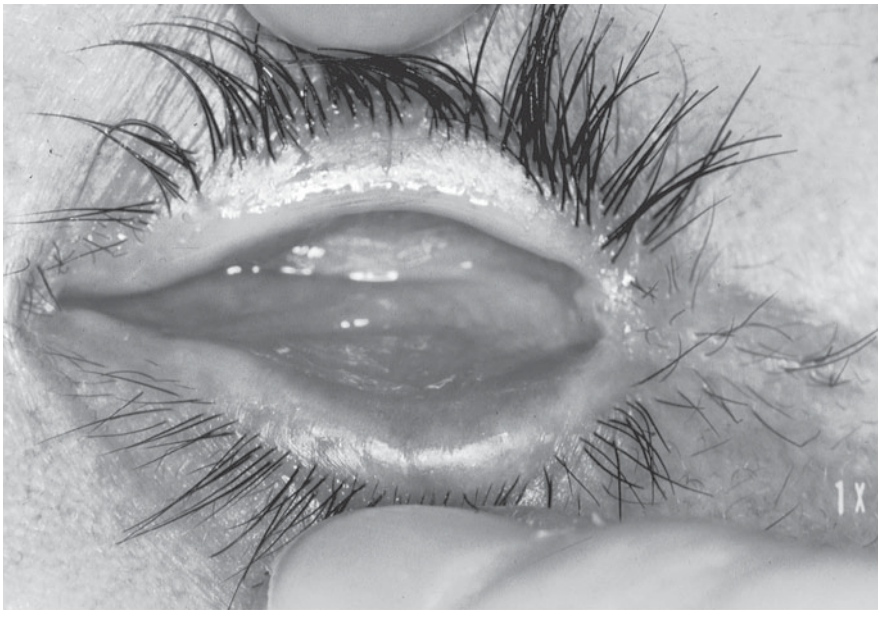

Figure 29-1 Absence of the globe with a normal appearance to the eyelids and eyelashes in anophthalmos. (*From Matsui H, Hayasaka S, Setogawa T. Congenital cataract in the right eye and primary clinical anophthalmos of the left eye in a patient with cerebellar hypoplasia.* Ann Ophthalmol *1993;25:315-318.*)

of affected infants had mild microphthalmia. Of the severely affected infants, 51% of cases were bilateral, other non-eye malformations were present in 65% of cases, and 72% had other eye malformations.

A Swedish health registry covering births during the years 1965 to 2001 observed a rate of 1.5/10,000 births for microphthalmia and 0.2/10,000 births for anophthalmia. Approximately 10% of the 432 children identified in this study had a chromosome abnormality (Källén and Tornquist, 2005). A recent epidemiologic study performed in California showed a twofold relative risk of bilateral anophthalmia if maternal age was 40 or more or if there was a multiple gestation (Shaw et al., 2005). After adjusting for other study factors, the relative risk was substantially lower if the mother has >12 years of education.

SONOGRAPHIC FINDINGS

The ability to measure the human fetal eye and orbits antenatally was first documented in 1982, when in two separate reports, sonographic measurements of fetal ocular diameters, interocular distance, and binocular distance were published (Jeanty et al., 1982; Mayden et al., 1982). Using transvaginal sonography, Bronshtein et al. (1991) detected fetal eyes within their orbits in 40% of screened fetuses at 11 weeks of gestation and 100% of fetuses at 12 weeks of gestation. They also noted the presence of a hypoechogenic ring that represented the fetal lens in 75% of fetuses at 12 weeks and 100% of fetuses at 14 weeks of gestation. Fetal eyelid motion was detectable by the beginning of the second trimester. This group recommended that the optimal section for the examination of the fetal eye is a transverse plane taken at the level of the skull at the orbits. An oblique tangential section taken from the fetal nasal bridge may detect hypoechogenic circles lateral to the nose consistent with the developing lens (Bronshtein et al., 1991).

Nomograms have been established for measurements of the fetal eye taken from 12 to 37 weeks of gestation using a combination of transvaginal and transabdominal high-resolution ultrasound techniques (Achiron et al., 1995). In this study, the fetal eye was evaluated by a coronal–facial view with the ultrasound probe positioned lateral to the fetal orbit. This group measured the transverse and superoinferior diameters of the vitreous, and the outer-edge to outer-edge measurement of the lens as a function of gestational age. Only one observer made the measurements, but three separate measurements were obtained on each fetal eye. An intraobserver variation of $3.1 \pm 1.5\%$ existed. This group studied 12 fetuses at risk for eye abnormalities and found 3 with vitreous and lens measurements above or below the 95% confidence intervals for gestational age (Achiron et al., 1995). An additional study documented the normal growth percentiles for intermalar and interethmoidal distances from 10 to 40 weeks of gestation (de Elejalde and de Elejalde, 1985).

Although routine study of the fetal face with prenatal sonography is recommended by most professional organizations, current guidelines do not recommend routine views of the fetal orbits or eyes (American College of Obstetricians and Gynecologists, 2008). Microphthalmia, even in the setting of a fetal face examination, may be difficult to detect antenatally. Bronshtein et al. (1991) reported two false-negative results for fetuses at prior genetic risk for microphthalmia. The sonographic diagnosis of anophthalmia can be equally challenging. Abnormalities in the fetal orbits are more easily recognized than abnormalities in the fetal globe. A specific finding appears to be flattened or concave eyelids when the fetal globes are missing (Figure 29-2).

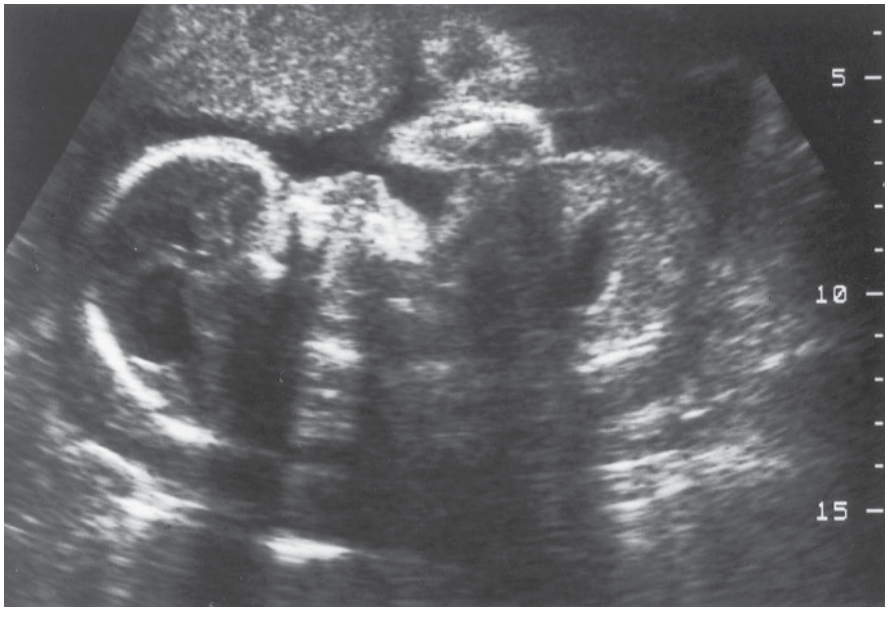

Figure 29-2 Antenatal sonogram, performed at 27 weeks of gestation, demonstrating anophthalmia and severe midface hypoplasia in a fetus with trisomy 13.

Table 29-2

Etiologic Classification of Microphthalmia

Genetic		Prenatally Acquired		Unknown	
Malformations and syndromes		Disruptions		Deformations	Associations
Single-gene disorder	Chromosomal abnormality	Drugs/radiation	Maternal disease	Encephalocele	VATER
Autosomal dominant Autosomal recessive CHARGE X-linked	Trisomy 13 Trisomy 18 18p− 13q− 4p− Triploidy Other deletions/duplications	Ionizing radiation (4–11 wk) Ethanol Thalidomide Isotretinoic acid	Diabetes Cytomegalovirus Rubella Toxoplasmosis Parvovirus B19 Influenza	Tumors	

Modified, with permission, from Warburg M. Classification of microphthalmos and coloboma. J Med Genet. *1993;30:664-669.*

DIFFERENTIAL DIAGNOSIS

The major consideration in the differential diagnosis is to determine whether the eye defects are isolated or part of a syndrome or association. Table 29-2 lists the etiologic classification of MAC. If the condition is isolated, it is important to determine whether other family members are also affected. Many chromosomal abnormalities include eye defects as part of a multiple congenital anomaly syndrome; trisomy 13 is one of the more common ones (Allen et al., 1977). MAC can be the consequence of exposure to certain drugs, ionizing radiation, or infectious agents. MAC can also be due to single-gene multiple congenital abnormality syndromes (Table 29-3), including Walker–Warburg syndrome (Crowe et al., 1986; Dobyns et al., 1990), Fraser syndrome (Schauer et al., 1990; Berg et al., 2001), Meckel–Gruber syndrome (Bateman, 1983), cerebro-oculo-facio-skeletal syndrome (Paladini et al., 2000), Lenz syndrome (Traboulsi et al., 1988), focal dermal hypoplasia (Goltz syndrome) (Gottlieb et al., 1973), Norrie disease, Hallermann–Streiff syndrome, oculodentodigital syndrome, frontonasal dysplasia, Fryns syndrome (Pierson et al., 2004), and microphthalmia with linear skin defects (Morleo et al., 2005). Any fetus diagnosed with MAC should have consideration of specific studies performed to rule out holoprosencephaly (see Chapter 14; Artman and Boyden, 1990). MAC can result from masses, such as encephalocele and tumors, pressing on the developing eye. Finally, MAC is seen in associations of congenital anomalies, such as CHARGE and VATER.

ANTENATAL NATURAL HISTORY

The overall fetal prognosis will depend to a large extent on the underlying cause of the microphthalmia or anophthalmia. Fetuses that have isolated eye malformations do well during gestation. Fetuses that have an underlying chromosomal abnormality will have a much worse prognosis. In a Japanese study, Amemiya and Nishimura (1977) studied 60 intact human fetal specimens that were selected on the basis of the presence of nonocular abnormalities. This study showed a very high association of eye abnormalities with other malformations. Overall, 18 (30%) of the fetuses had eye malformations and 12 (16.7%) had an asymmetric insertion of the recti muscles that would predispose the infant to severe strabismus later in life. The incidence of ocular malformation in fetuses with heart abnormalities was 40%, and central nervous system abnormalities was 37.5%. Abnormalities in the endocrine organs had a 31.6% chance of having associated ocular malformations. This study suggested that when severe malformations of other organs were detected early in fetal life, a specific study of the fetal eye was also indicated.

Microphthalmia is one of the most common consequences of ionizing radiation delivered to the pregnant woman. In a review of 26 cases of pregnant women who received large doses of radiation during pregnancy, Dekaban (1968) demonstrated that the fetus was especially vulnerable to development of severe microphthalmia between 4 and 11 weeks of gestation. Radiation after 12 weeks resulted in microcephaly, severe brain abnormalities, and growth restriction, but after 12 weeks the eyes were relatively protected. Maternal TORCH infections (herpes, varicella, and cytomegalovirus) are associated with MAC. More recently, maternal parvovirus B19 and influenza infection have also been shown to be positively associated with anophthalmia/microphthalmia (Busby et al., 2005). Any condition that affects development of the forebrain, such as maternal diabetes or maternal ingestion of ethanol, will also put the fetus at risk for abnormal eye development.

Table 29-3

Syndromes Associated with Microphthalmia

Syndrome	Associated Findings	Inheritance
Walker–Warburg	Pachygyria, cerebellar hypoplasia encephalocele, Dandy–Walker cyst, hydrocephalus, cataract	Autosomal recessive
Fraser	Mental retardation, syndactyly, genital abnormalities	Autosomal recessive
Meckel–Gruber	Microcephaly, encephalocele, polydactyly, cystic renal dysplasia, cleft lip and palate	Autosomal recessive
Cerebro-oculo-facio-skeletal	Microcephaly, cataracts, micrognathia, flexion contractures	Autosomal recessive
Fryns	Coarse face, cleft lip and palate, diaphragmatic hernia, genital malformations	Autosomal recessive
Lenz	Microcephaly, mental retardation, digital, skeletal, dental abnormalities	X-linked
Focal dermal hypoplasia (Goltz)	Microcephaly, syndactyly, skin lesions, dental anomalies	X-linked (lethal in males)
Microphthalmia with linear skin defects	Linear skin defects	X-linked
Norrie	Cataracts, deafness, mental retardation	X-linked
Hallermann–Streiff	Brachycephalus, micrognathia, cataracts, thin small nose, skin atrophy, hypotrichosis	Autosomal recessive
Oculodentodigital	Small nares, enamel hypoplasia, syndactyly, sparse hair	Autosomal dominant
Frontonasal dysplasia (median cleft face)	Hypertelorism, defect in midline frontal bone, cleft lip, notched nose	Unknown

MANAGEMENT OF PREGNANCY

Microphthalmia and anophthalmia are more commonly seen as part of a multiple malformation syndrome than as an isolated finding. In one study, six of eight cases of ocular malformations were associated with intracranial defects or other organ malformations (Bronshtein et al., 1991). It is therefore important to refer a patient in whom fetal microphthalmia is suspected to a center experienced in the detection of congenital malformations. In addition, a referral center is more likely to be familiar with the normal measurements of the fetal eye (Achiron et al., 1995). It is important to obtain a history from the mother regarding medication exposures, ethanol ingestion, and the results of glucose-tolerance testing to rule out maternal diabetes as a cause for microphthalmia. Isotretinoic acid, a commonly prescribed acne medication, can cause microphthalmia, so consideration should be given to the possibility of exposure to this medication in teenage patients or in older patients with severe cystic acne.

In the setting of isolated eye defects, it is important to examine both parents and to ask specifically about the history of visual difficulties and/or consanguinity. Because of the rarity of MAC and its association with severe abnormalities, we recommend obtaining a fetal karyotype to rule out the large number of chromosomal abnormalities that can result in microphthalmia. We also recommend obtaining TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes virus) titers.

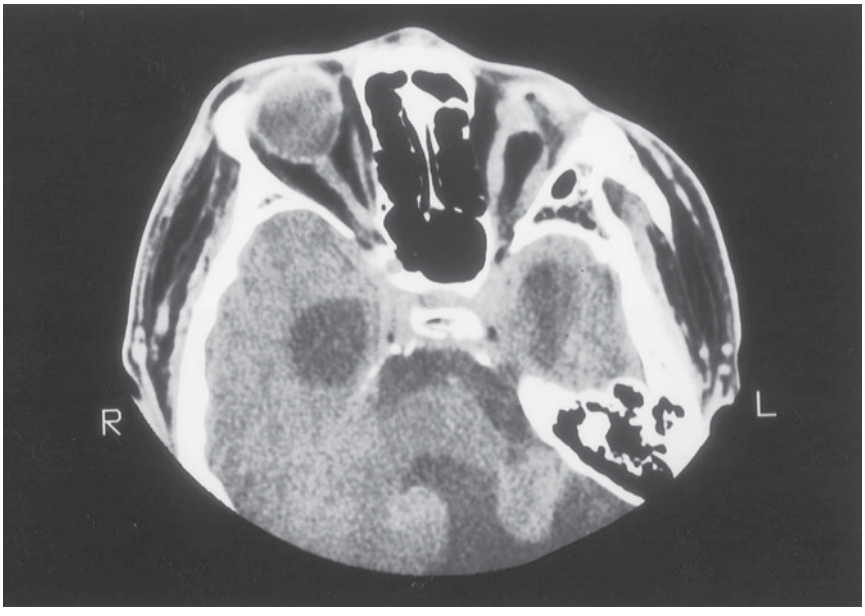

Figure 29-3 Postnatal CT scan showing, on the patient's left side, a small nodular mass with well-developed extraocular muscles in a case of primary anophthalmia. A normal eye is present on the right. (*From Matsui H, Hayasaka S, Setogawa T. Congenital cataract in the right eye and primary clinical anophthalmos of the left eye in a patient with cerebellar hypoplasia.* Ann Ophthalmol *1993;25:315-318.*)

FETAL INTERVENTION

There are no fetal interventions indicated for microphthalmia or anophthalmia.

TREATMENT OF THE NEWBORN

The newborn with unilateral or bilateral anophthalmia should have a complete physical examination to rule out associated congenital anomalies. A computed tomographic (CT) or magnetic resonance imaging (MRI) scan should be performed (Figure 29-3). If a fetal karyotype was not performed antenatally, it should be done postnatally. TORCH titers (if not obtained antenatally) should be performed on mother and infant. Newborn urine should be collected for cytomegalovirus culture. DNA should be analyzed for the presence of *SOX2* mutations, which are found in approximately 11% of individuals with bilateral anophthalmia (Fantes et al., 2003). A medical genetics consultation should be obtained. Consultation with a pediatric ophthalmologist should also be obtained to discuss plans for prosthetic fitting and plastic surgery.

Microphthalmia can be a subtle finding that can be missed during the newborn period. Asymmetry of the globes or an abnormal red reflex should prompt a pediatric ophthalmologic consultation. A newborn that has microphthalmia and a corneal diameter of 5 mm or less has a very poor prognosis for useful vision (Elder, 1994). The globe serves as a scaffold for further development of eyelids. Infants who have had severe microphthalmia in utero will have foreshortening of the palpebral fissure and flattening of the eyelids. The abnormal appearance becomes more apparent as facial growth occurs over the first year of life. Price et al. (1986) recommend fitting infants who have unilateral microphthalmia with cosmetic scleral shells. This permits the development of a symmetric ocular appearance without any need for surgery. They recommend initial fitting of the prosthesis at 2 months of age, with refittings twice or more yearly during the first 2 years of life. The adult eye size is normally reached at age 13 years, so fittings are required only throughout the childhood years.

SURGICAL TREATMENT

The normal development of the orbital region depends on orbital growth. Anophthalmia or severe microphthalmia leads to severely underdeveloped bony orbital growth and overall facial development (Chen and Heber, 2004). The resulting facial asymmetry is usually apparent at birth. The normal infant eye is approximately 70% of its adult size and grows most rapidly during the first 12 months of life. Therefore the long-term goal is to create a suitable pocket for a cosmetically acceptable prosthesis. Treatment usually consists of tissue expanders, orbital implants, and orbital reconstruction (Chen and Heber, 2004).

When microphthalmia is present with a cyst, the cyst may be aspirated repeatedly or surgically excised. Enucleation should be performed only if the cyst aspiration is unsuccessful. Once the eye is enucleated, laser orbital and eyelid reconstruction will become necessary. A lensectomy can be performed for congenital cataract if present. Corneal transplantation has successfully restored vision in some infants with microphthalmia (Feldman et al., 1987).

LONG-TERM OUTCOME

In a review of 15 patients with anophthalmia, those who had prosthetic therapy initiated during the first year of life had acceptable cosmetic results (Figure 29-4) (O'Keefe et al., 1987).

Figure 29-4 Patient with unilateral anophthalmos treated with early prosthetic therapy but no surgical eyelid revisions, demonstrating an acceptable cosmetic result. (*From O'Keefe M, Webb M, Pashby RC, et al. Clinical anophthalmos.* Br J Ophthalmol. *1987;71: 635-638.*)

Elder (1994) described 27 patients with bilateral microphthalmia, who had visual acuity of less than 6/60. All patients had nystagmus. Of the 27, 12 had congenital cataracts as their primary cause of blindness. An additional 6 had chorioretinal colobomas; 2 had degenerative myopia. There was no light perception in 8 of the 27. This study was performed in a very poor Middle Eastern area, where patients had no access to surgical treatment. Most patients with microphthalmia have high hyperopia and require lens correction. During adulthood, microphthalmic eyes are at high risk for glaucoma, retinal detachment, and spontaneous uveal effusion (Weiss et al., 1989). A retrospective follow-up study of 30 children with microphthalmia revealed that 7 had mental retardation, but a surprisingly high number of the others were described as extremely good students (Whiteman and Crawford, 1980). Long-term follow-up by a pediatric ophthalmologist is recommended.

GENETICS AND RECURRENCE RISK

Isolated microphthalmia usually occurs sporadically, although there have been reports of autosomal dominant inheritance (Vingolo et al., 1994) and autosomal recessive inheritance in a large inbred Arab kindred (Kohn et al., 1988), a Swiss Anabaptist kindred (Cross and Yoder, 1976), and an Iranian Jewish inbred community (Zlotogora et al., 1994). Additionally, X-linked forms have been reported (Warburg, 1981). Shulman et al. (1993) described a family initially thought to have microphthalmia presenting as an autosomal recessive condition, but later found to be autosomal dominant with incomplete penetrance.

Multiple chromosomal abnormalities have been associated with microphthalmia. These include triploidy; trisomies 13 and 18; deletion of the short arm of chromosome X (Xp22.2 to ter) (Ogata et al., 1998; Temple et al., 1990); deletion of 4p−, 4q−, 13q− (Gul et al., 2005), ring 13, ring 18q−, and 18 ring; and duplications of 4q+, 7p+, 9+, 10q+, 13q+, 22q+, and partial trisomy 22. In addition, microphthalmia has been found in at least 10 patients with trisomy 4p (Lurie and Samochvalov, 1994). Common chromosomal abnormalities to be suspected in the setting of microphthalmia with coloboma are trisomy 13, 13q−, triploidy, and trisomy 4p.

Many single gene (Mendelian disorders) are associated with microphthalmia and anophthalmia. Any patient with MAC should be referred to a medical genetics unit for complete pedigree interpretation and counseling regarding recurrence risk. Specific genetic counseling will depend on the underlying cause of the eye defect. If unbalanced chromosomal abnormalities are detected, parental blood samples should be obtained to study the parental karyotypes. Infants with MAC should be examined by a clinical geneticist to seek additional dysmorphic features to permit diagnosis of a genetic syndrome.

Recently, mutations in a number of developmental genes have been shown to be the cause of anophthalmia or microphthalmia. These include *SOX2*, *CHX10*, *RAX*, and *SIX3*. *PAX6* is considered to be a master control gene in eye development; mutations in *PAX6* and *PAX2* are more likely to result in colobomas than anophthalmia or microphthalmia (Morrison et al., 2002). *SOX2* is a transcription factor expressed in the early developing eye and nervous system. De novo heterozygous mutations in *SOX2* are present in 11% of individuals with bilateral anophthalmia (Fantes et al., 2003). Furthermore, it is now recognized that there are consistent nonocular abnormalities associated with *SOX2* mutations, including brain malformations, mild facial dysmorphism, seizures, learning disability, postnatal growth failure, and male genital abnormalities (Ragge et al., 2005). *SOX2*

mutation analysis is recommended for fetuses with bilateral anophthalmia. *CHX10* mutations are associated with an autosomal recessive syndrome of microphthalmia/anophthalmia that presents with iris colobomas and cataracts (Percin et al., 2000; Bar-Yosef et al., 2004).

The mouse microphthalmia (mi) gene encodes a protein whose mutations result in early onset deafness, reduced eye size, and loss of pigmentation in the eye, inner ear, and skin. A human homolog of this gene exists, microphthalmia-associated transcription factor gene, *MITF*, which maps to human chromosome 3p12–14 (Tachibana et al., 1994). *MITF* is responsible for Waardenburg syndrome, type 2, a dominantly inherited disorder with sensorineural hearing loss and heterochromic irides but no microphthalmia (Hughes et al., 1994). The gene for microphthalmia with linear skin defects (MLS) has been cloned and mapped to chromosome Xp22 (Ogata et al., 1998; Wapenaar et al., 1993; Morleo et al., 2005).

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Congenital High Airway Obstruction Syndrome

30
CHAPTER

Key Points

- Congenital high airway obstruction syndrome (CHAOS) is characterized by bilaterally enlarged lungs, flat or inverted diaphragms, dilated tracheobronchial tree, and massive ascites due to complete airway obstruction.
- CHAOS is often mistaken for bilateral congenital pulmonary airway malformations.
- MRI is helpful in diagnosing CHAOS and excluding potential associated findings.
- CHAOS can be associated with syndromes such as Fraser syndrome.
- The natural history of CHAOS may be divided in thirds: 1/3 die in utero; in 1/3 the hydrops remains stable; and in 1/3 the hydrops resolves following spontaneous perforation.
- Fetoscopic treatment of the tracheal or laryngeal obstruction is possible in select cases.
- EXIT procedure is indicated to deliver all cases of CHAOS due to critical airway obstruction.

CONDITION

Congenital high airway obstruction syndrome (CHAOS) is a prenatally diagnosed clinical syndrome manifested by the presence of extremely large echogenic lungs, flattened or inverted diaphragms, a dilated tracheobronchial tree, ascites, and other manifestations of nonimmune hydrops due to complete obstruction of the fetal airway (Hedrick et al., 1994). No fetus diagnosed prenatally with CHAOS associated with hydrops and complete airway obstruction has survived without intervention. The exception to this occurs when there is spontaneous perforation of the laryngeal or tracheal atresia, which may occur in up to one-third of cases and results in resolution of the hydrops.

The airway obstruction in CHAOS may be due to one of several causes, including laryngeal atresia, tracheal atresia, or laryngeal cyst, but the fetal clinical presentation is the same. Three types of laryngeal atresia are recognized: type I, in which the supraglottic and infraglottic parts of the larynx are atretic; type II, in which the atresia is infraglottic; and type III, which is glottic. A wide range of anomalies can be seen in association with laryngeal atresia (Table 30-1). Some fetuses, however, have atresia as an isolated anomaly (Fox and Crocker, 1964).

INCIDENCE

Congenital obstruction of the fetal airway resulting in CHAOS was initially thought to be extremely rare (Hedrick et al., 1994). Only 55 cases of this syndrome have been reported since 1989 (Wigglesworth et al., 1987; Delechotte et al., 1988; Silver et al., 1988; Tournier et al., 1988; Arizawa et al., 1989; Fang et al., 1989; Scurry et al., 1989; Didier et al., 1990; Schauer et al., 1990; Watson et al., 1990; Richards et al., 1992;

Table 30-1

Anomalies Associated with CHAOS

Hydrocephalus malformation of the aqueduct of Sylvius
Vertebral anomalies
Absent radius
Bronchotracheal fistula
Esophageal atresia
Tracheoesophageal fistula
Syndactyly
Genitourinary anomalies
Uterine anomalies
Imperforate anus
Cardiac anomalies
Anophthalmia

Weston et al., 1992; Hedrick et al., 1994). However, this syndrome may be more common than generally appreciated because many of the affected fetuses die in utero or are stillborn (Fox and Crocker, 1964; Smith and Bain, 1965; Cohen, 1971; Wigglesworth et al., 1987; Fang et al., 1989; Scurry et al., 1989; Schauer et al., 1990; Watson et al., 1990; Richards et al., 1992). The true incidence of this syndrome is unknown.

SONOGRAPHIC FINDINGS

The sonographic findings of CHAOS are due to complete obstruction of the upper airway. The lungs normally produce fluid that leaves the trachea at a rate estimated at 4 mL per kilogram of body weight per day as a result of fetal breathing movements. Complete obstruction of the upper trachea or larynx results in elevated intratracheal pressure and distention of the tracheobronchial tree due to accumulation of fetal lung fluid. The lungs become distended and appear sonographically to be extremely echogenic and diffusely enlarged (Tournier et al., 1988; Watson et al., 1990; Richards et al., 1992; Weston et al., 1992; Hedrick et al., 1994). The diaphragm becomes inverted and the mediastinal structures compressed (Figure 30-1). The heart may appear elongated, with a shift in its axis, and the chambers small and compressed by the large lungs (Figure 30-2). The dilation of the tracheobronchial tree can be traced up to the larynx or level of the tracheal obstruction. In a rare form of CHAOS, there may

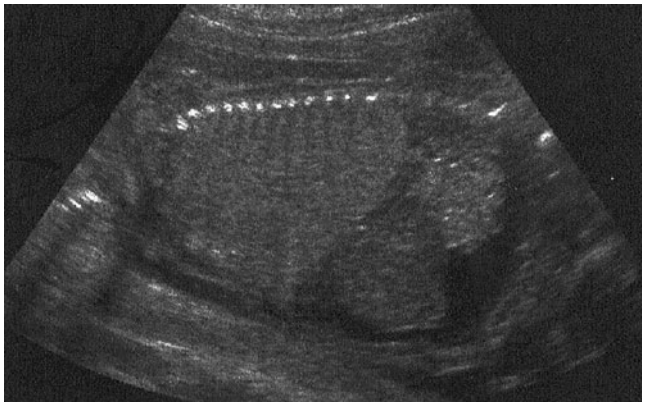

Figure 30-1 Sagittal sonographic image of a fetus with CHAOS at 20 weeks of gestation demonstrating extremely large homogenously echogenic lungs with inversion of the diaphragm.

be complete absence of the trachea (Vaikunth et al., 2009). In advanced cases, signs of nonimmune hydrops, including ascites, placentomegaly, and anasarca may be seen as a result of compromised venous return to the heart. Polyhydramnios may also be observed secondary to esophageal compression. The fetus with CHAOS may also exhibit qualitatively abnormally vigorous breathing movements. Baarsma et al. (1993) observed that a fetus with complete laryngeal atresia exhibited high-amplitude vigorous jerky breathing movements as it tried in vain to move tracheal fluid through an atretic larynx.

The cause of CHAOS may vary from laryngeal or tracheal obstruction or stenosis to an intraluminal web or cyst (Figure 30-3). However, it may be difficult, if not impossible, to distinguish these conditions sonographically. Recently, the use of half-Fourier acquisition single shot turbo spin echo sequence (HASTE) and echoplanar magnetic resonance imaging (MRI) has aided in the diagnosis of CHAOS. In the report by Crombleholme et al. (2000), fetal MRI was helpful in excluding bilateral cystic adenomatoid malformation as well as determining the level of obstruction (Figure 30-4).

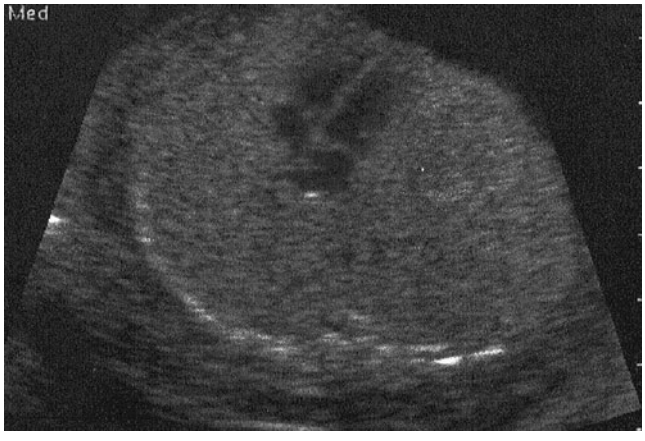

Figure 30-2 Cross-sectional view of same fetus in Figure 30-1, demonstrating extremely large echogenic lungs with narrowed compressed mediastinum and elongated heart.

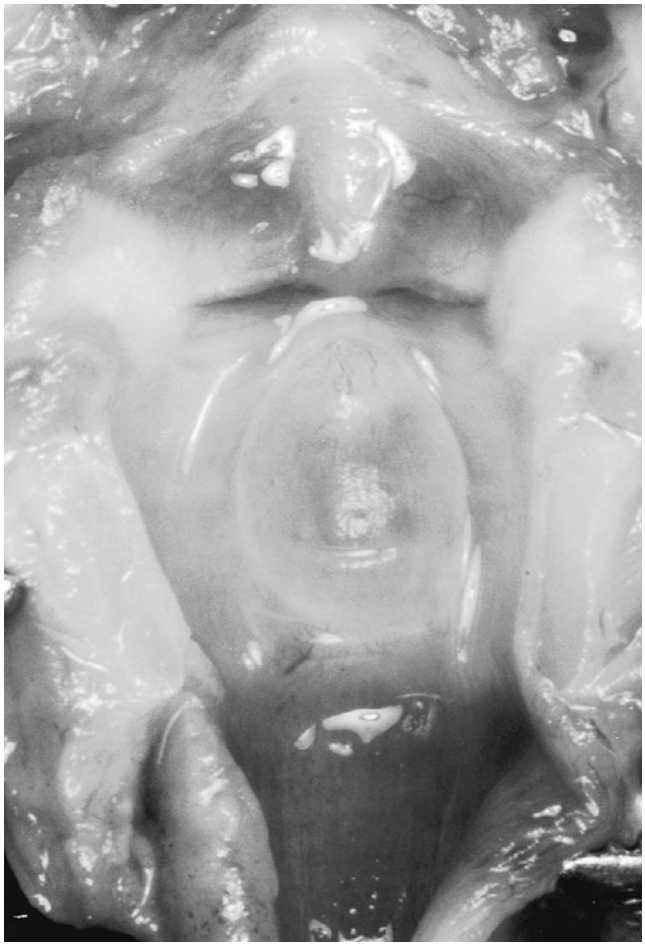

Figure 30-3 Autopsy of a 23-week-old fetus with CHAOS due to laryngeal cyst occluding the airway. The posterior view of the trachea and larynx is shown, with the back wall completely opened to reveal the laryngeal cyst.

DIFFERENTIAL DIAGNOSIS

The main diagnosis mistaken for CHAOS is bilateral cystic adenomatoid malformation (see Chapter 35). This is an even rarer finding than CHAOS, as cystic adenomatoid malformation is usually lobar, not involving the entire lung, and less than 2% of cases are bilateral. Cases of CHAOS are commonly misdiagnosed as bilateral CCAMS and this should raise suspicion that the diagnosis may, in fact, be CHAOS. An important distinguishing feature is the compressed rim of normal lung that can usually be seen in cystic adenomatoid malformation but not in CHAOS. The uniformly echogenic lungs, which are massively enlarged and associated with flattened or inverted diaphragms, a compressed mediastinum, and dilated trachea and mainstem bronchi allow CHAOS to be distinguished from cystic adenomatoid malformation.

CHAOS may be one fetal presentation of Fraser syndrome (cryptophthalmos–syndactyly syndrome) (see Chapter 29). This inherited disorder is characterized by variable expression of cryptophthalmos, renal agenesis, syndactyly, abnormalities of ears and external genitalia, and laryngeal stenosis or atresia (Fraser, 1962; Schauer et al., 1990). This syndrome has only been correctly diagnosed twice during the second trimester (Schauer et al., 1990; Feldman et al., 1995). Often a previously affected pregnancy will prompt sonographic surveillance for Fraser syndrome. The sonographic features of cryptophthalmos, renal agenesis, and syndactyly in a fetus with CHAOS suggest the diagnosis of Fraser syndrome.

ANTENATAL NATURAL HISTORY

Our understanding of the natural history of CHAOS is limited by the rarity of this entity. Only 48 cases of complete laryngeal

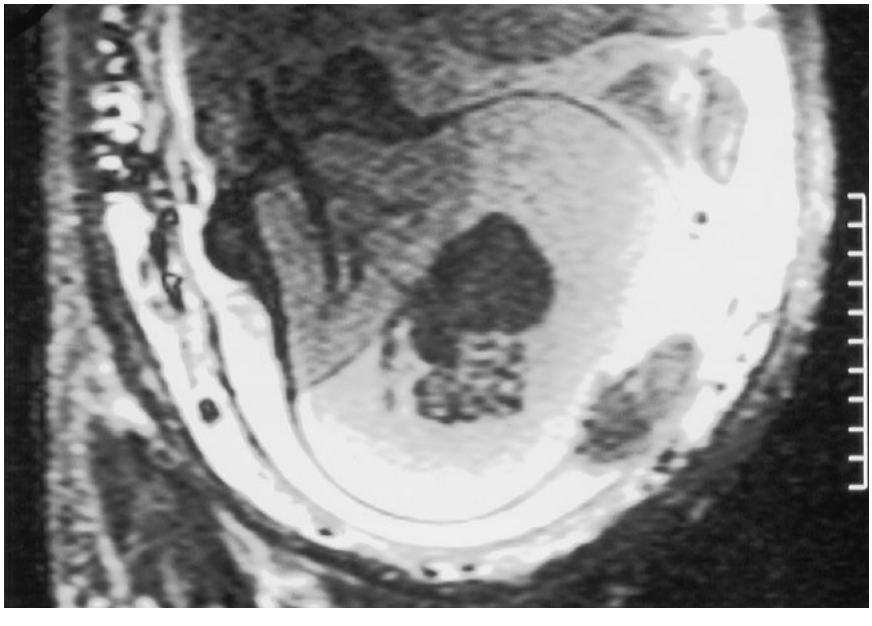

Figure 30-4 Fetal MRI demonstrating massively enlarged lungs, dilated tracheobronchial tree, inverted diaphragms, and massive ascites.

atresia and CHAOS have been reported to date. In 10 of these cases, the fetus was stillborn, suggesting that the fetus may be compromised in utero, not just at birth (Fox and Crocker, 1964; Smith and Bain, 1965; Cohen, 1971; Wigglesworth et al., 1987; Fang et al., 1989; Scurry et al., 1989; Schauer et al., 1990; Richards et al., 1992). Postnatal survivors with laryngeal atresia have been rare. Among the 16 most recently reported cases of prenatally diagnosed CHAOS, only 1 patient survived the immediate postdelivery period. In contrast to the nonsurvivors, this patient had incomplete subglottic stenosis, which may have lessened the effects of airway occlusion and contributed to the patient's survival.

A fetus identified with sonographic features of CHAOS should be presumed to be at significant risk of intrauterine fetal death and faces a high mortality should the pregnancy progress to delivery. Diagnosis in the middle of the second trimester appears to correlate with poor outcome. At least one case has been reported in which a 23-week-old fetus presented with CHAOS and polyhydramnios and fetal ascites, but no other manifestations of nonimmune hydrops. However, at 30 weeks of gestation, the amniotic fluid volume normalized and the ascites resolved. At birth, the infant was found to have a severe subglottic stenosis with only a 1-mm hole allowing passage of lung fluid (Richards et al., 1992).

Malformations of the esophagus and trachea, including tracheoesophageal fistula, which are commonly associated with laryngeal atresia, allow decompression of the obstructed tracheobronchial tree. With CHAOS, these fetuses are more commonly present at birth, as opposed to in utero.

The fetus with the characteristic features of diffusely enlarged lungs, polyhydramnios, and nonimmune hydrops is at high risk for perinatal death if no intervention takes place. Only one case has been reported in which CHAOS accompanied by ascites at 23 weeks of gestation progressed to delivery. Crombleholme et al. (2000) reported a case of CHAOS associated with massive ascites and other features of nonimmune hydrops at 20 weeks. The infant delivered by the ex utero intrapartum treatment (EXIT) procedure 11 weeks later. A fetus in the middle of the second trimester with isolated CHAOS presents a dilemma, as there is insufficient information about this condition to predict with certainty that fetuses will progress to hydrops and intrauterine fetal death versus premature delivery because of polyhydramnios, or will spontaneously perforate with resolution of hydrops.

Clinical experience suggests that fetuses diagnosed with CHAOS fall into one of three categories. Approximately one-third will develop progressive nonimmune hydrops and die in utero. Another third will spontaneously perforate through the tracheal or laryngeal atresia or less commonly decompress via a tracheoesophageal fistula. The remaining third tolerate hydrops reasonably well and remain hydropic until 30 to 32 weeks' gestation, at which point preterm labor or fetal distress prompt the need for an EXIT procedure.

A fetus presenting in the third trimester with CHAOS but without associated anomalies or hydrops likely has incomplete obstruction and will do well until delivery by EXIT procedure. These fetuses need to be managed by the EXIT procedure to secure the airway while being maintained on placental support, as laryngoscopy, bronchoscopy, and tracheostomy will be required immediately prior to delivery.

MANAGEMENT OF PREGNANCY

The fetus presenting with CHAOS should have a detailed sonographic examination to determine if there are associated anomalies present (see Table 30-1). Of particular interest are the features of Fraser syndrome, including cryptophthalmos, syndactyly, and genitourinary anomalies (see Chapter 29). An echocardiogram should be obtained because of the possibility of structural heart disease. A karyotype analysis should also be obtained to rule out aneuploidy or other serious chromosomal abnormalities that might preclude fetal intervention. The fetus should be followed closely for early signs of hydrops. Consultation with a medical geneticist and a pediatric surgeon is indicated.

Delivery in a tertiary care center experienced with the EXIT procedure is indicated. Under deep general anesthesia, which allows uterine relaxation and preserves uteroplacental circulation, a bloodless hysterotomy is performed using a uterine stapling device and the fetal head and chest are delivered in order to secure an airway (Figure 30-5). Stable uteroplacental gas exchange can be maintained for up to 60 minutes while an airway is secured (Liechty et al., 1997; Crombleholme et al., 2000). Previous reports in which vaginal delivery was performed without clamping the cord, to allow an airway to be secured, did not preserve uteroplacental circulation. Similarly, standard cesarean delivery results in uterine contraction and loss of uteroplacental circulation. Once the fetus is delivered, there is uterine contraction that shuts down uteroplacental gas exchange. During the EXIT procedure, laryngoscopy is performed initially to evaluate the larynx. In most instances, the level of obstruction will be distal to the vocal cords, and attempts to pass an endotracheal tube will be unsuccessful. Bronchoscopy should then be performed. The obstruction may be due to a simple laryngeal cyst or web, which may be amenable to bronchoscopic disruption, allowing passage into the trachea (Sylvester et al., 1998). If these efforts are unsuccessful, a formal tracheostomy should be performed. Once an airway is secured, the cord is clamped and the infant is handed over to the neonatologists. It is crucial that the timing of the delivery of the baby, after obtaining an airway, is carefully orchestrated with the anesthesiologist, because uterine relaxation is essential for an EXIT procedure. After delivery of the baby and placenta, massive uterine bleeding may occur unless uterine tone is rapidly reestablished. This is best accomplished by turning off the halogenated anesthetic agent to allow uterine tone to return to normal, as well as beginning an oxytocin infusion. After the infant and placenta are delivered, vigorous massage of the uterus stimulates contraction and minimizes blood loss (Langer et al., 1992; Skarsgard et al., 1996; Mychatisha et al., 1997; Sylvester et al., 1998).

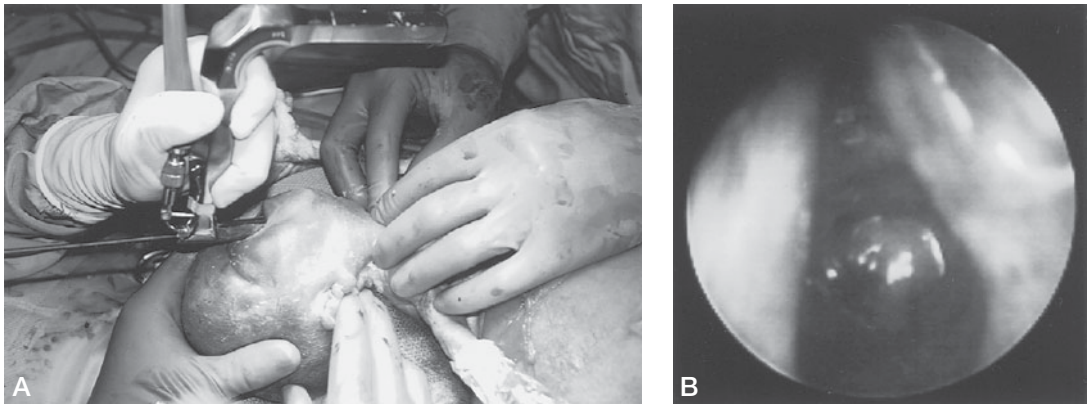

Figure 30-5 EXIT procedure for a fetus with CHAOS at 31 weeks of gestation. **A**. The fetus is monitored by pulse oximetry while undergoing laryngotracheoscopy. **B**. The tracheoscopic view of the obstructing tracheal atresia.

Crombleholme et al. (2000) reported the first successful salvage and long-term survival of a fetus with CHAOS due to complete tracheal atresia. The fetus was originally diagnosed with bilateral cystic adenomatoid malformation of the lung and nonimmune hydrops at 19 weeks of gestation. Although intrauterine fetal death was anticipated, 12 weeks after diagnosis the fetus was doing well, albeit with massive ascites and severe polyhydramnios. The EXIT procedure, performed at 31 weeks of gestation, demonstrated complete tracheal occlusion due to subglottic atresia (see Figure 30-5). A tracheostomy was performed and the newborn did well, requiring ventilatory support due to diaphragmatic dysfunction, but was weaned to room air in 24 hours. The child is developing normally now at 10 years of age.

FETAL INTERVENTION

The pathophysiology of CHAOS has been reproduced in a fetal lamb model (Crombleholme and Albanese, 2000). Tracheal ligation at 80 days of gestation produces extremely large hyperplastic fetal lungs, with secondary nonimmune hydrops and polyhydramnios. The fetal lambs die in utero if left untreated. Release of the tracheal ligation in utero reverses these changes and allows the lambs to be delivered at term. Fetal surgery to correct the airway obstruction has been performed by Kohl, et al. (2006). In this 25-week gestation fetus with characteristic signs of CHAOS, a fetoscopic laryngoscopy was performed. A balloon catheter was passed through the obstruction and pulled back. The catheter passed easily, which suggests that in this case, spontaneous perforation had already occurred and resolution of hydrops was due to the spontaneous perforation and not the fetoscopic procedure. Despite the likely spontaneous relief of obstruction, this case demonstrates the feasibility of treating CHAOS in utero. S. Hirose (personal communication, September 12, 2008) reported a similar case in which fetoscopic laryngoscopy allowed passage of a guide wire across the tracheal atresia. The importance of conversion of complete airway obstruction to partial airway obstruction should not be underestimated. In both instances an EXIT procedure will be necessary, but resolution of hydrops results in a much more easily managed premature infant. The baby with CHAOS has a profound capillary leak syndrome that may take weeks to resolve, with severe respiratory distress syndrome, hepatic and gastrointestinal dysfunction, all of which may contribute to significant morbidity and mortality. In marked contrast, the fetus with complete tracheal or laryngeal atresia and resulting CHAOS that spontaneously perforates or is fetoscopically decompressed will have resolution of hydrops and will be remarkably stable at birth. These infants do not have capillary leak syndrome, or respiratory distress, and are quite stable. Often their most significant clinical problem is diaphragmatic dysfunction due to stretch injury from massive lung enlargement and diffuse tracheobroncheomalacia due to softening of cartilage from distention of the trachea. Because of the possibility of a simple laryngeal web or cyst, in utero bronchoscopy should be performed first. If a more significant airway obstruction exists, laser perforation of the larynx or trachea can then be performed. CHAOS due to thick cartilaginous plaque is unlikely to respond to simple perforation, and fetal tracheostomy may be necessary to allow resolution of hydrops. Although there are many unanswered questions about the long-term effects of in utero tracheostomy on lung development, it is clear that CHAOS, when associated with hydrops carries a high risk of intrauterine fetal death. In addition, in a fetal lamb model of this condition, tracheostomy reversed the pathophysiology. However, the case reported by Crombleholme et al. (2000) suggests that in some cases hydrops can be tolerated for prolonged periods. If close monitoring is available, intervention may be deferred until after 30 weeks of gestation, when an EXIT procedure can be considered with acceptable risks of prematurity.

TREATMENT OF THE NEWBORN

In cases of CHAOS in which an EXIT procedure is performed, the infant should have an airway in place before being handed over to the neonatologist. It is important that a medical

geneticist examines the infant for possible associated anomalies. Blood for karyotype analysis should be sent if a karyotype was not obtained during the pregnancy. Depending on physical findings, plain radiography to exclude vertebral anomalies, sonography to exclude genitourinary anomalies, and echocardiography should all be considered. The possibility of a communication between trachea and esophagus must be excluded in all patients with CHAOS. The pathophysiology of CHAOS results in a capillary leak syndrome after delivery by EXIT procedure. Affected neonates require careful fluid management because of their capillary leak, and the massive ascites that may initially be refractory to diuretic therapy. Because of chronic tracheal obstruction, diffuse tracheobronchial malacia should be anticipated, which may require 7 to 12 cm H_2O positive end-expiratory pressure (PEEP) to maintain patency of the airway. In addition, diaphragmatic dysfunction, secondary to in utero stretch injury as a result of lung overdistention, may be severe at birth. Phrenic nerve stimulation can confirm that the neuromuscular unit is intact. Progressive improvement can be anticipated during the first 5 months of life. The infant can be weaned from mechanical as soon as diaphragmatic function is restored and tracheal reconstruction can be considered at 6 to 12 months of age. Because of the unusual nature of CHAOS, these patients are best managed at centers not only experienced in EXIT procedures, but also with the neonatal care of infants with CHAOS and the complex airway reconstructive surgery that will be required.

SURGICAL TREATMENT

The most important aspect of the care of the newborn diagnosed with CHAOS is securing and maintaining the airway. Once potential associated anomalies have been excluded, and the infant's cardiorespiratory status is stable, an elective approach to evaluating the newborn's airway can be taken. In the absence of tracheoesophageal fistula, the surgical management of CHAOS is elective. The initial evaluation should be directed toward diagnosing the level of obstruction to allow planning of definitive surgical repair. It is important that prospective parents understand that, depending on the nature of the malformation, perfect laryngeal reconstruction and adequate speech may not be possible. The ideal timing of reconstruction in these extremely rare cases has not been established. However, bronchoscopy performed during the newborn period will exclude simple causes of laryngeal obstruction, such as laryngeal cyst or web. The majority of webs are located at the level of the glottis or immediately subglottic and are readily diagnosed by laryngoscopy or bronchoscopy. These webs can occasionally be lysed endoscopically with a knife or laser. Although lasers can be used, the small airway of the newborn may make it difficult to avoid thermal damage to surrounding tissues. An infant urethral resectoscope with a narrow cutting loop can be used with brief bursts of cutting current. There are only anecdotal reports of successful reconstruction and long-term outcome in this condition (Smith and Bain, 1965; Richards et al., 1992; Crombleholme et al., 2000; Rutter, 2006; Vaikunth et al., 2009).

LONG-TERM OUTCOME

Because of the nature of the malformation in CHAOS, very little information exists regarding the long-term outcome for affected children. In cases of simple laryngeal cyst or web, normal laryngeal function can be anticipated. The outcome in cases of more significant laryngeal malformation is less certain. Most infants with this problem have not survived. The few long-term survivors of isolated CHAOS have had excellent glottic and airway function with normal neurodevelopmental outcome.

GENETICS AND RECURRENCE RISK

Most cases of CHAOS occur as sporadic, isolated malformations without a known risk of recurrence. In cases of CHAOS associated with Fraser syndrome, there is a 25% chance of recurrence, as this syndrome is inherited as an autosomal recessive disorder (Fraser, 1962). Two different genes have been shown to be associated with Fraser syndrome, *FRAS1* and *FREM2* (McGregor et al., 2003; Jadeja et al., 2005)

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Cystic Hygroma in Early Pregnancy

31 CHAPTER

Key Points

- Septated cystic hygroma in the first trimester is defined by extensive nuchal thickening extending along the entire length of the fetal back and in which septations are clearly visible.
- This finding is seen frequently in the first trimester, affecting more than one in 300 pregnancies.
- Given the 50% risk of fetal aneuploidy, definitive diagnostic testing with CVS should be offered immediately.
- Amongst the 50% of cases without aneuploidy, there is a one in two risk of major structural malformation, typically cardiac or skeletal abnormalities.
- If complete prenatal evaluation reveals no evidence of additional abnormality, a residual risk for abnormal pediatric outcome of 5% should be quoted.

CONDITION

Cystic hygroma refers to the finding of marked skin thickening extending along the entire length of the fetus at early ultrasound examination (Benacerraf and Frigoletto, 1987; Langer et al., 1990; Thomas, 1992; Gallagher et al., 1999). This finding is to be differentiated from simple increased nuchal translucency in which skin thickening is noted at the posterior aspect of the fetal neck only. Additionally, cystic hygroma in the first trimester has clearly visible septations running transversely between the fetal skin and underlying subcutaneous tissue. It

appears that the diagnosis of this finding early in pregnancy represents a completely different entity than the diagnosis of cystic hygroma in later pregnancy (Chapter 32). The latter condition is typically an isolated structural abnormality of lymphatic drainage and appears to have little or no association with chromosomal abnormality or other malformation.

The importance of this sonographic finding is its contribution to general population screening for fetal abnormalities and fetal aneuploidy in the first trimester of pregnancy. Given the pivotal role that nuchal translucency sonography at 11 to 13 weeks' gestation currently plays in general population screening for fetal abnormalities (Chapter 2), the finding of cystic hygroma will likely become more common. Once identified it is clear that such pregnancies are at significantly increased risk for a range of adverse outcomes. This includes up to a 50% chance of fetal aneuploidy (Malone et al., 2005a). Amongst euploid pregnancies there is almost a 50% chance of cardiac malformation or other major structural abnormality. Additionally, about one in four pregnancies with cystic hygroma in which a fetal abnormality has been excluded will result in spontaneous intrauterine fetal demise. Ultimately, only 15% to 20% of all cases of cystic hygroma identified in the first trimester will result in the birth of a healthy neonate at term (Malone et al., 2005a).

INCIDENCE

Until recently it was difficult to assess the population prevalence of first trimester cystic hygroma as most studies have included only selected patients identified from high-risk referral centers (Bernstein et al., 1991). However, a recent general population screening study evaluated more than 38,000 unselected pregnancies from throughout the United States with first trimester ultrasonography. The prevalence of cystic hygroma in this group was 1 in 285 first trimester pregnancies (Malone et al., 2005a). It is therefore likely that in a busy clinical practice performing routine first trimester ultrasonography, septated cystic hygroma will be encountered frequently.

SONOGRAPHIC FINDINGS

The key sonographic criteria for diagnosing cystic hygroma in the first trimester of pregnancy include the presence of a markedly enlarged nuchal translucency measurement that extends along the entire length of the fetal back, and in which septations are clearly visible in transverse section through the fetal neck. Figure 31-1 demonstrates a sagittal view through a fetus at 12 weeks' gestation in which skin thickening is seen to extend from the fetal head to the base of the fetal spine. Figure 31-2 illustrates the septations that are clearly visible in a transverse view through the fetal neck. Such septations tend to be more easily noted using the higher frequency imaging

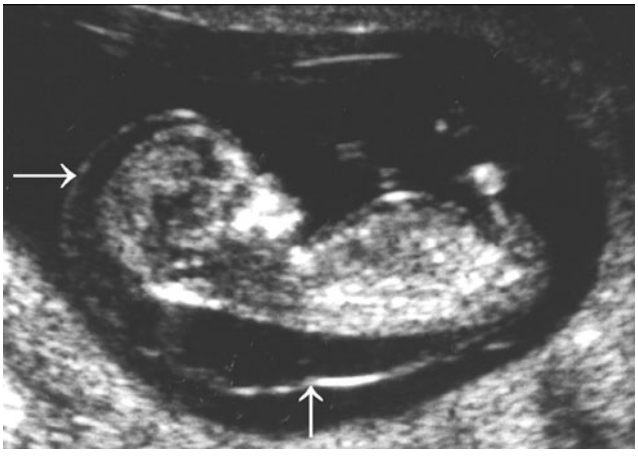

Figure 31-1 Septated cystic hygroma at 12 weeks' gestation, demonstrating midsagittal view through the fetus with increased nuchal translucency extending along the entire length of the fetal back.

provided by a transvaginal transducer. Figure 31-3 demonstrates a 3D ultrasound image of a septated cystic hygroma.

Given the strong association between first trimester cystic hygroma and various structural malformations, it is recommended that a careful sonographic evaluation is performed of the fetus following the diagnosis of cystic hygroma. Transvaginal sonography can be utilized to evaluate fetal long bones, skull, cardiac situs, cardiac axis, cardiac structure, and abdominal wall integrity in the first trimester.

DIFFERENTIAL DIAGNOSIS

The main differential diagnosis for first trimester enlarged nuchal thickening is to consider whether it meets criteria to

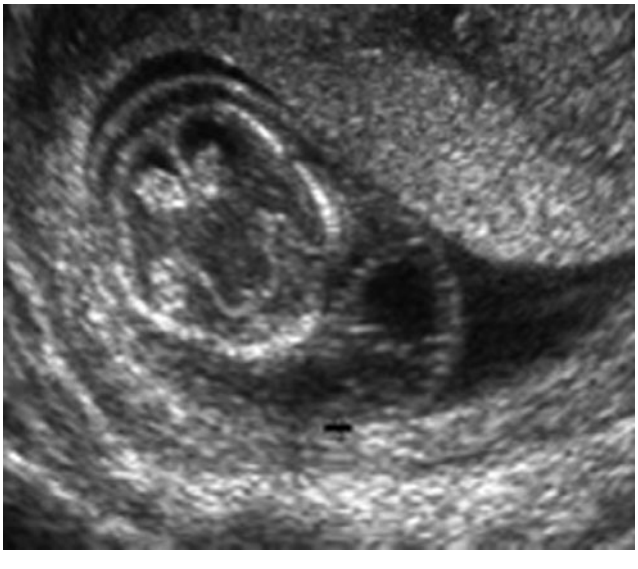

Figure 31-2 Septated cystic hygroma at 12 weeks' gestation, demonstrating transverse view through the fetal neck with septations being clearly visible between the fetal skin and underlying nuchal tissue.

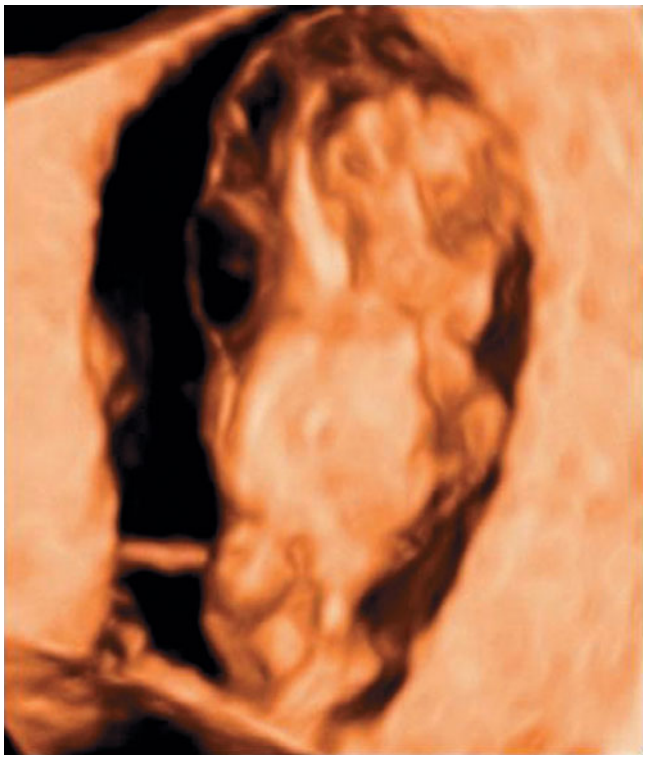

Figure 31-3 Three-dimensional surface-rendered view of fetus with septated cystic hygroma at 12 weeks' gestation.

be termed cystic hygroma or whether it should be considered a simple enlarged nuchal translucency. While some would consider these two entities to be part of the same spectrum of sonographic abnormalities, it is now clear that the outcomes following these two findings are clearly different. Septated cystic hygroma, using the definition as described above, can be easily identified in the first trimester and does not need the same degree of quality assurance required with general nuchal translucency screening programs. If the nuchal thickening does not extend along the entire length of the fetal back, and if transverse septations are not clearly visible, then the term nuchal translucency should be used. When an enlarged nuchal translucency is identified, it is generally advised that maternal serum markers, including free beta hCG and PAPP-A, be obtained before using risk-interpretative software to provide a patient-specific risk of fetal aneuploidy (Malone et al., 2005b). However, if a simple nuchal translucency measurement of 3 mm or greater is noted, there is little value in obtaining serum markers, and it is reasonable to immediately offer the patient definitive diagnostic testing with CVS (Comstock et al., 2006).

In a direct comparison of outcomes of cases of septated cystic hygroma and simple increased nuchal translucency, it is clear that the natural history of these two conditions is different (Table 31-1). Cystic hygroma has a fivefold higher risk of fetal aneuploidy compared with simple increased nuchal translucency, has a 12-fold increased risk of cardiac malformation, and a sixfold increased risk of spontaneous fetal or neonatal death (Malone et al., 2005a).

ANTENATAL NATURAL HISTORY

The natural history of septated cystic hygroma identified in the first trimester reveals a generally poor outcome (Table 31-1). In one series of 132 cases of cystic hygroma, 50% of fetuses were found to be aneuploidy (Malone et al., 2005a). Amongst aneuploidies, 40% were trisomy 21, 30% Turner syndrome, 20% trisomy 18, and 10% trisomy 13 or triploidy. Amongst the 50% of cases that are found to be euploid, approximately one-third will have a major structural malformation, most commonly cardiac malformation or skeletal abnormality. The most common cardiac malformations include hydrops, hypoplastic left heart syndrome, tetralogy of Fallot, and ventricular septal defect. The most common skeletal abnormalities include Roberts syndrome and Cornelia de Lange syndrome (Malone et al., 2005a). Additionally, amongst euploid fetuses

Table 31-1

Comparative Outcome of Septated Cystic Hygroma and Simple Increased Nuchal Translucency

	Septated Cystic Hygroma	Simple Nuchal Translucency $\geq$ 3.0 MoM	*P*	OR (95% CI)
Number	132	140		
Aneuploidy	67/132 (51%)	23/140 (16%)	<0.001	5.2 (2.9–9.6)
Cardiac malformation	16/65 (25%)	3/117 (3%)	<0.001	12.4 (3.2–56.3)
Fetal or neonatal death	5/20 (25%)	6/114 (5%)	0.003	6.0 (1.4–26.2)

MoM = multiples of median; OR = odds ratio.
From Malone FD, Ball RH, Nyberg DA, et al. First trimester septated cystic hygroma. Prevalence, natural history, and pediatric outcome. Obstet Gynecol. *2005a;106:288-294.*

without structural malformation, there is a 25% risk of spontaneous fetal demise. Ultimately, only 15% to 20% of all cases of septated cystic hygroma diagnosed in the first trimester will result in a normal liveborn neonate at term.

Also of note, in almost 80% of cases of first trimester cystic hygroma followed expectantly, the cystic hygroma can be expected to resolve spontaneously at a mean gestational age of 18 weeks (Malone et al., 2005a).

MANAGEMENT OF PREGNANCY

Following the diagnosis of septated cystic hygroma in the first trimester, counseling regarding pregnancy management can be provided in three steps. Once the initial diagnosis is made, patients should be counseled of a one in two risk of fetal aneuploidy and therefore should be offered the opportunity for immediate definitive diagnostic testing by means of CVS. There is no benefit in delaying diagnosis further by awaiting first trimester serum markers or performing computerized risk assessment. If CVS confirms no evidence of aneuploidy, patients should then be counseled of a one in two residual risk of major structural malformation. Since these malformations are most likely to be cardiac or skeletal, a targeted ultrasound evaluation of fetal anatomy and fetal echocardiography should be provided at 16 to 20 weeks' gestation. Finally, if such targeted fetal evaluation confirms a structurally normal fetus, patients should be counseled of a 95% likelihood of normal short-term pediatric outcome. A residual risk of 5% for abnormal pediatric outcome, despite complete prenatal evaluation, should be described.

FETAL INTERVENTION

Other than prenatal diagnostic testing by means of CVS in the first trimester and appropriate detailed fetal anatomical evaluation at 16 to 20 weeks' gestation, there is no indication for specific fetal intervention following the diagnosis of cystic hygroma.

TREATMENT OF THE NEWBORN

Once prenatal evaluation has confirmed normal fetal karyotype and no evidence of structural cardiac or skeletal malformation, there is generally no need for specific treatment or intervention in the neonatal period. It is recommended that all such neonates should be examined carefully by a pediatric geneticist or dysmorphologist as rarer genetic conditions such as Noonan syndrome have been described following cystic hygroma (Achiron et al., 2000). This is especially important given the acknowledged difficulties in making the diagnosis of Noonan syndrome in the neonatal period. Additionally, despite a normal fetal echocardiogram it would be reasonable to repeat an echocardiographic examination for the neonate, given the difficulties in excluding certain cardiac abnormalities prenatally, such as ventricular septal defect and aortic or pulmonary stenosis.

SURGICAL TREATMENT

In contrast to the third trimester diagnosis of cystic hygroma (Chapter 32), no specific surgical intervention is recommended following the early pregnancy diagnosis of cystic hygroma.

LONG-TERM OUTCOME

Minimal data are currently available to counsel patients regarding the long-term outcome of first trimester cystic hygroma, once fetal aneuploidy and major structural malformation are excluded. In a study of 132 cases of first trimester cystic hygroma, median longer term outcome extended to 25 months of age, with a range of 12 to 50 months (Malone et al., 2005a). In only 1 of 23 cases followed for this length of time was an additional pediatric abnormality diagnosed (one case of spastic diplegia with developmental delay). It seems reasonable therefore to counsel patients with cystic hygroma and normal prenatal evaluation of a 5% residual risk of longer term abnormal pediatric outcome. However, caution should be exercised in implying normal outcome beyond 2 years of age.

GENETICS AND RECURRENCE RISK

It is clear that 50% of cases of first trimester cystic hygroma are associated with fetal aneuploidy. Recurrence risk for such cases should be provided based on the individual chromosomal abnormality. For example, for cases of fetal trisomy, recurrence risk is generally quoted as 1%, or the maternal age–related risk, whichever is higher. In contrast, for cases of fetal Turner syndrome, patients should generally be counseled that there is no significant increased risk of recurrence beyond the general population risk (Chapter 134). Similarly, if a cardiac malformation is diagnosed, specific recurrence risks should be quoted based on the individual cardiac abnormality.

There have been a number of case reports of recurrence of first trimester cystic hygroma, both in the setting of normal fetal karyotype and as a sonographic marker of other recurrent fetal abnormalities. One report described three consecutive pregnancies complicated by cystic hygroma with nonimmune hydrops with normal karyotype (Teague et al., 2000). Another described recurrent cases of Fryns syndrome (diaphragmatic hernia and digital hypoplasia) presenting in the first trimester as cystic hygroma (Hosli et al., 1997). It has

been suggested that there may be rare cases of recurrent cystic hygroma inherited in an autosomal recessive pattern (Dallapiccola et al., 1984).

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Cystic Hygroma in Late Pregnancy

32 CHAPTER

Key Points

- Cystic hygroma and lymphangioma are older commonly used terms for a specific type of vascular malformation.
- Most often seen in the soft tissue of the neck, axilla, thorax, and lower extremities.
- Different prenatal natural history if diagnosed in the first trimester versus the third.
- Lymphangiomas presenting in the third trimester usually seen in the anterior or anterolateral neck are not usually associated with other anomalies or hydrops.
- Lymphatic vascular malformations consisting of cysts separated by fine septa.
- While the mortality of lymphatic vascular malformations prior to 30 weeks' gestation is high, due to hydrops and karyotype abnormalities, those presenting later have an excellent prognosis.
- Cervical lymphangiomas are at risk for airway compromise, and an EXIT procedure should be considered if there is evidence of airway compression or displacement.

CONDITION

Traditionally referred to as lymphangioma or if in the neck cystic hygroma, these are currently considered a form of vascular malformation of the lymphatic system characterized by localized or diffuse malformations of lymphatic channels that can be characterized as microcystic, macrocystic, or both (Christison and Fishman, 2006).

Lymphangioma is a benign type of vascular malformation composed predominantly of dilated cystic lymphatics (Isaacs, 1997). These malformations are often present at birth and are second only to hemangioma as a cause of

soft tissue mass in the newborn (Potter and Craig, 1975; Isaacs, 1983, 1991, 1997). Lymphangiomas can occur in almost any location but are most commonly seen in the soft tissue of the neck, axilla, thorax, and lower extremities (Isaacs, 1997). Isaacs reported a series of 97 consecutive lymphangiomas seen at Children's Hospital of Los Angeles in which 45 occurred in the neck, 22 in the chest wall, 12 in the extremities, and 4 in the abdominal wall. Other less common sites included the omentum, mesentery, larynx, tongue, bowel, retroperitoneum, mediastinum, conjunctiva, and mouth (Isaacs, 1991). These lesions can vary in size from tiny subepidermal skin blebs to large dilated cystic fluid filled–masses that, when presenting in the neck, are commonly referred to as cystic hygromas.

There is a disparity between lymphangiomas that are diagnosed at birth as isolated findings in otherwise healthy infants and those detected prenatally during the first or second trimester (see chapter 31). Prenatal sonographic examination in the first and second trimester identifies a group of fetuses with cystic hygroma in which 60% have associated chromosomal abnormalities and are often associated with other structural anomalies that have an extremely high mortality rate (Romero et al., 1988; Cohen et al., 1989; Welborn and Timm, 1994). In this group of fetuses, cystic hygromas are distinguished by posterior triangle location of the lymphangioma, chromosomal abnormalities, structural anomalies, hydrops fetalis, a high incidence of intrauterine death, and rare postnatal survival. In contrast, isolated cystic hygroma presenting during the third trimester, often with previously normal sonographic studies earlier in gestation, is usually located anteriorly or anterolaterally in the anterior cervical triangle. These two groups of fetuses appear to have lymphangiomas of differing origin, pathophysiology, natural history, and most importantly, prognosis (Lyngbye et al., 1986; Benacerraf and Frigoletto, 1987; Langer et al., 1990).

The lymphatic system develops at the end of the 5th week of gestation with sprouting from the six primary lymph sacs situated in the neck, iliac region, and retroperitoneum. Goetsch (1938) suggested that lymphangiomas are developmental defects secondary to sequestration of lymphatic tissue in early embryonic life. Cystic hygromas are thought to arise because of the failure of the jugular lymph sacs to join the lymphatic system. The hygroma develops fibrillike sprouts from the existing cystic spaces. These endothelial-lined cystic spaces secrete lymphlike fluid, which causes local distention and gradual enlargement of cysts. The walls may become thicker with time, with connective tissue septae separating large cysts (Chervenak et al., 1983; Isaacs, 1997).

Lymphangiomas diagnosed in utero are commonly seen in association with Turner syndrome, hydrops, oligohydramnios, single-vessel umbilical cord, Noonan syndrome, fetal alcohol syndrome, Fryns syndrome, and trisomies 18 and 21 (Stephens and Shepard, 1980; Chervenak et al., 1983; Pijpers et al., 1988; Golden et al., 1989; Welborn and Timm, 1994). Chromosomal abnormalities are found in more than 60% of fetuses with cystic hygroma. The majority have a 45,X karyotype (Romero et al., 1988; Cohen et al., 1989; Welborn and Timm, 1994), although Trisomies 13, 18, and 21 and Klinefelter syndrome have all been reported (Chervenak et al., 1983; Greenberg et al., 1983; Marchese et al., 1985; Stephens and Shepard, 1980). Conversely, fetuses with a normal karyotype appear to have a much higher incidence of consanguinity or a previous family history of abnormal fetuses (Langer et al., 1990). Cystic hygromas in these patients are more likely to be associated with familial conditions such as Noonan syndrome, multiple pterygium syndrome, polysplenia syndrome, Roberts syndrome, or an isolated autosomal recessive trait (Chen et al., 1982; Cowchock et al., 1982; Graham et al., 1983; Zarabi et al., 1983; Zelante et al., 1984).

Isolated cystic hygromas presenting late in gestation appear to be a completely different entity (Lyngbye et al., 1986; Benacerraf and Frigoletto, 1987; Langer et al., 1990; Fujita et al., 2001; Tanriverdi et al., 2005; Gedikbasi, 2007). These cases had cystic hygromas located in the anterior and lateral location and were not generally associated with other anomalies or hydrops. Langer et al. suggested that in these cases lymphangioma developed much later in gestation. In one of his cases, the fetus had a normal sonographic examination at 17 weeks of gestation (Langer et al., 1990). If this is true, it is unlikely that the mechanism would be similar in the late presenting group of cystic hygromas and the early gestation group. Cystic hygromas may also regress in utero, presumably due to development of collateral lymphatic and venous connections. Webbing of the neck and puffiness of the hands and feet are characteristic features of Turner syndrome, which is thought to be due to fetal cystic hygromas that spontaneously resolve.

INCIDENCE

Precise estimates of the incidence of cystic hygroma and lymphangioma are difficult to come by and depend on whether prenatal or postnatal data are evaluated. Fonkalsrud estimated the incidence of cystic hygroma to be 1 in 12,000 births, with 50% to 65% of cases presenting at birth, and 80% to 90% presenting by the second year of life (Bill and Sumner, 1965; Fonkalsrud, 1980). A total of 52 confirmed diagnoses of cystic hygroma were reported to the South East Thames Regional Congenital Malformation Registry in a region with an annual birth rate of 52,000, yielding an incidence of 1 in 1000 births. This series included terminations, intrauterine fetal death, stillbirths, and postnatal deaths to give a more accurate account of the incidence of cystic hygroma (Fisher et al., 1996). The incidence of cystic hygroma was as high as 1 in 300 among spontaneous abortuses reported by Byrne et al. (1984).

SONOGRAPHIC FINDINGS

The sonographic features of cystic hygroma include fluid-filled cystic spaces divided by fine septae commonly observed in the nuchal region and anterior and posterior triangles of the neck (Figure 32-1). They often have a dense midline posterior

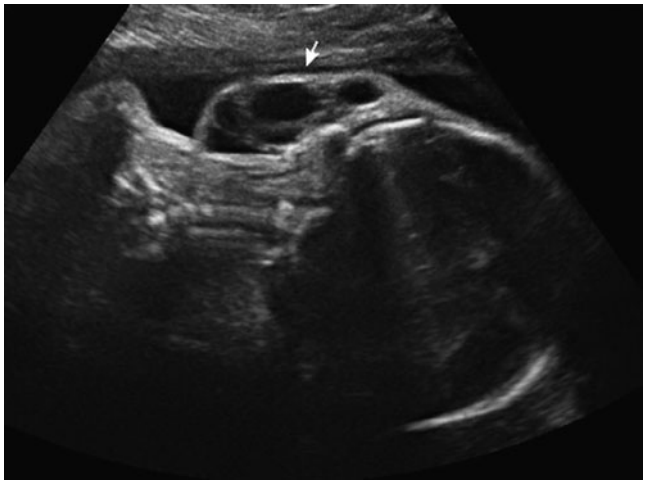

Figure 32-1 Cystic mass along lateral aspect of fetal head at 31 weeks consistent with cystic hygroma.

septum extending from the fetal neck across the full width of the hygroma. This septum is the sonographic equivalent of the nuchal ligament (Chervenak et al., 1985). In order to differentiate cystic hygroma from other diagnoses, it is important to exclude a bony defect in the skull or vertebral column as would be seen with encephalocele. Solid components should be excluded to distinguish cystic hygroma from a cystic teratoma. Cysts separated by septae are helpful in distinguishing nuchal edema from cystic hygroma.

Lymphatic malformations may be diagnosed in the chest, abdomen, retroperitoneum or inguinal region. Rasidaki et al. (2005) have reported a chest wall lymphatic malformation in which MRI in addition to ultrasound was used to make the diagnosis. Similarly, there have been several reports of prenatal diagnoses of axillary lymphatic malformations (Song et al., 2002; Zanotti et al., 2001).

Once cystic hygroma has been detected, a search for other potential associated signs of nonimmune hydrops such as fetal skin edema, ascites, and pleural or pericardial effusions should be sought. In addition, structured anomalies seen in association with cystic hygroma should be sought, including cardiac, facial, vertebral, and genitourinary anomalies and diaphragmatic hernia (Bulas et al., 1992) (Table 32-1).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of cystic neck masses includes nuchal edema, encephalocele or other neural tube defects, cystic teratoma, and twin sac of a blighted ovum. The approach to each of these conditions differs, highlighting the importance of accurate prenatal diagnosis. The presence of skull or vertebral column defects suggests the diagnosis of encephalocele, especially if associated with hydrocephalus. The distinction between cystic hygroma and cervical teratoma can be extremely difficult. Teratomas usually have a more complex sonographic appearance, with solid as well as cystic components. Calcifications within the mass are thought to be diagnostic of teratoma (see Chapter 110). Fetal magnetic resonance imaging (MRI) may be very helpful in distinguishing cystic hygroma from cervical teratoma (Liechty et al., 1997; Hubbard et al., 1998) (Figures 32-2A and 32-2B). Nuchal edema is usually without septae except the midline nuchal ligament and is a few millimeters in thickness (see Chapter 31).

Table 32-1

Associated Structured Anomalies in 19 Fetuses with Cervical Cystic Hygroma

Cardiac defects	6
Hydronephrosis	3
Neural tube defect	3
Cleft lip and palate	2
Multiple pterygium syndrome	2
Skeletal anomalies	1
Imperforate anus	1
Ambiguous genitalia	1

Source: Langer JC, Fitzgerald PG, Desa D, et al. Cervical cystic hygroma in the fetus: clinical spectrum and outcome. J Pediatr Surg. *1990;25:58-62.*

ANTENATAL NATURAL HISTORY

The natural history of prenatally diagnosed cystic hygroma appears to depend on gestational age at diagnosis, location of the cystic hygroma, and most particularly, whether or not there are associated chromosomal or structural abnormalities (Langer et al., 1990).

The mortality rate for cystic hygromas diagnosed prior to 30 weeks of gestation, with posterior location, is extremely high because of the high incidence of nonimmune hydrops and associated chromosomal defects (see Chapter 128). In the report by Langer et al. of 27 cases diagnosed prior to 30 weeks of gestation, all but 2 fetuses died. Of the 25 that did not survive, nonimmune hydrops developed in 21, 4 spontaneously aborted, and 21 were electively terminated. The only 2 survivors had spontaneous regression and were subsequently diagnosed with Noonan syndrome at birth (Langer et al., 1990). Cystic hygroma associated with nonimmune hydrops is almost uniformly fatal. There are chromosomal abnormalities in approximately 80% of these cases. Fetuses with normal chromosomes have a higher incidence of consanguinity (Langer et al., 1990). These cases of cystic hygroma are also

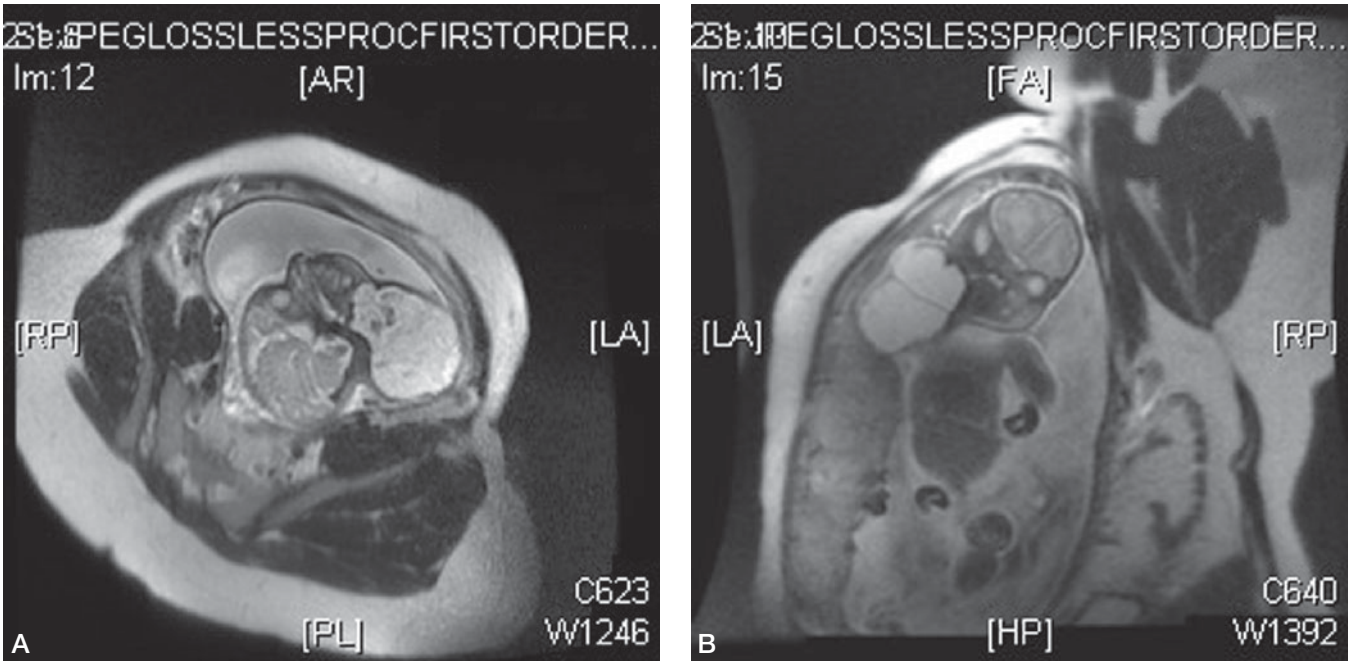

Figure 32-2 **A**. Sagittal view of fetus with large right-sided lymphangioma resulting in hyperextension of the neck and compression and distortion of the airway. **B**. Coronal view of the same fetus with a large lymphangioma.

more likely to be associated with familial conditions, such as Noonan syndrome (Zarabi et al., 1983), multiple pterygium syndrome (Chen et al., 1982), polysplenia syndrome, Roberts syndrome (Graham et al., 1983), or an isolated recessive trait (Cowchock et al., 1982). In a review of 100 fetuses with nuchal thickening or cystic hygroma detected sonographically at 10 to 15 weeks of gestation, Nadel et al. (1993) found that a good prognosis could be expected if the karyotype was normal, there were no separations in the mass, and there were no associated hydrops.

In marked contrast to cystic hygromas with associated karyotypic abnormalities, there is a small group of fetuses with an isolated cystic hygroma without chromosomal abnormality, structural anomaly, or familial condition and in which hydrops does not develop. These cystic hygromas usually develop in the third trimester and have an excellent prognosis. The major concern in fetuses with large cystic cervical masses later in gestation is airway compromise at birth. The fetuses often require delivery by EXIT procedure (see below).

MANAGEMENT OF PREGNANCY

The management of a pregnancy complicated by a fetus with cystic hygroma depends on the presence or absence of nonimmune hydrops, chromosomal abnormalities, or other associated anomalies. Once a cystic hygroma has been detected, a detailed sonographic examination should be performed to search for fetal skin edema, ascites, and pleural or pericardial effusions. In addition, other structural anomalies should be excluded, especially genitourinary and cardiac defects. Genetic amniocentesis is recommended in all cases of cystic hygroma because of the high incidence of associated chromosomal abnormalities. In the presence of nonimmune hydrops the prognosis is grim, and appropriate counseling is indicated. In the presence of severe associated anomalies or a chromosomal abnormality prior to 24 weeks of gestation, elective termination may be offered. Echocardiography should be obtained in cases in which no chromosomal abnormalities are detected to exclude cardiac defects. An isolated cystic hygroma diagnosed in the third trimester has a much more favorable prognosis, and attention should be focused on site and mode of delivery. Because of risks of airway compromise, delivery in a tertiary care center with neonatologists and pediatric surgeons standing by is recommended. Because of the risks of airway compromise, consideration should be given to the EXIT procedure (Liechty et al., 1997; Marwan and Crombleholme, 2006). While a cervical mass of any size can cause airway compromise, masses sufficiently large enough to cause polyhydramnios can obstruct the pharynx or larynx, making intubation exceedingly difficult. Pregnancies with a cystic hygroma should be followed closely for the development of polyhydramnios and secondary uterine irritability. Polyhydramnios in fetuses with large cystic hygromas may be so severe as to require amnioreduction to treat maternal respiratory difficulties and preterm labor.

FETAL INTERVENTION

A few cases of lymphangioma have undergone in utero drainage by ultrasound-guided cyst aspiration. Chen et al. (1996) reported two fetuses that underwent multiple cyst aspirations. In each case karyotype analysis was normal and

there were no associated structural anomalies. The rationale for this approach is to prevent polyhydramnios, irreversible facial deformity, and progression to hydrops fetalis. It is unclear, however, that these multiple cyst aspirations had any effect on outcome. While cyst aspiration as an adjunct to securing an airway at birth may be indicated, there are few data to support in utero decompression to prevent progression to nonimmune hydrops or facial deformity. The lack of benefit and risk of repeated aspirations make this fetal intervention difficult to justify. Kaufman et al. (1996) did report successful percutaneous decompression of a large axillary lymphangioma that would have caused skeletal dystocia. Ultrasound-guided aspiration was followed by normal spontaneous vaginal delivery. Figure 32-3 demonstrates an axillary lymphangioma detected antenatally and aspirated prior to birth to allow vaginal delivery.

Several groups in Japan have attempted intrauterine sclerotherapy using OK-432 between 27 and 28 weeks' of gestation (Wattori et al., 1996; Ogita et al., 2001). OK-432 is a lyophilized mixture of a low-virulence strain of *Streptococcus pyogenes* of human origin incubated with penicillin G. The fetuses had involution of the cystic hygroma, and at birth only a slight skinfold was noted. Cases of lymphatic vascular malformations with normal chromosomes and no associated anomalies with hydrops were considered candidates for in utero sclerotherapy with OK-432 (Ogita et al., 2001). Those lesions with very large lymphangiomas even in the absence of hydrops may also be candidates for OK-432 in Japan. To date there have been no reports of in utero sclerotherapy with OK-432 being used in this country. There are few data on the use of this agent postnatally and none are available on its potential effects in the developing fetus. Currently, the only

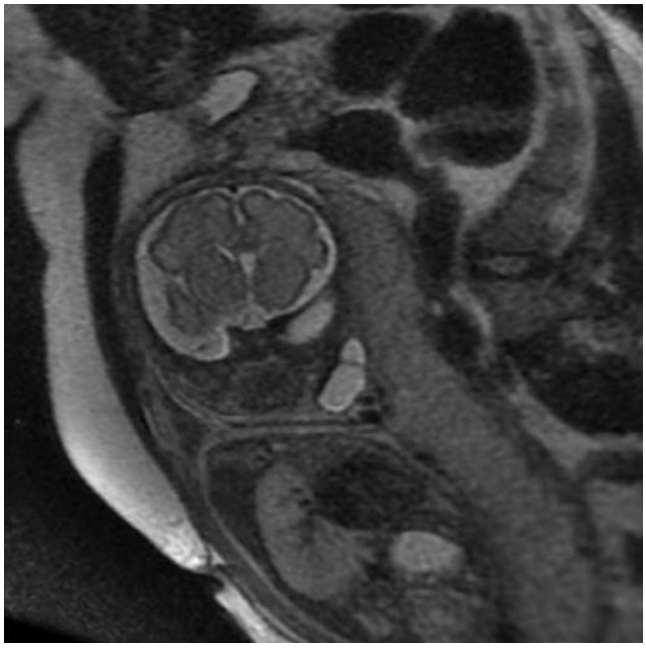

Figure 32-3 Fetal MRI demonstrating unilateral cystic mass at lateral aspect of fetal neck consistent with cystic hygroma.

fetal procedure indicated for large cystic hygromas is EXIT (ex utero intrapartum treatment), which involves placement of an endotracheal tube before the fetus is separated from placental support (Liechty et al., 1997).

Treatment of the fetus with a large cystic hygroma includes an EXIT procedure to secure the airway (Liechty et al., 1997). The EXIT procedure allows up to 1 hour with excellent uteroplacental gas exchange for laryngoscopy, bronchoscopy and, if necessary, tracheostomy with or without partial resection of the mass (Liechty et al., 1997). As fetuses with prenatally diagnosed fetal airway obstruction reach viability, they should be monitored closely for the development or progression of hydrops or cardiac decompensation. If the development or progression of hydrops is noted sonographically, open fetal surgery may be necessary to salvage patients younger than 30 weeks' gestation. If hydrops is noted later than 30 weeks' gestation, the fetus should be delivered by using the EXIT strategy.

A number of important considerations must be taken into account when applying the EXIT procedure in the setting of giant fetal neck masses. The most pressing issue is the successful securing of the fetal airway. Although fetal neck masses can cause polyhydramnios and preterm labor, the most significant aspect of their management is treating a compromised airway at the time of delivery. The timing of the EXIT is often dictated by severity of polyhydramnios and preterm labor. The mean gestational age of fetuses with neck masses undergoing EXIT procedure is 34 weeks. Airway compromise is a function of the location of the mass and distortion of the airway, not necessarily the absolute size of the neck mass. As mentioned previously, the surgeon must be prepared for every possible airway contingency. All the available modalities to secure the fetal airway are detailed under the description of the EXIT procedure and are outlined in the algorithm in Figure 32-4. Other important issues to consider when performing an EXIT procedure for giant neck masses include: (1) the possibility of wedging of the lungs in the apex of the chest as a result of the neck hyperextension (despite the fact that a successful EXIT strategy can be applied in these cases, significant morbidity and mortality should be anticipated because of the associated lung hypoplasia); (2) the chance of the trachea being pulled up into the neck may lead to the underestimation of the site of tracheostomy, leading to an inappropriately low tracheostomy site; (3) the occurrence of polyhydramnios as a result of esophageal compression (this may lead to underestimation of the proximity of the placental edge to the site of hysterotomy with increased risk of bleeding); and (4) some fetal neck masses are caused by a cystic mass lesion. In such cases, decompression of the mass before the hysterotomy under US guidance will help in fashioning the hysterotomy and in delivering the fetal head and neck. Based on our cumulative experience in the application of the EXIT procedure in different clinical situations, we have summarized pitfalls and lessons learned to provide guidance when applying the EXIT approach (See Chapter 5, Table 5-6). If the fetus is premature and at increased risk for respiratory distress syndrome, surfactant replacement therapy can be administered while on

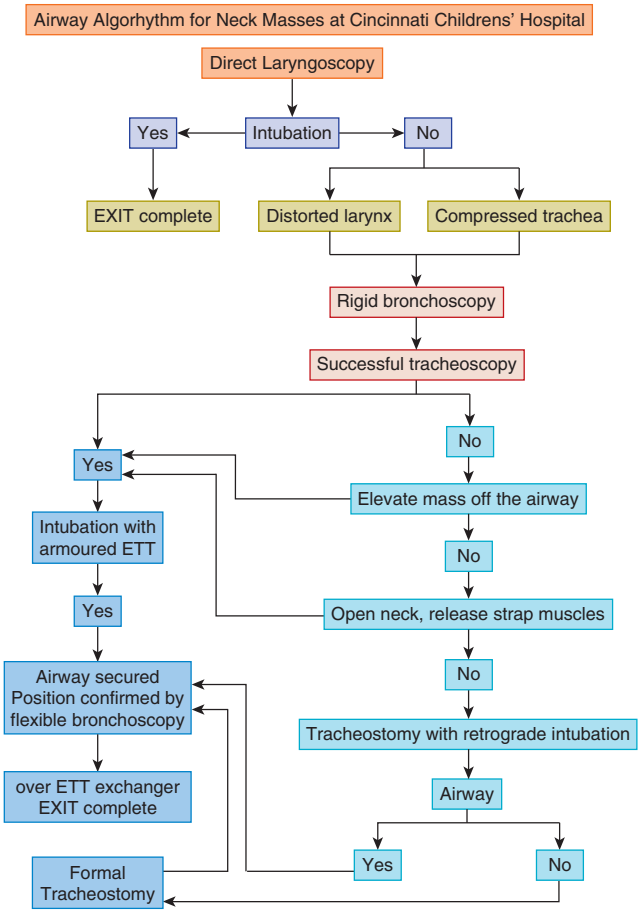

Figure 32-4 Algorithm for EXIT-to-Airway intraoperative decision-making.

placental support. In addition, in a three-vessel cord, and umbilical artery catheter, and even an umbilical venous catheter can be placed while on placental support to facilitate newborn resuscitation.

Once an airway has been established, the care of the newborn should focus on any underlying lung disease and exclusion of any associated anomalies and chromosomal abnormalities, if this has not already been done. Once the newborn is able to be transported to a tertiary care facility, a computed tomographic (CT) scan and MRI scan with magnetic resonance angiography should be obtained of the infant's head and neck to confirm the diagnosis of lymphangioma and to determine the extent of the hygroma (Figures 32-5A and 32-5B). Of particular concern is to define whether there is extension into the mediastinum or the floor of the mouth and tongue.

TREATMENT OF THE NEWBORN

The infant with a large cystic hygroma has an intrinsically unstable airway, and resection should proceed as soon as the diagnostic evaluation is completed. Cystic hygromas of a modest size can be dealt with on a more elective basis if they do not pose a risk for airway compromise. The nature of the lymphangioma often precludes a complete resection. The surgical approach is focused on resection of as much of the mass as possible without sacrificing vital structures. Some surgeons have recommended a conservative approach in asymptomatic lymphangiomas because of occasional spontaneous regression. More commonly, these lesions grow proportionately with the growth of the infant. There may also be acute increases in the size of the cyst due to hemorrhage or infection. Because of difficulty in achieving a complete resection, alternative treatments have been tried with variable results.

SURGICAL TREATMENT

Cystic aspiration is of little benefit except in the rare instance of a large dominant cyst as a means of emergency decompression. However, the cysts rapidly reaccumulate. Sclerosing agents have been used as an alternative to resection, using boiling water or sodium morrhuate, with disappointing results. Bleomycin has been used as microspheres in oil bleomycin fat emulsions (BLM), and seems more effective than other preparations (Tanigawa et al., 1987; Tanaka et al., 1990). After cyst aspiration, injection into the lymphangioma via fine needle of 0.3 to 0.6 mg of BML per kilogram of body weight is recommended. This treatment requires admission to the hospital for observation and is contraindicated in infants younger than 6 months or in the presence of airway compromise or mediastinal involvement due to significant tissue edema that results. Side effects of bleomycin include fever, diarrhea, vomiting, infection, and bleeding. In addition, the incidence of long-term complications such as pulmonary fibrosis is unknown.

The sclerosing agent OK-432 is the product of incubating *S. pyogenes* of human origin with penicillin G (Ogita et al., 1996). Intracystic injection of 0.1 mg of OK-432 in 10 mL of saline solution following cyst aspiration is recommended. If necessary, the treatment can be repeated 3 to 4 weeks later. No prospective trials confirming the efficiency of this treatment have been reported. Laser treatment of lymphangioma has also been reported, but again with mixed results (Ogita et al., 1996).

LONG-TERM OUTCOME

The mortality of cystic hygroma diagnosed prior to 30 weeks of gestation and associated with nonimmune hydrops is virtually 100%. There is also a high incidence of associated chromosomal abnormalities that may, as in trisomy 18 and 13, be lethal. The outcome for isolated cystic hygroma presenting in the third trimester, however, is quite different. The overall mortality in this group is very low. However, complete resection is possible in only 75% of cases (Hancock et al., 1982). Despite complete resection, recurrence can occur in as many as 10% to 27% of cases. In cases in which only a partial

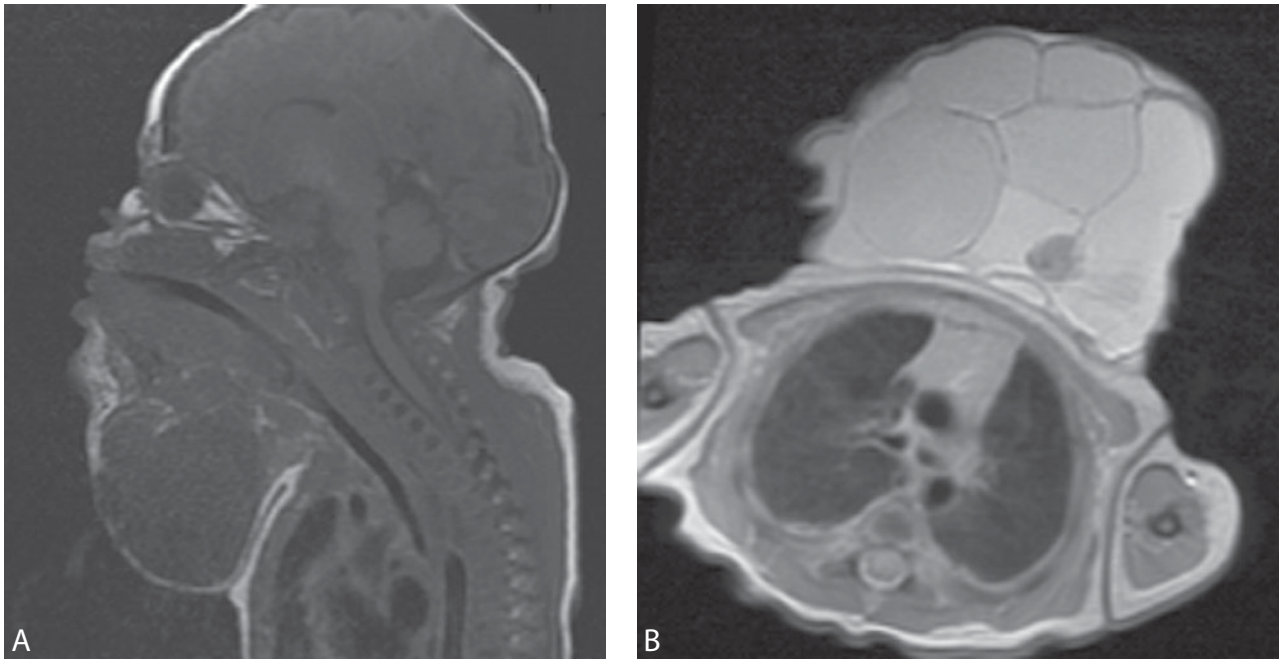

Figure 32-5 **A and B.** Postnatal MRI images demonstrating large submental cystic mass resting on the anterior surface of the fetal chest.

resection can be achieved, recurrence is observed in 50% to 100% of patients. Significant complications can occur in up to 30% of patients. Significant neurologic problems can result from injury to cranial nerves, especially the facial nerve (VII). However, injuries to the 9th, 10th, 11th, and 12th cranial nerves have also been reported. In addition, Horner syndrome due to injury to the sympathetic chain and diaphragmatic paralysis from phrenic nerve injury has occurred during resection of the cystic hygroma. Extensive involvement of the larynx, trachea, or extensive involvement of the floor of the mouth may necessitate tracheostomy tube placement. Often multiple operations are required to bring lymphangiomas under control. The long-term outcome depends on the ability to achieve a complete resection. This becomes unlikely in the face of extensive involvement of the floor of the mouth, tongue, larynx, or trachea.

GENETICS AND RECURRENCE RISK

Prenatally diagnosed cystic hygroma has a 50% to 60% incidence of abnormal karyotype. The most common associated chromosomal abnormalities are listed in Tables 32-1 and 32-2. Because some fetuses with cystic hygroma may have chromosomal mosaicism, it may be necessary to study several tissues to make a diagnosis. There are two reports of familial cystic hygroma occurring in eight patients in three families (Tricoire et al., 1993; Teague et al., 2000). In the first family, two fetuses with normal karyotypes and cystic hygromas had camptomelic dysplasia (see Chapter 91). Only one other fetus had anomalies—meningomyelocele and cleft palate. In all cases parental consanguinity was found, suggesting an autosomal recessive mode of inheritance. In another report, a 19-year-old gravida 3 para 0 was diagnosed with a large cystic hygroma at 11 weeks' gestation. The fetal subsequently developed increasing sign of a septated nuchal mass and ascites. A 46XX fetal karyotype had been noted on two prior pregnancies, both of which had also been complicated by cystic hygroma and hydrops. Cystic hygroma associated with a normal karyotype can be inherited as an autosomal recessive (Teague et al., 2000).

Table 32-2

Chromosomal and Nonchromosomal Abnormalities Associated with Cystic Hygroma

Chromosomal
45,X
Trisomy 18
Trisomy 13
Trisomy 21
13q deletion
18p deletion
Partial 11q:22q trisomy
Trisomy 22 mosaicism
Nonchromosomal
Noonan syndrome
Fetal alcohol syndrome
Distichiasis-lymphedema syndrome
Congenital diaphragmatic hernia

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33 Goiter

CHAPTER

Key Points

- Goiter in the fetus, a rare condition, can occur as part of a hypothyroid, hyperthyroid, or euthyroid state.
- Hypothyroid fetal goiter may be secondary to transplacental passage of antithyroid medication, iodine deficiency, iodine intoxication, transplacental passage of antithyroid antibodies, congenital metabolic disorders of thyroid hormone synthesis, or hypothalamic-pituitary hypothyroidism.
- Congenital hypothyroidism is a serious condition, which if not treated in the first 3 months of life is likely to result in irreversible mental retardation.
- Hyperthyroid fetal goiter is most often caused by transplacental passage of a thyroid-stimulating IgG antibody from the mother. Such antibodies are present in approximately 95% of women with Graves disease.
- Thyroid-stimulating antibody levels in Graves disease may not reflect maternal thyroid status because they are detectable in women who are clinically hyperthyroid, euthyroid, or hypothyroid.
- The typical sonographic appearance of a fetal goiter is a symmetric, homogenous mass in the anterior neck, with an echogenic consistency, and with some lobulation.
- The diagnosis of fetal goiter is rarely made prior to 24 weeks' gestation. The fetal neck may be hyperextended and the trachea and esophagus may become compressed or displaced resulting in polyhydramnios.
- It is extremely important to thoroughly evaluate and treat a fetal goiter.
- Because ultrasound methods of differentiating between hypothyroidism and hyperthyroidism may not be reliable, fetal cord blood sampling may be required. Amniotic fluid thyroid hormone values may not be reliable.
- If fetal hypothyroidism is diagnosed, intra-amniotic injection with levothyroxine will be required.
- Little information is available to guide patient counseling regarding the antenatal natural history of fetal goiter. The clinical course will depend on whether or not the fetus is hyperthyroid, euthyroid, or hypothyroid.
- Serial sonographic surveillance is suggested due to the fact that fetal goiter may be associated with polyhydramnios, intrauterine growth restriction, hydrops, and intrauterine fetal demise.
- A neonatologist should be present in the delivery room because problems securing an airway may be encountered. In the most severe cases of fetal goiter, the ex utero intrapartum treatment (EXIT) procedure may be needed to maximize the ability to promptly secure an airway at delivery.
- There is little data available to counsel patients on the long-term prognosis of antenatal fetal goiter.

CONDITION

Fetal goiter, or thyromegaly, is a diffuse enlargement of the fetal thyroid gland. Goiter in the fetus can occur as part of a hypothyroid, hyperthyroid, or euthyroid state. Hypothyroid fetal goiters are more common than those associated with either the hyperthyroid or euthyroid states.

Goiter associated with fetal hypothyroidism can be caused by transplacental passage of antithyroid medications being used by a mother with hyperthyroidism, iodine deficiency, iodine intoxication, transplacental passage

of antithyroid antibodies, congenital metabolic disorders of thyroid hormone synthesis, or hypothalamic-pituitary hypothroidism (Weiner et al., 1980; Romero et al., 1988; Noia et al., 1992; Soliman et al., 1994; Van Loon et al., 1995; Bruner and Dellinger, 1997; Vicens-Calvet et al., 1998). Most cases of hypothyroid goiter will not become apparent until the neonatal period. When goiter associated with hypothyroidism is recognized in utero it is most likely to be secondary to transplacental passage of drugs or congenital dyshormonogenesis because of an inherited enzymatic deficiency (Romero et al., 1988). Congenital hypothyroidism is a serious condition, which if not treated within the first 3 months of life is likely to result in irreversible mental retardation. Although newborn screening programs for congenital hypothyroidism have been extremely successful in reducing the incidence of mental retardation associated with this condition, it is possible that the presence of a hypothyroid state in utero may result in some degree of hearing, speech, and other intellectual impairment, despite early neonatal therapy (Rovet et al., 1987). This emphasizes the importance of thorough evaluation and treatment of fetal goiter whenever it is suspected prenatally.

Goiter associated with fetal hyperthyroidism is almost always caused by transplacental passage of a thyroid-stimulating IgG antibody from the mother (Wenstrom et al., 1990; Belfar et al., 1991; Hatjis, 1993; Hadi and Strickland, 1995; Heckel et al., 1997). Such antibodies are present in at least 95% of women with Graves disease. Thyroid-stimulating antibody levels in Graves disease may not reflect maternal thyroid status, as they are detectable in women who are clinically hyperthyroid, euthyroid, or hypothyroid. Therefore, whenever a patient with a history of Graves disease becomes pregnant, the fetus is at risk for hyperthyroid goiter, irrespective of the mother's clinical thyroid state. The fetal thyroid gland becomes fully responsive to thyroid-stimulating substances, such as maternal IgG, only in the second trimester, so the detection of a fetal goiter before 20 to 24 weeks of gestation is unlikely.

INCIDENCE

Fetal goiter is extremely rare, with no published series sufficient to allow an estimation of its incidence. Hypothyroid goiter is more common than hyperthyroid goiter. Congenital hypothyroidism has an incidence of 1 in 4000 livebirths. Only a small fraction of these will be complicated by fetal goiter, because in the vast majority of cases goiter becomes clinically apparent only during neonatal life (Fisher et al., 1979). Inborn errors of thyroid hormone biosynthesis that result in congenital dyshormonogenesis and cause hypothyroid fetal goiter are rare, being present in 1 in 30,000 livebirths. Graves disease is seen in approximately 1% of pregnant women, and hyperthyroidism or hypothyroidism will develop in 2% to 12% of these fetuses or neonates (Hatjis, 1993). However, only a small fraction of this number of at-risk fetuses will be diagnosed prenatally with a fetal goiter.

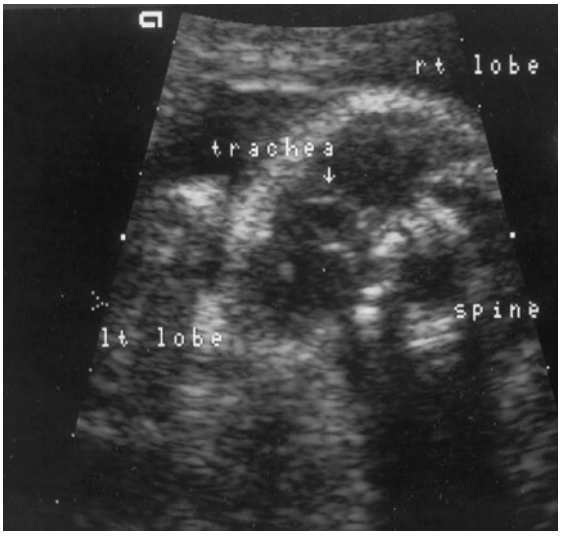

Figure 33-1 Prenatal sonographic image of a fetal neck demonstrating symmetric bilateral enlargement of the thyroid gland.

SONOGRAPHIC FINDINGS

The typical sonographic appearance of a fetal goiter is a symmetric, homogeneous mass in the anterior neck, with an echogenic consistency, and with some lobulation (Figure 33-1) (Heckel et al., 1997). The diagnosis is rarely made prior to 24 weeks of gestation. The fetal neck is often maintained in a state of hyperextension (Figure 33-2), and the

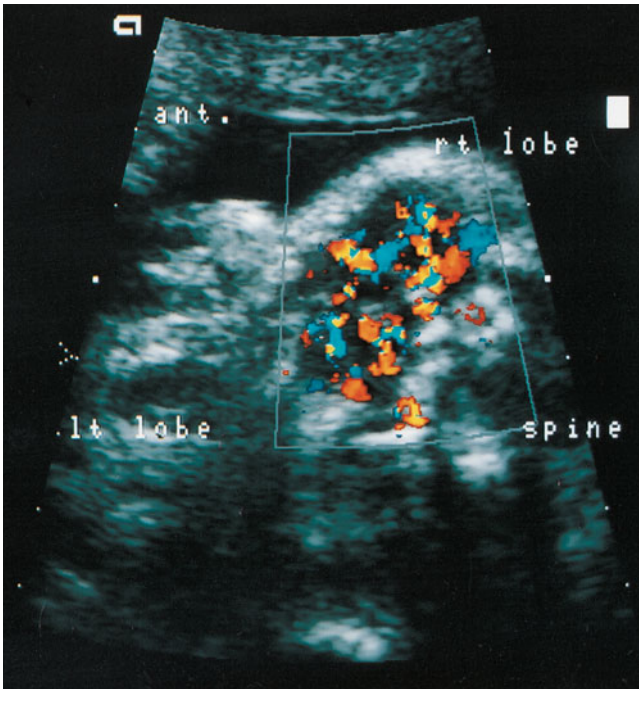

Figure 33-2 Sonographic image of the same fetal goiter shown in Figure 33-1 demonstrating increased vascularity in the neck mass.

trachea and esophagus may be compressed or displaced. Later in gestation, this compression may be associated with polyhydramnios, as swallowing becomes more difficult (Abuhamad et al., 1995). Color Doppler sonography can be used to aid in the diagnosis of a fetal goiter. The presence of a high flow pattern helps to confirm the diagnosis of goiter but does not necessarily imply a hyperthyroid state, as hypothyroid fetal goiters may also have increased vascularity (Soliman et al., 1994). Color Doppler sonography may also be useful in monitoring the response of a hyperthyroid fetus to antithyroid therapy, with a decrease in vascularity accompanying the resolution of the hyperthyroid state (Luton et al., 1997).

Sonographic screening for fetal goiter may be difficult because of problems in accurately identifying the fetal thyroid during early gestation. Nevertheless, normograms have been published for thyroid volume across a range of gestational ages, including transverse width and circumference of the gland, which may be helpful in diagnosing fetal goiter in patients at high risk for fetal thyroid dysfunction (Bromley et al., 1992).

After the sonographic diagnosis of a fetal goiter, a careful sonographic survey should be performed for other features suggestive of hyperthyroidism or hypothyroidism. Sonographic signs suggestive of fetal hyperthyroidism include cardiac hypertrophy, fetal tachycardia, hydrops, intrauterine growth restriction, advanced bone age with craniosynostoses, and hepatosplenomegaly. Sonographic signs of fetal hypothyroidism include cardiomegaly and fetal heart block. However, none of these additional sonographic features are sufficiently specific to reliably predict the fetal thyroid status. Magnetic resonance imaging (Figure 33-3) and 3D ultrasound imaging may help confirm the diagnosis (Figure 33-4) (Karabulut et al., 2002; Nath et al., 2005).

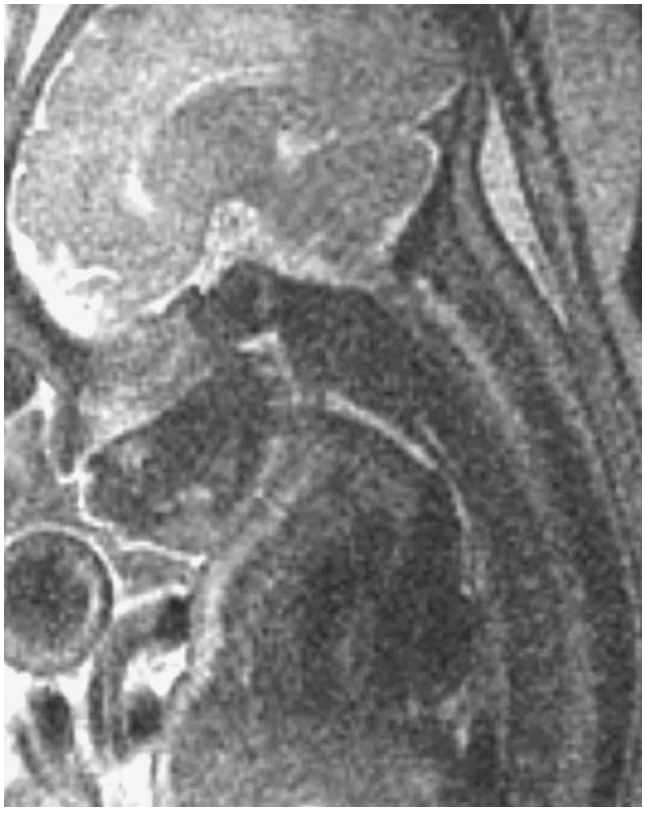

Figure 33-3 Magnetic resonance image of a prenatally diagnosed fetal goiter. (*Courtesy of Nancy Budorick, MD*).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for a fetal goiter includes a determination of whether the fetus is hypothyroid, hyperthyroid, or euthyroid. A presumptive diagnosis of fetal hyperthyroidism may be considered in the setting of a fetal goiter in a mother with autoimmune Graves disease. Sonographic findings suggestive of fetal hyperthyroidism include cardiac hypertrophy, hydrops, or fetal tachycardia. Sonographic findings suggestive of fetal hypothyroidism include cardiomegaly and fetal heart block. Because other methods of differentiation between hypothyroidism and hyperthyroidism may not be reliable, fetal blood sampling may be required to evaluate the fetal thyroid state. Amniotic fluid thyroid hormone values may also not be reliable (Abuhamad et al., 1995; Van Loon et al., 1995; Heckel et al., 1997).

Other structural abnormalities that may mimic a fetal goiter include a thyroid cyst, hemangioma, cervical neuroblastoma, teratoma, ectopic thymus, branchial cleft cyst, cervical meningocele, or cystic hygroma (Heckel et al., 1997). Anterior neck masses other than a fetal goiter, such as a teratoma

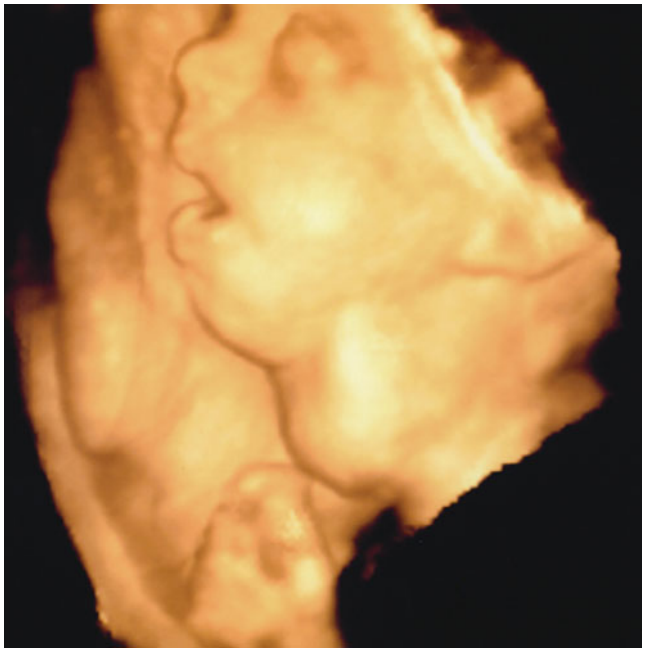

Figure 33-4 Twenty-seven-week fetus with goiter: three-dimensional multiplanar surface-rendered image of the fetal neck and face. *(From Nath CA, Oyelese Y, Yeo L, et al. Three-dimensional sonography in the evalution and management of fetal goiter.* Ultrasound Obstet Gynecol. *2005;25:312-314.)*

or neuroblastoma, tend to be asymmetric and extend above or below the thyroid region.

ANTENATAL NATURAL HISTORY

Little information is available to guide patient counseling regarding the antenatal natural history of fetal goiter. The literature to date consists almost entirely of single case reports. The antenatal natural history of a goiter will depend in large part on the thyroid status of the fetus. In the euthyroid fetus, the main potential problem associated with the presence of a goiter is obstruction of trachea and/or esophagus as the goiter enlarges in later pregnancy. This may lead to polyhydramnios, which may precipitate preterm contractions that are due to uterine overdistention (Abuhamad et al., 1995). In addition, fetal goiter may result in hyperextension of the fetal neck, which can result in dystocia (Romero et al., 1988).

Fetal goiter associated with hyperthyroidism may result in significant fetal changes in utero as the pregnancy progresses. Fetal effects may include tachycardia, cardiac hypertrophy, hydrops, fetal death, intrauterine growth restriction, craniosynostoses, advanced bone age, intellectual impairment, and preterm birth (Wenstrom et al., 1990; Belfar et al., 1991; McKenzie and Zakarija, 1992; Hatjis, 1993; Heckel et al., 1997). Fetal tachycardia is the most common presentation of fetal hyperthyroidism, and the most common cause of intrauterine death is secondary to hydrops. Congenital hyperthyroidism is associated with a 15% to 25% mortality rate.

Fetal goiter secondary to hypothyroidism may result in fetal bradycardia, heart block, or cardiomegaly. However, in the majority of cases of fetal hypothyroidism there are no additional sonographic findings other than the presence of a goiter. Given the strong association between mental retardation and untreated neonatal hypothyroidism, there is logical concern that prolonged untreated fetal hypothyroidism may also lead to intellectual impairment during the prenatal period (Abuhamad et al., 1995; Bruner and Dellinger, 1997).

MANAGEMENT OF PREGNANCY

After the prenatal diagnosis of a fetal goiter, a careful sonographic survey of the entire fetal anatomy is indicated to evaluate for sonographic signs consistent with fetal hypothyroidism or hyperthyroidism. A detailed maternal history should be obtained to evaluate for an antecedent diagnosis of thyroid dysfunction and for any exposure to drugs that may affect fetal thyroid function, such as propylthiouracil, iodide preparations, or amiodarone. It should be noted that the mother may be unaware of possible iodide exposure in the form of expectorant medications or certain radiopaque dyes (Romero et al., 1988). A physical examination of the mother should be performed to evaluate for clinical signs of hypothyroidism or hyperthyroidism. Maternal serum should be assayed for thyroxine (T_4) levels, thyroid-stimulating hormone (TSH) levels, and for the presence of thyroid-stimulating antibodies.

Because of the difficulty in predicting fetal thyroid status in the absence of clear sonographic signs of thyrotoxicosis, serious consideration should be given to percutaneous fetal blood sampling to evaluate fetal serum thyroid hormone levels directly. A maternal history of Graves disease does not imply that fetal goiter will be associated with fetal hyperthyroidism, as goiter may be secondary to either fetal hypothyroidism from transplacental passage of antithyroid medications or fetal hyperthyroidism from transplacental passage of thyroid-stimulating antibodies. An alternative to fetal blood sampling may be amniocentesis, which in the presence of severe fetal hypothyroidism may demonstrate elevated TSH levels. However, this approach is controversial, with many authors suggesting that there is no reliable correlation between amniotic fluid thyroid hormone levels and fetal serum levels (Abuhamad et al., 1995; Van Loon et al., 1995; Bruner and Dellinger, 1997; Heckel et al., 1997).

When the fetal thyroid status is known, decisions can be made regarding options for fetal intervention. These options are described in detail in the section on "Fetal Intervention." Prenatal consultation with a neonatologist is recommended to discuss potential difficulties with neonatal airway management. Careful sonographic surveillance every 2 weeks is recommended following the diagnosis of fetal goiter, because of the association with polyhydramnios, growth restriction, hydrops, and intrauterine death. Antenatal testing with twice-weekly nonstress tests or biophysical profiles is recommended in the presence of fetal hyperthyroidism.

Because of the possibility of significant tracheal compression, all fetuses with a goiter should be delivered in a tertiary care center with the immediate availability of experienced neonatology, pediatric anesthesiology, or pediatric otolaryngology personnel. Securing an adequate airway is crucial and, in cases of severe tracheal compression from a goiter, may require maintenance of the uteroplacental circulation until intubation, bronchoscopy, or tracheotomy procedures are performed (Stocks et al., 1997). The timing of delivery should not be altered simply because a fetal goiter is present. However, if the fetus has significant hypothyroidism or hyperthyroidism, consideration should be given to elective induction of labor at 39 weeks of gestation, because of the potential adverse pregnancy outcome associated with these conditions. The mode of delivery should be dictated by standard obstetric indications, although there may be a high likelihood of cesarean delivery in cases of severe fetal neck hyperextension leading to dystocia.

FETAL INTERVENTION

After the diagnosis of a fetal goiter, consideration should be given to percutaneous fetal blood sampling to accurately document the thyroid status of the fetus, and to guide options

for fetal intervention. Many case reports have described successful prenatal therapy of fetal hyperthyroid goiter, with resolution or improvement in the size of the thyroid gland (Wenstrom et al., 1990; Hatjis, 1993; Hadi and Strickland, 1995; Heckel et al., 1997; Yanai and Shveiky, 2004; Lembert et al., 2005). Propylthiouracil (PTU) is considered the drug of choice for the treatment of hyperthyroidism in pregnancy, because of an apparently slightly better safety profile as compared with carbimazole or methimazole. However, carbimazole and methimazole have much more rapid and complete transplacental transfer as compared with PTU (Marchant et al., 1977). If carbimazole or methimazole is used for fetal therapy, the lowest possible dose that produces a clinical effect should be used. All three agents are considered class D for use in pregnancy. Adequacy of dose can be documented by return of fetal heart rate to a normal range. Repeat fetal blood sampling may also be considered after therapy to confirm normalization of fetal serum thyroid hormone profiles. If the mother is clinically euthyroid, maternal thyroxine replacement may also be required, as an antithyroid medication used for fetal therapy may render the mother hypothyroid.

Many case reports have also described successful prenatal therapy of fetal hypothyroid goiter, with resolution or improvement of the goiter (Weiner et al., 1980; Noia et al., 1992; Abuhamad et al., 1995; Van Loon et al., 1995; Bruner and Dellinger, 1997; Vicens-Calvet et al., 1998). However, since thyroxine does not cross the placenta, more invasive methods of therapy are required to treat fetal hypothyroidism. The most commonly used approach is the periodic intra-amniotic injection of levothyroxine, 90% of which is adsorbed in animal models within 24 hours of instillation (Abuhamad et al., 1995). The dose used in the various reports described to date has varied from 250 to 500 mg of levothyroxine. The intra-amniotic injection of levothyroxine can be repeated weekly as often as needed until sonographic resolution of the fetal goiter occurs, or until repeat fetal blood sampling has confirmed normalization of the fetal thyroid hormone status. In one case report, intra-amniotic injections of levothyroxine were repeated for seven consecutive weeks, from 29 to 37 weeks of gestation, with documented normalization of fetal thyroid hormone status and reduction in size of the fetal thyroid gland (Abuhamad et al., 1995).

TREATMENT OF THE NEWBORN

A neonatologist should be present in the delivery room whenever a prenatal diagnosis of fetal goiter is suspected, as problems securing an adequate airway may be encountered. Although it is possible that emergency tracheotomy or bronchoscopy may be required in cases of severe tracheal compression from a large goiter, such occurrences are extremely rare. Once an airway is secured the neonate should be transferred to a neonatal intensive care unit for a thorough evaluation of thyroid status. This should include careful physical examination and serum thyroid hormone profiles.

Neonatal thyrotoxicosis can be treated with PTU, carbimazole, or methimazole, as in the adult patient. Additional therapy with a β-blocker such as propranolol may also be required to control heart rate. Iodide should be administered, in the form of Lugol solution. In most cases of maternal Graves disease with subsequent neonatal thyrotoxicosis, the hyperthyroid features are transient and ameliorate over time, as there is no longer a source of thyroid-stimulating autoantibodies. Therefore, medical supportive therapy is generally needed only for a short period, usually for no longer than 12 weeks. Neonatal features of hyperthyroidism may not appear during the first week of life, presumably due to a residual therapeutic effect of any maternal antithyroid medications that may be present in the neonatal circulation during the first days of life. Infants with hyperthyroid goiter should therefore be followed closely during the first 2 weeks of life to evaluate for possible clinical deterioration. The infant should be examined for any evidence of premature craniosynostoses, which can accompany fetal hyperthyroidism and may require surgical correction.

The infant with hypothyroid goiter is usually asymptomatic at birth, but may also present with profound lethargy, hypotonia, hyporeflexia, and bradycardia. Subsequent development may be delayed, with delayed bone age and epiphyseal dysgenesis. Replacement therapy with levothyroxine should be started immediately and is usually successful at reducing the incidence of intellectual impairment and developmental delay associated with congenital hypothyroidism. Any delay in therapy may lead to a significantly poorer neurologic outcome for the child.

SURGICAL TREATMENT

Surgical treatment for fetal goiter is rarely required. Occasionally, a massive fetal goiter may cause such extreme compression of the trachea that an adequate airway cannot be secured. In that case, surgical options include emergency tracheotomy in the delivery room or bronchoscopy. In the most severe cases of fetal goiter, the EXIT (ex utero intrapartum treatment) procedure may be another option to maximize the ability to promptly secure an airway at delivery. Using this technique during cesarean delivery, the fetal face and neck are exposed at the uterine incision prior to delivery of the fetus, thus preserving uteroplacental perfusion for up to 1 hour and allowing time for surgical attainment of an adequate airway (Liechty et al., 1997). Additional surgical resection of an enlarged thyroid gland in infancy may be required rarely, if interference with swallowing and breathing continues despite medical therapy.

LONG-TERM OUTCOME

Minimal data are available to counsel parents on the long-term prognosis in childhood following the prenatal diagnosis

of a fetal goiter. In almost all cases however, it can be expected that shrinkage of the goiter will occur during the neonatal period as appropriate medical therapy is initiated. In addition, most cases of hyperthyroid goiter will improve spontaneously during the first 1 to 3 months of life as thyroid-stimulating antibodies from a mother with Graves disease are no longer present. Failure to replace levothyroxine adequately in a timely fashion in infants with congenital hypothyroidism will greatly increase the risk of profound and irreversible intellectual impairment and developmental delay.

GENETICS AND RECURRENCE RISK

Recurrence of fetal goiter in subsequent pregnancies is a significant possibility when a mother has thyroid dysfunction. It is estimated that there will be some hypothyroid effects on the fetus in 1% of all mothers with hyperthyroidism who are taking PTU (Romero et al., 1988). Between 2% and 12% of all infants of mothers with Graves disease will have hypothyroidism or hyperthyroidism (Hatjis, 1993). Inborn errors of thyroid hormone biosynthesis that result in congenital dyshormonogenesis and cause hypothyroid fetal goiter are rare, but are inherited as an autosomal recessive trait. Therefore, the recurrence risk for such conditions is 25%.

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Bronchopulmonary Sequestration

34
CHAPTER

Key Points

- Bronchopulmonary sequestration (BPS) is a mass of nonfunctioning lung tissue that does not communicate with the bronchial tree.
- Prenatal diagnosis is possible by noting an echodense triangular area of tissue, often with an obvious systemic feeding vessel, such as from the descending aorta.
- BPS can be intralobar (same pleural cover as normal lung) or extralobar (separate pleural cover), and can be intrathoracic or extrathoracic.
- Main differential diagnosis for intrathoracic BPS includes type III CCAM, teratoma, and diaphragmatic hernia, while the differential for intra-abdominal BPS includes mesoblastic nephroma and neuroblastoma.
- At least 75% of prenatally diagnosed cases of BPS resolve spontaneously, while those associated with hydrops, pleural effusions, or mediastinal shift have a much worse prognosis.
- Fetal intervention by means of thoracoamniotic shunting may be an option for cases with coexisting pleural effusions prior to 30 weeks' gestation.
- For large lesions that persist prenatally, and for those associated with hydrops, delivery should occur in a tertiary care center.
- Elective surgical excision is recommended for most cases of asymptomatic BPS that persist postnatally.

CONDITION

Bronchopulmonary sequestration (BPS) is a mass of nonfunctioning pulmonary tissue that lacks an obvious communication with the tracheobronchial tree and receives all or most of its blood supply from anomalous systemic vessels (Carter, 1959). There appears to be a spectrum of sequestration with, at one extreme, an abnormal vessel supplying a nonsequestered lung and, at the other extreme, abnormal pulmonary tissue but without anomalous vascular supply. Terminology has become increasingly complicated with terms such as congenital bronchopulmonary foregut malformation (CBPFM) and malinosculation used (Gerle et al., 1968; Heithoff et al., 1976; Clements and Warner, 1987). CBPFM refers to intralobar or extralobar BPS associated with a communication with the gastrointestinal tract. The spectrum of CBPFM includes intralobar sequestration, extralobar sequestration, congenital cystic adenomatoid malformation (CCAM), bronchogenic cyst, Scimitar syndrome, and duplication cyst. Malinosculation describes the spectrum of congenital lung anomalies, in which there is abnormal connection of one or more of the four major components of the lung tissue (Clements and Warner, 1987). While much emphasis has been placed in the past in differentiating between

BPS and CCAM, it is now clear that both can coexist in the same lesion, where it is referred to as a hybrid lesion. Extralobar sequestration and CCAM type II coexisting together has been reported in 25% to 50% of extralobar sequestration cases (Conran and Stocker, 1999) (see Chapter 35).

There are two forms of BPS: intralobar and extralobar. Intralobar is the more common malformation seen in infants and children, accounting for 75% of cases of BPS, and it shares the same pleural investment with the normal lung (Savic et al., 1979; Collin et al., 1987). Extralobar BPS accounts for 25% of cases in infants and children, has a separate pleura from the lung, and may be either intrathoracic or subdiaphragmatic in location (Savic et al., 1979; Collin et al., 1987).

The most widely accepted theory about the embryogenesis of BPS is that a supernumerary lung bud arises caudal to the normal lung bud and migrates caudally with the esophagus. If this lung bud arises prior to the development of the pleura, the bud is invested with adjacent lung and becomes an intralobar BPS. If supernumerary development occurs subsequent to pleura formation, the bud will grow separately and become invested with its own pleura, forming an extralobar BPS (Carter, 1959).

INCIDENCE

BPS is seen in 0.8% to 1.4% of all pulmonary resections (Carter, 1959). There is no familial predisposition. There is a slight male predominance, which is more obvious in extralobar BPS (male to female ratio of 3:1) compared with intralobar BPS (male to female ratio of 1.5:1) (Warner et al., 1958; Carter, 1959; Williams and Enumah, 1968). Extralobar BPS is much more common in the fetus and neonate than intralobar BPS (Buntain et al., 1977; Moulik et al., 1987; Panicek et al., 1987; Felker and Tonkin, 1990; Sauerbrei, 1992).

Intralobar BPS is located within the lower lobe in 98% of cases. Extralobar BPS is usually located in the posterior lower chest and 90% of extralobar BPS is located on the left side. Up to 15% of extralobar BPS can be found either within or below the diaphragm (Berrocal et al., 2004).

SONOGRAPHIC FINDINGS

BPS is a solid, highly echogenic mass (Figure 34-1) with a clearly defined systemic feeding vessel (Figure 34-2). There have now been many reports of the prenatal sonographic diagnosis of BPS (Newman, 1970; Jaffe et al., 1982; Romero et al., 1982; Jouppila et al., 1983; Kritstoffersen and Ipsen, 1984; Mariona et al., 1986; Thomas et al., 1987; Adzick et al., 1998; Baumann et al., 1988; Davies et al., 1989a; Morin et al., 1989; Siffling et al., 1989; Weinbaum et al., 1989; Slotnick et al., 1990; Stern et al., 1990; Boiskin et al., 1991; Heranz-Schulman et al., 1991; Dolkhart et al., 1992; Eisenberg et al., 1992; Sauerbrei, 1992; Luetic et al., 1995). The sonographic hyperechogenicity of BPS is thought to result from the interfaces created by numerous dilated bronchioles (Jaffe et al., 1982). The demonstration of the systemic blood supply to the mass by color Doppler sonography usually confirms the diagnosis (Figures 34-2 to 34-4). Occasionally, these vessels cannot be demonstrated sonographically, making it difficult to distinguish BPS from type III congenital cystic adenomatoid malformation (CCAM) of the lung (see Chapter 35). Even if an anomalous systemic blood supply to a thoracic mass can be demonstrated, which confirms the diagnosis of BPS, intralobar and extralobar BPS usually cannot be distinguished by prenatal ultrasound. Several cases of extralobar BPS have been reported prenatally because of the finding of echogenic suprarenal abdominal masses (Mariona et al., 1986; Baumann et al., 1988; Davies et al., 1989b; Dolkhart et al., 1992).

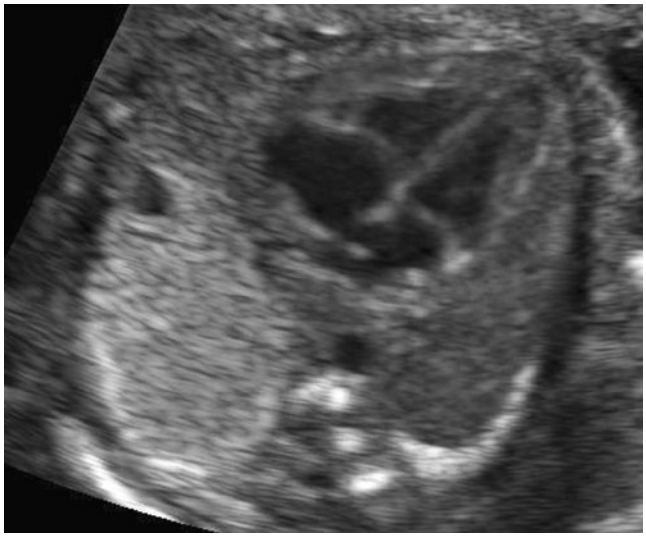

Figure 34-1 Ultrasound of the fetal chest at 23 weeks' gestation, demonstrating a homogeneous echodense triangular wedge-shaped thoracic mass, consistent with either type III cystic adenomatoid malformation or bronchopulmonary sequestration.

Additional sonographic findings seen in association with BPS include pleural effusion, mediastinal shift, hydrops, and polyhydramnios (Morin et al., 1989, 1994a, 1994b; Gross et al., 1992). Extralobar BPS may undergo torsion of its vascular pedicle, causing venous and lymphatic obstruction, leading to pleural effusion and hydrops due to systemic venous obstruction (Vode and Kramer, 1989; Morin et al., 1994a). Fetal hydrops may result from a compressive effect of the sequestration on the inferior vena cava with venous obstruction and compromised cardiac output. Polyhydramnios may be seen in association with BPS due to esophageal obstruction or decreased swallowing. BPS associated with hydrops uniformly results in fetal or neonatal death if untreated. There have been anecdotal reports of cases treated successfully in utero by thoracoamniotic shunting of the associated pleural effusion. To date, open fetal surgery has not been reported for a BPS in contrast to hybrid CCAM (see Chapter 35).

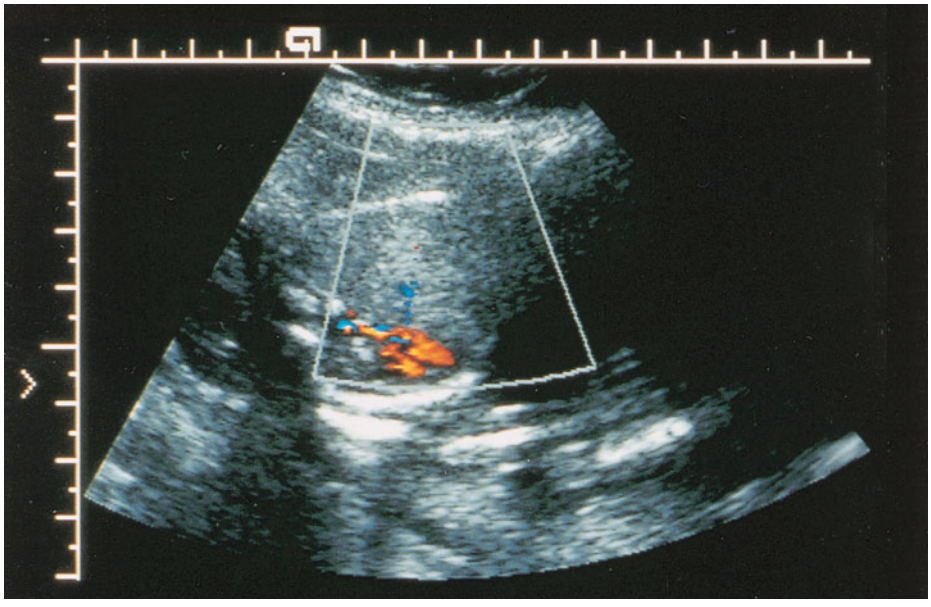

Figure 34-2 Color flow Doppler examination of the same fetus as in Figure 34-1, demonstrating systemic blood supply to the mass arising from the descending aorta, confirming the diagnosis of bronchopulmonary sequestration. (*Reprinted, with permission, from Morin L, Crombleholme TM, Louis F, et al. Bronchopulmonary sequestration: prenatal diagnosis with chinisopathologic correlation*. Curr Opin Obstet Gynecol. *1994b;6:479-481.*)

In postnatal series of BPS, there is a high incidence of associated anomalies, especially in extralobar BPS (60% of cases) (Warner et al., 1958; Carter, 1959; Gerle et al., 1968; Sade et al., 1974; Buntain et al., 1977; Savic et al., 1979; Collin et al., 1987). The most commonly associated anomalies include congenital diaphragmatic hernia (CDH), pectus excavatum, tracheoesophageal fistula, esophageal duplication, and congenital heart disease (Warner et al., 1958; Carter, 1959; Gerle et al., 1968; Buntain et al., 1977). The intralobar type has a lower incidence of associated anomalies (10% of cases) (Carter, 1959; Gerle et al., 1968; Sade et al., 1974; Buntain et al., 1977).

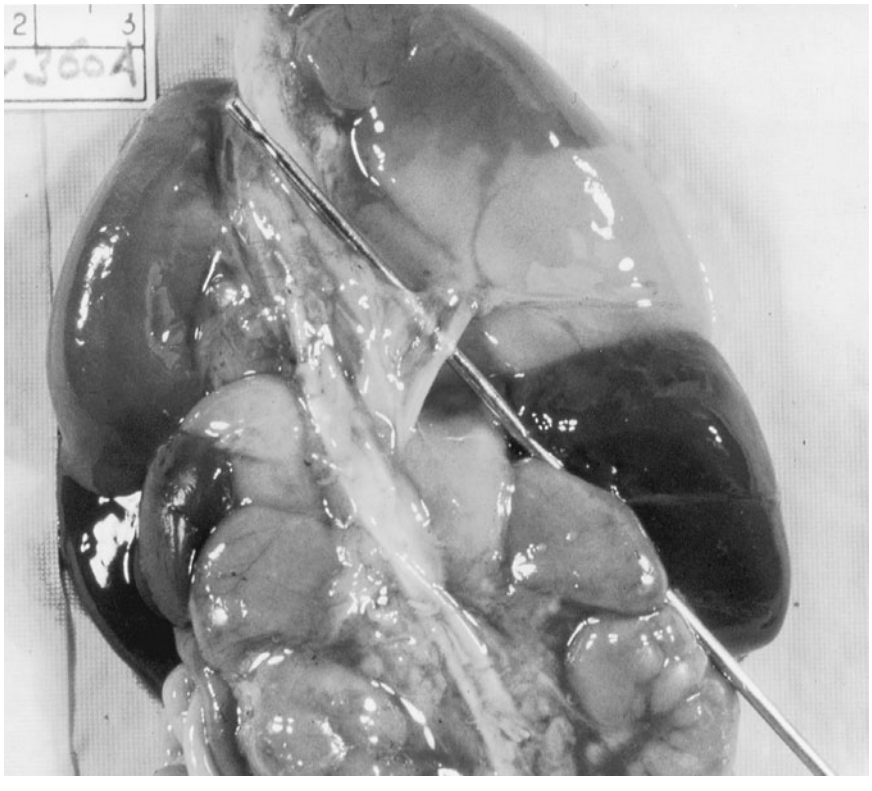

Figure 34-3 Autopsy confirmation of the systemic blood supply to an intralobar bronchopulmonary sequestration. The vessel is demonstrated by the probe.

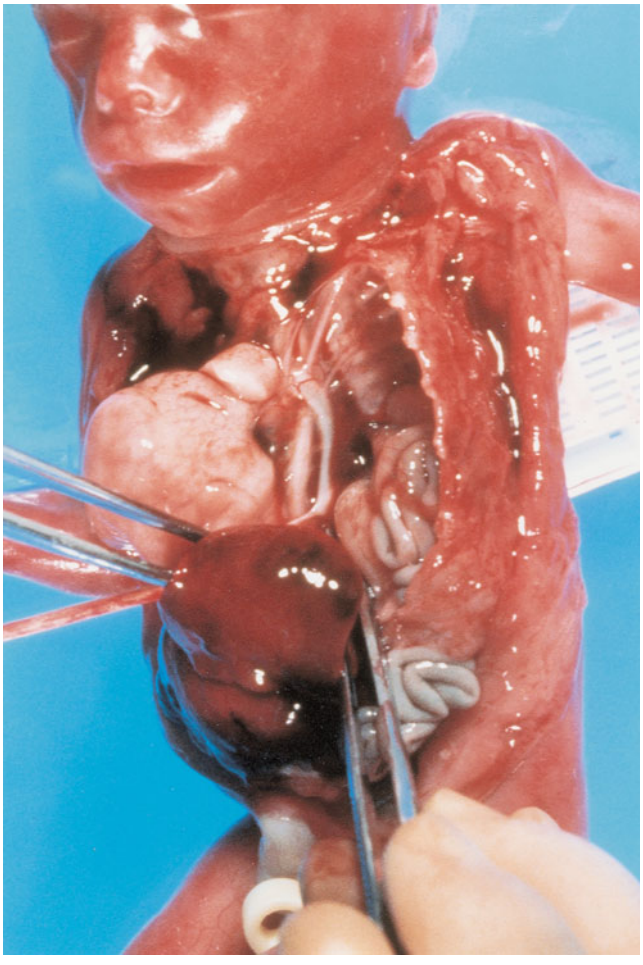

Figure 34-4 Photograph taken at autopsy, demonstrating systemic blood supply arising from the descending thoracic aorta to supply an extralobar BPS.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of intrathoracic BPS includes type III CCAM, mediastinal or thoracic teratoma, and CDH (Moulik et al., 1987; Morin et al., 1994a) (Table 34-2). Type I or II CCAMs have a characteristic cystic appearance that clearly distinguishes them sonographically from BPS, while type III CCAMs have a dense hyperechoic appearance that may be indistinguishable from BPS. Mediastinal teratomas usually have a higher density, causing acoustic shadowing behind the mass (Golladay and Mollitt, 1984). Prenatal diagnosis of BPS may be quite difficult. In a review of cases diagnosed antenatally, only 29% were diagnosed correctly (Dolkhart et al., 1992). The other cases of BPS were documented variously as tumor, diaphragmatic hernia, CCAM, neuroblastoma, collapsed lung, and abdominal mass (Siffling et al., 1989; Dolkhart et al., 1992). The distinction between CCAM and BPS when a systemic feeding vessel is not demonstrated usually comes down to the echotexture of the mass. The presence of cysts suggests CCAM, whereas solid triangular lesions are more consistent with BPS, especially in the lower thoracic region. In lesions that are without cysts, it may not be possible to distinguish type III hybrid CCAM from BPS.

The main considerations in the differential diagnosis of intra-abdominal extralobar BPS are mesoblastic nephroma and neuroblastoma (see Chapters 112 and 113) (Mariona et al., 1986; Baumann et al., 1988; Davies et al., 1989b; Ohnichi et al., 1989; Weinbaum et al., 1989; Sauerbrei, 1992). Intra-abdominal extralobar BPS can occur on as a discrete suprarenal echogenic mass with a systemic blood supply. This mass can be mistaken for neuroblastoma or mesoblastic nephroma (Ohnichi et al., 1989; Oh et al., 1993). However, mesoblastic nephroma can usually be seen arising from the kidney (Ohnichi et al., 1989). Neuroblastomas arising from the adrenal glands are most commonly cystic lesions, which distinguish them from BPS (Oh et al., 1993). There has been one case of gastric duplication in association with BPS that gave a cystic appearance to the intra-abdominal BPS (Thilenius et al., 1983).

ANTENATAL NATURAL HISTORY

The natural history of BPS depends on whether it is an intralobar or an extralobar BPS, whether it has a thoracic or abdominal location, and the presence or absence of hydrops and other associated anomalies (Adzick et al., 1993). Older reports suggested survival among cases of prenatally diagnosed intrathoracic BPS of only 36% (van Nayenberg, 1914; Williams and Enumah, 1968; Newman, 1970; Buntain et al., 1977; Rodgers et al., 1986; Panicek et al., 1987; Felker and Tonkin, 1990; Stern et al., 1990). However, a more recent report from the Children's Hospital of Philadelphia reported a survival of 95% (Adzick et al., 1998). This difference likely reflects the fact that today's more advanced ultrasound techniques are picking up milder cases that would never have been apparent prenatally in the past, as well as the fact that older case reports described successful prenatal diagnosis in only the most severe cases. BPS associated with hydrops is uniformly fatal if untreated (Weiner et al., 1986). The survival rate for BPS associated with pleural effusions was 22%, but the only survivors were those in whom the pleural effusions were decompressed in utero by thoracoamniotic shunts (Kritstoffersen and Ipsen, 1984; Boiskin et al., 1991; Dolkhart et al., 1992). The survival rate for BPS associated with polyhydramnios was only 30%.

Our understanding of the natural history of this lesion when diagnosed prenatally is still evolving. It was once thought that in fetuses with BPS, hydrops invariably developed and the fetus died in utero or during the neonatal period (Warner et al., 1958; Williams and Enumah, 1968). However, MacGillivray et al. (1993) subsequently reported six cases of BPS associated with contralateral mediastinal shift that dramatically decreased in size over the course of the pregnancy and spontaneously resolved, leading to a good neonatal outcome. Postnatally, the lesions could be detected only by computed tomographic (CT) scan or magnetic resonance imaging (MRI). There were no signs of hydrops in any of these cases.

Adzick et al. (1994, 1998) subsequently reported that 75% of cases of BPS diagnosed prenatally resolve spontaneously. The mechanism by which these lesions shrink is unknown. Adzick (1993) speculated that the lesions may decompress themselves into the normal tracheobronchial tree or that the lesions outgrow their vascular supply and partially involute (Rodgers et al., 1986). Another possibility is that the "disappearing" malformations are actually extralobar BPSs that undergo complete torsion about their vascular pedicle and infarct (Morin et al., 1994a).

Intra-abdominal extralobar BPS has an outcome that is somewhat better than that for intrathoracic lesions and is rarely associated with hydrops. However, polyhydramnios may still develop secondary to esophageal or gastric compression.

The BPS associated with hydrothorax is usually of the extralobar type. It is thought that torsion of the extralobar BPS about its vascular pedicle may result in venous and lymphatic obstruction, causing fluid accumulation in the ipsilateral hemithorax (Golladay and Mollitt, 1984). Tension hydrothorax in the fetus with BPS is fatal unless there is intervention. An alternative explanation for nonimmune hydrops, especially in intralobar BPS, is the "left-to-left" shunting that may occur due to anomalous systemic artery and venous drainage via the pulmonary veins (Thilenius et al., 1983). This "left-to-left" shunt, which occurs in no other clinical entity, results in high-output failure and nonimmune hydrops (White et al., 1974).

MANAGEMENT OF PREGNANCY

The fetus with an echodense chest mass should be evaluated to exclude CDH (see Chapter 37), mediastinal teratoma, and CCAM (see Chapter 35). In most cases of BPS, the vascular supply from the aorta can be defined with color Doppler studies (see Figure 34-2). The adrenal glands and kidneys should be delineated to distinguish an abdominal extralobar BPS from mesoblastic nephroma (see Chapter 112) and neuroblastoma (see Chapter 113). It is noteworthy that most cases of BPS diagnosed prenatally are isolated sequestrations without associated anomalies (Felker and Tonkin, 1990). Despite this observation, it is recommended that a detailed sonographic survey for possible associated anomalies be performed in every case.

Ultrafast fetal MRI may be very useful in sorting out the differential diagnosis, demonstrating the feeding vessels and excluding other potential associated anomalies. Normal fetal lungs are homogenous and, on MRI, have a relatively high T2 signal intensity because they are filled with amniotic fluid. A sequestration cyst typically appears as a well-defined mass in the chest with a T2 signal intensity that is higher than that of the normal lung (Hubbard et al., 1999). The efficacy of MRI for detecting systemic feeding vessels is no better than that of Doppler ultrasonography. However, MRI has some advantages over ultrasound in differentiating complex cases associated with other anomalies (Table 34-1).

Table 34-1

Anomalies Associated with Bronchopulmonary Sequestration

Scimitar syndrome
Goldenhar syndrome
Gastrointestinal duplications
Hirschsprung's disease
Esophageal atresia with tracheoesophageal fistula
Neuroenteric cysts
Vertebral anomalies
Pulmonary hypoplasia
Congenital diaphragmatic hernia
Diaphragmatic eventration
Cardiac anomalies
Aberrant pancreatic tissue
Pectus excavatum
Bronchogenetic cyst
Pericardial malformation
Cardiac anomalies
Congenital lobar emphysema

A fetal karyotype should be obtained to exclude associated chromosomal anomalies if they might influence the decision to continue the pregnancy or for cases in which fetal treatment is contemplated (see Table 34-2). Because of the reported association of BPS with congenital heart disease, fetal echocardiography should be performed (White et al., 1974). The family may choose not to continue the pregnancy if the diagnosis of BPS is made prior to 24 weeks and there are other life-threatening anomalies.

Arrangements should be made for delivery at a center with appropriate neonatal and pediatric surgical expertise. The fetus with isolated BPS, of either the intrathoracic or intra-abdominal type, has a good chance of survival in the absence of hydrops, polyhydramnios, or pleural effusion and when there is a planned delivery at an appropriately staffed facility with immediate resuscitation and surgery available. BPS may regress in size in 75% of cases, even when it is associated

Table 34-2

Differential Diagnosis for Fetuses with Chest Masses

Anterior mediastinum	Thymoma, teratoma, cystic hygroma
Posterior mediastinum	Gastric duplication, teratoma, neuroblastoma, Wilms' tumor
Left hemithorax	CCAM, accessory lobe
Right hemithorax	Bronchogenic cyst, hamartoma, CDH, CCAM, teratoma, accessory lobe
Diaphragm	CDH, duplication cyst
Left upper quadrant	Gastric duplication, adrenal cyst and tumors, accessory spleen, neuroblastoma, Wilms' tumor
Right upper quadrant	Adrenal cyst and tumors, liver tumor, neuroblastoma, Wilms' tumor

with mediastinal shift (MacGillivray et al., 1993; Adzick et al., 1995).

FETAL INTERVENTION

The management of intrathoracic BPS in the fetus with hydrops depends on the gestational age (Figure 34-5). Fetuses at 30 weeks' gestation or more should be considered for early delivery and resection ex utero. The fetus with hydrops and intrathoracic BPS diagnosed prior to 30 weeks' gestation may however be a candidate for fetal intervention. Hydrops may be seen in cases of BPS with tension hydrothorax, causing mediastinal shift, compromised venous return to the heart, and cardiac output. Thoracoamniotic shunting in these cases may correct the pleural effusion, mediastinal shift, polyhydramnios, and hydrops. Shunting is not an option for the fetus with intrathoracic BPS associated with mediastinal shift and hydrops from a large thoracic mass without pleural effusion. Because BPS associated with hydrops is uniformly fatal, fetal surgery should be considered in these cases. Adzick et al. have reported excellent results with fetal surgery for pulmonary resection in cases of CCAM. It is anticipated that similar results may be observed with BPS (Adzick, 1993; Adzick et al., 1998).

The prognosis for isolated intra-abdominal BPS is better than that for intrathoracic BPS because the intra-abdominal location does not result in pulmonary hypoplasia. Polyhydramnios may be observed due to compression of the esophagus or stomach, which may cause preterm labor and delivery. The role of reduction amniocentesis remains undefined but may be considered in such cases.

TREATMENT OF THE NEWBORN

Ideally, a fetus diagnosed with a large BPS should be delivered in a setting where vigorous resuscitation and appropriate therapy for a newborn with pulmonary hypoplasia can be initiated immediately. In contrast, small lesions do not require a change in delivery plans, and delivery in a community setting may be appropriate. The infant should be examined carefully to confirm the presence or absence of associated anomalies. There is a wide range of severity with BPS; the degree of pulmonary hypoplasia is the primary determinant of outcome. The newborn with intra-abdominal BPS usually has no respiratory compromise and can undergo elective resection. The treatment of the newborn with an intrathoracic BPS is determined by the severity of pulmonary hypoplasia. Therapeutic needs may vary from minimal (not requiring ventilatory support) to severe [requiring ventilatory and vasopressor support, high-frequency oscillatory ventilation, and/or extracorporeal membrane oxygenation (ECMO)]. Large pleural effusions should be treated immediately by tube thoracostomy. In the infant with pulmonary hypoplasia secondary to BPS, thoracotomy should be deferred until it is clear the infant has stabilized, as in the management of CDH (see Chapter 37) (Hazebrock et al., 1989; Langer et al., 1989). The infant's condition often deteriorates after surgery because of changes in chest wall compliance, pulmonary vascular resistance, and pulmonary hypertension superimposed on pulmonary hypoplasia.

SURGICAL TREATMENT

The surgical approach to BPS is straightforward, with the exception of the management of anomalous blood supply. These vessels are often huge, thin-walled, and elastic, rather than muscular, arteries. In 20% of cases, these vessels are subdiaphragmatic in origin; in 15%, more than one vessel is present (Carter, 1959). Subdiaphragmatic origin of anomalous vessels is more common with right-sided lesions (Gottrup and Lund, 1978). These vessels can retract into the mediastinum or diaphragm and continue to bleed. Intraoperative death due to hemorrhage from unrecognized anomalous vessels has been reported (Harris and Lewis, 1940). Of note, one series reported that 60% of right-sided intralobar sequestrations had anomalous venous return compatible with the Scimitar syndrome (Collin et al., 1987). The importance of preoperative assessment of venous drainage, as well as arterial supply, is underscored by the reports of postoperative fatalities due to ligation of anomalous veins that constituted the sole or major venous drainage of the entire ipsilateral lung (O'Mara et al., 1978; Thilenius et al., 1983).

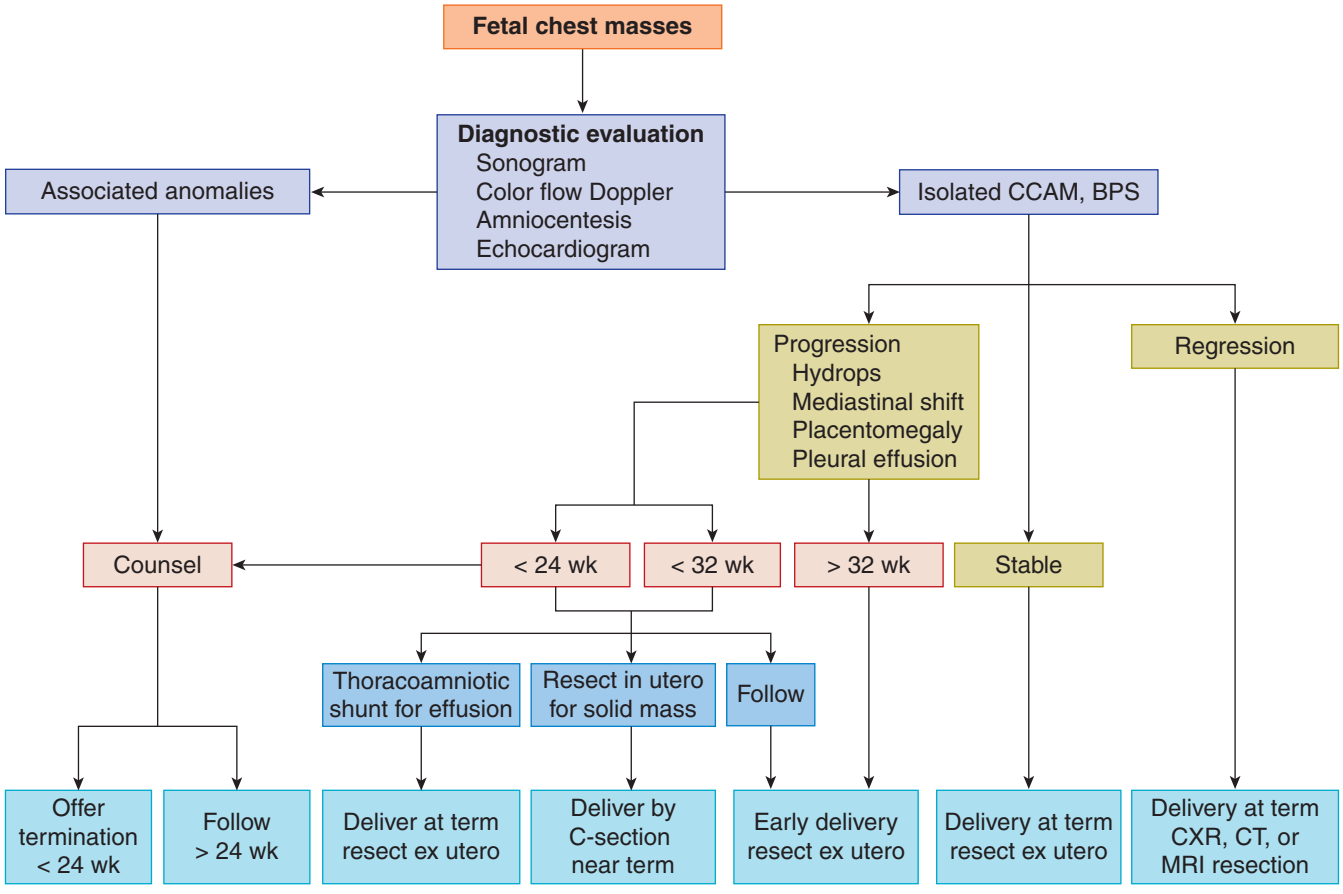

Figure 34-5 Algorithm for the management of fetal chest masses.

In the rare case of the prenatally diagnosed BPS that appears to regress, postnatal imaging studies should be obtained. If the lesion is evident on plain chest radiography, surgical resection should be planned. If chest radiography does not demonstrate the malformation, a CT or MRI scan should be performed. Even though these lesions are asymptomatic, postnatal resection should be considered because of the risks of infection, hemorrhage, and malignant transformation (Elias and Aufses, 1960; Juettner et al., 1987). When cardiac decompensation is the result of BPS, embolization of the feeding vessels may be considered. This technique can be used either as definitive treatment or in combination with resection. Complications reported after embolization include pain and pyrexia, pleural effusion, transient ischemia of the lower limb, recanalization of the artery, and persistent chest radiography changes (Corbett et al., 2004).

LONG-TERM OUTCOME

The resection of the intra-abdominal extralobar BPS has no affect on the pulmonary parenchyma, and the operative risks and long-term complications are the same as those for laparotomy in the newborn. The long-term outcome of intrathoracic BPS is determined by the extent of pulmonary hypoplasia. In extralobar BPS, resection results in no loss of pulmonary parenchyma. Resection of intralobar BPS requires at least segmentectomy or lobectomy, and the loss of pulmonary tissue may compound the underlying pulmonary hypoplasia in the short term. In the long term, removal of the BPS will provide room for compensatory lung growth in the remaining pulmonary tissue. It has been suggested that infants treated for BPS are at increased risk for gastroesophageal reflux, pneumonia, and pectus exconation (Corbett et al., 2004).

GENETICS AND RECURRENCE RISK

There is no known genetic predisposition to the development of BPS. Although BPS is not known to have a familial pattern of recurrence and occurs as a sporadic anomaly, there has been a case reported of BPS recurring in male siblings (Abuhamed et al., 1996).

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Cystic Adenomatoid Malformation

35 CHAPTER

Key Points

- CCAM is cystic malformation of pulmonary tissue and, unlike BPS, typically has a pulmonary blood supply.
- CCAM has been subdivided into five types, depending on the number and size of cystic changes; additionally hybrid lesions in which features of BPS coexist have been described.
- Prenatal ultrasound can detect either cystic or solid mass in the chest without a systemic vascular supply.
- Differential diagnosis includes BPS, diaphragmatic hernia, and bronchogenic cyst.
- Cases of CCAM with a dominant large cyst, or with a CCAM volume ratio greater than 1.6, appear to be at most risk of developing hydrops in utero, which is associated with very poor prognosis; in contrast, some cases of CCAM also regress spontaneously in utero.
- Fetal intervention is possible by means of thoracoamniotic shunting for cases of hydrops with a dominant cyst, or by means of open fetal surgical resection for cases of hydrops with a microcystic appearance; additionally a course of antenatal corticosteroids may also be beneficial.
- Delivery should occur electively, at term, in a tertiary care center with adequate pediatric surgical facilities available.

CONDITION

Congenital cystic adenomatoid malformation (CCAM) of the lung is a lesion characterized by a multicystic mass of pulmonary tissue with a proliferation of bronchial structures (Stocker et al., 1977; Miller et al., 1980). It may represent a failure of maturation of bronchiolar structures, occurring at approximately the 5th or 6th week of gestation during the pseudoglandular stage of lung development (Stocker et al., 1977; Miller et al., 1980; Shanji et al., 1988). Alternatively, it may represent focal pulmonary dysplasia, since skeletal muscle has been identified within the cyst walls (Leninger and Haight, 1973). Others have suggested that it may be the result of airway obstruction (Demos and Teresi, 1975; Cochia and Sobonya, 1981; Moerman et al., 1992; Langston, 2003). The gestational age and location of the airway obstruction may determine whether CCAM, bronchopulmonary sequestration, or lobar emphysema results (Keswani et al., 2005; Kunisaki et al., 2006).

CCAM is slightly more common in males and may affect any lobe of the lung (Hernanz-Schulman, 1993). The lesion is unilobar in 80% to 95% of cases and bilateral in fewer

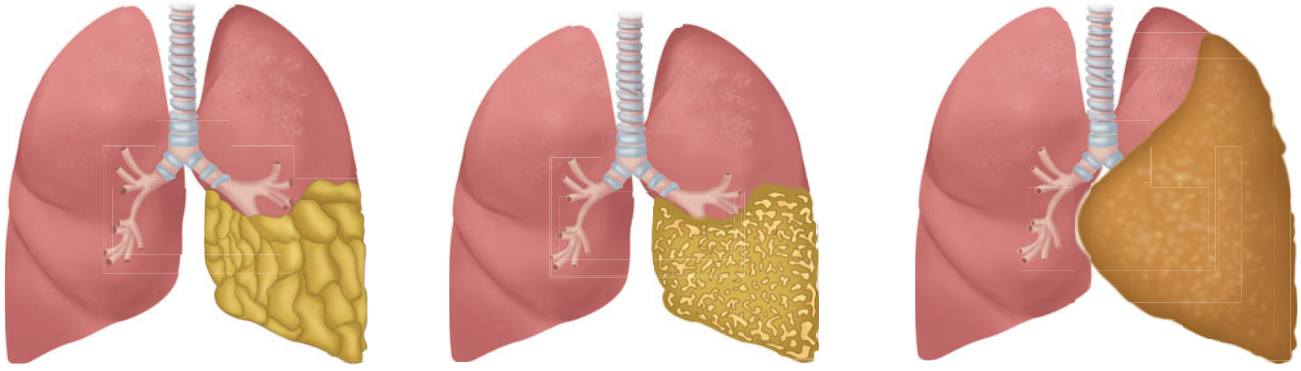

Figure 35-1 Depiction of Stocker's classification of type I, II, and III CCAM.

than 2% (Stocker et al., 1977). Unlike bronchopulmonary sequestration (BPS), CCAMs have a communication with the tracheobronchial tree, albeit via a minute tortuous passage. In contrast to BPS, CCAMs derive their arterial blood supply and venous drainage from normal pulmonary circulation, but anomalous arterial and venous drainage of CCAM have also been reported (Rashad et al., 1988) as well as the so-called "hybrid" CCAMs that have a systemic blood supply (Cass et al., 1997).

Stocker et al. (1977) originally subdivided CCAM into three types based on their pathologic characteristics (Figure 35-1). More recently, Stocker revised this classification to include five types. Stocker initially recommended that CCAM be classified as type I, II, and III and later added type 0 and IV (Stocker et al., 1977; Stocker, 2002). The five types were intended to represent the spectrum of malformations of five successive groups of airways. Type 0, a condition previously described as acinar dysplasia (Davidson et al., 1998) is described as bronchial; type I as bronchial/bronchiolar; type II as bronchiolar; type III as bronchiolar/alveolar dust; and type IV as peripheral. Because of the broad spectrum of malformations covered by this expanded classification system, Stocker (1994) suggested the term congenital pulmonary airway malformation (CPAM), and both CCAM and CPAM are in common usage. Stocker's classification is a histologic one, although commonly applied to sonographic appearance.

Type I lesions account for 50% of postnatal cases of CCAM, and consist of single or multiple cysts lined by ciliated pseudostratified epithelium. These cysts are usually quite large (3–10 cm) and few in number (1–4). Type I lesions are usually associated with a favorable outcome. Type II lesions account for 40% of postnatal cases of CCAM and consist of more numerous cysts of smaller diameter (usually less than 1 cm) lined by ciliated, cuboidal, or columnar epithelium. Respiratory bronchioles and distended alveoli may be present between these cysts. There is a high frequency of associated congenital anomalies with type II lesions. The prognosis for type II lesions often depends on the severity of associated anomalies. The most commonly associated anomalies include genitourinary, such as renal agenesis or dysgenesis; cardiac, including truncus arteriosus and tetralogy of Fallot; jejunal atresia; diaphragmatic hernia; hydrocephalus; and skeletal anomalies (Stocker et al., 1977). The high incidence of associated anomalies has led to speculation that this type of CCAM may occur as a result of events occurring prior to 31 days of gestation (Walker and Cudmore, 1990). The type III lesions account for only 10% of cases and are usually large homogeneous microcystic masses that cause mediastinal shift. These lesions have bronchiole-like structures lined by ciliated cuboidal epithelium, separated by masses of alveolar-sized structures lined by nonciliated cuboidal epithelium. The mixture of epithelial and mesenchymal structures in type III lesions has led to speculation that its development is related to events occurring prior to 28 days of gestation, after the formation of the lung buds (Walker and Cudmore, 1990). The prognosis in type III CCAMs is variable but can in severe cases present with nonimmune hydrops in utero and cardiorespiratory compromise in the newborn (Adzick et al., 1985b; Harrison et al., 1990a). Type IV CCAMs account for approximately 15% of cases and are characterized by very large cysts up to 10 cm lined by flattened epithelium resting on loose mesenchyme. These lesions can have areas of focal stromal hypercellularity with histologic overlap with grade I pleuropulmonary blastoma (McSweeney et al., 2003; Hill and Dehner, 2004).

Adzick et al. (1985b) have proposed a modification of Stocker's classification of CCAMs based on anatomy and sonographic appearance to assist in predicting prenatal outcome. In this classification, macrocystic CCAMs have single or multiple cysts >5 mm in diameter. Microcystic CCAMs are more solid and bulky, with cysts that are <5 mm in diameter. This distinction can easily be made sonographically in the fetus. Macrocystic lesions appear sonographically as fluid-filled cysts, while microcystic lesions appear solid with an almost homogeneous appearance (Adzick et al., 1985b). This is a useful sonographic distinction, because microcystic lesions are at increased risk for the development of hydrops. The high mortality rate of microcystic lesions is due to the large size these lesions attain and secondary sequelae, including mediastinal shift, pulmonary hypoplasia, polyhydramnios, and nonimmune hydrops (Adzick et al., 1985b, 1993, 1998; Harrison et al., 1990a).

INCIDENCE

CCAM has been considered a relatively rare lesion, although in more recent years, with the widespread use of obstetrical ultrasound, there has been a rapid increase in the number of cases detected prenatally (Nicolaides et al., 1987; Adzick et al., 1998). A commonly quoted incidence of CCAM lesions is between 1:25,000 and 1:35,000 livebirths (Laberge et al., 2001).

SONOGRAPHIC FINDINGS

CCAM is diagnosed by prenatal ultrasound demonstrating a lung tumor that may be solid or cystic, and with an absence of systemic vascular flow (Figure 35-2) (Dann et al., 1981; Bezzuti and Isler, 1983; Diwan et al., 1983; Cone and Adam, 1984; Johnson et al., 1984; Morcos and Lobb, 1986; Mendoza et al., 1986; Deacon et al., 1990). Types I and II CCAM appear as cystic or echolucent pulmonary masses, and may appear similar to diaphragmatic hernia, cystic hygroma, and other cystic lesions, such as bronchogenic or enteric cysts, and pericardial cysts (Boulot et al., 1991). In contrast, type III CCAM typically appears as a large hyperechogenic mass, often associated with mediastinal shift and, in advanced cases, hydrops (Adzick et al., 1985b).

The sonographic appearance of CCAMs can range from solid echodense mass filling the chest to a lesion with a single dominant cyst with a compressive effect on the mediastinum. The vast majority of CCAMs derive their blood supply from the pulmonary circulation and drain via the pulmonary veins. However, color Doppler should be used to search for the presence of a systemic feeding vessel. This may be observed in most BPSs (the main differential diagnosis in CCAMs) and in "hybrid" CCAM lesions (Cass et al., 1997). The systemic feeding vessel in hybrid CCAM lesions usually comes directly off the descending aorta; however, transdiaphragmatic systemic feeding vessels have also been observed in CCAMs.

A change in the echogenicity of type III CCAMs may occur between 30 and 34 weeks in which they become isoechogenic with adjacent normal lung. Although sonographically invisible, such cases of CCAM are still readily apparent on MRI. Occasionally, postnatal imaging with CT scanning reveals no evidence of CCAM, which may be due to the presence of lobar emphysema instead.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of fetal thoracic masses includes congenital diaphragmatic hernia (CDH) (see Chapter 37), bronchogenic or enteric cysts, BPS (see Chapter 34), mediastinal cystic hygroma (see Chapter 32), bronchial atresia or stenosis, neuroblastoma, and brain heterotopia (Adzick et al., 1985a; Hobbins et al., 1979; Gonzalez-Cuezzi et al., 1980; Romero et al., 1982; Chinn et al., 1983). The sonographic appearance of CCAM will influence the differential diagnosis. Type I CCAMs are more likely to be confused with a CDH. Observing peristalsis in the loops of herniated intestine or emptying of the stomach herniated through the diaphragm may help to differentiate the two (May et al., 1993). Fetal magnetic resonance imaging (MRI) may be helpful in evaluating fetal chest masses and distinguishing them from diaphragmatic hernia (Figure 35-3) (Hubbard and Crombleholme, 1998). It is also worth noting that CCAM can coexist with CDH (Stocker et al., 1977). The microcystic type III CCAMs are highly echogenic. This is helpful in distinguishing CCAM from solid tumors such as neuroblastoma. Bronchogenic cysts

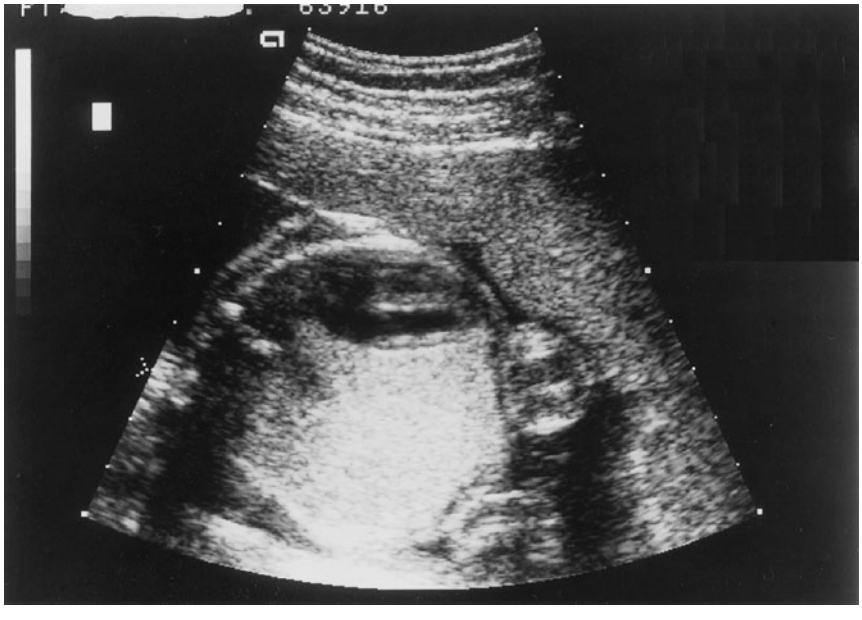

Figure 35-2 Prenatal sonographic cross-sectional image of the fetal chest, demonstrating a large homogeneous type III CCAM filling the right chest, displacing the mediastinum to the left. The four-chamber view of the heart is seen displaced against the left chest wall. (*Courtesy of Dr. Marjorie Treadwell.*)

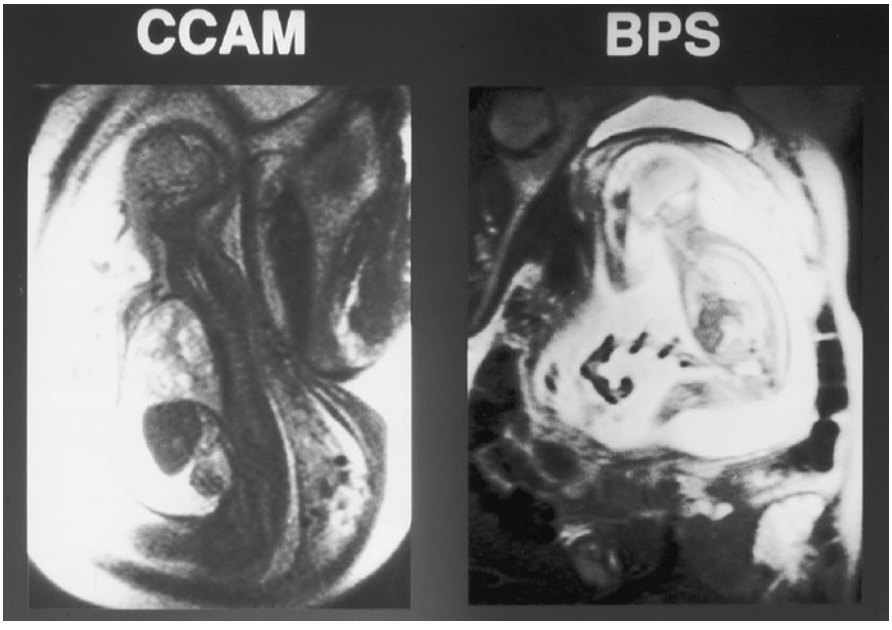

Figure 35-3 Fetal MRI in CCAM and BPS. The left panel is a sagittal section of a fetus with complex multicystic adenomatoid malformation with associated hydrops and ascites. The right panel is a sagittal section of a fetus with a hyperechogenic, homogeneous, wedge-shaped mass due to bronchopulmonary sequestration.

are unilocular and are usually adjacent to major bronchi, which may be confused with a type I CCAM. However, the main differential diagnosis in type III CCAM is usually BPS. Unlike most CCAMs, BPS derives its blood supply from the systemic circulation (Carter, 1959). This systemic blood supply to BPS can often be demonstrated with the use of color flow Doppler studies (Figure 35-4) (Hernanz-Schulman et al., 1991; Morin et al., 1994). There has been an anecdotal report of CCAM associated with anomalous blood supply (Rashad et al., 1988). With the exception of this case, the demonstration of systemic blood supply to a thoracic mass has been thought to be pathognomonic of BPS. More recently, Cass et al. (1997) described six cases of cystic adenomatoid malformation that had systemic blood supply. These lesions were called "hybrid" lesions as they had features of both CCAMs and BPSs and their natural history was also a mixture of the two lesions. The prognosis in hybrid CCAM is much more favorable than "pure" CCAM (Crombleholme et al., 2002).

ANTENATAL NATURAL HISTORY

The postnatal natural history of CCAM can be quite variable (Adzick, 1993, 1998). The lesion can be completely asymptomatic and come to medical attention only when chest radiography is performed for other reasons, such as a history of mild respiratory complaints with recurrent infections in infancy or childhood. However, most postnatal patients will present at birth with severe cardiorespiratory compromise

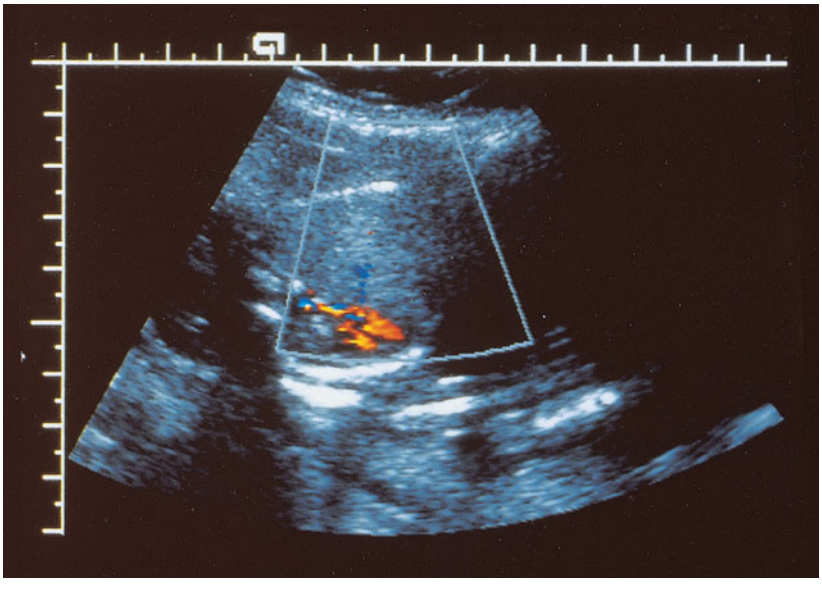

Figure 35-4 Color Doppler sonogram demonstrating systemic feeding vessel arising from the aorta supplying an echogenic lung mass, in this case a bronchopulmonary sequestration.

due to severe pulmonary hypoplasia (Atkinson et al., 1972; Stocker et al., 1977; Nishibayashi et al., 1981; Pulpeiro et al., 1987; Heij et al., 1990; Hernanz-Schulman et al., 1991; Neilson et al., 1991; Kuller et al., 1992; Cloutier et al., 1993). Even before the advent of obstetrical sonography, it was recognized that up to 14% of cases of CCAM result in stillbirths (Stocker et al., 1977). This observation hinted at the different prenatal natural history of CCAM.

Our understanding of the natural history of CCAM is still evolving. The worst outcome is observed in fetuses in which hydrops develops (Adzick et al., 1985b, 1998; Harrison et al., 1990a; Adzick, 1993). Hydrops is usually seen in very large lesions, often type III lesions, which cause mediastinal shift and vena caval obstruction (Figure 35-5). Hydrops may also be exacerbated by the loss of protein from the CCAM into the amniotic fluid, thus reducing the fetal colloid oncotic pressure from hypoproteinemia (Hernanz-Schulman et al., 1991). Anecdotal reports exist of fetuses with CCAM surviving after the onset of hydrops (Golladay and Mollitt, 1984; Graham et al., 1982; Glaves and Baker, 1983; Heydanus et al., 1993; Meagher et al., 1993; Etches et al., 1994; Dommergues et al., 1997; Higby et al., 1998; Bunduki et al., 2000; Diamond et al., 2003). Diamond et al. (2003) suggested that resolution by 30 weeks' gestation may be more common than is appreciated. The reason for this unexpected resolution of hydrops in CCAM was not apparent until the natural history of CCAM was defined by Crombleholme (Crombleholme et al., 2002). CCAMs plateau in their growth at an average of 26 weeks' gestation after which the fetus grows around the CCAM allowing hydrops to resolve (Crombleholme et al., 2002).

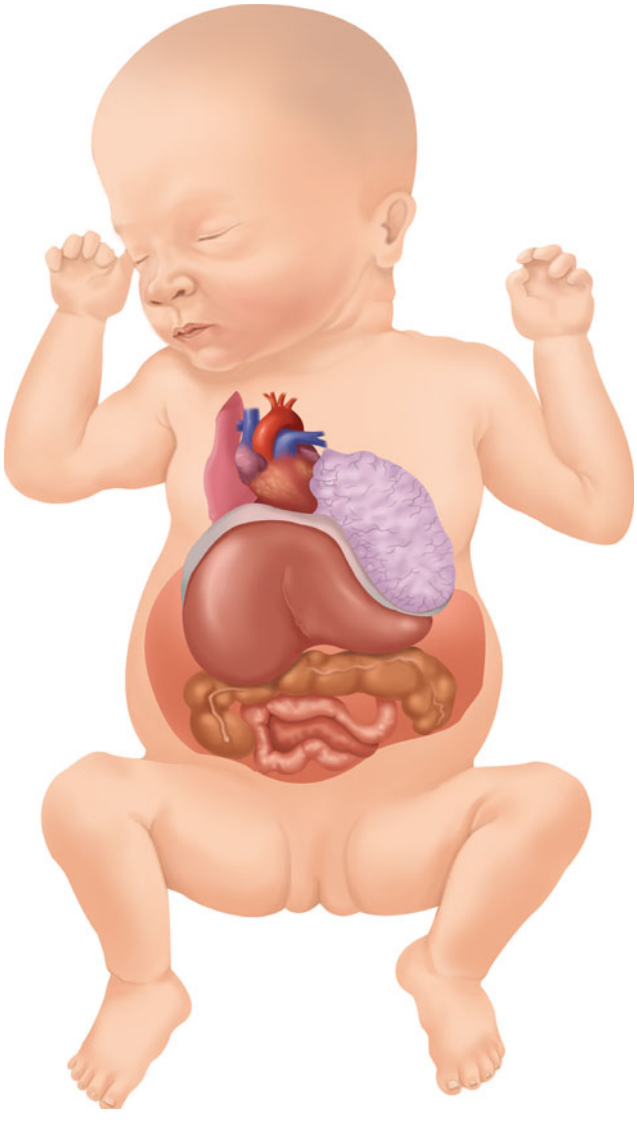

Figure 35-5 Schematic illustration of the pathophysiology of large CCAMs. The rapid growth of the chest mass compresses the lungs, depresses the diaphragm, and shifts the mediastinum, compromising venous return to the heart. Ascites, placentomegaly, and nonimmune hydrops develop.

The overall prognosis depends primarily on the size of the lesion, as well as whether it is predominantly macrocystic or microcystic. Polyhydramnios is seen in up to 70% of CCAMs diagnosed antenatally (Adzick et al., 1998). The pathogenesis of polyhydramnios is not completely understood but is thought to relate to esophageal obstruction from mediastinal shift and interference with fetal swallowing of amniotic fluid (Miller et al., 1980; Murayama et al., 1987). This is supported by the absence of fluid in the fetal stomach in such cases.

The diagnosis of CCAM may also have implications for the health of the mother. The mother with a fetus with CCAM may develop the "mirror syndrome," a hyperdynamic pre-eclamptic state that may be life-threatening. The "mirror syndrome" has also been seen in molar pregnancies, sacrococcygeal teratoma, and in fetal conditions that result in poor placental perfusion, which leads to endothelial cell injury (Creasy, 1979; Roberts et al., 1989). The only treatment for this syndrome is immediate delivery of the baby and placenta.

The antenatal diagnosis of a large CCAM might at first appear to be an ominous finding; however, several reports have described disappearing fetal lung masses (Fine et al., 1988; Saltzman et al., 1988; Budorick et al., 1992; Adzick and Harrison, 1993; Adzick et al., 1993; MacGillivray et al., 1993). MacGillivray et al. (1993) have reported six cases of large CCAM with associated mediastinal shift that progressively decreased in size over the course of gestation. These lesions were all of the microcystic, or type III, variety but none was associated with hydrops. The percentage of cases that will undergo spontaneous regression is not known, but may occur in 6% to 11% of cases (MacGillivray et al., 1993; Adzick et al., 1998). The reason for regression of fetal CCAM is not understood. Decompression of the fluid from the CCAM into the tracheobronchial tree or outgrowing its blood supply has been suggested as possible mechanisms (Adzick et al., 1993). There has been no biochemical or sonographic marker that allows differentiation between a CCAM that will regress and one that will progress to hydrops.

Recently, Crombleholme et al. (2002) reported the use of CCAM volume and the CCAM volume ratio as a predictor of the development of hydrops. The CCAM volume

is calculated using the formula for the volume of an ellipse ($h \times w \times l \times 0.52$ in cm^3) with the measurement of the greatest length in the sagittal section and the width and height taken at 90 degrees to the sagittal measurement. The CCAM volume ratio (CVR) is obtained by dividing the CCAM volume by the head circumference (in cm) to correct for any differences in gestational age. Based on 32 fetuses with CCAMs, the CCAM volume and the CVR were found to be significantly higher in fetuses destined to develop hydrops. Of those fetuses with CVRs > 1.6, 80% developed hydrops. The CVR may therefore be a useful criterion to select fetuses at greatest risk for the development of hydrops and those at low risk for development of hydrops (Crombleholme et al., 2002).

One of the largest experiences with prenatally diagnosed CCAMs has been reported by Adzick et al. (1998) who described 134 fetuses with CCAM. Of these, 14 pregnancies were terminated, 101 cases were managed expectantly, 13 women underwent open fetal surgery, and 6 fetuses underwent thoracoamniotic shunt placement. In the fetuses that did not develop nonimmune hydrops, the postnatal survival was 100%. In contrast, of 25 large CCAMs that developed hydrops and were managed expectantly, there was 100% mortality, with death in utero or immediately after birth. Among the 76 fetuses with CCAMs that were not associated with hydrops, the uniform survival was, in part, due to planned near-term delivery at a tertiary care center. Many of the babies with large lesions required substantial ventilatory support, and four needed treatment with extracorporeal membrane oxygenation (ECMO).

Fifteen CCAM lesions appeared large at 20 to 26 weeks of gestation with an associated contralateral mediastinal shift, but then clearly decreased in size during the third trimester with return of the position of the heart toward midline. Although four of these shrinking lesions were associated with polyhydramnios, including one case with fetal ascites, these phenomena resolved as the masses decreased in size.

MANAGEMENT OF PREGNANCY

The initial evaluation of the patient with a suspected fetal CCAM should include a detailed ultrasound examination to confirm the diagnosis, including color flow Doppler studies to demonstrate or exclude systemic blood supply as seen in BPS (see Chapter 34). The size of the cysts within the lesion should be noted, as well as the size and location of the CCAM. Evidence of mediastinal shift and subtle signs of hydrops should be sought. The incidence of chromosomal anomalies in CCAM is uncertain. In the report by Adzick et al. (1998), among 134 prenatally diagnosed CCAMs, there was only one fetus with a chromosomal abnormality (trisomy 21), for an incidence of only 0.7%. Amniocentesis for karyotype analysis may be reasonable if fetal treatment is anticipated (D'Alton and DeCherney, 1993). Fetal echocardiography should be performed in all cases of suspected CCAM because of an increased incidence of associated cardiac anomalies, particularly truncus arteriosus and tetralogy of Fallot (Stocker et al., 1977; Miller et al., 1980). In addition, there is impaired cardiac function in large CCAMs that shifts the mediastinum causing compression of the ventricles, elevating central filling pressures, altering ventricular inflow patterns, and causing reversal of IVC flow with atrial contractions. This pattern of restrictive ventricular filling associated with flow reversals in the IVC with atrial contractions may be a harbinger of the development of hydrops (Mahle et al., 2000). Prenatal consultation should be obtained from a pediatric surgeon, a neonatologist, and a pediatric cardiologist.

If there are associated life-threatening congenital anomalies, the family may choose not to continue the pregnancy. The development of the maternal "mirror syndrome" warrants immediate delivery. A fetus with an isolated CCAM but no hydrops should be followed closely by serial sonography. Occasionally, these lesions will regress during gestation, but this is not predictable, and CCAMs should be observed for signs of hydrops. All fetuses with CCAMs should be referred for delivery at a tertiary care center, preferably with ECMO capability, where a planned delivery with appropriate resuscitation and surgery can be performed. There is no need for cesarean delivery of a baby with CCAM except for standard obstetrical indications.

FETAL INTERVENTION

The management of CCAM and hydrops depends on the CVR value that is obtained at presentation. If the CVR is less than 1.6 and there is no evidence of a dominant cyst, the CCAM has only a 2% risk for the development of hydrops (Crombleholme et al., 2002). The fetus should have weekly sonograms to measure the CAM volume and CVR in order to identify early signs of hydrops or more likely that the plateau in growth has been reached. Once the growth plateau is reached, the pregnancy is no longer at risk for the development of hydrops. The surveillance of the fetus can be reduced but one should continue to assess the size of the CCAM, the risk of pulmonary hypoplasia, or air trapping that would influence delivery management.

If there is a dominant cyst, even if the CVR is less than 1.6, the fetus remains at significant risk for acute enlargement of the cyst and development of hydrops. A thoracoamniotic shunt may be considered in these cases at the very earliest sign of hydrops.

If the CVR is more than 1.6 at presentation, with or without a dominant cyst, there is an 80% chance of hydrops developing. Twice weekly sonographic surveillance should be started to help detect the earliest signs of hydrops, in which case fetal surgery may be considered. Maternal administration of antenatal corticosteroids should be considered in all cases with a CVR of 1.6. There are now two small series of apparent resolution of hydrops in patients with CCAMs that were not candidates for open fetal surgery (Tsao et al., 2003;

Perenteau et al., 2008). It is thought that steroids may arrest the growth of the solid component of the CCAM inducing an early growth plateau allowing the fetus to grow around the CCAM and hydrops to resolve. However, it is not proven that steroids truly affect the growth of CCAMs and the observations reported may simply reflect CCAMs naturally entering a growth plateau regardless of steroid administration.

Fetuses with CCAM and a dominant cyst in which hydrops develops prior to 32 weeks can be considered for treatment in utero. There now have been at least 28 CCAMs treated by thoracoamniotic shunting (Clark et al., 1987; Nicolaides et al., 1987; Bernaschek et al., 1994; Miller et al., 1996; Dommergues et al., 1997; Bunduki et al., 2000; Laberge, 2001; Wilson et al., 2004; Viggiano et al., 2006) with survival of 19 (70%) fetuses. However, these survivors often have marked respiratory insufficiency and some have required ECMO or high-frequency ventilation. The most challenging antenatal presentation is large microcystic CCAM with hydrops that does not lend itself to catheter decompression. Fetal surgical resection of massively enlarged microcystic CCAM with associated hydrops has been performed in at least 25 patients at 21 to 29 weeks' gestation (Figure 35-6) (Harrison et al., 1990b; Adzick et al., 1993, 1998). In this series, of the 16 fetuses that survived, CCAM resection led to hydrops resolution in 1 to 2 weeks, return of the mediastinum to the midline within 3 weeks, and impressive in utero lung growth. There were also nine fetal deaths in this series.

While open fetal surgery remains the best treatment option for type III CCAMs associated with hydrops, some patients may not be suitable or may decline such intervention. In these cases, a course of maternal steroids (betamethasone or dexamethasone) may be effective in arresting the growth of the CCAM (Tsao et al., 2003; Peranteau et al., 2008; Morris et al., 2009). We have treated several patients in the Fetal Care Center of Cincinnati with resolution of hydrops. The fetus remains at high risk, however, for significant pulmonary hypoplasia. In some instances, the size of the CCAM remains substantial with significant mediastinal shift and cardiac compression. In these cases, delivery by EXIT-to-Resection may be indicated. The rationale for this approach is that the mediastinal shift and compression by the CCAM will make ventilation difficult and will similarly impair venous return if ECMO was attempted. During EXIT-to-Resection, a thoracostomy for resection of the CCAM is performed on placental support during an EXIT procedure. In this approach when the infant is born the trachea is decompressed facilitating ventilation, and if ECMO is needed venous return will be unobstructed (Hedrick et al., 2005).

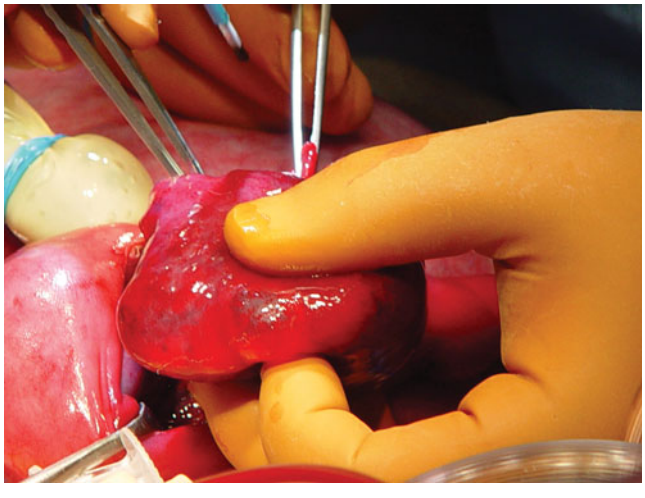

Figure 35-6 Intraoperative view of a fetus at 23 weeks' gestation undergoing resection of a large left lower lobe CCAM. The uterus has been opened, and the left fetal chest has been opened through a left thoracoabdominal incision; the left lower lobe CCAM has been delivered from the chest and is held in the surgeon's fingers. The forceps hold the tip of the hypoplastic left upper lobe. The 7 Hz fetal echocardiography probe seen in the background is used for continuous intraoperative fetal cardiac monitoring.

TREATMENT OF THE NEWBORN

The fetus with CCAM should be referred for delivery at a center with an intensive care nursery and appropriate staff available to resuscitate a newborn with potentially severe pulmonary hypoplasia. The newborn should be evaluated in the nursery to confirm the prenatal diagnosis and exclude other associated anomalies. The infant with type I or II CCAM may be at significant risk for air trapping in the CCAM, which may acutely worsen the respiratory status (Stocker et al., 1977; Bailey et al., 1990). In cases of unilateral CCAM, selective intubation of the contralateral bronchus may be a useful temporizing measure until resection of the CCAM can be accomplished. Pneumothorax is an additional concern in CCAM, especially in the type I or II lesions, and may require tube thoracostomy (Bentur et al., 1991).

SURGICAL TREATMENT

CCAM is usually confined to a single lobe. Rare cases have been reported of multilobar involvement of one lung or bilateral lesions (Rempen et al., 1987). Complete resection of the CCAM, usually by lobectomy, is the treatment of choice in CCAM. In cases of extensive involvement of nearly the entire lung, resection of multiple lobes or pneumonectomy may be necessary. There are several reports, however, detailing potentially lethal problems associated with pneumonectomy in newborns resulting from mediastinal shift with vascular compression of the trachea and remaining bronchus (Szarnicki et al., 1978). Because of these risks, some groups advocate a nonanatomic resection to preserve as much pulmonary parenchyma as possible to allow postoperative compensatory growth and avoid postpneumonectomy complications (Mentzer et al., 1992).

The newborn with a CCAM detected antenatally that subsequently regresses, also needs careful postnatal evaluation (MacGillivray et al., 1993; Adzick et al., 1998). Often

subtle abnormalities will be evident on chest radiography, but chest CT or MRI scanning may be necessary to detect residual CCAM tissue. Several authors have recommended that as long as these lesions are asymptomatic, they be observed closely and managed without resection (Adzick et al., 1993; MacGillivray et al., 1993; Aziz et al., 2004; Hsieh et al., 2005). The argument against this approach includes the reported cases of myxosarcoma, embryonal rhabdomyosarcoma, pleuropulmonary blastoma, and bronchoalveolar carcinoma arising in CCAMs (Stephanopoulos and Catsaros, 1963; Wecla et al., 1977; Benjamin and Cahill, 1991; d'Agostino et al., 1997). While primary lung tumors are rare during the first two decades of life, 4% of those reported were associated with congenital cystic lesions of the lung, including CCAM (Benjamin and Cahill, 1991). While CCAM-associated malignancies often arise only after decades, the youngest patient reported with a malignancy was only 13 months of age (Ozcan et al., 2001). Because there is an anomalous connection to the tracheobronchial tree, infection is an additional potential complication (Stephanopoulos and Catsaros, 1963; Ueda et al., 1977; Weinberg et al., 1980; Krous and Sexauer, 1981; Weinblatt et al., 1982; Prichard et al., 1984; Sheffield et al., 1987; Hedlund et al., 1989; Domizio et al., 1990; Benjamin and Cahill, 1991; Morresi et al., 1995; Ribet et al., 1995; d'Agostino et al., 1997; Kaslovsky et al., 1997; Granata et al., 1998; de Perrot et al., 2001; Federici et al., 2001; Ozcan et al., 2001; Hasiotou et al., 2004; Doladzas et al., 2005; Pai et al., 2005). Some have argued that asymptomatic CCAMs should be followed expectantly, and that the risks of surgery in infancy outweigh the potential benefits (Aziz et al., 2004). However, the continued presence of CCAM represents a lifelong risk of both infection and malignant transformation. In centers with significant experience in lung resection in infants, CCAMs can be safely resected with no mortality and virtually no morbidity (Tsai et al., 2007). Our approach is to obtain a postnatal CT scan and perform a muscle-sparing thoracotomy for lobectomy or nonanatomic resection whenever possible to retain normal lung tissue. An added benefit to resection over observation is that the remaining lung undergoes significant compensatory growth within months of the surgery. This does not occur if the CCAM is left in situ.

LONG-TERM OUTCOME

The long-term outcome of infants with CCAM following resection is excellent. If residual CCAM is left behind or the mass is not resected, the child will be at risk for infectious and potentially malignant complications. Also as noted above, infants usually have remarkable compensatory growth of the residual lung following resection, with continued alveolization for several years. We also recommend prophylaxis against respiratory syncytial virus (RSV) in infancy in children with significant pulmonary hyperplasia, pulmonary hypertension, or chronic lung disease. Children who survived open fetal surgery for CCAMs associated with hydrops appear to be still doing well from 1 to 7 years postoperatively.

GENETICS AND RECURRENCE RISK

CCAM has no known genetic defect responsible for its development and is thought to be an early developmental anomaly of uncertain cause. CCAM is not known to be specifically associated with chromosomal abnormalities, although one case of the 134 CCAMs reported by Adzick et al. (1998) had trisomy 21. No cases of recurrence of CCAM in a sibling or offspring have been reported.

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Other Cystic Lesions of the Chest

36 CHAPTER

Key Points

- Differential diagnosis includes bronchogenic cyst, pericardial cyst, thymic cyst, esophageal duplication, and neurenteric cysts.
- Sonographic features may be used to differentiate between various cystic masses that may be found in the fetal chest.
- MRI scanning is often a useful adjunctive imaging modality to ultrasound that may allow more accurate diagnosis and recognize mass effect on adjacent structures.
- Fetal intervention may be indicated by thoracoamniotic shunting for hydrops.
- EXIT-to-ECMO or EXIT-to-Resection may be indicated in cases in which the cystic lesion is very large and the airway is compromised.

CONDITION

Cystic lesions of the fetal chest include a broad list of anomalies that differ in origin, prenatal natural history, pathophysiology, and implications for management of the fetus. The most common lesions of the fetal chest include congenital pulmonary airway malformation (CPAM) (see Chapter 35) and bronchopulmonary sequestration (BPS) (see Chapter 34). This chapter focuses on other less common causes of fetal thoracic cysts including bronchogenic cysts, congenital lobar emphysema, pericardial cyst, thymic cyst, esophageal duplication cysts, and neurenteric cysts.

Bronchogenic cysts result from premature foregut remnants that originate in embryonic bud tissue prior to the formation of the bronchi. While bronchogenic cysts can share common features with esophageal duplication cysts, they are histologically characterized by the presence of cartilage, smooth muscle, and glands in the cyst wall (McAdams et al., 2000; Stocker, 2002; Langston, 2003). Most bronchogenic cysts occur in the mediastinum adjacent to the distal trachea or mainstem bronchi (McAdams et al., 2000; Stocker, 2002). Bronchogenic cysts can also be found within the lung parenchyma (McAdams et al., 2000; Langston, 2003). However, this is a controversial point, as some have considered these lesions a form of type I CPAM (Stocker, 2002). Bronchogenic cysts are unilocular and do not communicate with the tracheobronchial tree and are usually filled with mucus. Bronchogenic cysts can enlarge to produce airway compression and may ulcerate the cyst wall lining due to ectopic gastric mucosa (Eber, 2007). Histologically, bronchogenic cysts are lined with ciliated columnar epithelium and contain bronchial mucous glands, elastic tissue, and hyaline cartilage (Maier, 1948) (Figure 36-1).

Congenital lobar emphysema is characterized by overinflation, either by retained fluid produced in the lobe or segment prenatally or by air trapped in the lobe or segment postnatally (Clements, 1999). Congenital lobar emphysema is thought to be a consequence of bronchial valve mechanism from localized malformations or deficiencies of bronchial cartilage, mucosal folds, or extrinsic bronchial compression (Clements, 1999). This same appearance may be due to an increase in the number of normally expanded alveoli, called a polyalveolar lobe (Hislop and Reid, 1970; Mani et al., 2004). Almost half of all cases involve the left upper lobe (Eber, 2007), and the right middle lobe is the next most often affected. These lesions rarely contain cysts and appear homogeneous by ultrasound and MRI.

Some authors have suggested that both congenital lobar emphysema and polyalveolar lobe may be two outcomes of a similar inciting lesion during lung development (Mani et al., 2004). The timing of the lesion during lung development may account for different anatomical and functional bronchial abnormalities (Mani et al., 2004). Prenatally, lobar emphysema appears as a homogeneously enlarged lobe or segment that may be impossible to distinguish from a type III CPAM. Lobar emphysema tends to follow a different prenatal history from type III CPAM and can continue to enlarge slowly throughout gestation with resulting mediastinal shift and compression of

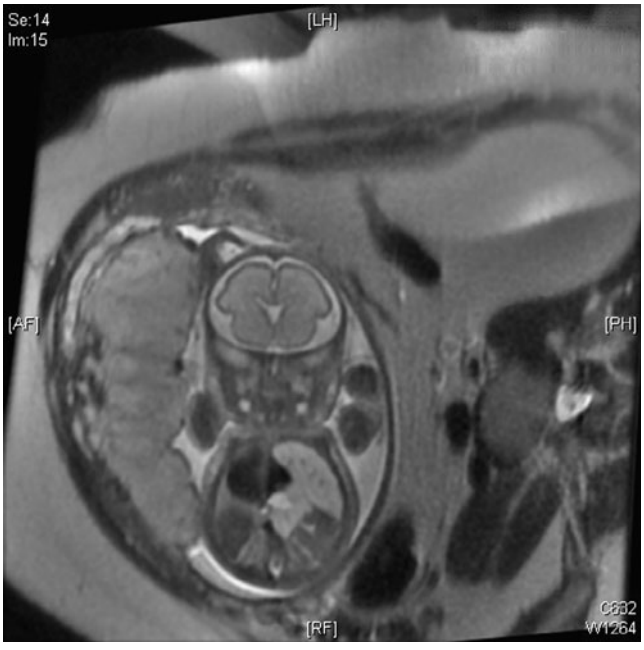

Figure 36-1 A T_1-weighted fetal MRI attained at 28 weeks' gestation demonstrating lobar emphysema of the LUL that was due to a bronchogenic cyst compressing the left mainstem bronchus and the take off of the left upper lobe bronchus. The bronchogenic cyst could not be detected prenatally as the cyst fluid was of the same signal intensity as that of adjacent mediastinal tissues.

adjacent normal lungs. Congenital lobar emphysema may be associated with other anomalies including cardiac anomalies in 12% to 14% of patients (Stocker et al., 1977; Kuga et al., 2001).

Pericardial cysts are rare lesions that are typically located at the cardiophrenic angle. Approximately 50% to 70% of pericardial cysts occurring in the costophrenic angle occur on the right side, whereas 28% to 38% occur on the left. More rarely, pericardial cysts may occur in other mediastinal locations not adjacent to the diaphragm (8–11%) (Stoller et al., 1986; Patel et al., 2004). Pericardial cysts are mesothelial lined with clear watery fluid. Pericardial cysts are usually asymptomatic but may cause compression of adjacent structures. Bernasconi et al. (2007) reported a small case series of prenatally diagnosed pericardial cysts that all spontaneously resolved without intervention by 28 weeks' gestation. However, there have been larger pericardial cysts that have been associated with fetal hydrops or with cardiac or respiratory compromise at birth due to impaired cardiac filling or airway compression (Fernandes et al., 1991; Muraskas et al., 1993; Rizalar et al., 1995; Daher et al., 1996; Macaulay et al., 1997; Wilkinson et al., 1999; Jung et al., 2000). Aspiration of cyst fluid has been associated with resolution of hydrops caused by a pericardial cyst (Gulrajani et al., 1993; Muraskas et al., 1993; Macaulay et al., 1997).

Thymic cysts are rare, accounting for less than 4% of all anterior mediastinal masses postnatally (Kelley et al., 1997; Tollefson et al., 2001). Thymic cysts arise from remnants of the thymopharyngeal duct that can occur anywhere from the hyoid bone to mediastinum (McEwing and Chaoui, 2005). Thymic cysts are usually asymptomatic and are usually an incidental finding but respiratory complications, vocal cord paralysis, and dysphagia have been reported (Rudick and Wood, 1980; Dunne and Weksberg, 1983; Graeber et al., 1984; Wernicke and Diederich, 1994; Tollefson et al., 2001). Prenatal diagnosis of asymptomatic thymic cysts has been reported (de Miguel Campos et al., 1997; McEwing and Chaoui, 2005).

Enteric duplication cysts of the mediastinum may or may not communicate with the gastrointestinal lumen, either in the chest or below the diaphragm (Jaggers and Balsara, 2004). There can be associated vertebral anomalies, but there is no communication with the spinal cord or meninges. Enteric duplication cysts may have ectopic gastric mucosa that can cause pain or bleeding due to peptic ulceration. In contrast, a neurenteric cyst that contains both ectodermal and endodermal or neurogenic elements is characterized by a connection to the meninges and spinal cord by a narrow stalk. Neurenteric cysts are associated with spinal anomalies such as congenital scoliosis, hemivertebrae, or spina bifida.

INCIDENCE

All of the cystic lesions described above are rare conditions for which only anecdotal reports of prenatal diagnosis exist. There are no reliable estimates of their incidence.

SONOGRAPHIC FINDINGS

Bronchogenic cysts are rarely diagnosed prenatally but may be suspected from the sonographic appearance of a unilocular fluid-filled cyst in the middle or posterior mediastinum (Avni et al., 1986). Alternatively, a bronchogenic cyst may be suggested by mass effect on adjacent structures (Figure 36-1). Patel et al. (2004) diagnosed a cystic mass at the time of fetal echocardiogram compressing the left atrium. Bronchogenic cysts can also present in atypical locations such as in the neck or subdiaphragmatic but retain the unilocular fluid-filled cystic appearance (Bagolan et al., 1999).

Esophageal duplication cysts are second only to those of the ileum comprising 15% to 20% of all reported duplications (Benson et al., 1985; Berrocal et al., 1999). Esophageal duplications may be tubular or sausage-shaped but most often are spherical cysts that have a thick wall of smooth muscle and an inner lining of gastrointestinal mucosa that may include gastric mucosa (Tam et al., 1987). These duplications are intimately associated with the esophagus but may appear as an isolated posterior mediastinal unilocular cyst on ultrasound. On T_1-weighted fetal MRI images, esophageal duplications may appear as a discrete, sharply defined low signal intensity mass and high signal intensity on T_2-weighted images (Berrocal et al., 2003). Esophageal duplications may enlarge sufficiently to obstruct the esophageal lumen and cause polyhydramnios (Gul et al., 2004).

Only a few thymic cysts have been diagnosed prenatally, usually recognized as an intrathoracic cyst and confirmed

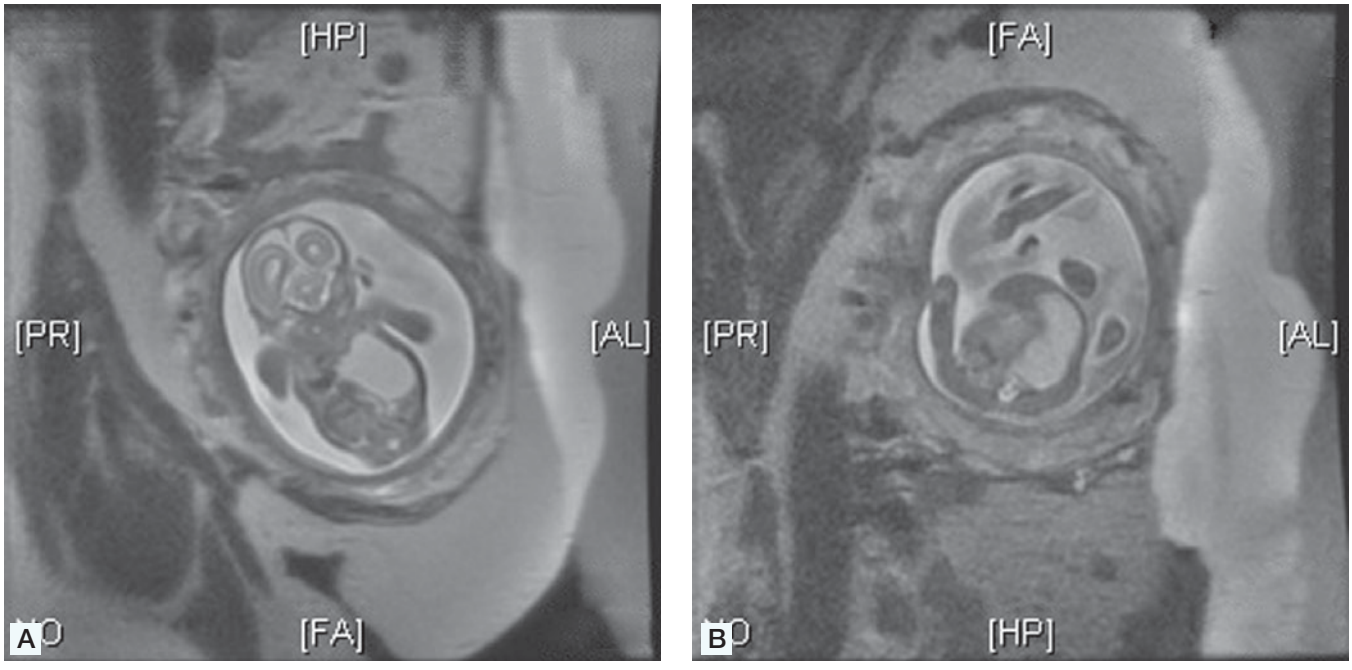

Figure 36-2 **A**. A T_1-weighted fetal MRI demonstrating a very large neurenteric cyst compressing adjacent structures. **B**. A narrow stalk communicating with the spinal canal can be seen.

to be thymic postnatally (de Miguel Campos et al., 1997; McEwing and Chaoui, 2005). The normal fetal thymus, lying immediately posterior to the sternum, can be either hyperechoic or hypoechoic with a tendency to become more hypoechoic as the gestation progresses (Felker et al., 1989). Thymic cysts arise from remnants of the thymopharangeal duct and may appear from the level of the hyoid bone to the carina (Han et al., 2001). These cysts tend to present in the anterior mediastinum and are usually small. If completely surrounded by thymic tissue, a diagnosis of thymic cyst can be made. However, in a large mediastinal cyst, it may be difficult to differentiate a thymic cyst from other etiologies such as lymphangioma, thyroid cyst, parathyroid cyst, bronchogenic cyst, or pericardial cyst (Tollefson et al., 2001).

Pericardial cysts are rare lesions adjacent or originating from the pericardium that are thin-walled anechoic masses (Bernasconi et al., 2007). There have been a number of prenatally diagnosed cases (Newnham et al., 1984; Zalel et al., 1992; Muraskas et al., 1993; Rahmani et al., 1995; Wu et al., 1995; Lewis et al., 1996; Jung et al., 2000; Simsek et al., 2003; Bernasconi et al., 2007) allowing some understanding of their presentation and natural history. Pericardial cysts are usually diagnosed at midgestation during routine sonography. In the report from Bernasconi et al. (2007), all had a benign course without impingement on adjacent structures and half resolved by 28 weeks' gestation. In contrast, other case reports have documented large cysts with secondary impaired cardiac filling and hydrops or airway compression (Muraskas et al., 1993; Jung et al., 2000). Pericardial cysts are characteristically unilocular, fluid filled arising from pericardial fat along the left or right cardiophrenic angle either inside or outside the pericardium or both (Feigin et al., 1977). The cyst wall consists of a single layer of mesothelial cells surrounded by fibroconnective tissue and may communicate with the pericardial space. It has been speculated that spontaneous resolution may occur as a result of rupture into the pericardial space (Bernasconi et al., 2007).

Neurenteric cysts are presumed to arise from incomplete separation of the notochord from the foregut during embryogenesis. The extraspinal neurenteric cysts are usually located in the right posterior chest and are associated with vertebral anomalies with a stalklike connection to the meninges or spinal canal (Figure 36-2). At least eight cases of neurenteric cysts have been diagnosed prenatally (Fernandes et al., 1991; Gulrajani et al., 1993; Rizalar et al., 1995; Daher et al., 1996; Macaulay et al., 1997; Perera and Milne, 1997; Wilkinson et al., 1999; Bernasconi et al., 2007). Neurenteric cysts may become quite large with impingement on adjacent structures. In five of the prenatally diagnosed cases, respiratory distress occurred soon after delivery due to mass effect on the airway resulting from posterior mediastinal cysts up to 6 cm in diameter (Fernandes et al., 1991; Rizalar et al., 1995; Daher et al., 1996; Wilkinson et al., 1999). In addition, two of these prenatally diagnosed neurenteric cysts developed hydrops from cardiac compression (Macaulay et al., 1997; Wilkinson et al., 1999).

DIFFERENTIAL DIAGNOSIS

The location, size, and involvement of adjacent structures may be used to help distinguish the underlying etiology of cystic thoracic masses. Bronchogenic cysts are almost uniformly found in close proximity to the trachea or mainstem bronchi. In some cases, a bronchogenic cyst may be found completely surrounded by lung parenchyma that may make it difficult to distinguish from a type I CPAM (Stocker, 2002).

The typical location of pericardial cysts is in the cardiophrenic angle on the right more often than left and rarely seen in sites not adjacent to the diaphragm (Stoller et al., 1986). These cysts may have an intra- and extrapericardial sac component and can seriously compromise fetal cardiac function. These lesions may spontaneously resolve by 28 weeks' gestation. In contrast to other cystic lesions, thymic cysts are usually confined to the anterior mediastinum and are often completely surrounded by thymic tissue allowing a specific diagnosis to be made (de Miguel Campos et al., 1997; McEwing et al., 2004).

Thoracic enteric duplication cysts can communicate with the enteric lumen and extend below the diaphragm. They are most commonly seen intimately involved with the esophagus. Neurenteric cysts are usually seen in the posterior mediastinum and are characterized by their associated vertebral anomalies. Although communication with the meninges or spinal canal is typical of these lesions, this may be difficult to demonstrate on prenatal imaging. Although ultrasound is the primary imaging modality to help with the differential diagnosis of cystic thoracic masses, MRI may be extremely helpful in defining involvement of adjacent structures and may provide clues to the true etiology of the cysts.

ANTENATAL NATURAL HISTORY

The rare occurrence of cystic lesions of the chest limits our understanding of the natural history of these congenital anomalies. Most are likely to be asymptomatic, but some will pose a risk for development of complications usually due to compression of adjacent structures. For example, esophageal duplication cysts can cause polyhydramnios from esophageal obstruction. Bronchogenic cysts may increase in size and cause compression on the trachea or mainstem bronchi, but this does not cause symptoms in utero. After birth, however, these compression effects may result in airway compromise and respiratory distress at the time of delivery. Pericardial cysts and neurenteric cysts have both been reported to result in hydrops due to compression of the fetal heart. The pericardial cysts by their location do not need to be excessively large to compromise fetal cardiac function. In the case of pericardial cysts, up to half of these may spontaneously resolve by 28 weeks of gestation (Bernasconi et al., 2007). In contrast, neurenteric cysts have resulted in hydrops because they can be extremely large. Thoracic cysts of other etiologies such as thymic cysts infrequently cause any symptoms and are usual incidental findings. A precise diagnosis may not always be possible but is helpful in defining complications if any, from the cyst for which the fetus is at risk.

MANAGEMENT OF PREGNANCY

The pregnancy in which a cystic lesion of the chest is diagnosed should be evaluated by a combination of ultrasound, echocardiography, and MRI. The latter may be useful in narrowing the differential diagnosis and help define impingement on adjacent structures. If the cyst is in close proximity to the heart and a pericardial cyst is suspected, fetal echocardiography is indicated. However, a large cyst in close proximity to the heart should prompt fetal echocardiography to exclude cardiac compromise no matter the suspected etiology. Prenatal consultation with a pediatric surgeon, cardiac surgeon, or neurosurgeon may be indicated depending upon whether the cyst is thought to be bronchogenic or a duplication cyst, pericardial cyst or neurenteric cyst. Orthopedic consultation may be indicated if there are associated hemivertebrae or kyphoscoliosis. The indications for genetic amniocentesis should be based on maternal age and associated anomalies detected as none of the cysts discussed have a particular association with karyotype anomalies. Close sonographic and echocardiographic surveillance should be recommended for signs of progressive cyst growth, polyhydramnios, or the development of hydrops until the cyst size stabilizes or resolves. Ultrasound close to the time of delivery is indicated to be certain that there is no impingement on the fetal airway that may have implications for delivery management.

FETAL INTERVENTION

There are few reports of fetal interventions for thoracic cysts. To date, there have only been three reports of cyst decompression in utero with resolution of hydrops (Muraskas et al., 1993; Macauley et al., 1997; Wilkinson et al., 1999). In one case, the etiology was a mediastinal lymphatic vascular malformation (Muraskas et al., 1993). In the other two cases, large neurenteric cysts causing hydrops responded to cyst drainage at 25 and 28 weeks' gestation, respectively. Kunisaki et al. reported the use of EXIT-to-ECMO to manage a fetus with a bronchogenic cyst completely obstructing the carina resulting in bilateral lung distention. The use of the EXIT strategy allowed the newborn to be evaluated by CT scan, undergo a right thoracotomy resection of the bronchogenic cyst, and repair of the trachea while on ECMO support (Kunisaki et al., 2007). The anecdotal nature of fetal interventions for thoracic cysts precludes defining indications for interventions. However, the presence of hydrops or significant airway compromise as in the cases noted above appears to be reasonable indications for treatment in utero.

TREATMENT OF THE NEWBORN

The newborn with a thoracic cyst should be evaluated to exclude airway compromise prior to delivery. Postnatal studies to evaluate the cyst will depend on the nature of the cyst. Cases of bronchogenic cysts, thymic cysts, duplication cysts may be best evaluated by bronchoscopy and chest CT or MRI. Echocardiography may be better to evaluate a suspected pericardial cyst and its effect on cardiac function.

In some instances, such as in known thymic cysts or pericardial cysts, simple observation alone is indicated in the

absence of significant compression on adjacent structures. In some instances such as neurenteric cysts, plane radiographs may also be indicated to evaluate possible associated vertebral anomalies. Potential communication with the meninges or spinal cord should also be evaluated by CT scan. In most instances, surgery to resect the cyst is indicated to prevent complications including infection or hemorrhage into the cyst or simply cyst growth with impingement on adjacent structures. If a complete resection can be performed, this reduces the chances of cyst recurrence.

SURGICAL TREATMENT

In most instances, surgical resection of cystic thoracic lesions will be indicated due to risk of infection, cyst enlargement, airway compromise, impingement on the heart, esophageal obstruction, or because the etiology of the cyst is unknown. In some instances, observation alone is indicated when the diagnosis is known and the risk of cyst enlargement is small as in thymic cysts. The operative approach to resecting these cysts depends on location and involvement of adjacent structures. Bronchogenic cysts can involve the trachea or mainstem bronchi and resection may require cross-field ventilation or cardiopulmonary bypass. Thoracoscopic resection may be possible in some cases but most will require open thoracotomy. The assistance of a pediatric neurosurgeon may be required for resection of a neurenteric cyst because of communication with meninges or spinal canal. In virtually all instances, complete excision of neurenteric cysts is possible that eliminates the risk of cyst recurrence. In the case of duplication cysts and neurenteric cysts, communication with the lumen of the gastrointestinal tract should be sought and addressed to avoid postoperative complications. Unless a decision has been made to observe as in the case of pericardial or thymic cysts, resection should be performed as early as practical in order to prevent complications.

LONG-TERM OUTCOME

In almost all instances, these cystic lesions do not recur and cause no other problems once resected. In some instances, as in large bronchogenic cysts or large neurenteric cysts tracheobronchial malacia may take 1 to 2 years to improve. In the case of neurenteric cysts, the associated vertebral anomalies may require spinal surgery to prevent progressive kyphoscoliosis.

In most instances, complete resection of the cyst prevents long-term complications and these children do very well long-term follow-up. Those patients with spinal abnormalities may have problems related to these vertebral anomalies such as kyphosis or scoliosis but not related to the cyst itself.

GENETICS AND RECURRENCE RISK

None of the cystic lesions discussed in this chapter are associated with karyotype abnormalities or recognized syndromes. There has been only a single report of familial thymic cysts (Joshua et al., 2004). In all other cases, these lesions are thought to be sporadic and recurrence with subsequent pregnancies has not been reported.

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37 CHAPTER Congenital Diaphragmatic Hernia

Key Points

- Defect in formation of diaphragm that is associated with pulmonary hypoplasia.
- Incidence is around 1 in 2200 with 85% to 90% being left sided, 10% to 15% right sided, and 2% bilateral.
- Approximately 60% of cases are isolated and 40% are complex or syndromic.
- Multiple sonographic and MRI techniques have been described to predict lung volume, which is an important predictor of survival. Liver position is also very important with regard to outcome.
- In the most severe cases of congenital diaphragmatic hernia (CDH), the fetal tracheal occlusion (FETO) with a balloon is removed prior to delivery "or EXIT-to-ECMO offers the best hope for survival."
- All fetuses with CDH should be delivered in a tertiary center with specific neonatal and surgical expertise in this condition and ECMO capability.

Key Points (cont.)

- Cesarean section delivery is indicated only for standard obstetrical reasons.
- Approximately a dozen single-gene disorders have CDH as a major feature. With increased cytogenetic resolution through array cGH, more syndromic cases are being recognized as being associated with a chromosome abnormality. Fetal karyotype is indicated.

CONDITION

Congenital diaphragmatic hernia (CDH), a defect in the diaphragm, is thought to be due to failure of the pleuroperitoneal canal to close by 9 to 10 weeks of gestation and results in varying degrees of pulmonary hypoplasia from compression of the developing lungs by the herniated viscera (Harrison et al., 1993b). The traditional view that the diaphragm forms by fusion of the septum transversum, the esophageal mesentery, the pleuroperitoneal folds, and ingrowth of musculature from the lateral body wall, is now being questioned (Pober, 2008). In model organisms, recent work suggests that a nonmuscular diaphragmatic anlage first develops, and that the diaphragmatic musculature derives from muscle precursors that migrate through the pleuroperitoneal folds at approximately day 37 of gestation (Babiuk and Greer, 2002; Pober, 2008).

During the development of the diaphragm, the peritoneal cavity is quite small and the midgut is normally present in the umbilical cord as physiologic herniation of the cord. If closure and muscularization of the pleuroperitoneal canal has not occurred by 9 or 10 weeks of gestation, when the midgut returns to the abdomen to undergo its normal 270-degree rotation, the viscera may herniate into the thorax through the posterolateral diaphragmatic defect because of limited intra-abdominal space (Areechon et al., 1963). If herniation occurs before the closure of the pleuroperitoneal canal there is no hernia sac. However, if pleuroperitoneal membrane has formed but is not muscularized, a hernia sac will be present and is observed in 10% to 15% of cases (Areechon et al., 1963). Occasionally, a "transient" herniation may occur later in gestation, with little effect on pulmonary development (Adzick et al., 1985a; Stringer et al., 1995).

The clinical course of an infant with isolated CDH depends entirely on the degree of pulmonary hypoplasia and severity of pulmonary hypertension. The degree of pulmonary hypoplasia depends on the timing of herniation during development, the volume of viscera herniated, and duration of herniation, that is, whether or not the viscera slide in and out of the thorax (Harrison et al., 1993a; Stringer et al., 1995).

An appreciation of the pathophysiology of CDH requires an understanding of the normal growth and development of the tracheobronchial tree and pulmonary vasculature. Reid (1977) has described four overlapping stages of normal histologic development: embryonic (from conception to 5 weeks); pseudoglandular (5–16 weeks); canalicular (16–24 weeks); and terminal sac or alveolar (24 weeks to postnatal life). The bronchial tree is almost completely developed by 16 weeks of gestation, at which time the adult complement of airways is established. However, alveoli continue to develop after birth, increasing in number until about 8 years of age (Boyden, 1977).

The severity of pulmonary developmental abnormalities depends on the time and the extent to which the herniated viscera compress the adjacent lung. A large intrathoracic mass effect that develops during the formation of the conducting airways (pseudoglandular stage) will reduce the number of bronchial divisions, decreasing the thoracic volume available for lung development (Geggel and Reid, 1984). The herniation of viscera in CDH usually occurs during the pseudoglandular stage of lung development (5–16 weeks) (Reid et al., 1977). In fetuses with CDH, the major bronchial buds are already present, but the number of bronchial branches is pruned and greatly reduced (Companale et al., 1955). The number of alveoli per acinus may be normal, but the absolute number of alveoli is decreased because of the reduced number of bronchial divisions. These morphologic changes are more pronounced in the lung ipsilateral to the diaphragmatic hernia, but the contralateral lung is similarly affected by compression from the shifted mediastinum (Figure 37-1) (Harrison et al., 1980a, 1980b, 1981, 1990, 1993a; O'Rourke et al., 1984; Adzick et al., 1985b; Hasegawa et al., 1990). Persistent mass lesions during later stages of lung development (canalicular or alveolar stages) will result in a reduction not only in airway size, but in the number and size of saccules, alveoli, and preacinar and intra-acinar vessels (Areechon et al., 1963). Concomitant with these changes in the fetal tracheobronchial tree is an increase in the thickness of the arterial media and extension of muscle peripherally into the small preacinar arteries (Levin et al., 1978). The pulmonary hypoplasia that is associated with CDH is one of the major determinants of morbidity and mortality (Figure 37-1). Some have suggested a "two-hit" theory in which pulmonary underdevelopment occurs first but is then made worse by subsequent mechanical compression (Keijzer et al., 2000). In addition, the pulmonary vasculature is abnormal with overmuscularized vessels. In addition to the increased muscularization of the preacinar arteries, Geggel et al. have demonstrated that there is a reduction in size of the pulmonary vascular bed in CDH (Geggel et al., 1985). These changes in the pulmonary vascular bed are the histologic correlate of the pulmonary hypertension seen in experimental models of CDH and newborns with pulmonary hypoplasia.

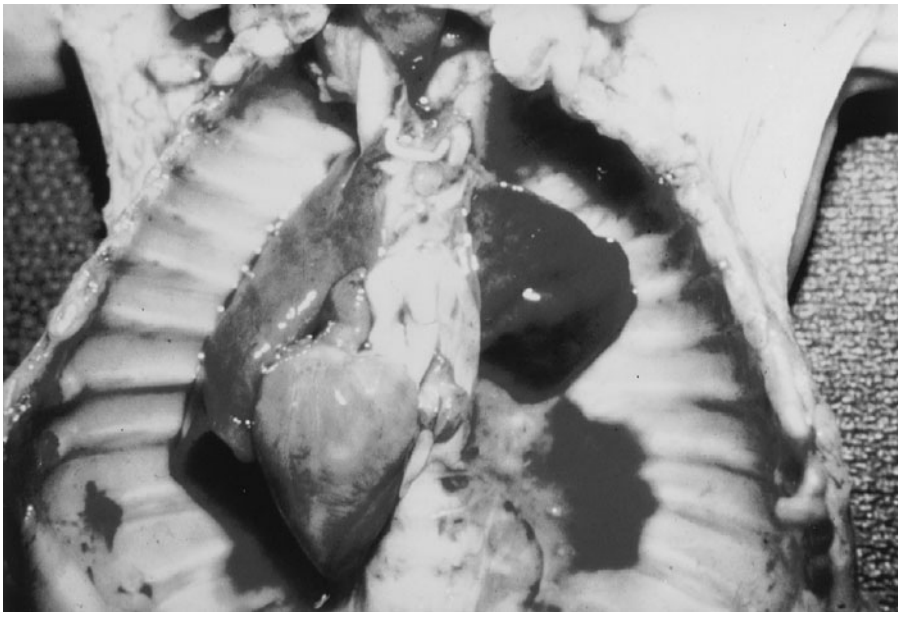


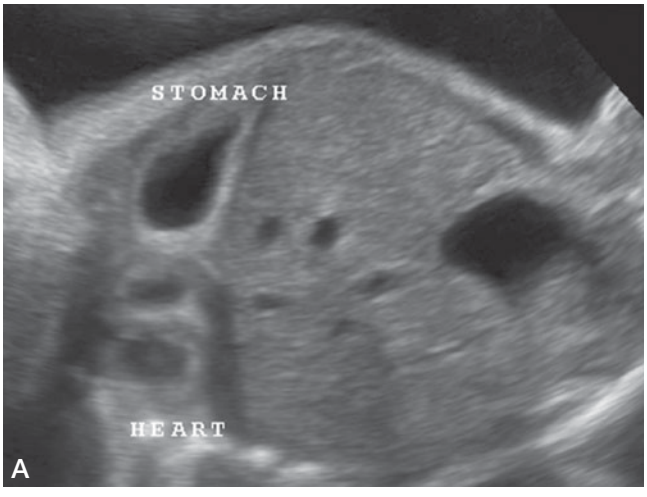
Figure 37-1 Autopsy photograph demonstrating the shift of the heart to the right side of the chest and bilateral lung hypoplasia due to diaphragmatic hernia.

There is evidence that mutations in specific genes that are involved in diaphragmatic development and/or the vitamin A pathway may play a role in the etiology of CDH and pulmonary hypoplasia (Ackerman and Pober, 2007). Key genes that are mutated in teratogenic mouse models of CDH include the transcription factors *Fog2*, *couptf2*, *wt1*, *slit3*, and *GATA4*, and molecules involved in cell migration and signaling such as *slit3* (Bielinska et al., 2007). It is not clear that this teratogenic model from which these mutations have been identified apply to human CDH. Interestingly, in the human, these genes map to areas that have been consistently shown to have chromosome abnormalities that are associated with CDH. There has also been one case in a human mutation in *FOG2* in which there was pulmonary hypoplasia and a diaphragmatic abnormality consistent with eventration, but no CDH (Ackerman et al., 2005).

INCIDENCE

Approximately 85% to 90% of diaphragmatic hernias occur on the left side, 10% to 15% are on the right side, and a few are bilateral. In 60% of cases, the diaphragmatic hernia is either isolated or associated with malformations that are due to hemodynamic or mechanical consequences of the CDH. In 40% of cases the CDH is nonisolated or part of a syndrome. All studies have shown that infants with syndromic (or "complex") CDH have higher mortality (Pober, 2007). The incidence of CDH has been estimated at between 1 in 3000 and 1 in 5000 livebirths (Puri and Gorman, 1984). These estimates ignore the significant numbers of intrauterine fetal death, stillbirths, and neonatal deaths that occur before transfer to a tertiary care facility. An accurate incidence of CDH is more likely around 1 in 2200 births (Fitzgerald, 1979; Harrison et al., 1979; Reynolds et al., 1984; Puri, 1989). In years past, the postnatal survival rate of infants with CDH has traditionally been quoted as 50% (Adzick et al., 1981), but this figure represents survival in a favorably selected group of patients who survive not only to term, but also transfer to a referral center for further treatment (Harrison et al., 1979, 1990, 1993a, 1994; O'Rourke et al., 1984; Adzick et al., 1985a). The most severely affected neonates die before they are transferred to a tertiary care center. Harrison has referred to this discrepancy as the "hidden mortality" of CDH (Harrison et al., 1979). A more recent meta-analysis found that the average mortality for prenatally diagnosed cases was 75%, for cases ascertained as part of a population-based study it was 48%, and for cases transferred to a tertiary facility it was 45% (Skari et al., 2000).

The cause of CDH is unknown but it has been reported in association with maternal ingestion of thalidomide, Bendectin, quinine, and antiepileptic drugs (Hobolth, 1962; Kup, 1967; Hill, 1974; Greenwood et al., 1976; Tubinsky et al., 1983). Associated anomalies are seen in 25% to 57% of all cases of CDH, but this figure rises to 95% in stillborn infants (Crane et al., 1979; Tubinsky et al., 1983; Puri, 1984). The associated anomalies may include congenital heart defects, hydronephrosis or renal agenesis, intestinal atresias, extralobar sequestrations, and neurologic defects, including hydrocephalus, anencephaly, and spina bifida (Crane et al., 1979; Tubinsky et al., 1983). CDH has been described as a finding in Fryns, Beckwith–Wiedemann, and Pierre–Robin syndromes as well as in congenital choanal atresia (Thorburn et al., 1970; Evans et al., 1971; Harrison et al., 1991). Chromosomal anomalies are diagnosed in 10% to 20% of cases of CDH diagnosed prenatally. The most common diagnoses include



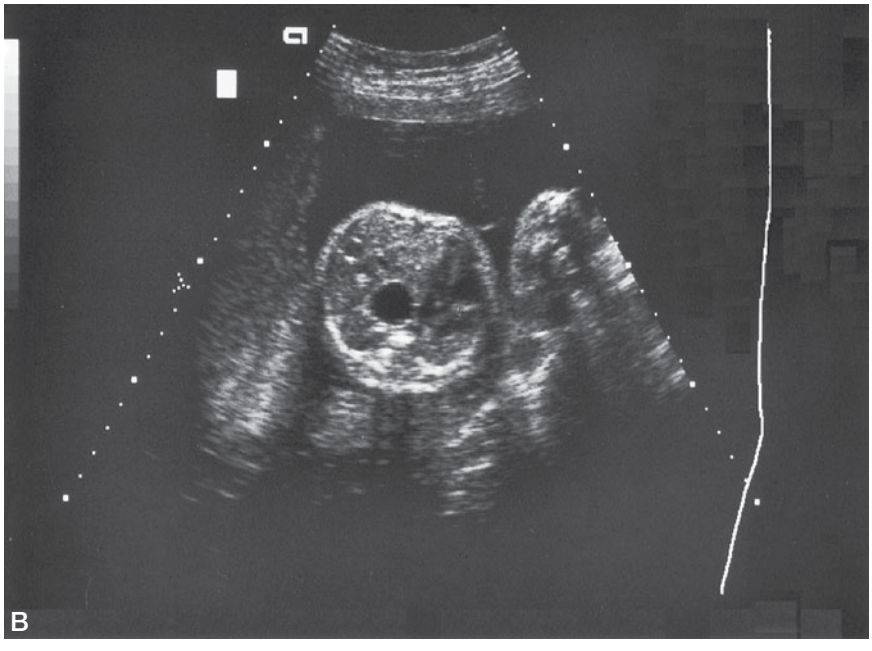


Figure 37-2 **A.** Coronal image of a fetus with a left congenital diaphragmatic hernia demonstrating the stomach in the left chest and the heart deviated into the right chest. **B.** An axial image demonstrating the four-chamber view of the heart and adjacent herniated loops of bowel. (*Reprinted, with permission, from Morin L, Crombleholme TM, Dalton ME. Prenatal diagnosis and management of fetal thoracic lesions.* Semin Perinatol. *1994;18:228-253.*)

trisomies 21, 18, and 13 (Lesk et al., 1959; Crane et al., 1979; Tubinsky et al., 1983).

SONOGRAPHIC FINDINGS

Approximately 60% to 90% of cases of CDH are detected prenatally by sonography or MRI depending on the center reporting ascertainment (Pober, 2008). The diagnosis of CDH should be suspected if the stomach bubble is not observed in its normal intra-abdominal location. The fetal chest should be viewed in the true transverse plane, and landmarks such as the inferior margin of the scapula should be used to identify the abdominal viscera in the chest (Lesk et al., 1959). Abdominal viscera that are seen cephalad to the inferior margin of the scapula or at the same level of the four-chamber view of the heart are herniated, confirming a diagnosis of CDH (Figures 37-2 to 37-4). The herniated abdominal viscera associated with a left-sided CDH may be the easiest to detect. The fluid-filled stomach and small bowel contrast strikingly with the more echogenic fetal lung.

Liver Herniation

The position of the fetal liver is one of the most significant and reproducible independent prognostic factors, with liver herniation predictive of poor outcome (Harrison et al., 1990; Cannie et al., 2006; Hedrick et al., 2007; DePrest et al., 2009). Kinking of the sinus venosus is a reliable sign of left-sided CDH with herniated left lobe of the liver (Figure 37-5). In a retrospective review of 16 fetuses with left CDH, Boostaylor et al. (1995) found that bowing of the umbilical segment of the portal vein (the portal sinuses) to the left of midline and coursing of portal vessels to the lateral segment of the left hepatic lobe toward or above the diaphragmatic ridge are the best predictors for liver herniation into the left chest. Another subtle finding is an echodense space between the left border

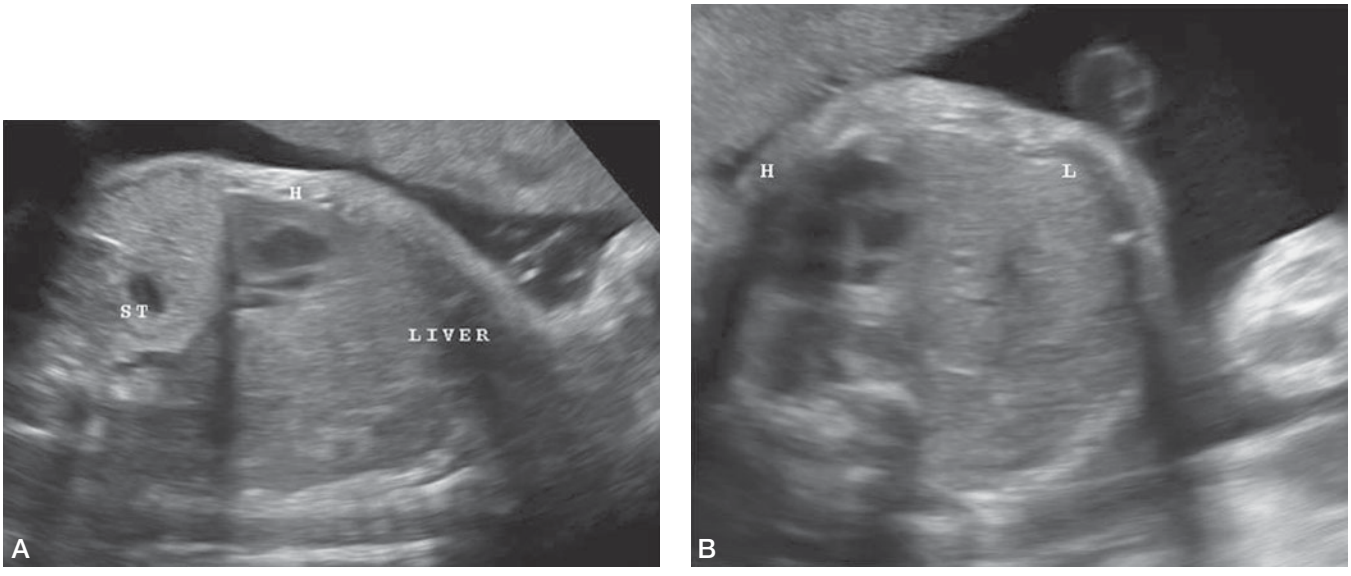


Figure 37-3 **A.** Sagittal image of a fetus with a right congenital diaphragmatic hernia demonstrating the liver above the diaphragm. **B.** An axial image demonstrating a right congenital diaphragmatic hernia with the liver filling the right fetal thorax and the heart deviated against the left chest wall.

of the heart and the stomach, which is due to interposed herniation of the left lobe of the liver. Sonographic or MRI delineation of the diaphragm is not always possible. Even identifying the diaphragm cannot exclude CDH because only a portion of the diaphragm may be missing.

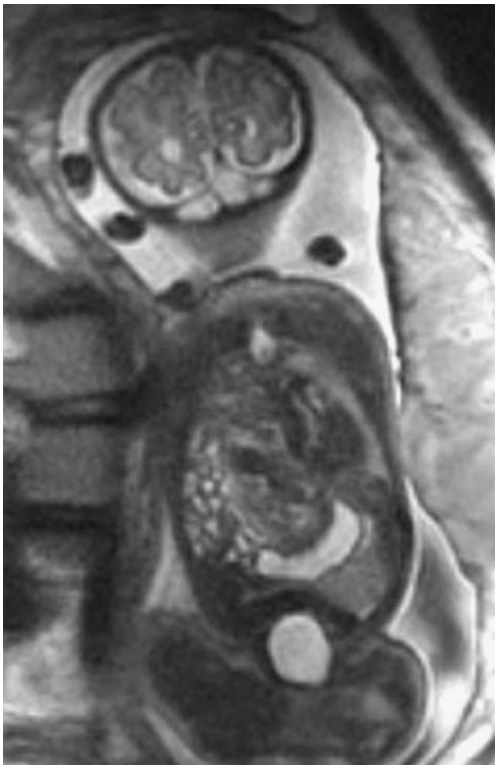


Figure 37-4 Fetal MRI demonstrating a right diaphragmatic hernia; note the liver, gallbladder, and small intestine filling the right thorax and the stomach below the diaphragm.

The location of the gallbladder may also be helpful in diagnosing CDH because it may be herniated in the right chest in right-sided CDH or displaced to the midline or left upper quadrant with left-sided CDH. A large-volume herniation will result in mediastinal shift with polyhydramnios. Mediastinal shift is thought to interfere with swallowing, thus resulting in polyhydramnios (Harrison et al., 1991). Since the stomach is often rotated 180 degrees counterclockwise from its normal anatomic position up into the chest, it is more likely that there is partial gastric outlet obstruction due to kinking at the gastroduodenal junction. The stomach position is also a good predictor if observed in a posterior or midthoracic location if the liver is herniated (Boostaylor et al., 1995). CDH has been also reported in association with concomitant bronchopulmonary sequestration cystic adenomatoid malformation, and teratomas. These may be noted as echogenic masses seen in association with the CDH.

The extent of pulmonary hypoplasia is the most important determinant of survival in CDH. Hasegawa et al. (1990) have proposed using a ratio of the cross-sectional area of the lung to thorax (L:T ratio) in sonographic transverse section of the fetal chest at the level of the four-chamber view of the heart to assess the likelihood of pulmonary hypoplasia. They found, in a small series of eight fetuses with CDH, that the L:T ratio was below 2 SD from the mean ratio obtained in 156 normal controls. There was also an inverse correlation between the L:T ratio in the fetus and in the postnatal A-aDO_2 (alveolar-to-alveolar oxygen difference) values (Hasegawa et al., 1990).

Metkus et al. (1996) reported the use of the right-lung to head circumference ratio (LHR) as a sonographic predictor of survival in fetal diaphragmatic hernia. The LHR is the two-dimensional area of the right lung taken at the level of the four-chamber view of the heart. This is divided by the

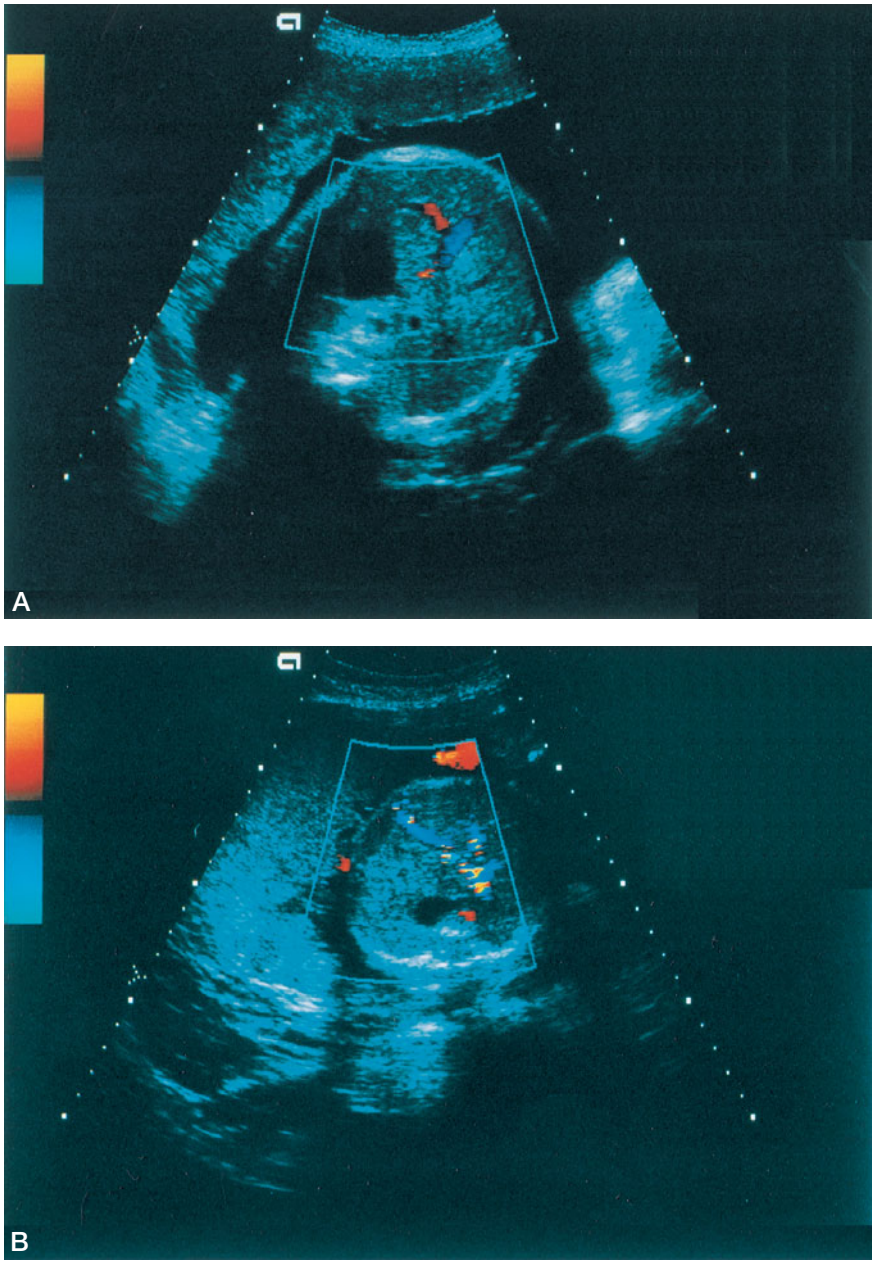


Figure 37-5 **A.** Color flow Doppler images demonstrating normal course of sinus venosus on left. **B.** ''Kinked" sinus venosus on right in CDH.

head circumference. In a retrospective review of 55 fetuses diagnosed with left-sided CDH, the LHR was found to be predictive at its extremes. At low values (i.e., small right lung), fetuses with LHRs <0.6 did not survive with postnatal therapy. But in fetuses with LHRs >1.35, survival was 100% with conventional postnatal therapies, including ECMO (Cannie et al., 2006; DePrest et al., 2006). The survival of fetuses with LHRs between 0.6 and 1.35 was 61%. At an NIH symposium, Harrison et al. (2003) provided additional data in the group of fetuses with values between 0.6 and 1.35. Survival with an LHR <1.0 was only 11%. The accuracy of the LHR described by Metkus et al. (1996) was validated in two subsequent prospective studies (Flake et al., 2000). The LHR has not been widely adopted due to the difficulty in accurately and reproducibly obtaining the LHR.

There now have been three different techniques reported for obtaining lung:head circumference ratio and a fourth modification in which the observed LHR is normalized to an expected LHR. The only two of these methods have been validated in prospective studies. In the technique first reported by the University of California San Francisco (UCSF) group, the largest transverse width of the right lung is obtained from the cross-sectional view of fetal chest at the level of the four-chamber view of the heart. This transverse measurement is taken parallel to the sternum from the right side of the Ao to the edge of the lung at the right chest wall. The anterior-posterior (AP) measurement is obtained perpendicular to this measurement. A second technique obtains the longest transverse measurement at the level of the four-chamber view of the heart independent of the orientation

of the sternum. The third technique captures the image of the cross-sectional view of the chest at the level of the four-chamber view and traces the outline of the right lung to obtain the area and divides by the head circumference. Each of these techniques yields slightly different results that may alter the perceived prognosis. These techniques are not only highly user-dependent, but the prognosis based on these results may not translate from one center that sees a high volume of fetuses with CDH to one that sees only a few cases each year. Case in point, Crombleholme et al. (2009) have reported the Cincinnati Children's experience with LHR, finding a survival of 100% when LHR was >1.0 and 50% with LHR <1.0. These findings are in contrast to older reports of prognosis based on LHR that indicates the institutional-specific nature of the utility of LHR in predicting survival. The accuracy of the LHR in predicting outcome has been challenged by the Columbia group (Arkovitz et al., 2007), who reported that the LHR in their series was not predictive of outcome. Methodical problems with LHR acquisition may be an issue, but this does point to concern regarding how easily translatable use of LHR is from one center to another.

Between 12 and 32 weeks' gestation, normal lung area increases four times more than head circumference (DePrest et al., 2009). For this reason, Jani et al. (2007) proposed referencing LHR to gestational age by expressing the observed LHR as a ratio to the expected mean LHR for that gestational age. In a study from the CDH antenatal registry of 354 fetuses with isolated left and right CDH between 18 and 38 weeks, Jani et al. found that observed/predicted LHR predicted postnatal survival. The O/E LHR tended to be more accurate at 32 to 33 weeks than at 22 to 23 weeks' gestation. The O/E LHR was also found to correlate with short-term morbidity indicated (Jani et al., 2007).

A novel approach was reported by Mahieu-Caputo et al. (2001) using the thoracic volume minus the mediastinal volume to yield an estimate of what the lung volume would be expected to be if there was no CDH and dividing the actual lung volume by this estimate to yield the percent predicted lung volume (PPLV). Mahieu-Caputo et al. (2001) found that the observed/expected fetal lung volume ratio was significantly lower in CDH patients who died with a mean of 26% compared to those who survived with a mean of 46%. This same group reported a larger experience from a 4-year prospective multicenter study of 77 fetuses with isolated CDH diagnosed between 20 and 33 weeks' gestation (Gorincour et al., 2005). They found that the observed/expected lung volume was significantly lower in fetuses with CDH that died (23%) compared to those that survived (36%). When the observed to expected fetal lung volume ratio was below 25%, there was a significant decrease in postnatal survival to 19% versus 40.3%. While these survival rates are lower than usually reported in the United States, they still support the utility of this prognostic technique.

Using this same technique that she termed PPLV, Barnewolt et al. (2007) reported their preliminary experience in Boston with 14 patients with CDH in which there was a clear break point at a PPLV of 15%. Fetuses with PPLV more than 20% had 100% survival while those with PPLV <15% had a 40% survival and all required prolonged ECMO. However, Crombleholme et al. (2009), in reporting the Cincinnati Children's experience with PPLV with 28 patients, found that PPLV was not as predictive of outcome as LHR (Crombleholme et al., 2009). In this series, three of the four deaths occurred in patients with PPLV more than 15%. In contrast, survival with LHR >1.0 was 100% and all deaths occurred in patients with LHR <1.0.

Fetal MRI has been also applied to directly measure total lung volumes to predict outcome in CDH. Hubbard et al. (1997) found that fetal lung volumes obtained by MRI at midgestation did not accurately predict postnatal outcome. Kilian et al. (2006) reported a series of fetal MRI-derived lung volumes at 34 to 35 weeks' gestation. They noted that most of the growth in lung volume occurs in late gestation, as reflected in the later sharp upward sweep of lung volume normograms. They reasoned that in the presence of a large CDH there would not be the normal increase in lung growth. In a series of 38 cases of CDH, both right-sided and left-sided, they correlated lung volume with survival and the need for ECMO. They found that the mean lung volume of survivors was 35 cc, while mean lung volume of nonsurvivors was 9 cc. The mean lung volume of those infants requiring ECMO was 18 cc, while 25 cc was the mean lung volume of those that did not require ECMO.

At the time of 34 weeks' gestation MRI, measurement of the branch pulmonary artery diameter and the descending Ao allows calculation of the modified McGoon index. Vuletin et al. (2009) have shown that the modified McGoon <1.0 and the prenatal pulmonary hypertensive index (PPHI, branch pulmonary arteries divided by the cerebellum to normalize for age) correlates with severe postnatal pulmonary hypertension at 3 weeks of age.

Cystic diseases of the chest, such as type I congenital cystic adenomatoid malformation (CCAM) of the lung, bronchogenic cysts, neurenteric cysts, and cystic mediastinal teratoma, may also be mistaken for the herniated bowel of CDH (Harrison et al., 1991). The demonstration of normal upper gastrointestinal anatomy helps to distinguish cystic thoracic masses from CDH. Peristalsis of bowel loops within the chest may also help distinguish these two diagnoses. In right-sided lesions the liver is often the only organ herniated. This may be more difficult to identify, due to the similar echodensities of the fetal liver and lung. It may also be difficult to distinguish herniation of the liver into the chest from a type III CCAM.

ANTENATAL NATURAL HISTORY

It was once thought that prenatal detection of CDH might improve outcome by allowing transport of the mother to an appropriate facility, planned delivery, immediate resuscitation, and sophisticated postnatal intervention with "gentilation" strategies, high-frequency ventilation and/or ECMO. Reviews of prenatally diagnosed CDH, however, have consistently shown a 76% to 80% mortality rate despite this

optimized approach to management (Adzick et al., 1981; O'Rourke et al., 1984; Reynolds et al., 1984; Harrison et al., 1990, 1993a, 1993b, 1994; Puri and Gorman, 1984).

There has been a trend toward improved survival even among the most severely affected fetuses with CDH in which there is liver herniation and LHR <1.0. In the NIH study reported by Harrison et al. (1997), the survival in fetuses regardless of treatment was 30%. Although the numbers were small, this is an improvement from 11% previously reported by this group. Similarly, the CHOP group has reported 40% survival in this high-risk category. The improvement in survival in general for CDH has shifted innovative strategies of management to only those patients with LHR <1.0 and liver herniation. These innovative strategies include reversible tracheal balloon occlusion (DePrest, 2007; DePrest et al., 2009), EXIT-to-ECMO (Kunisaki et al., 2007), and aggressive management of pulmonary hypertension with off-label use of inhaled nitric oxide and inhaled prostacyclin (Lim, 2007). This aggressive management of pulmonary hypertension in CDH has resulted in 100% survival in isolated CDH with LHR >1.0. Even with LHR ≤1.0, the group at Cincinnati Children's have observed a 50% survival and have reduced the need for ECMO to only 8% in patients not sufficiently severe for EXIT-to-ECMO.

MANAGEMENT OF PREGNANCY

The evaluation of the fetus with suspected CDH should include a detailed ultrasound examination to confirm the diagnosis and detect possible associated anomalies. If possible, measurement of LHR should be obtained. Prenatal karyotyping is indicated in all cases of CDH because of the high incidence of associated chromosomal anomalies (16–37% of cases) (Adzick et al., 1981; Puri, 1984; Sharland et al., 1992). Even if termination of the pregnancy is not an option because of gestational age or parental choice, the diagnosis of a chromosomal anomaly may influence the management of labor and the plan for neonatal resuscitation. Array comparative genomic hybridization (CGH) has also been recommended by some for all cases of prenatally diagnosed CDH due to limitations in completely ascertaining all anomalies in utero (Pober, 2008).

The most common chromosome abnormalities associated with CDH are trisomy 18 (see Chapter 130), and tetrasomy 12p (Pallister–Killian syndrome) (see Chapter 138), and trisomy 21 (see chapter 131). Other chromosome rearrangements that have been reported in association with multiple cases of CDH include del(15)(q26.1-q26.2), del (8)(p23.1), del (4)(p16), partial and full trisomy 22, del (1)(q41-q42.12), and rearrangement of 8q23 (Holder et al., 2007; Pober, 2008).

CDH is found in at least a dozen single-gene disorders, including Cornelia de Lange syndrome, craniofrontonasal syndrome, Donnai–Barrow syndrome, multiple vertebral segmentation defects, Simpson–Golabi–Behmel syndrome, Denys–Drash syndrome, and Frasier syndrome. Although a diagnosis of Fryns syndrome is commonly made, there is likely to be etiologic heterogeneity with Fryns, and no gene that causes this condition has been identified to date (Pober, 2008). If the CDH is suggested to be syndromic, consultation with a medical geneticist is advised.

Fetal echocardiography is also recommended in all cases because of the 16% incidence of associated congenital heart disease (Sharland et al., 1992).

The diagnosis of CDH at less than 25 weeks of gestation with long-standing large-volume herniation (indicated by mediastinal shift and dilated intrathoracic stomach, herniated liver, or LHR <1.0 and associated polyhydramnios) indicates a fetus at risk for severe pulmonary hypoplasia and a poor outcome. The severity of pulmonary hypoplasia and CDH seems to correlate with the timing, duration, and volume of herniation. A few mildly affected fetuses will have minimal developmental effects on the lungs because of herniation late during gestation, small-volume hernia, minimal mediastinal shift, and greater lung volume as indicated by an L:T ratio >0.5 or LHR >1.4 (Hasegawa et al., 1990; Metkus et al., 1996; Stringer et al., 1995). These fetuses should be followed closely by serial ultrasound examinations and delivered at term in an ECMO center staffed with pediatric surgeons and neonatologists, expert in management of infants with CDH.

The majority of fetuses with prenatally diagnosed CDH are detected early in gestation (less than 25 weeks), with a large-volume herniation with mediastinal shift and intrathoracic stomach, polyhydramnios, low L:T ratio (<0.5), and low LHR (<1.35). The management of the fetus depends on the gestational age at diagnosis. If the fetus is less than 24 weeks, then the parents may choose to terminate the pregnancy, continue the pregnancy with conventional postnatal care at term, or consider fetoscopic tracheal balloon occlusion procedure in utero (if available). At the time of publication, no FDA-approved device for fetal tracheal balloon occlusion was available in the United States, and tracheal occlusion is being offered in Europe. Several centers including UCSF and Cincinnati Children's are offering this therapy on an FDA-approved investigational device exemption. After 28 weeks of gestation, CDH is managed by conventional postnatal management or EXIT-to-ECMO (Figure 37-6).

Cesarean delivery is not indicated for CDH. There are no data to support elective preterm delivery. However, elective induction at 37 weeks allows a planned delivery in the appropriate center with suitable resources for the care of a fetus with severe pulmonary hypoplasia. There has been controversy as to whether CDH fetuses are surfactant deficient with reports on both sides of the argument. Recently however, Benachi (2007) from France reported definitive results in autopsy specimens in fetuses with CDH near term, as demonstrated by the presence of type II pneumocytes both bronchoalveolar lavage and histology that were no different from normal-term control fetuses. There is, however, another reason to administer prenatal steroids within 48 hours up to 7 days prior to delivery. Davey et al. (2007) have demonstrated in a sheep model of CDH that steroid administration close to the time of delivery can reverse the extensive muscularization of the preacinar capillary bed responsible for pulmonary.

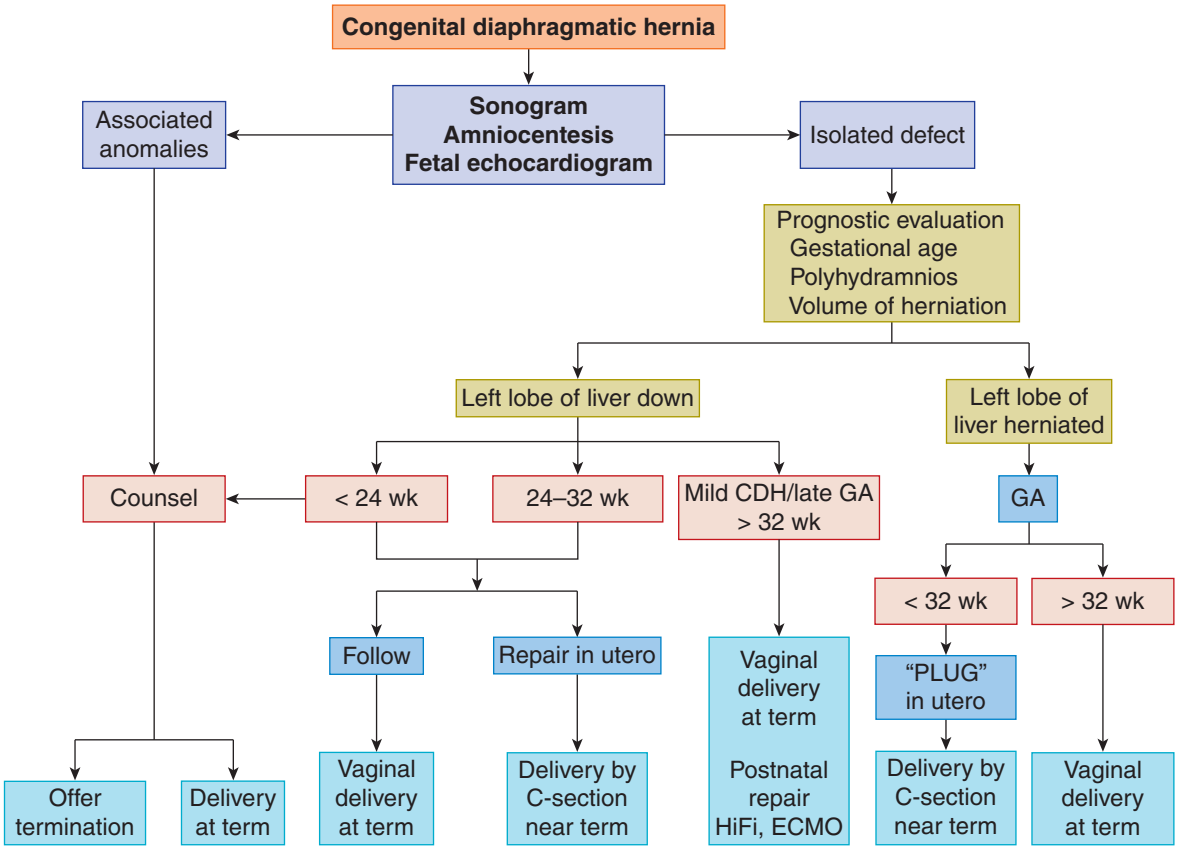


Figure 37-6 Algorithm for the management of prenatally diagnosed CDH.

FETAL INTERVENTION

Compensatory lung growth and development are possible after repair of CDH, but weeks or months may be required to achieve this. Postnatal support by ECMO is usually limited to 2 to 6 weeks, which may be an inadequate period of support for the most severely affected infants (O'Rourke et al., 1984). It has been demonstrated experimentally that reduction and repair of the hernia in utero allows the lungs adequate time for compensatory growth (Harrison et al., 1980a, 1980b, 1981; Adzick et al., 1985b). In a series of experiments in fetal sheep and rhesus monkeys, the techniques of open fetal surgery and perioperative tocolytic therapy were established before clinical trials of open fetal surgery for CDH were undertaken (Harrison et al., 1980a, 1980b, 1981, 1991; Adzick et al., 1985b; Adzick and Harrison, 1994).

Although the survival rate with in utero repair of CDH in initial clinical trials was not encouraging (Harrison et al., 1990, 1993a, 1993b), the dramatic results observed in surviving infants prompted an NIH-sponsored trial (Harrison et al., 1997). The results of this trial, limited to diaphragmatic hernia without herniation of the left lobe of the liver, showed no survival benefit of fetal surgery over postnatal treatment. As a result, there is currently no indication for complete repair of diaphragmatic hernia without herniation of the left lobe of the liver. However, cases of diaphragmatic hernia associated with herniation of the left lobe of the liver remain the most severely affected cases, with profound pulmonary hypoplasia. Ironically, although considered an exclusion criterion for complete repair of diaphragmatic hernia, it is now one of the selection criterions for fetal tracheal occlusion (FETO; Deprest et al., 2009).

It was recognized long ago that occlusion of the fetal trachea results in markedly enlarged and hyperplastic lungs (Carmel et al., 1965; Lanman et al., 1971; Alcorn et al., 1976). This observation was applied to the problem of diaphragmatic hernia. Throughout gestation the fetal lung produces fluid that exits the trachea during normal breathing movements. External drainage of this fluid, bypassing the glottic mechanism, results in retarded lung growth and pulmonary hypoplasia (Carmel et al., 1965; Lanman et al., 1971; Alcorn et al., 1976). Conversely, tracheal occlusion results in accelerated lung growth and pulmonary hyperplasia (Carmel et al., 1965; Alcorn et al., 1976; Moessinger et al., 1990; Hedrick et al., 1993; Hooper et al., 1993; DeFiore et al., 1994; Bealer et al., 1995; Luks et al., 1995; Beierle et al., 1996). In the fetal lamb model of diaphragmatic hernia, tracheal obstruction accelerates lung growth, pushing the viscera back into the abdomen resulting in larger lungs with significant functional improvement at birth as compared with controls (Hedrick et al., 1993; Wilson et al., 1993; DeFiore et al., 1994; Bealer et al., 1995; Luks et al., 1995; Beierle et al., 1996). The results of experimental work were so impressive that this strategy was employed by Harrison in fetuses with herniation of the left lobe of the liver (Harrison et al., 1997).

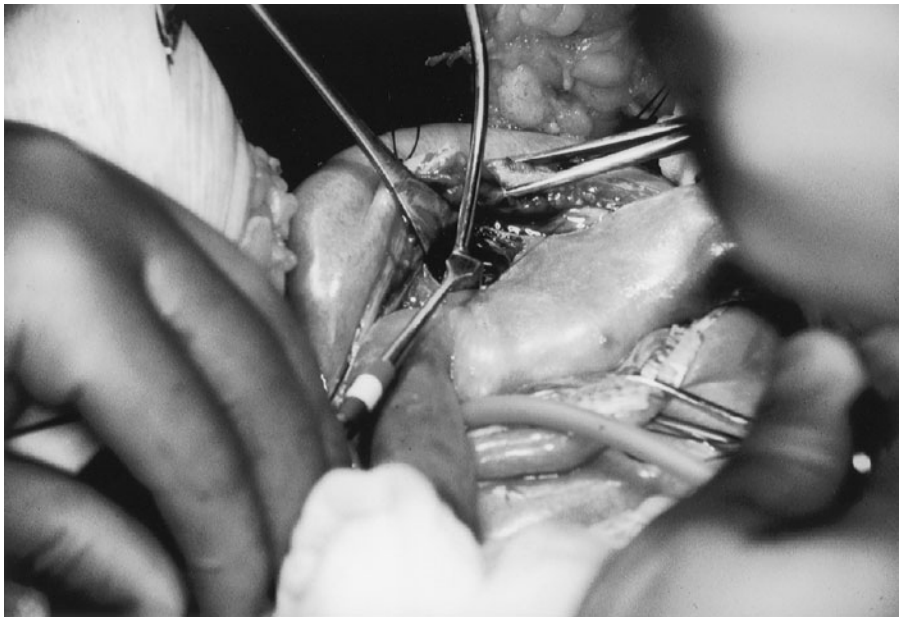


Figure 37-7 Intraoperative view of a fetus at 26 weeks of gestation undergoing fetal tracheal clip application. The fetal arms are retracted down through the hysterotomy and the head is extended within the uterus. The fetal neck is opened above the sternal notch to expose the fetal trachea.

Despite an excellent biologic response with complete tracheal occlusion, there was only one survivor in the initial series of patients treated by tracheal occlusion. The group at The Children's Hospital of Philadelphia had similar problems when the procedure was performed at 28 weeks of gestation (Figure 37-7). Survival increased to 40% in fetuses with a predicted mortality rate in excess of 90% when fetal tracheal clip application was performed at 26 weeks of gestation (Flake et al., 2000).

Due to difficulties with open fetal surgery for tracheal clip application as well as fetoscopic tracheal clip application, the UCSF group began performing tracheal occlusion by detachable endoluminal balloon placement.

The results with fetoscopic balloon tracheal occlusion were evaluated by the UCSF group in an NIH-sponsored randomized trial that compared fetoscopic tracheal occlusion to conventional postnatal therapy in fetuses with isolated left-sided CDH with liver herniation and LHR <1.4 (Harrison et al., 2003). The investigators' preliminary data suggested an anticipated survival with conventional therapy of 50% and with fetoscopic tracheal occlusion of 75%. A crucial aspect of the trial was that patients from both arms of the trial were born and treated postnatally at UCSF. The trial was stopped after randomization of only 24 patients because of an unexpectedly high survival rate with standard care. Eight of the 11 fetuses (73%) randomized to tracheal occlusion survived and 10 of 13 fetuses (77%) randomized to standard care survived to 90 days of age. There was a significant difference in gestational age at delivery for FETO (30.8 weeks) compared to conventional therapy (37 weeks). This trial demonstrated a significant improvement in survival compared to historical controls in the same center. However, the inclusion of fetuses with LHR > 1 < 1.4 biased the study toward the less severe end of the spectrum with insufficient power to analyze the effects in the subset of patients with LHR <1.0.

The tracheal occlusion procedure currently in use in Europe is done using maternal percutaneous access under local or regional anesthesia with a single 3.3 mm port and a balloon to occlude the trachea (DePrest et al., 2009). The balloon is inserted at 26 to 28 weeks and removed at 34 weeks. If patients deliver prior to 34 weeks they require emergency peripartum balloon removal, which requires the availability of trained clinicians at all times. The Eurofoetus group reports in their experience of more than 150 cases a survival rate with tracheal occlusion of 50% to 57% (DePrest et al., 2009). However, these studies have been criticized due to lack of contemporary controls. Nonetheless, no maternal complications have been reported, but iatrogenic preterm rupture of the membranes has occurred in 20% of cases. Long-term follow-up study of infants is in progress. DePrest and his Eurofoetus colleagues have achieved survival of 83% with tracheal occlusion at 26 to 28 weeks' gestation followed by reversal of tracheal occlusion performed either by popping the balloon by an ultrasound-guided needle or by a second fetoscopic procedure. While no randomized trial comparing fetoscopic tracheal occlusion to conventional care is planned. The Eurofoetus study will soon begin randomizing patients to different gestational ages to determine the best timing of tracheal occlusion. In the United States, no center is currently offering FETO due to the lack of an FDA-approved device. The only fetal surgery offered for high-risk CDH is EXIT-to-ECMO. In preliminary results reported by Kunisaki et al. (2007), fetuses with liver herniation and PPLV or <20% are offered EXIT-to-ECMO, with a 65% survival. Similar results have been observed at Cincinnati Children's and Vanderbilt. This therapeutic innovation remains unproven but may hold

promise in these high-risk CDH cases given survival with conventional treatment is significantly lower.

TREATMENT OF THE NEWBORN

All fetuses with CDH are at high risk for severe pulmonary hypoplasia and are optimally managed by delivery in a perinatal center with neonatal and pediatric surgical expertise in CDH immediately available, preferably in a center capable of performing ECMO (Harrison et al., 1990; Marwan and Crombleholme, 2006). The resuscitation of a newborn includes immediate endotracheal intubation, "gentilation" limited, positive-pressure ventilation with PIPs. The infant should have a sump-style nasogastric tube inserted in the delivery room to perform continuous suction to avoid dilation of the intrathoracic bowel from the infant swallowing air. In the delivery room the infant should have umbilical arterial and umbilical venous catheters placed to monitor arterial blood gases and provide venous access. In the face of liver herniation, however, umbilical venous lines are rarely successfully placed. Preductal and postductal transcutaneous oxygen saturation monitors can help to continuously monitor right-to-left shunting across the ductus arteriosus.

Judicious volume resuscitation is important, and many infants with diaphragmatic hernia require vasopressor support with dopamine, milrinone, or epinephrine. Occasionally vasopressor refractory hypotension may require the use of steroids or even vasopressin.

The use of inhaled nitric oxide in CDH has met with mixed results. Inhaled nitric oxide has not clearly been shown to benefit newborns with diaphragmatic hernia. However, inhaled nitric oxide has been beneficial in preventing the need for ECMO during the postoperative period (Frostell et al., 1993; Dillon et al., 1995). At Cincinnati Children's an aggressive approach for pulmonary hypertension includes inhaled nitric oxide combined with inhaled prostacyclin. While this approach has not been proven yet to affect outcome, preliminary results with this approach have been promising, and resulted in 90% overall survival in CDH and 100% survival in cases with LHR >1.0. (Crombleholme et al., 2009)

SURGICAL TREATMENT

It was once believed that immediate operation to decompress the chest was necessary. However, in recent years, it has been recognized that this is not the case. The more important variable is the degree of underlying pulmonary hypoplasia. Emergency surgical repair may, in fact, be detrimental to the infant's tenuous pulmonary and hemodynamic status after birth and relative pulmonary artery hypertension (Hazebrock et al., 1989; Langer et al., 1989). It is better to delay repair until the infant has stabilized. This may take hours, days, or weeks. If the infant deteriorates during this so-called "honeymoon" period, ECMO can be initiated. The infant can undergo repair of CDH while on ECMO and be weaned from the circuit postoperatively (Connors et al., 1990). An alternate strategy is to perform early repair on ECMO to facilitate remodeling of the hypoplastic lung following repair of the diaphragmatic defect. The rationale here is that relieving compression of the lung is beneficial for pulmonary hypertension. The risk of this approach is postoperative bleeding while anticoagulated on ECMO prior to a time when ECMO decannulation would be possible.

Repair of CDH is usually performed via a left-upper-quadrant transverse or subcostal incision, which allows exposure of the defect and reduction of the herniated viscera. The diaphragm can occasionally undergo primary repair, but in severe cases, the defect is large or there may be complete diaphragmatic aplasia, both of which require a prosthetic patch. Because reherniation may occur in up to 50% of cases with gortex patch repair, there is growing interest in the use of the transversus abdominus muscle flap as a patch. Because the tissue is autologous there is decreased risk of infection, and because it grows with the infant, it is believed to prevent dehiscence and reherniation. A chest tube may be inserted after repair of CDH. If used, the chest tube is placed only to water seal, and no suction is applied.

LONG-TERM OUTCOME

The long-term outcome of infants with isolated CDH who survive the neonatal period depends on the severity of pulmonary hypoplasia, and the degree of bronchopulmonary dysplasia resulting from long-term ventilatory support (Bales and Anderson, 1979). In addition, extrapulmonary complications are noted more commonly in survivors of CDH (Glass et al., 1989; Lund et al., 1994). There is a high incidence of neurologic problems in children with CDH, independent of exposure to ECMO. Other complications such as reactive airway disease, sensorineural hearing loss due to prolonged need for antibiotics and/or furosemide (Lasix), seizures, and developmental delay, may be seen in up to 20% to 30% of patients (Lund et al., 1994). Long-term follow-up evaluation and early intervention are indicated in this group of high-risk patients.

Failure to thrive has been noted in many survivors of diaphragmatic hernia (Cunniff et al., 1990; Atkinson and Poon, 1992; Van Meers et al., 1993; D'Agostino et al., 1995). Many infants with isolated diaphragmatic hernia have feeding difficulties that may require gavage feedings and may contribute to failure to thrive. The causes of failure to thrive may be multifactorial, but Nobuhora et al. (1996) noted that 30% of infants remained below the fifth percentile despite optimization of caloric intake; 68% of the patients in this group were ECMO survivors. Van Meers et al. (1993) also noted a high percentage (50%) of CDH survivors supported with ECMO who had failure to thrive.

Gastroesophageal reflux may affect as many as 50% to 62% of diaphragmatic hernia survivors (Koot et al., 1993; Kieffer et al., 1995). While some have reported good response to medical therapy (Stolar et al., 1990), the need for antireflux

surgery varied from 9.6% to 14.8% (Nagaya et al., 1994; Kieffer et al., 1995).

Musculoskeletal deformities, such as pectus excavatum and scoliosis, may also develop in survivors of diaphragmatic hernia. The cause of these deformities may be the asymmetric lung size, the diaphragmatic repair, or the increased work of breathing some patients may have. In the series reported by Nobuhora et al. (1996), the incidence of pectus excavatum was 21% and scoliosis was 10.5%.

The most worrisome finding is the incidence of neurodevelopmental delays, which may be present in up to 40% of survivors with CDH. While in general the risk of neurodevelopmental delay is thought to be proportional to the severity of the infant's NICU course, this has not been proven.

GENETICS AND RECURRENCE RISK

In recent years, there have been multiple lines of evidence that suggest that many cases of CDH may have a genetic etiology. These include: (1) recurring chromosome abnormalities in unrelated individuals that reveal CDH "hot spots"; (2) single-gene disorders in which the causative gene is known and provides insight into pathways that are critical for diaphragmatic development; (3) multiple families in which CDH recurs (Pober, 2008).

For all fetuses in which a CDH is detected, a complete family history should be obtained and the parents should be examined. The first consideration should be whether the CDH is isolated or nonisolated. Anomalies such as pulmonary hypoplasia, bowel malrotation, patent ductus arteriosus, dextraposition of the heart, tricuspid or mitral valve regurgitation, or undescended are considered to be mechanical or hemodynamic consequences of the CDH, so if present, they do not preclude a diagnosis of isolated CDH (Pober, 2008). A truly isolated CDH carries a multifactorial recurrence risk of at most 2% (Pollock and Hall, 1979; Norio et al., 1984).

All fetuses with CDH should have a minimum of a metaphase karyotype, and ideally, an array cGH study. If a chromosome abnormality is detected, the prognosis and recurrence risk will be those of the specific abnormality.

If associated anomalies are detected the prospective parents should meet with a medical geneticist. The single-gene disorders in which CDH is a major feature are listed in Table 37-1. If the geneticist suspects one of the conditions listed, DNA diagnosis is possible on amniocytes. Special note

Table 37-1

Major Single-Gene Disorders Associated with CDH

Syndrome	Pattern of Inheritance	Causative Gene	Chromosome Location	Prenatal Sonographic Findings*
Cornelia de Lange	Autosomal dominant X-linked	*NIPBL* *Smc1 A*	5p13.1 Xp11.2	Growth restriction Limb anomalies
Craniofrontonasal dysplasia	X-linked	*EFNB1*	Xq12	Craniosynostosis, hypertelorism
Donnai–Barrrow	Autosomal recessive	*LRP2*	2q24.3-2q31.1	Agenesis of corpus callosum, hypertelorism
Fryns	Unknown Autosomal recessive			CNS, renal, cardiac anomalies
Matthew–Wood	Autosomal recessive	*STRA6*	15q24.1	Micro- or anophthalmia, cardiac and GU anomalies
Multiple vertebral segmentation defects	Autosomal recessive	*DLL3*	19q13	Hemivertebrae, fused vertebrae, rib anomalies
Simpson–Golabi–Behmel	X-linked	*GPC3*	Xq26	Overgrowth, limb, and renal anomalies
Denys–Drach/ Frasier/Meacham	Autosomal dominant	*WT1*	11p13	Ambiguous genitalia, cryptophthalmos, renal anomalies

** In addition to diaphragmatic hernia.*

should be made of Fryns' syndrome, an autosomal recessive condition that is commonly considered for fetuses with CDH (Moerman et al., 1988; Bamforth et al., 1989; Cunniff et al., 1990). The gene responsible for this condition is not known. For a diagnosis of Fryns syndrome to be made, Lin et al. (2005) propose that at least four of the following six findings are present: diaphragmatic defect, pulmonary hypoplasia, specific facial dysmorphic features, distal digital hypoplasia, and affected sibling, or "other anomalies" (typically, septal or conotruncal cardiac defects, renal cystic dysplasia, or agenesis of the corpus callosum). If a single-gene disorder is diagnosed, either by molecular testing or by physical examination of the neonate, the recurrence risk and prognosis are that of the condition.

In cases of perinatal loss, every attempt should be made to have autopsy studies performed to document the presence of additional anomalies not detected on sonographic examination. A follow-up meeting with a clinical geneticist is useful to summarize autopsy results and discuss possible genetic diagnoses. A fibroblast cell line should be established as a source of DNA for molecular studies. If karyotype and CGH analysis were not performed earlier, they should be done on cultured cells.

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38 CHAPTER Hydrothorax

Key Points

- May be primary, due to chylous leak, or secondary, in which effusions are part of generalized fluid retention. Secondary hydrothorax is more common in the fetus than the neonate.
- Sonography demonstrates an anechoic space peripherally around the compressed lungs. If effusion is large there may be mediastinal shift. Polyhydramnios is present in 60% to 70% of cases. Extrathoracic anomalies are frequently present.
- Prior to 32 weeks of gestation fetal treatment options include: thoracentesis, thoracoamniotic shunting, and thoraco-maternal cutaneous drainage. Thoracentesis should be performed to determine if the effusion is chylous and to obtain a cell count, differential, and culture.
- Decompression of the fetal chest immediately prior to delivery is controversial.
- Delivery should occur in a tertiary care center.
- Up to 5% of cases are associated with a chromosome abnormality, such as Down and Turner syndromes.

CONDITION

Fetal hydrothorax (FHT), either unilateral or bilateral, is a pleural effusion that may be primary, due to chylous leak, or secondary, in which the effusions are part of a generalized fluid retention associated with immune or nonimmune hydrops (Holzgreve et al., 1985; Longaker et al., 1989; Laberge et al., 1991). The management of pleural effusion in the fetus is complicated by the difficulty in distinguishing primary from secondary FHT. Secondary FHT is far more common in the fetus than in the neonate (Holzgreve et al., 1985; Hagay et al., 1993). Secondary FHT may be due to a wide variety of maternal and fetal disorders, including chromosomal anomalies, cardiovascular, hematologic, gastrointestinal, pulmonary, metabolic, infectious, and neoplastic, and malformations of the placenta and umbilical cord (Chernick and Reed, 1970; Petres et al., 1982; Gardner et al., 1983; Grena-Ansotegui et al., 1984; Van Gerde et al., 1984; Foote and Vickers, 1986; Nicolaides and Azar, 1990). While the underlying cause of a secondary FHT may be evident from detailed sonographic examination and karyotype analysis, in many instances the cause of the effusion remains obscure even after a postmortem examination (Keeling et al., 1983; Nicolaides et al., 1985).

INCIDENCE

Cases of secondary FHT may occur as frequently as 1 in 1500 livebirths (Hutchison et al., 1982; Im et al., 1984; Castillo et al., 1986). The true incidence of primary FHT is uncertain. In a review of cases from five obstetrical hospitals in Montreal between 1980 and 1987, Longaker et al. (1989) estimated that the incidence of primary FHT is 1 case per 12,000 livebirths. The actual incidence of primary FHT may be even higher if one considers that in many cases the condition may remain undiagnosed, it may resolve spontaneously, the fetus may be aborted, or death may occur soon after birth in outlying hospitals before transfer to a tertiary care center (Longaker et al., 1989; Laberge et al., 1991). In a review of reported cases of FHT, Weber and Philipson (1992) found that there was a 2:1 male to female ratio, which is similar to the ratio in neonates with chylothorax (Chernick and Reed, 1970; Broadman, 1975; Weber and Philipson, 1992).

SONOGRAPHIC FINDINGS

The first sonographic diagnosis of FHT was made by Carroll in 1977, followed shortly thereafter by Defoort and Thiery (1978). Although the earliest gestation age at which prenatal diagnosis has been made sonographically is 17 weeks, the majority of cases are not diagnosed until after 30 weeks (Laberge et al., 1991). Reports of prenatally diagnosed FHT have continued to appear, and hundreds of cases have been described in the literature (Defoort and Thiery, 1978; Peleg et al., 1985; Wilson et al., 1985; Benacerraf et al., 1986; Calisti et al., 1986; Roberts et al., 1986; Weiner et al., 1986; Castillo et al., 1987; Murayoma et al., 1987; Reece et al., 1987; Adams et al., 1988; Blott et al., 1988; Bruno et al., 1988; Yaghoobian and Comrie, 1988; Longaker et al., 1989; Landy et al., 1990; Lien et al., 1990; Eddleman et al., 1991; Hernanz-Schulman et al., 1991; Parker and James, 1991).

In FHT, sonography demonstrates an anechoic space located peripherally around the compressed lungs (Figure 38-1). If the effusion is sufficiently large, there may be some degree of tension noted, with shift of the mediastinum away from the FHT and flattening or eversion of the ipsilateral diaphragm. The heart may be shifted into the contralateral hemithorax and appear smaller than normal. The presence of septations or solid components within the intrathoracic fluid collection suggests alternative diagnoses (Sydorak et al., 2002; Tsao et al., 2003). FHT has been reported in association with congenital diaphragmatic hernia, congenital cystic adenomatoid malformation of the lung, and bronchopulmonary sequestration, but it can usually be differentiated from simple hydrothorax by its more echogenic appearance (Smith, 1982; Longaker et al., 1989; Hernanz-Schulman et al., 1991; Laberge et al., 1991). Blott et al. (1988) reported FHT in association with a right-sided congenital diaphragmatic hernia and ascites. The hydrothorax resulted from a fluid-filled peritoneal sac in the right chest. The association with FHT has been reported in up to 20% of cases of congenital diaphragmatic hernia and should be considered in the differential diagnosis of FHT (Liew, 1974; Sydorak et al., 2002; Khalil et al., 2005), although the effusion in these cases is usually small.

FHT may be the first sign of nonimmune hydrops, and a careful sonographic inspection should be made to detect subtle signs of this. Congenital heart disease is observed in up to 5% of cases of prenatally diagnosed FHT (Hagay et al., 1993). Large effusions with shift of the mediastinum and compression of the heart may limit delineation of cardiac anatomy on fetal echocardiography (Rodeck et al., 1988). Evacuation of the pleural cavity by fetal thoracentesis will shift the heart to the midline, which may facilitate adequate imaging of the heart (Bigras et al., 2003).

Polyhydramnios is associated with FHT in 60% to 70% of cases (Defoort and Thiery, 1978; Peleg et al., 1985; Wilson et al., 1985; Calisti et al., 1986; Roberts et al., 1986; Weiner et al., 1986; Castillo et al., 1987; Murayoma et al., 1987; Reece et al., 1987; Adams et al., 1988; Blott et al., 1988; Bruno et al., 1988; Yaghoobian and Comrie, 1988; Lien et al., 1990; Longaker et al., 1989; Landy et al., 1990; Nicolaides and Azar, 1990; Eddleman et al., 1991; Parker and James, 1991). This often prompts referral for prenatal sonography because of discordant size and dates. The cause of polyhydramnios in FHT is not known for certain, but it has been suggested that large FHT associated with mediastinal shift may interfere with fetal swallowing (Hagay et al., 1993). This view is supported by one study that demonstrated a lack of contrast agent in the gastrointestinal tract after intra-amniotic instillation (Urografin) (Murayoma et al., 1987). Alternatively, Petres et al.

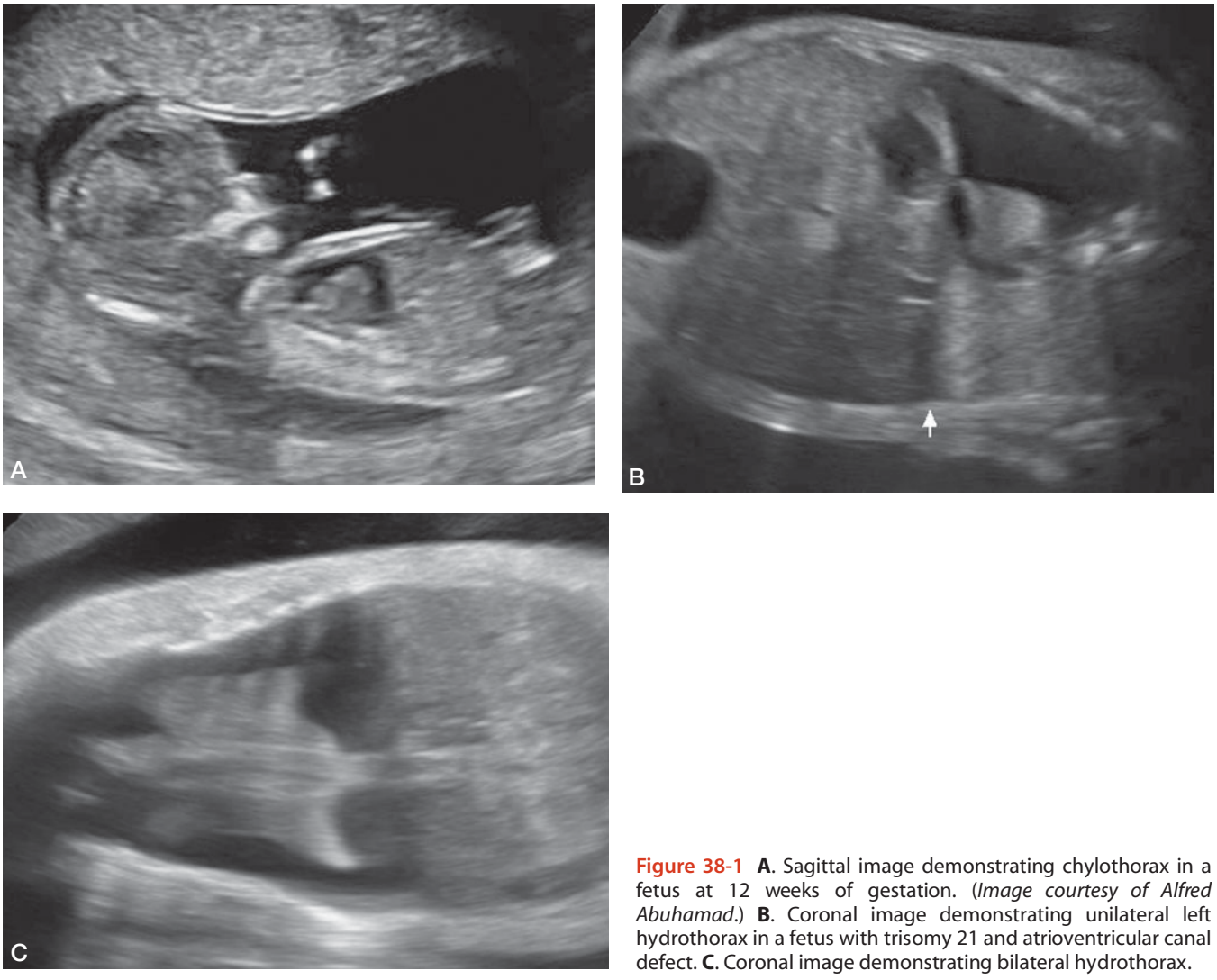

Figure 38-1 **A**. Sagittal image demonstrating chylothorax in a fetus at 12 weeks of gestation. (*Image courtesy of Alfred Abuhamad.*) **B**. Coronal image demonstrating unilateral left hydrothorax in a fetus with trisomy 21 and atrioventricular canal defect. **C**. Coronal image demonstrating bilateral hydrothorax.

(1982) suggested that the cause of polyhydramnios in FHT may be an alteration in the production of amniotic fluid by the compressed lungs.

A thorough search should be made for associated extrathoracic malformations, such as cystic hygroma or other features suggesting Turner syndrome (Smith, 1982; Foote and Vickers, 1986). Down syndrome has been associated with congenital pleural effusion (Puntis et al., 1987). Both Turner and Noonan syndromes include malformations of lymphatic vessels, but only rarely are these syndromes associated with congenital chylothorax (Van Gerde et al., 1984).

DIFFERENTIAL DIAGNOSIS

The most important factor in the differential diagnosis of fetal pleural effusions is distinguishing primary from secondary FHT. A detailed sonographic examination will reveal a major congenital anomaly in up to 40% of cases of secondary FHT (Hutchison et al., 1982). In most instances, however, a fetal thoracentesis is needed to distinguish primary from secondary FHT (Broadman, 1975). A pleural-fluid differential cell count that consists of more than 80% lymphocytes is considered pathognomic for chylothorax, which is a characteristic finding in neonates (Puntis et al., 1987; Longaker et al., 1989; Pijpess et al., 1989). Eddleman et al. (1991) have questioned the accuracy of a lymphocyte count as an indicator of chylothorax in the presence of a viral infection. However, the serositis that results from viral infection is usually not limited to the pleural cavities, and pericardial effusion and ascites are also often observed. A predominance of atypical lymphocytes on differential cell count may also suggest a viral infection.

Chylothorax has been described in association with diffuse congenital lymphangiomatosis (Berberich et al., 1975; Roth, 1984; Smelzer et al., 1986), diffuse hemangiomata, chylopericardium (Bhatti et al., 1985), congenital lymphedema (Pearl and Wilson, 1981; Kitohara, 1985; Lev-Sagie et al., 2003), pulmonary lymphangiectasia (Jauppela et al., 1983; Hunter and Becroft, 1984; Kerr-Wilson et al., 1985), bronchopulmonary sequestration (Kristofferson and Ipsen, 1984; Hook et al., 1987), congenital diaphragmatic hernia (Liew,

1974; Sydorak et al., 2002; Khalil et al., 2005) atresia of thoracic duct, generalized pleural oozing, and other malformations (Manning and O'Brien, 1983; Lazarus and McCurdy, 1984). In many cases no underlying cause for the chylothorax is found.

ANTENATAL NATURAL HISTORY

The natural history of FHT is significantly different from chylothorax in the newborn and carries a much poorer prognosis. The mortality rate for chylothorax in the newborn is at most 15%, but the mortality rate for prenatally diagnosed FHT is 53% (Broadman, 1975; Longaker et al., 1989; Klam et al., 2005).

Several features of primary FHT are associated with a more favorable outcome. Unilateral FHT, without evidence of tension, such as mediastinal shift or diaphragmatic eversion, is associated with 100% survival (Longaker et al., 1989; Laberge et al., 1991). This contrasts with a survival rate of only 52% in bilateral FHT (Longaker et al., 1989). Survival is also observed in all cases of FHT that spontaneously resolve (Longaker et al., 1989; Laberge et al., 1991). Spontaneous resolution of FHT has occurred in approximately 5% to 22% of cases (Carroll, 1977; Jaffe et al., 1986; Blott et al., 1988; Yaghoobian and Comrie, 1988; Longaker et al., 1989; Landy et al., 1990; Lien et al., 1990; Nicolaides and Azar, 1990; Eddleman et al., 1991; Klam et al., 2005). Because of the possibility of spontaneous regression, a period of observation is warranted in all cases of FHT.

The development of hydrops in the fetus with primary FHT is a poor prognostic sign, with a mortality rate of up to 52% (Longaker et al., 1989). It is thought that hydrops develops from mediastinal shift, cardiac compression, and vena caval obstruction, which diminishes venous return to the heart, resulting in a low-cardiac-output state (Bessone et al., 1971). The mortality rate associated with primary FHT is still significantly better than the 95% to 98% mortality rate observed in secondary FHT (Inselman and Mellins, 1981). In cases of FHT diagnosed prior to 33 weeks, the survival rate is only 43%, versus 80% if it was diagnosed after 33 weeks (Carroll, 1977; Longaker et al., 1989). Similarly, a gestational age of less than 35 weeks at delivery has a survival rate of only 30%, versus 79% if delivered after 35 weeks (Carroll, 1977; Longaker et al., 1989; Laberge et al., 1991). Polyhydramnios has no independent prognostic significance, except that it can result in uterine overdistention, which predisposes to preterm labor and delivery (Broadman, 1975; Carroll, 1977; Defoort and Thiery, 1978).

Even in the absence of hydrops, large pleural effusions can cause pulmonary hypoplasia due to compression. Pulmonary hypoplasia is a well-known complication of space-occupying lesions in the chest, such as cystic adenomatoid malformation of the lung and congenital diaphragmatic hernia (Areechon and Reid, 1963; Levin, 1978; Geggel and Reid, 1984; Adzick et al., 1985; Geggel et al., 1985; Lange et al., 1989; Morin et al., 1994). It is likely that the time of onset, size, and duration of the pleural effusion probably influence the development of pulmonary hypoplasia. The earlier in gestation a large pleural effusion develops, the greater the degree of pulmonary hypoplasia is likely to be. Klam et al. (2005) suggested that unrelieved compression of the lung by bilateral FHT for 8 to 9 weeks associated with hydrops was sufficient to cause lethal pulmonary hypoplasia. The most common cause of neonatal death in patients diagnosed with FHT is respiratory insufficiency due to pulmonary hypoplasia (Carroll, 1977; Longaker et al., 1989; Laberge et al., 1991).

MANAGEMENT OF PREGNANCY

FHT is frequently associated with extrathoracic anomalies. The risk of an abnormal karyotype in FHT is small but significant (Chen, 2005). Prenatal karyotyping is recommended, especially if fetal intervention is considered. The incidence of Down syndrome in FHT is 4.9% (Weber and Philipson, 1992). Because the incidence of associated congenital heart disease may be as high as 5%, we recommend that every fetus diagnosed with FHT undergoes fetal echocardiography. Rodeck reported treating a fetus with a thoracoamniotic shunt. The fetus was subsequently shown to have congenital heart disease that was appreciated only after the effusion was drained (Rodeck et al., 1988).

The fetus with a pleural effusion is at risk for the development of polyhydramnios and preterm labor. We recommend that these pregnancies be followed closely, with ultrasound examination every 1 to 2 weeks for early detection of signs consistent with tension hydrothorax, such as mediastinal shift, diaphragmatic eversion, development of hydrops, and polyhydramnios.

The fetus with FHT is at significant risk for pulmonary hypoplasia and respiratory distress following delivery. We recommend that the fetus with a large pleural effusion be delivered in a tertiary care center. Prenatal consultations with a pediatric surgeon, neonatologist, geneticist, and pediatric cardiologist are indicated. The presence of FHT does not influence the mode of delivery. Cesarean delivery should be reserved for obstetrical indications. There have been several reports of fetal thoracentesis prior to delivery to improve respiratory function. Some neonatologists believe that prenatal decompression facilitates resuscitation of the newborn (Bessone et al., 1971; Petres et al., 1982). Others believe that the fluid reaccumulates so rapidly that the patient will be hypovolemic at birth and that this will compromise resuscitation. The latter group advocates thoracentesis after delivery, when venous access can be established and boluses of colloid or crystalloid can be given. There are no data to support one approach over the other, but delay of thoracentesis until after delivery will minimize maternal and fetal risks (Wilson et al., 1985). If the effusion is large and long-standing, thoracentesis is unlikely to have much benefit because of underlying pulmonary hypoplasia. The benefit at the time of delivery, before

or after, is to facilitate ventilation by removing compression of the lung by the hydrothorax.

The development of polyhydramnios may precipitate preterm labor. Antenatal treatment of the FHT may reduce the amniotic fluid and eliminate the preterm labor. In cases in which treatment of the FHT fails to improve the polyhydramnios, reduction amniocentesis may be considered. If tocolysis is necessary, it may be appropriate to administer indomethacin (Lange et al., 1989).

FETAL INTERVENTION

There are several options in the management of the fetus with isolated FHT; the options depend on gestational age, severity of effusion, evidence of progression, and the presence or absence of hydrops, polyhydramnios, or mediastinal shift (Figure 38-2). A period of observation is recommended in each fetus with FHT because of the real possibility of spontaneous resolution. Simple observation may be the best option when the effusion is small and unilateral and there is no evidence of tension. In a fetus diagnosed with FHT prior to 24 weeks of gestation, termination of pregnancy is an option. In the fetus of greater than 32 weeks' gestational age, observation with postnatal thoracentesis may be the best option, but shunting may still be considered.

There are three forms of treatment available for managing the fetus with FHT prior to 32 weeks: thoracentesis, thoracoamniotic shunting, and thoraco-maternal cutaneous drainage. Thoracentesis is a diagnostic maneuver to obtain pleural fluid for cell count, differential, and culture and to establish whether the effusion is chylous. Even repeated thoracenteses provide inadequate decompression of the fetal chest.

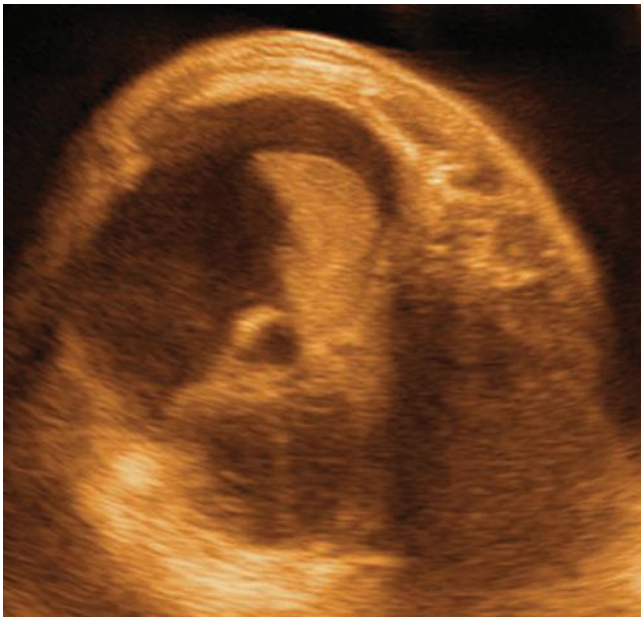

Figure 38-2 Axial image demonstrating unilateral right hydrothorax with significant mediastinal shift.

There have been several reports of thoracentesis for FHT, performed with either complete resolution or a good outcome despite reaccumulation (Petres et al., 1982; Kurjak et al., 1985; Benacerraf et al., 1986). Others have had disappointing results with repeated thoracentesis for FHT because of rapid accumulation of the effusion and neonatal death from respiratory insufficiency (Longaker et al., 1989; Nicolaides and Azar, 1990; Weber and Philipson, 1992). Thoracentesis cannot adequately decompress the fetal chest to allow pulmonary expansion and prevent pulmonary hypoplasia (Longaker et al., 1989).

Thoracoamniotic shunting provides continuous decompression of the fetal chest, allowing lung expansion (Figure 38-3). If instituted early enough, this allows compensatory lung growth and prevents neonatal death from pulmonary hypoplasia. In a review of reported cases of thoracoamniotic shunting for FHT, the survival rate was 38 of 59 (65%) (Weber and Philipson, 1992). Nicolaides and Azar (1990) subsequently reported 48 cases of thoracoamniotic shunting, but there was no attempt to distinguish isolated primary FHT from secondary FHT. Despite intervention, the mortality rate was high. Four of the deaths were due to termination of pregnancy after a chromosomal abnormality was diagnosed. In addition, there were 12 neonatal deaths despite thoracoamniotic shunt placement, but these fetuses appeared to have severe nonimmune hydrops and secondary FHT. Two fetuses that died in utero also appeared to have had secondary FHT and severe hydrops. If the cases of secondary FHT are eliminated, the survival of cases with thoracoamniotic shunting is 38 of 41 (92%) (Gardner et al., 1983; Nicolaides and Azar, 1990; Weber and Philipson, 1992). This is a striking improvement as compared with the survival rate without treatment (50%). Wilson et al. (2004) recently reviewed experiences with thoracoamniotic shunting for pleural effusions reporting a survival rate of 67%. A similarly lower survival rate is observed if secondary cases of FHT are excluded.

The initial step in the management of all fetuses with FHT is a diagnostic thoracentesis for cell count, differential, and culture. The rapidity with which the effusion reaccumulates provides an indication of the severity of the FHT. Drainage of FHT also provides a better view of the heart for fetal echocardiogram. If hydrops is present and thought to be due to mediastinal shift from a unilateral FHT under tension, then thoracoamniotic shunting should be performed without delay. Since spontaneous regression is possible, a second thoracentesis should be performed in cases without hydrops. Drainage of the pleural effusion may allow apposition of visceral and parietal pleura to seal the chylous leak. If the effusion rapidly reaccumulates despite the second thoracentesis, then more definitive drainage is indicated.

The indications for thoracoamniotic shunting are not well defined. Most authors consider the presence of FHT-induced hydrops or polyhydramnios to be indications for shunting (Rodeck et al., 1988; Longaker et al., 1989; Weber and Philipson, 1992). In addition, we recommend

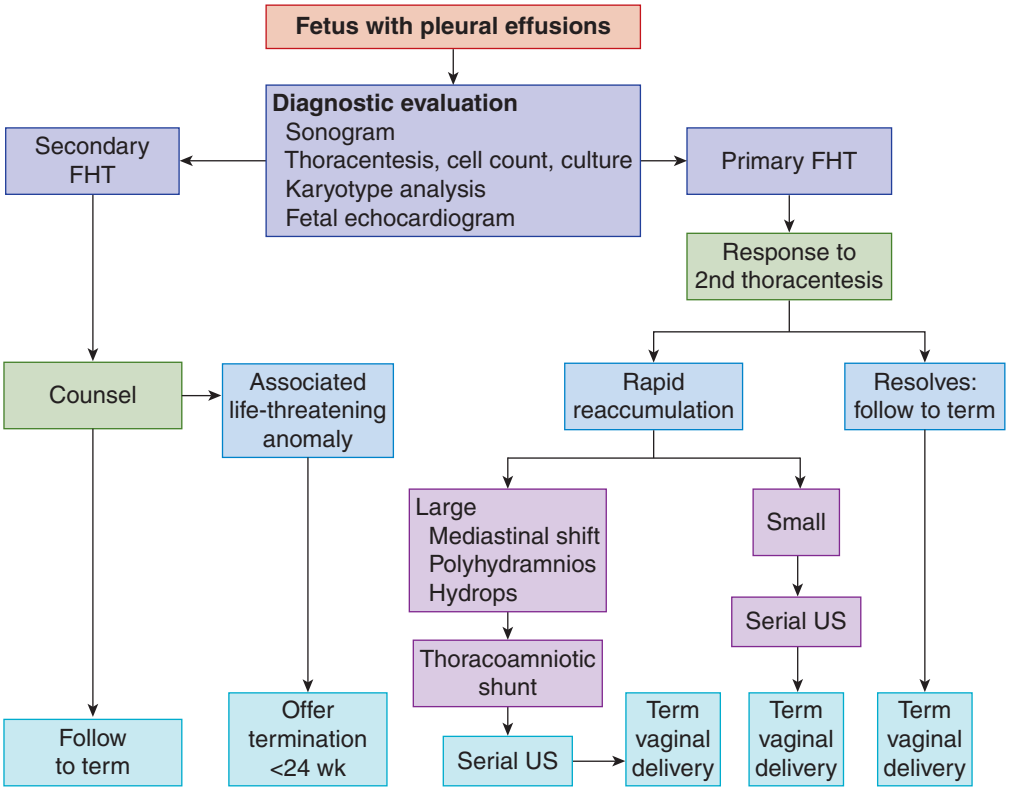

Figure 38-3 Algorithm for the management of fetal pleural effusions.

thoracoamniotic shunting for primary FHT with evidence of effusion under tension even in the absence of hydrops or polyhydramnios (Rigsby et al., 1998). Because spontaneous resolution has been observed even in severe cases of FHT, we reserve thoracoamniotic shunting for cases in which a tension hydrothorax persists after two thoracenteses. The two currently available catheters are the Harrison double-pigtail catheter (Cook Inc., Bloomington, IN) and the Rocket catheter (Rocket Co. Inc., Branford, CT). We have had excellent results with both catheters, which have pigtails at 90 degrees to each other so that the outer coil sits flush against the fetal chest. The trocar used for insertion is smaller for the Cook catheters that make it preferable to the Rocket catheter for earlier gestation fetuses. Laceration of an intercostal artery is possible with either catheter system. This is usually lethal (Wilson et al., 2004). The thoracoamniotic shunt is placed under ultrasound guidance after administering prophylactic tocolytic agents (terbutaline) to the mother; antibiotics (cefazolin, 1 g) are delivered to the amniotic cavity at the conclusion of the procedure. The mother may be admitted to the hospital overnight for serial ultrasound examinations to assess regression of FHT and improvement of hydrops and to be monitored for preterm labor. Weekly sonography is recommended to ensure continued function of the shunt.

Another therapeutic option is thoraco-maternal cutaneous drainage, as reported by Roberts et al. (1986). Adapting a technique first used by Liggins (1986) for intraperitoneal blood transfusions, a catheter was inserted into the fetal pleural cavity. This single case report is of historical interest, in which a chylothorax was successfully decompressed and external drainage maintained for 7 days, with complete resolution. The catheter was subsequently removed and there was a good neonatal outcome. Although no adverse effects were reported, infection remains a significant risk of this procedure and no other cases have been reported.

Large effusions, diagnosed early in gestation, are likely to progress to tension hydrothorax, hydrops, and neonatal death from pulmonary hypoplasia. We do not yet know what percentage of second trimester FHTs require intervention. We believe that evidence of tension, hydrops, or polyhydramnios indicates a worse prognosis. The limited experience with thoracoamniotic shunts suggests that they are extremely effective in decompressing the effusion and improving survival. The risks of thoracentesis and shunt placement to mother and fetus have been minimal and far outweighed by the potential benefits. Few complications have been reported for either fetal thoracentesis or thoracoamniotic shunts. There have even been cases of FHT occurring in twins that have been successfully treated (Grisaru-Granovsky et al., 2000; Lam et al., 2003; Van Mieghem et al., 2006). There has been a procedure-related fetal death due to torsion of the umbilical cord as a result of thoracentesis (Longaker et al., 1989). One case of migration of the shunt under the fetal skin has been reported, but required no intervention when the infant was born (Rodeck et al., 1988). There has been one reported case in which the trocar used to place the shunt lacerated the intercostal artery resulting in fetal demise (Wilson et al., 2004). There have been

no maternal complications reported with either thoracentesis or thoracoamniotic shunting. It should be recognized, however, that these procedures have the potential for infection, bleeding, premature rupture of membranes, preterm labor, and injury to the fetus (Rodeck et al., 1988; Longaker et al., 1989; Tsao et al., 2003; Wilson et al., 2004).

TREATMENT OF THE NEWBORN

We recommend delivery of the fetus with FHT in a tertiary-care setting, where appropriate neonatal resuscitation can be instituted immediately. The infant with an undrained pleural effusion may have pulmonary hypoplasia and is at risk for respiratory insufficiency. We do not see any advantage to fetal thoracentesis immediately prior to delivery. We recommend neonatal thoracentesis in the delivery room to avoid risk to mother and fetus. Fluid shifts caused by thoracentesis can be treated with volume infusion once intravenous access is established in the newborn. The infant who undergoes thoracoamniotic shunt placement should have the shunt clamped or removed during the delivery to prevent pneumothorax. Occasionally, the shunt will become dislodged during delivery. After the infant is resuscitated, chest radiography should be performed to exclude pneumothorax and evaluate the size of residual effusion.

SURGICAL TREATMENT

In the infant with congenital chylothorax without respiratory distress, a period of close observation is indicated. The majority of patients treated in utero do not require postnatal treatment. In the infant with modest effusions, a period of observation and diet manipulation should be initiated. A formula high in medium-chain triglycerides (e.g., Portogen) will bypass the lymphatic system by direct absorption into the bloodstream. This reduces thoracic duct lymphatic flow, which normally has a basal rate of 4 mL per kilogram of body weight per hour (Acevedo, 1943). In some patients, even modest enteral feedings may stimulate marked increases in lymphatic flow. If the chylothorax rapidly reaccumulates and requires repeated thoracentesis on this diet, then central access for total parenteral nutrition and bowel rest are indicated. This regimen is successful in the majority of cases of chylothorax. Tube thoracostomy should be reserved for large effusions that cause respiratory embarrassment despite repeated thoracentesis. Octreotide can be used as an adjunct to bowel rest and total parenteral nutrition and has been successful in treating chylous effusions. Prolonged continuous chest tube drainage can result in relative lymphopenia and an immunocompromised state. In the rare instances in which the chylothorax fails to resolve, thoracotomy for thoracic-duct ligation becomes necessary if chest tube drainage, bowel rest, total parenteral nutrition, and octreotide fail. The duration of nonoperative management in newborns should be at least 1 month because congenital chylothorax tends to close spontaneously. If severe lymphopenia results from long-term chest tube drainage or difficulty maintaining lung inflation is encountered, surgical intervention should be undertaken sooner.

The approach to ligation of the thoracic duct should be on the side of the chylothorax. The surgical objective should be ligation of the leaking tributary or ligation of the main trunk of the thoracic duct above and below the site of the leak, in addition to the overlying pleura at the site of the leak (Reynolds, 1998). In some instances, tissue adhesions such as fibrin glue may be helpful in sealing thoracic duct leaks in congenital chylothorax (Stenzl, 1983). In cases in which thoracic duct ligation fails, the use of pleuroperitoneal shunts for chylothorax has been effective in up to 75% of cases and can be accomplished thoracoscopically (Milsom et al., 1985; Murphy et al., 1989).

LONG-TERM OUTCOME

The majority of cases of congenital chylothorax due to primary FHT resolve spontaneously (Laberge et al., 1991). In Broadman's series, 19 of 20 patients were normal at an average follow-up period of 15 months (Broadman, 1975).

GENETICS AND RECURRENCE RISK

Primary FHT may be associated with a chromosomal abnormality in up to 5% of cases (Weber and Philipson, 1992). This is most often Down syndrome, but cases of Noonan and Turner syndromes have also been reported in FHT (Van Gerde et al., 1984). To date there have been no reports of primary FHT occurring in siblings or the subsequent offspring of an affected fetus.

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39 CHAPTER Pulmonary Agenesis

Key Points

- Pulmonary agenesis is defined as complete absence or severe hypoplasia of one or both lungs.
- Pulmonary agenesis may be found in isolation or in association with other malformations.
- Bilateral agenesis of the lung is rare, and is incompatible with life; unilateral agenesis occurs more commonly, and may be compatible with normal life.
- Sonographically, the mediastinum is shifted toward the affected side and the diaphragm on the ipsilateral side is elevated.
- Detailed sonography and fetal magnetic resonance imaging (MRI) may distinguish unilateral pulmonary agenesis from other causes of mediastinal shift.
- Unilateral or bilateral pulmonary agenesis is not thought to be associated with chromosomal abnormalities.

CONDITION

Pulmonary agenesis is a rare developmental condition in which there is complete absence or severe hypoplasia of one or both lungs (Oyamada et al., 1953; Valle, 1955; Booth and Berry, 1967; Borja et al., 1970; Yaghmai, 1970; Costas et al., 1977; Boxer et al., 1978; McCormick and Kuhns, 1979; Shenoy et al., 1979; Mygind and Paulsen, 1980). Although quite rare, it was initially recognized by dePozzi in 1673 (Skandalakis and Gray, 1994). Munchmeyer was the first to diagnose unilateral agenesis of the lung clinically in 1885 (Ferguson and Neuhauser, 1944). There have since been more than 200 cases of unilateral agenesis of the lung reported. However, only 14 cases have been reported of bilateral agenesis of the lung (Allen and Affelbach, 1925; Tuynman and Gardner, 1952; Claireaux and Ferreira, 1957; Devi and More, 1966; Ostor et al., 1978; Faro et al., 1979; Diaz et al., 1989; Engellenner et al., 1989). In some cases, bilateral pulmonary agenesis was an isolated finding. In other cases, pulmonary agenesis was found in association with other anomalies in the gastrointestinal, genitourinary, and ocular systems (Tuynman and Gardner, 1952; Claireaux and Ferreira, 1957; Devi and More, 1966; Ostor et al., 1978).

A number of theories have been advanced to explain the pathogenesis of lung aplasia. Lung aplasia has been observed in experimental animals fed a diet deficient in vitamin A (Warkany et al., 1948). Some authors have suggested that there may be a vascular cause of pulmonary agenesis, similar to that invoked for intestinal atresia (Louw, 1959). Other authors have suggested a genetic cause for the pulmonary agenesis. Booth and McKenzie and their colleagues linked unilateral pulmonary agenesis to ipsilateral facial and jaw abnormalities, an association noted more recently by several authors (McKenzie and Craig, 1955; Booth and Berry, 1967; Kenawi and Dickson, 1976; Maymon et al., 2001; Dorchy, 2004; Priolo et al., 2004). The gene involved may have a variable expressivity and penetrance. However, the actual cause of this type of pulmonary agenesis remains obscure.

Bilateral agenesis of the lung is incompatible with life and, fortunately, is exceedingly rare (Engellenner et al., 1989). Unilateral agenesis occurs approximately 25 times more commonly, and it may be compatible with a normal life (Booth and Berry, 1967; Maltz and Nadas, 1968). Maymon et al. (2001) proposed a classification for the degree of underdevelopment of the lung that has been adopted by many authors. In Class I, there is agenesis of the lung or total absence of the bronchus and lung. In Class II, there is aplasia in which there is a rudimentary bronchus without lung tissue. In Class III hypoplasia there is bronchial hypoplasia and a variably reduced amount of lung tissue present. This classification scheme is most appropriately referred to as agenesis and hypoplasia, with Class I and II representing cases of agenesis, and Class III representing cases of hypoplasia.

Unilateral pulmonary agenesis is associated with a broad range of anomalies of other organ systems. The most common cardiac defect associated with unilateral agenesis is patent ductus arteriosus (PDA). Although PDA is a common neonatal finding, it may or may not relate directly to the nature of the underlying cause of the pulmonary agenesis. Another common finding is anomalous pulmonary venous drainage, either to the azygos vein or to a persistent left superior vena cava. Other cardiovascular anomalies that have been reported include left pulmonary artery posterior to the left bronchus, aorta anterior to the trachea and compressing it with the left pulmonary artery posterior to the trachea, an anomalous pulmonary venous drainage of the left lung to the right atrium, and four pulmonary veins on the right side. In addition, atrial and ventricular septal defects have been reported in association with pulmonary agenesis.

Although tracheoesophageal anomalies may accompany unilateral pulmonary agenesis, only 14 cases have been recorded thus far, one of which was tracheoesophageal fistula (Kitagawa et al., 1995; Steadland et al., 1995; Vittraino et al., 2003). Other gastrointestinal anomalies associated with pulmonary agenesis include duodenal atresia, annular pancreas, malrotation, Meckel diverticulum, and imperforate anus. Barium contrast studies may demonstrate deviation of the esophagus to the agenetic side, particularly when the right lung is absent. Occasionally the diaphragm may be deficient on either the ipsilateral or contralateral side, allowing eventration of the abdominal viscera. However, this diaphragmatic anomaly is more commonly seen accompanying pulmonary hypoplasia than agenesis.

The most common spinal abnormality seen in association with pulmonary agenesis is hemivertebrae (see Chapter 88). This can be seen in both agenesis of the lung and hypoplasia of the lung. The resulting scoliosis may be quite severe and produce an additional handicap in the child already suffering from recurrent respiratory infection. Such scoliosis may also be due to a rudimentary rim of lung tissue on the affected side. An abnormality of the spine or ribs in the cervical or thoracic regions may be attended by a more prominent scapula on the affected side.

In at least six cases, there have been associated facial or jaw abnormalities ipsilateral to the side of the pulmonary agenesis or hypoplasia (David et al., 1996; Cunningham and Mann, 1997). These abnormalities have included hemifacial microsomia, deformed left external ear, seventh nerve paralysis, small deformed right ear without a patent external auditory canal, facial asymmetry, torticollis, and unilateral mandibulofacial dysostosis (see Chapter 24).

Ipsilateral limb abnormalities have also been observed in many of these cases. These usually involve the upper extremity on the ipsilateral side (Cunningham and Mann, 1997; Aggarwal et al., 2002). While abnormalities of both the ulna and the radius and malformation of the carpus result in a smaller, less powerful hand and arm, the most characteristic abnormalities have been noted in the ipsilateral thumb. These included triphalangia; angulated thumb, in which the middle phalanx is hypoplastic; a preaxial polydactyly; and an abnormal thumb with a short first metacarpal. Some of these digital radial dysplasias fit the pattern of the Holt–Oram syndrome (Holt and Oram, 1960) and the ventriculoradial

dysplasia syndrome (Harris and Osborn, 1966). Because of the association of pulmonary agenesis, or vascular anomalies, gastrointestinal anomalies (tracheoesophageal fistula, imperforate anus), vertebral anomalies (fetal vertebrae or hemivertebrae), urogenital anomalies (renal agenesis, horseshoe kidney, hemiuterus), radial ray anomalies, and ipsilateral craniofacial anomalies (microtic facial asymmetry and hemifacial microsomia) have suggested that pulmonary agenesis should be considered part of the VACTERL Association (Knowles et al., 1988; David et al., 1996; Cunningham and Mann, 1997). At least 13 cases of unilateral pulmonary agenesis have now been reported as part of the VACTERL Association (Knowles et al., 1988; David et al., 1996; Bromley and Benacerraf, 1997; Cunningham and Mann, 1997; Chen et al., 2003).

INCIDENCE

The incidence of agenesis, either unilateral or bilateral, is uncertain. Based on a report of four cases among 114,569 hospital admissions Borja et al. (1970) suggested a prevalence of 0.0034%. During a 6-year period, four other patients were noted with unilateral agenesis among 41,403 admissions to the King Feisel Specialist Hospital and Research Center, which would represent a prevalence of 0.0097% or approximately 1 in 10,000 admissions, or 0.67% of the 596 patients who underwent cardiac catherization at that center (Mardini and Nyhan, 1985). Agenesis of the right lung and agenesis of the left lung are about equally common. Females are affected slightly more commonly than males, and the condition may be inherited (Schechter, 1968; Mardini and Nyhan, 1985).

There is no estimate of the prenatal incidence of pulmonary aplasia; however, Schechter (1968) has estimated an incidence of 1 in 15,000 based on autopsies. Both lungs are affected with equal frequency, although patients with left lung aplasia are thought to have a much better prognosis.

SONOGRAPHIC FINDINGS

The diagnosis of pulmonary agenesis is often made only at the time of autopsy. However, in recent years cases of unilateral pulmonary agenesis have been recognized prenatally (Engellenner et al., 1989; Becker et al., 1993; Yancey and Richards, 1993; Bromley and Benacerraf, 1997; Maymon et al., 2001; Viora et al., 2002; Chen et al., 2003). Sonographically, the mediastinum is shifted toward the affected side and the diaphragm on the ipsilateral side is elevated. Care should be taken to distinguish pulmonary hypoplasia caused by compression from a diaphragmatic hernia or cystic adenomatoid malformation from unilateral agenesis. The sonographic features of unilateral pulmonary agenesis include medial mediastinal shift to the agenetic side and enlarged echogenic lung herniating into the contralateral chest anterior and/or posterior to the mediastinum. There may be associated scoliosis with a curve toward the agenetic side with or without hemivertebrae. Because of the frequency of associated anomalies in pulmonary agenesis affecting other organ systems, a careful sonographic examination should be performed, including scanning of the vertebrae, heart, and limbs and the genitourinary and central nervous systems. There is an association with ipsilateral radial ray defects and hemifacial microsomia. The presence of bilateral facial or radial ray anomalies may be seen in bilateral pulmonary agenesis (Cunningham and Mann, 1997). Renal abnormalities including dysplasia, pelvic kidney, and horseshoe kidney have been reported with unilateral pulmonary agenesis, as has encephalocele (Becker et al., 1993; Cunningham and Mann, 1997; Eroglu et al., 2005). Both polyhydramnios and oligohydramnios have been reported in pulmonary agenesis (Engellenner et al., 1989). In the single case of nonimmune hydrops reported in a fetus with unilateral pulmonary agenesis, it was thought to be due to partial closure of the ductus arteriosus in an otherwise structurally normal heart (Engellenner et al., 1989).

While opacification of the ipsilateral hemithorax occurs with displacement of the mediastinum in the direction of the agenetic lung, Roque et al. (1997) reported a postnatal patient in which this was not the case. In that patient the mediastinum was not displaced, but the liver and the intact diaphragm were displaced cephalad. Fetal magnetic resonance imaging (MRI) has been helpful in distinguishing unilateral pulmonary agenesis from other causes of mediastinal shift (Hubbard and Crombleholme, 1998). MRI clearly demonstrates the compensatorily enlarged unilateral lung shifting over into the contralateral hemithorax with shift of the heart and mediastinal structures to the agenetic side (Figures 39-1 and 39-2).

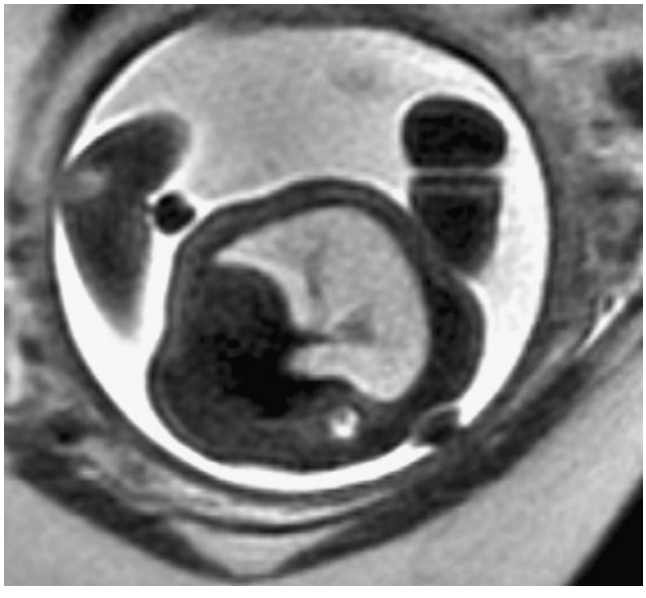

Figure 39-1 Axial image on fetal MRI demonstrating the compensatorily enlarged single lung with shift of mediastinum away from the lung toward the side of the agensis.

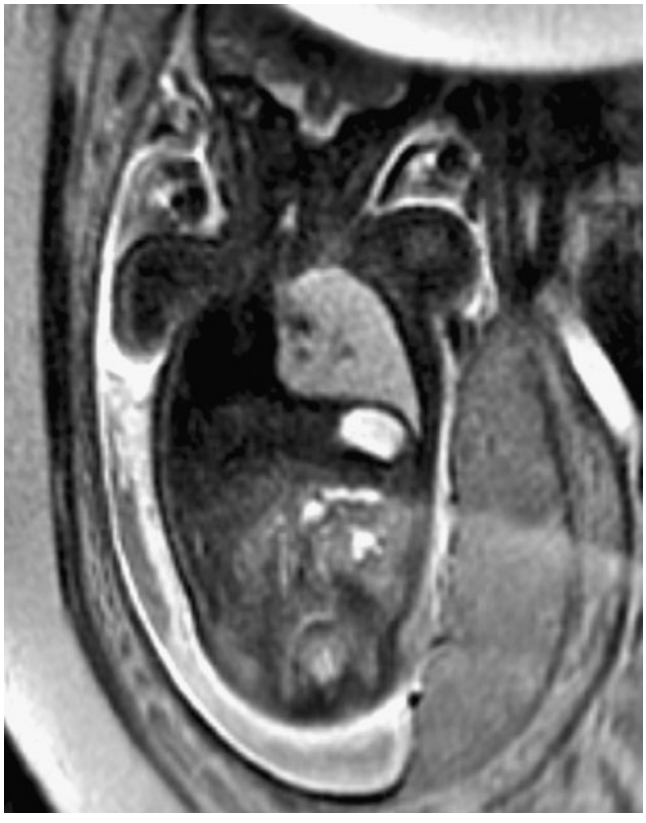

Figure 39-2 The same fetus on sagittal MRI image demonstrating the shift of the heart to the right.

DIFFERENTIAL DIAGNOSIS

Bilateral pulmonary agenesis is not generally mistaken for other conditions. However, at least one case report raised bilateral diaphragmatic hernia in the differential of bilateral pulmonary agenesis (Vittraino et al., 2003). Unilateral agenesis, however, must be distinguished from other conditions that cause mediastinal shift, including diaphragmatic hernia, cystic adenomatoid malformation, and bronchopulmonary sequestration (Bromley and Benacerraf, 1997) (see Chapters 34–37) as well as emphysema.

ANTENATAL NATURAL HISTORY

The coexistence of pulmonary agenesis with other malformations suggests that an interference with embryologic development in the 4th week of fetal life is responsible for these defects. The primitive lung buds are forming at the fourth week of embryonic life, when the pulmonary venous system is changing from its early association with systemic venous circulation to make a connection with the left atrium. An insult occurring at this time, along with the laryngotracheal groove on the ventral surface of the foregut, could interrupt lung-bud development and interfere with the establishment of normal pulmonary venous return. This could account for the frequently observed anomalous pulmonary venous return seen in association with pulmonary agenesis. While the bilateral cases of lung agenesis are incompatible with life, a better prognosis exists for unilateral agenesis. As noted by Maltz and Nadas (1968), 24 of 36 patients followed since 1954 were alive at the time of their report in 1968. In unilateral agenesis there is an uncertain incidence of fetal death, stillbirth, and death during the immediate neonatal period from respiratory distress. These infants remain at risk for recurrent bronchopulmonary infections, which is the leading cause of death. The second most common cause of death is related to associated congenital anomalies, primarily cardiac in cause. While studies have demonstrated that resting pulmonary arterial pressures are normal in these infants, there have been questions raised about the ability for the pulmonary vascular bed to accept increases in cardiac output when stressed. However, it has been recognized that, in the absence of increased pulmonary blood flow related to anomalous pulmonary venous return or other congenital heart defect, the pulmonary vascular bed behaves relatively normally in these children. Ryland and Reid (1971) have performed detailed morphometric analysis of a child who died at 3 months of age from infectious causes with unilateral pulmonary agenesis (Ryland and Reid, 1971). The findings that they reported included a decrease in the number of pulmonary vascular generations, as well as tracheobronchial divisions. However, there was a normal complement of alveoli for two lungs that had been concentrated in the single lung. Right-sided pulmonary agenesis carries a worse prognosis than that of left-sided lesions (Oyamada et al., 1953; Schaffer and Rider, 1957; Smith and Beck, 1958; Steinberg and Stein, 1966; Gabarre et al., 2005). Right-sided lesions result in death earlier and at a greater frequency. This is thought to be due to the fact that 50% of cases of right-sided pulmonary agenesis have associated anomalies—including severe cardiac abnormalities (Gabarre et al., 2005), whereas left-sided lesions are more often isolated. This higher mortality may also be due to the greater mediastinal shift produced by right-sided agenesis, leading to more significant distortion of the tracheobronchial and vascular structures (Thurlbeck, 1975).

MANAGEMENT OF PREGNANCY

Any fetus in which bilateral pulmonary agenesis is suspected should have a detailed sonographic assessment to confirm the diagnosis. MRI may be particularly helpful in distinguishing pulmonary agenesis from congenital cystic adenomatoid malformation of the lung and labor emphysema. In addition, MRI may complement ultrasound in distinguishing unilateral pulmonary agenesis from aplasia (in which, unlike agenesis, the bronchial trunk is seen as a rudimentary stump) and hypoplasia, in which there is arrest of fetal bronchial development (Gabarre et al., 2005). If bilateral pulmonary agenesis is confirmed, the parents should be advised of the uniformly

fatal outcome. Termination is an option if the pregnancy is at less than 24 weeks. If the diagnosis is made at a later gestational age, the delivery should be planned without monitoring for fetal distress. In addition, the neonatologist should be aware of the diagnosis so that no futile heroic resuscitative efforts are made.

In the case of unilateral pulmonary agenesis, detailed sonographic and MRI examination should be performed to confirm the diagnosis and to exclude any associated abnormalities. Of particular interest is the ipsilateral upper extremity, kidneys, face, and mandible. In addition, spinal and rib abnormalities may be seen in unilateral agenesis. The volume of amniotic fluid is important to note, as both esophageal atresia and tracheoesophageal fistula have been reported with unilateral pulmonary agenesis, which may cause polyhydramnios (Thomas and Boyden, 1952). Conversely, oligohydramnios has been observed in one case of unilateral pulmonary agenesis associated with bilateral renal agenesis. Because of the frequency of associated cardiac anomalies in unilateral pulmonary agenesis, echocardiography should be performed in every patient. Unless there are other indications, such as an abnormal serum screen or sonographic markers of aneuploidy, there is no need to perform amniocentesis because pulmonary agenesis is not associated with an increased incidence of chromosomal abnormalities.

FETAL INTERVENTION

There are no fetal interventions for pulmonary agenesis.

TREATMENT OF THE NEWBORN

Fifty percent of children with pulmonary aplasia are stillborn or die within the first few years of life. Because of potential problems with the airway or pulmonary hypoplasia, delivery in a tertiary care center with neonatologists in attendance and a pediatric surgeon available is advisable. Once respiratory status has been assessed, a nasogastric tube should be inserted to exclude esophageal atresia. A detailed physical examination should be performed to evaluate possible VACTERL-associated anomalies. A plain chest radiogram will show shift of the mediastinum toward the affected side (Figure 39-3). There may be bony spinal anomalies and a thoracic asymmetry not appreciated on the physical examination. The diaphragm may be quite high on the ipsilateral side, but it is not paralyzed and it functions normally. The agenetic hemithorax is opaque in contrast to the contralateral side, which may appear overinflated. In contrast, in cases of cystic adenomatoid malformation of the lung and bronchopulmonary sequestration, the ipsilateral hemithorax is cystic or opaque. In addition, unilateral pulmonary agenesis should be distinguished from severe scoliosis by the presence of two lungs. Symptoms may develop in infants with

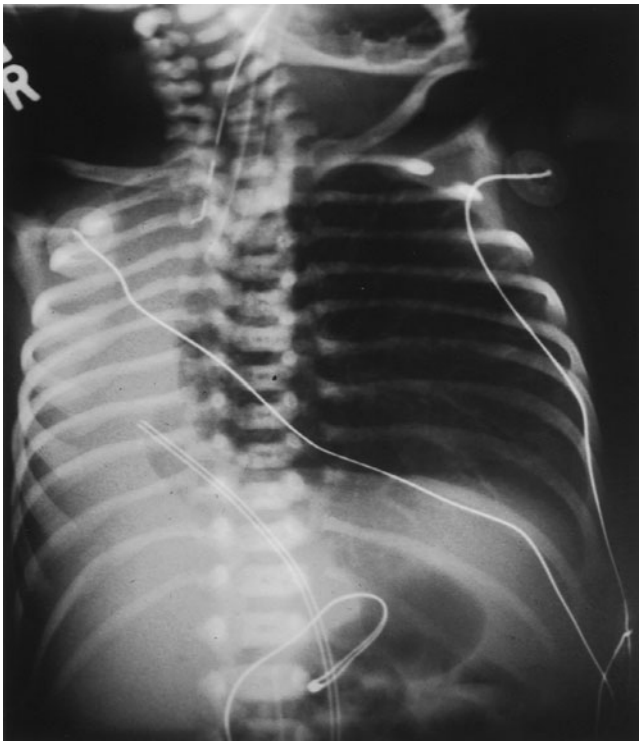

Figure 39-3 Plain chest radiogram of an infant with unilateral right pulmonary agenesis. The left lung appears hyperinflated and rotated into the right hemithorax. The agenetic side is radiopaque and there is mediastinal shift toward the agenetic side.

lung agenesis because of distortion of the airway from severe shift or vascular compression (Harrison and Hendren, 1975; Newman and Gandor, 1997). Three-dimensional chest computed tomography (CT) or MRI scanning may be valuable in defining airway and vascular anatomy for planning a surgical strategy (Wu et al., 1996).

LONG-TERM OUTCOME

Patients who survive with unilateral lung aplasia are thought to be at risk for recurrent respiratory infections due to the rudimentary bronchus. Patients with pulmonary agenesis do not appear to be at increased risk of infectious complications. There have been at least three children with pulmonary aplasia who have died from aspiration of a foreign body, which obstructed their only bronchus (Thomas and Boyden, 1952). Schaffer and Rider (1957) suggested that the survival of patients with pulmonary aplasia was worse with absence of the right lung as compared with absence of the left. The incidence of respiratory infections is higher in patients with Class II and III defects, in which there is interrupted formation of the bronchial tree with absence of alveoli or the entire lung is reduced in size or one lobe of the lung is absent. Schaffer (1960) suggested that the remaining bronchi on the affected side provide a constant source of infection for the contralateral normal lung.

In a detailed morphometric analysis of a child with right pulmonary aplasia, Ryland and Reid found several abnormalities in the remaining lung. There was a reduction in the number of branches in the tracheobronchial tree, which they suggested may be due to an intrinsic abnormality that had affected the two lung buds unequally (Ryland and Reid, 1971). However, despite abnormalities in this lung, it achieved a compensatory cell population appropriate for two normal lungs. The patients with pulmonary agenesis may be at risk for the development of progressive mediastinal shift over time that may present as the equivalent of postpneumonectomy syndrome (Dobremez et al., 2005).

GENETICS AND RECURRENCE RISK

Unilateral or bilateral pulmonary agenesis is not thought to be associated with chromosomal abnormalities. An exception to this is a single case of unilateral pulmonary agenesis associated with velocardiofacial syndrome due to deletion of 22q 11.2 (Conway et al., 2002). While no familial tendency has been recognized, there is one case reported in which pulmonary agenesis occurred in offspring of an affected patient. In addition, unilateral pulmonary aplasia has been reported in both members of two sets of identical twins (Yount, 1948).

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40 CHAPTER Esophageal Atresia and Tracheoesophageal Fistula

Key Points

- Occurs in 1 in 3000 livebirths.
- Fifty percent of cases have associated anomalies, most commonly cardiac, but also genitourinary, anorectoal, and musculoskeletal.
- Sonographic diagnosis is inferred by absence of the fetal stomach with polyhydramnios.
- Differential diagnosis includes congenital diaphragmatic hernia, situs inversus, and musculoskeletal or neurologic abnormalities.
- Chromosome abnormalities are present in 6% to 10% of cases. Fetal karyotype is indicated. Fetal echocardiogram should be performed.
- Delivery is not mandated at a tertiary care center.
- Long-term outcome may be complicated by esophagitis, recurrent strictures, and the development of Barrett's mucosa.
- Mutations in the genes *N-MYC*, *CHD7*, and *SOX2*, which cause Feingold syndrome, CHARGE syndrome, and anophthalmia, esophageal atresia, and genital (AEG) syndrome, respectively, are important genetic causes of esophageal atresia.

CONDITION

Tracheoesophageal anomalies probably arise as a result of events that occur around the 4th week of gestation. The trachea and esophagus first develop as a ventral diverticulum off of the foregut at 22 to 23 days of gestation (Skandalakis et al., 1994). This diverticulum elongates and there is an influx of endodermal cells that form ridges of tissue, which divide the foregut into esophageal and tracheal lumens beginning at the carina and progressing cephalad. By the 26th day of gestation the esophagus and trachea have become completely separated up to the level of the larynx. Interruption in the ingrowth of ectodermal ridges is thought to result in tracheoesophageal fistula. However, the cause of esophageal atresia when associated with tracheoesophageal fistula is less well understood. One theory suggests that rapid caudal elongation of the trachea, in the presence of a distal tracheoesophageal fistula, produces fixation of the distal esophagus to trachea (Smith, 1957; Moore and Pessaud, 1993). The dorsal wall of the esophagus is drawn forward and downward to be incorporated with the trachea, and esophageal atresia results. Consequently, the esophageal atresia associated with tracheoesophageal fistula occurs as a direct result of the presence of the fistula. In contrast, isolated, or pure, esophageal atresia is thought to arise as a result of a vascular deficiency.

More recently, mutations in the hedgehog (Hh) signaling pathway have been implicated in the development of tracheoesophageal fistula (Lees et al., 2005). Studies in transgenic mouse models examining the effects of homozygous sonic hedgehog (*Shh*) knockout mutations demonstrate esophageal atresia and tracheoesophageal fistula (Litingtung et al., 1998; Ramalho-Santos et al., 2000). The foregut abnormalities become evident as early as embryonic day 9.5 in the mouse when the tracheal diverticulum is developing. The role of hedgehog signaling in esophageal atresia and tracheoesophageal fistula is further supported by *Gli* 2−/− and *Gli* 3+/− double knock out mice. These mutations are downstream from sonic hedgehog and also result in esophageal atresia and tracheoesophageal fistula (Lees et al., 2005). Studies performed on biopsies of proximal and distal esophagus in infants undergoing repair of esophageal atresia (EA) and tracheoesophageal fistula (TEF) demonstrated that *Shh* expression was present in the proximal esophagus, but absent in the distal esophagus by both immunohistochemistry and RT-PCR (Spilde et al., 2003).

INCIDENCE

The various forms of esophageal atresia constitute one of the most common gastrointestinal anomalies, occurring in 1 in 3000 livebirths (Holder et al., 1964). The embryologic events at approximately 28 days of gestation that result in esophageal atresia can result in a spectrum of anomalies (Figure 40-1). Isolated esophageal atresia occurs in only 1 in 15,000 livebirths (Figure 40-1A), but esophageal atresia is most commonly seen in association with distal esophageal fistula (Figure 40-1C), in 86% of the observed cases (Holder et al., 1964). Approximately one half of patients with esophageal atresia have anomalies of other organs. Cardiac malformations are the most common, occurring in approximately 25% of cases. They are responsible for most of the mortality and morbidity associated with esophageal atresia (Landing, 1975; Greenwood and Rosenthal, 1976). Atrial and ventricular septal defects are the most common cardiac abnormalities. Genitourinary, additional gastrointestinal, anorectal, and musculoskeletal anomalies occur in approximately 10% of the cases (David and O'Collaghan, 1975; Manning et al., 1986; Spitz et al., 1993) (Table 40-1). These anomalies tend to cluster in groups as part of the "VACTERL" association—*v*ertebral, *a*norectal, *c*ardiac, *t*racheal, *e*sophageal, *r*enal, and *l*imb anomalies.

Maternal exposure to the teratogen methimazole is associated with esophageal and tracheal defects (Shaw-Smith, 2006).

SONOGRAPHIC FINDINGS

It is important to recognize that the diagnosis of esophageal atresia is inferred from the presence of polyhydramnios and

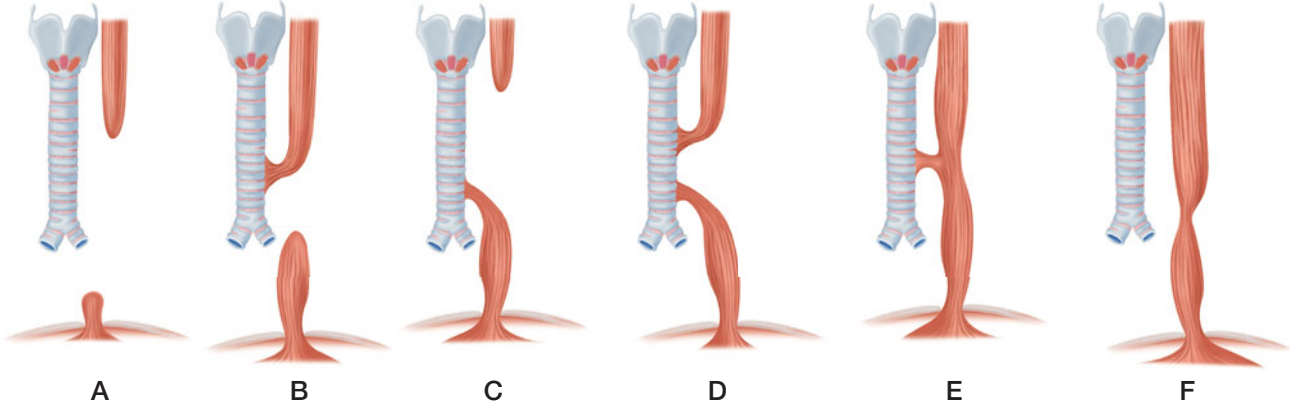

Figure 40-1 Types of esophageal anomalies.

Table 40-1

Incidence of Associated Anomalies in Esophageal Atresia

Anomalies	Percent
Cardiovascular	35
Gastrointestinal	15
Neurologic	5
Genitourinary	5
Skeletal	2
VACTERL association	25
Overall incidence	50–70

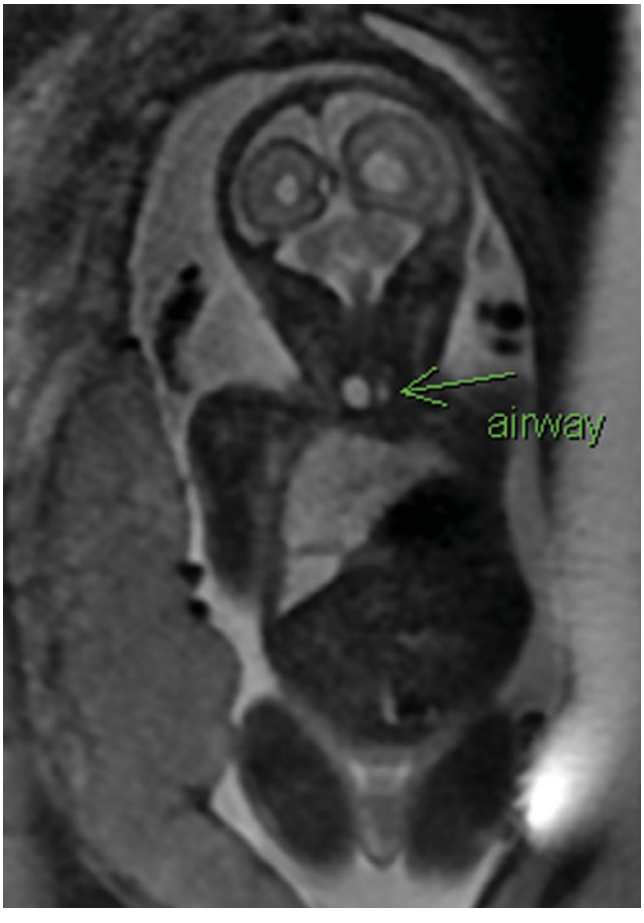

Figure 40-2 Sagittal fetal MRI image in a baby with esophageal atresia and tracheoesophageal fistula demonstrating a dilated esophageal pouch. The arrow indicates the fluid in the immediately adjacent trachea.

the absence of a fetal stomach. This combination of findings has a positive predictive value ranging from 30% to 70% for esophageal atresia (Pretorius et al., 1987; Stringer et al., 1995; Crombleholme et al., 1996). Observation of the dilated proximal pouch is a far more specific finding for esophageal atresia, but this is difficult to see in most fetuses with esophageal atresia (Figure 40-2).

Sonographic observation of fetal breathing movements, swallowing, and general muscular activity should be assessed whenever the stomach bubble is not observed, in order to exclude a neuromuscular cause. Failure to observe the fetal stomach may also occur in normal fetuses because of variations in swallowing and gastric emptying. Serial ultrasound examinations are useful to distinguish this cause of absent fetal stomach. However, visualization of a normal-appearing stomach does not exclude the diagnosis of esophageal atresia. Even in isolated esophageal atresia, gastric secretions alone may be sufficient to distend the stomach and make it visible on prenatal sonography. In esophageal atresia associated with a distal tracheoesophageal fistula, amniotic fluid may be inhaled and passed into the stomach. When the size of the tracheoesophageal fistula is small and limits flow of fetal lung fluid, polyhydramnios develops (Bovicelli et al., 1983).

DIFFERENTIAL DIAGNOSIS

Prenatal diagnosis of esophageal atresia is suspected when polyhydramnios is seen in association with an absent stomach bubble (Figure 40-3) (Farrant, 1980; Zemlyn, 1981; Bovicelli et al., 1983). Considerations in the differential diagnosis of these findings include congenital diaphragmatic hernia,

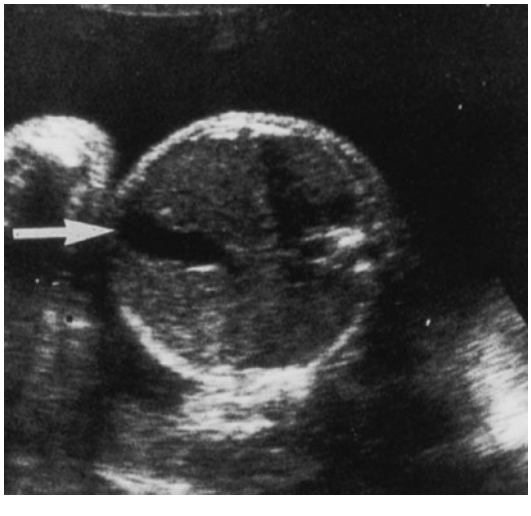

Figure 40-3 Sonographic image of absent stomach with polyhydramnios in fetus with esophageal atresia. *(From Robertson FM, Crombleholme TM, Paidas M, et al. Prenatal diagnosis and management of gastrointestinal anomalies.* Semin Perinatol. *1994;18:182-195.)*

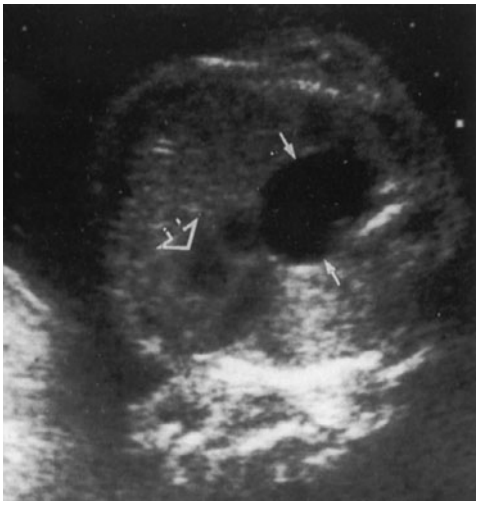

Figure 40-4 Sonographic image of a fetus with esophageal atresia, demonstrating dilated proximal esophageal pouch. *(From Estroff JA, Parad RB, Share JC, et al. Second trimester prenatal findings in duodenal and esophageal atresia without tracheoesophageal fistula.* J Ultrasound Med. *1994;13:375-379.)*

situs inversus, and musculoskeletal or neurologic anomalies that result in fetal inability to swallow. Some authors argue that prenatal diagnosis of esophageal atresia is possible only in isolated esophageal atresia, which accounts for only 10% to 15% of esophageal anomalies. Rarely, a dilated proximal esophageal pouch may be visualized, which is diagnostic of esophageal atresia (Estroff et al., 1994) (Figure 40-4). A dilated proximal esophageal pouch ending at the point of atresia with regurgitation after swallowing has been observed on prenatal ultrasound examination in cases of pure esophageal atresia (Bowie and Clair, 1982; Eyheremendy and Pfister, 1983). Absence of the stomach on ultrasound examination is commonly seen in isolated esophageal atresia, but may also be observed in esophageal atresia with tracheoesophageal fistula. Prenatal sonographic absence of the fetal stomach may also be seen in neuromuscular disorders due to absence of normal fetal swallowing. Severe central nervous system disorders can diminish fetal swallowing and breathing, resulting in an absent stomach bubble and polyhydramnios (Bowie and Clair, 1982).

ANTENATAL NATURAL HISTORY

It remains controversial as to whether prenatal diagnosis of EA with or without TEF alters the prognosis of this condition. Some have argued that early detection allows appropriate counseling of parents, screening for potential associated anomalies, and appropriate delivery setting for postnatal care (Kalish et al., 2003). Despite these theoretical advantages of prenatal diagnosis, some studies have shown no improvement in neonatal outcomes. Increases in perinatal loss rates have been demonstrated among antenatally detected cases of EA/TEF (Nicolaides et al., 1992; Stringer et al., 1995). It has therefore been suggested that prenatally diagnosed cases have a higher incidence of associated anomalies and attendant morbidity. Sparey et al. (2000) also attributed the worse prognosis in prenatally detected cases to the high incidence (60%) of associated anomalies, including cardiac, genitourinary, skeletal, and chromosomal abnormalities. These additional abnormalities may make it more likely that the cases would be identified prenatally.

MANAGEMENT OF PREGNANCY

All pregnant women in whom a fetus with esophageal atresia is suspected because of observed polyhydramnios and absent stomach or dilated proximal pouch should undergo a thorough sonographic survey for potential associated anomalies (see Table 40-1). In particular, evidence of spinal, limb, genitourinary, and cardiac anomalies should be sought. Each fetus should undergo echocardiography to exclude associated structural heart disease.

The fetal karyotype should be determined because chromosomal abnormalities in 6% to 10% of cases (Shaw-Smith, 2006). The most common chromosomal abnormalities observed have been trisomies 18 and 21 (Felix et al., 2007). Esophageal atresia and/or tracheoesophageal fistula are found in 1% of infants with trisomy 21 and up to 25% of infants with trisomy 18. Other chromosome abnormalities that are associated with esophageal atresia and tracheoesophageal fistula include deletions of bands 17q22-23, 13q32, and 22q11 (Shaw-Smith, 2006).

Polyhydramnios may complicate up to 62% of cases of esophageal atresia. This usually develops during the third trimester (Pretorius et al., 1987). Polyhydramnios predisposes to preterm labor, and active measures to continue the pregnancy may be required, including bed rest, administration of tocolytic agents, and/or reduction amniocenteses. The role of reduction amniocentesis in this setting is undefined, but in general is reserved for cases of maternal respiratory compromise. In cases of uterine irritability caused by polyhydramnios, betamethasone can be administered to hasten fetal lung maturity before delivery. The overall prognosis of tracheoesophageal anomalies depends on the presence of associated anomalies, the infant's physiologic status, respiratory complications, and gestational age. In the absence of severe cardiac anomalies and chromosomal abnormalities, survival is greater than 95% in infants weighing more than 2.5 kg following repair of esophageal atresia and tracheoesophageal fistula (Spitz et al., 1993).

The pregnancy should be monitored during the third trimester for the development of worsening polyhydramnios and secondary preterm labor. Once appropriate screening has been performed to exclude potential associated anomalies, the delivery plan can be made. In general, there is no need to transfer care to a tertiary care center. However, the patient should be aware that if esophageal atresia is confirmed postnatally the newborn will require immediate transport to a tertiary care center with pediatric surgeons capable of

reconstructing the anomaly. The presence of esophageal atresia has no implications for the mode of delivery. Cesarean section should be reserved for obstetric indications and there is no need to alter the timing of delivery.

FETAL INTERVENTION

There are no fetal interventions for esophageal atresia and tracheoesophageal fistula.

TREATMENT OF THE NEWBORN

At birth, Replogle sump tube should be positioned in the proximal esophageal pouch and placed to low, continuous suction to prevent aspiration of secretions. Chest radiography showing the sump tube coiled in the proximal pouch is consistent with a diagnosis of esophageal atresia. Rarely a Replogle tube will coil in the pharynx of a normal infant. In isolated esophageal atresia, plain radiography reveals a gasless abdomen. If a tracheoesophageal fistula is present, bowel gas will be seen. The infant should be maintained in an upright position and given antibiotics, and H_2 blockers intravenously. Because of the reported 7% incidence of proximal esophageal pouch–tracheal fistulas (Figure 40-1D) and the possibility of coiling of a sump tube in the pharynx, despite a normal esophagus, some groups perform contrast studies or bronchoscopy/esophagoscopy at the time of repair.

SURGICAL TREATMENT

After considering gestational age, birth weight, pulmonary function, and the presence of other associated anomalies, a decision is made whether to perform a reconstructive procedure or a staged repair. In the extremely premature infant, or a newborn of any gestational age with tracheoesophageal fistula complicated by pneumonia, a feeding gastrostomy can be performed, with or without closure of the tracheoesophageal fistula, and definitive repair can be deferred until the infant's clinical status improves (Louhimo and Lindahl, 1983; Spitz, 1996; Orford et al., 2004).

In cases of isolated esophageal atresia, the gap between proximal and distal pouches is usually prohibitively long (Figure 40-1A). In these cases, a gastrostomy tube is placed to allow enteral feeding. Bolus feedings are employed to encourage gastroesophageal reflux to facilitate growth and dilation of the distal pouch. The growth of the proximal and distal pouches will be maximal between 10 and 12 weeks of postnatal age (Puri et al., 1981). In the meantime, nasopharyngeal suction is maintained to clear saliva, and H_2 blockers are administered to prevent severe esophagitis. Serial contrast studies are performed every few weeks to assess growth of the pouches so that reconstruction may be undertaken as soon as possible. One risk of this approach is aspiration pneumonia. If the infant's respiratory status has been compromised because of aspiration of secretions, this form of therapy must be abandoned. A cervical esophagostomy is then performed to drain salivary secretions. This results in foreshortening of the proximal esophageal pouch and necessitates an esophageal replacement procedure using either colon interposition or a gastric tube. These procedures are usually not performed until approximately 1 year of age.

The prolonged hospitalization, expense, risk of salivary aspiration, and, most importantly, lost opportunity to reconstruct the infant's native esophagus have led some surgeons to attempt a primary repair during the newborn period. Spitz et al. (1987) have reported some success with the gastric pullup of so-called long-gap esophageal atresia. The advantages of this approach include briefer hospitalization, lower cost, and early return to normal feeding. The use of this procedure in the United States is not widespread because of the ongoing risk of aspiration from pooling of secretions in the intrathoracic gastric reservoir and compromise of respiratory function secondary to mass effect of the gastric pullup in the posterior mediastinum.

A basic tenet of all reconstructive esophageal surgery is the preservation of the native esophagus whenever possible. True to this tenet, Kimura and Soper (1994) have proposed an ingenious operation for long-gap esophageal atresia. The infant's proximal esophagus is mobilized through an incision into the right neck and a spiral myotomy is performed to lengthen the esophagus. The esophagus telescopes like a "barber shop pole" and the muscular layers are reapproximated. This gives sufficient length to create an esophagostomy at the level of the nipples. A gastrostomy tube is placed for enteral feeding, but sham feedings can be commenced to preserve the coordination of normal swallowing. In addition, an esophagostomy positioned on the chest instead of at the clavicle allows placement of an ostomy appliance for ease of care. Normal neck movement then stretches the proximal esophagus. In a series of two or three procedures, the stoma is advanced 1.5 to 2.5 cm to lengthen the proximal esophagus. When sufficient length has been obtained, the esophagus can be reconstructed through a right thoracotomy. The advantages of this approach include discharge from hospital within the first 10 days of life, maintenance of normal swallowing coordination by sham feedings, cost reduction, and, most importantly, a reconstruction that preserves the infant's native esophagus. There is limited experience with this approach and no data on long-term outcome are yet available.

LONG-TERM OUTCOME

In cases of esophageal atresia, the motor function of the distal esophageal pouch never becomes normal because of its interruption during embryologic life. Manometric studies of the distal esophageal pouch have demonstrated that it lacks normal peristalsis and the stripping activity usually observed after

reflux of acid into the distal esophagus. In addition to motor disturbances, the sensory innervation of the distal esophagus does not appear to be as robust as that of the normal esophagus. Also, due to foreshortening of the intra-abdominal esophagus, the lower esophageal sphincter appears to be less competent than in normal infants. All these factors predispose to gastroesophageal reflux and the potential for severe esophagitis. A more significant consequence is the development of strictures at the anastomosis, which occurs as a result of acid injury in this area. To prevent these complications, all infants with tracheoesophageal fistula should be on H_2-blocker therapy to prevent injury from gastroesophageal reflux. In instances in which recurrent anastomotic strictures occur despite repeated dilation and adequate medical therapy, antireflux procedures, such as Nissen fundoplication, are often indicated.

As experience has grown with repair of esophageal atresia and tracheoesophageal fistula, it has become more widely recognized that these children are at risk for the subsequent development of Barrett's mucosa from prolonged and severe gastroesophageal reflux. Barrett's mucosa is the result of metaplastic changes in the mucosa of the distal esophagus. This is a premalignant condition and requires close endoscopic surveillance with biopsies to detect dysplastic changes that precede the development of esophageal carcinoma. Esophageal carcinoma has developed after repair of tracheoesophageal fistula in patients as young as 21 years of age (Adzick et al., 1989). It is presumed that these malignancies arose within areas of Barrett's mucosa, which were caused by severe untreated gastroesophageal reflux. While both Barrett's mucosa and esophageal carcinoma are rare in children with repair of esophageal atresia and tracheoesophageal fistula, the incidence is uncertain. It is recommended that all children with this anomaly undergo endoscopic surveillance periodically to ensure that clinically silent gastroesophageal reflux has not resulted in severe esophagitis predisposing to the development of Barrett's mucosa.

Because of the abnormal motility in the reconstructed esophagus of the child with esophageal atresia with tracheoesophageal fistula, the motility in this organ is never quite normal. These children are prone to the impaction of food boluses at the anastomosis. This may occur even in the absence of a true anastomotic stricture. The reason for this is the disordered motility in the distal esophageal pouch, which does not move the food bolus normally into the stomach. All parents should be advised that once their infant begins eating solid food the pieces should be small and that they should learn to chew their food very well. This problem with impaction of food in the esophagus usually becomes less frequent as the child grows and the caliber of the esophagus increases.

GENETICS AND RECURRENCE RISK

The birth of an infant with an isolated esophageal atresia and/or tracheoesophageal fistula and a negative family history carries a low recurrence risk, on the order of 1% (Van Staey M et al., 1984; Pletcher et al., 1991; Shaw-Smith, 2006). The recurrence risk for a chromosome abnormality depends on the parental age and their chromosome status, if a chromosome deletion was found in the fetus or infant.

Recently, mutations in three different genes, *N-MYC*, *CHD7*, and *SOX2*, have been shown to be causative in syndromes that include esophageal atresia as one feature. The first condition, Feingold syndrome, is an autosomal dominant disorder in which 40% of patients have a gastrointestinal atresia. Esophageal atresia is the most frequent GI atresia in this syndrome. Affected individuals have other subtle anomalies, including microcephaly, shortening of the second and fifth fingers, hypoplastic thumbs, and syndactyly of the toes (Brunner and van Bokhoven, 2005; Shaw-Smith, 2006). The condition results from heterozygous mutations in the *N-MYC* gene. It is thought that this syndrome is underdiagnosed (Layman-Pleet et al., 2007). Diagnostic DNA mutation testing is available. If a mutation is identified, the parents should have their DNA studied.

Approximately 10% of patients with CHARGE syndrome (coloboma, heart malformation, choanal atresia, growth and/or mental retardation, genital abnormalities, ear anomalies and/or deafness) have esophageal atresia. Charge syndrome is due to haploinsufficiency of the gene *CHD7*. DNA testing is also available for this condition. Lastly, anophthalmia, esophageal atresia, and genital (AEG) syndrome have been shown to be due to loss of function mutations in the *SOX2* gene.

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Tachyarrhythmias

41
CHAPTER

Key Points

- Fetal tachyarrhythmias include isolated extrasystoles, supraventricular tachycardia, and atrial flutter.
- Approximately 1% of fetuses are diagnosed with an arrhythmia.
- Isolated extrasystoles are the most common tachyarrhythmias and are for the most part benign.
- Supraventricular tachycardia is the most common serious dysrhythmia detected prenatally. The majority are re-entrant and are identified by a fetal heart rate of greater than 200 beats per minute with one-to-one atrial-to-ventricular activity. Congenital heart disease is associated with this arrhythmia 5% to 10% of cases.
- The rate with atrial flutter is usually between 300 and 500 beats per minute. The ventricular response depends on the degree of atrioventricular block. This dysrhythmia has a poor prognosis due to the fact that it is associated with hydrops and with congenital heart defects.
- Fetal dysrhythmias have the potential for serious sequelae including fetal hydrops.
- Fetal arrhythmias are diagnosed by fetal echocardiography that includes M-mode assessment and Doppler analysis. A full anatomical survey including a detailed survey of the fetal heart should also be performed.
- Although premature atrial and ventricular contractions are considered benign, sustained tachyarrhythmia may develop in up to 1% of fetuses diagnosed with this condition. Thus, serial fetal heart rate auscultation is suggested.
- Spontaneous resolution of supraventricular tachycardia has been reported.
- For the most part, fetal supraventricular tachycardia associated with congenital heart defects has been associated with a poor prognosis.
- Gestational age is an important factor when determining how best to manage a fetal dysrhythmia.
- Digoxin is the first-line therapy for isolated fetal tachyarrhythmia. Procainamide, flecainide, and sotolol are reserved for second-line treatment.
- If hydrops is concomittent, the tachyarrhythmia may take longer to resolve.
- Intermittent fetal tachycardia without evidence of fetal hemodynamic compromise can be observed closely instead of undergoing medical therapy.
- Refractory cases to maternal medical management have been treated with direct fetal therapy.
- The newborn should be evaluated thoroughly for signs of cardiac abnormalities. Approximately 50% of infants will relapse after birth.

CONDITION

Fetal tachyarrhythmias detected in utero include irregular cardiac rhythm resulting from isolated extrasystoles, supraventricular tachycardia, and atrial flutter. The most common of the above arrhythmias is an irregular cardiac rhythm resulting from isolated extrasystoles (Silverman et al., 1985; Kleinman, 1986; Copel et al., 2000). Most of these extrasystoles originate in the atria and resolve spontaneously (Kleinman, 1986; Reed et al., 1987). An increased frequency of premature beats has been attributed to the maternal use of caffeine, tobacco, and alcohol (De Vore, 1984). Although premature atrial or ventricular contractions have not been considered a risk factor for anomalies in the past, more recent reports suggest that a fetal structural cardiac abnormality may be found in up to 2% of such cases (Beall and Paul, 1986; Reed, 1991).

Supraventricular tachycardia is the most common serious dysrhythmia detected prenatally (Bergmans et al., 1985; Kleinman et al., 1985a). The majority of supraventricular tachycardias are considered to be re-entrant dysrhythmias and are identified by a fetal heart rate of more than 200 beats per minute (bpm) with one-to-one atrial-to-ventricular activity (Figure 41-1) (Simpson and Marx, 1994). Paroxysmal supraventricular tachycardia may also occur as part of the Wolff–Parkinson–White syndrome, together with a short P–R interval, prolonged QRS, and presence of a delta wave on electrocardiogram. Typically, supraventricular tachycardia has not been associated with congenital heart disease; however, in 5% to 10% of cases, structural cardiac abnormalities can be found (Beall and Paul, 1986; Reed, 1989). The presence of structural heart disease in addition to supraventricular tachycardia is associated with a poor fetal outcome (Bergmans et al., 1985).

Fetal atrial flutter has been diagnosed and reported less commonly than supraventricular tachycardia (Kleinman, 1986). The atrial rate in flutter can be estimated between 300 and 500 bpm with a variable ventricular response dependent on the degree of atrioventricular block (Figure 41-2). Fetal atrial flutter has a poor prognosis, due in part to its association with structural heart disease (in up to 20% of cases) and with the development of hydrops fetalis (Kleinman, 1986; Reed, 1991; Simpson and Marx, 1994).

In contrast to benign arrhythmias such as isolated extrasystoles, fetal dysrhythmias have the potential for serious sequelae. It has been well described that fetuses with tachyarrhythmias have decreased cardiac output and are at risk for hydrops fetalis (Reed et al., 1987; Reed, 1989). Protracted supraventricular tachycardia can lead to cardiac failure in a matter of days (Allan, 1984). The exact mechanism for the development of cardiac failure and hydrops remains unclear. The progression to hydrops in utero seems to follow right heart failure with tricuspid regurgitation and right ventricular dilatation, signifying impending decompensation (Allan et al., 1983; Chao et al., 1992; Gembruch et al., 1993). It has been postulated that either passive liver congestion associated with cardiac failure or decreased hepatic perfusion from decreased cardiac output may result in hypoalbuminemia, leading to decreased oncotic pressure and transudation of fluid into interstitial spaces (Johnson et al., 1992). Pericardial and pleural effusions, fetal ascites, and subcutaneous edema are probably late manifestations of cardiac decompensation.

INCIDENCE

Arrhythmias are identified in approximately 1% of all fetuses; however, the actual incidence of fetal arrhythmias is expected

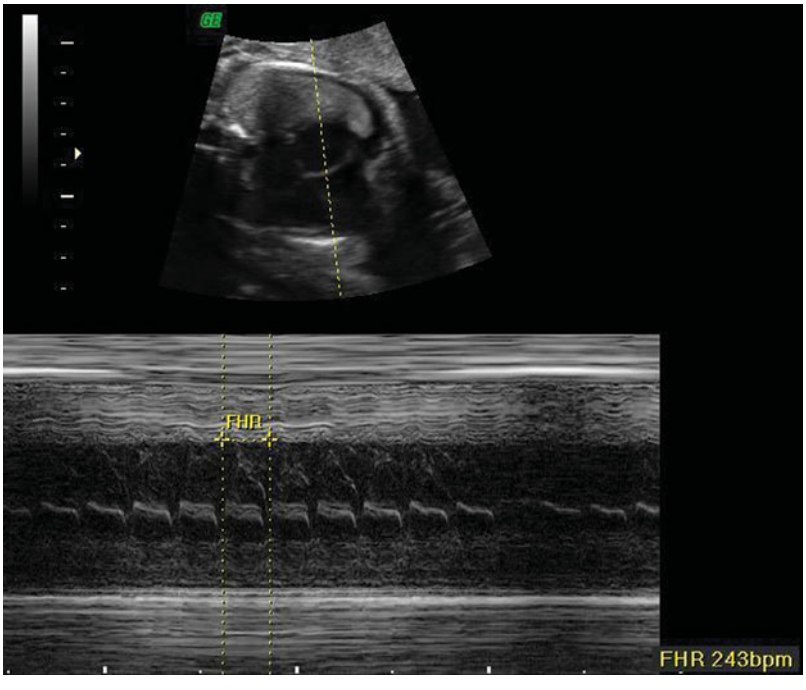

Figure 41-1 M-mode imaging in a fetus with supraventricular tachycardia demonstrating a ventricular rate of 243 bpm.

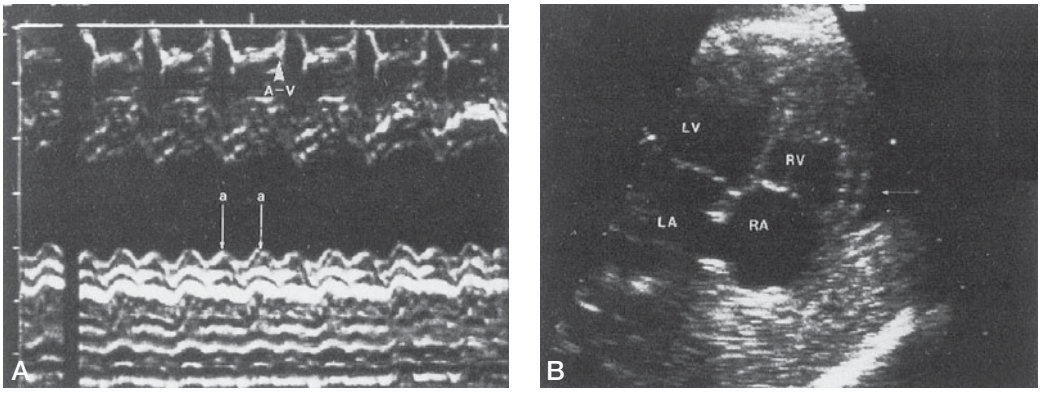

Figure 41-2 **A**. Fetus in atrial flutter as shown by an atrial contraction rate of 480 bpm (arrowhead labeled A-V for atrioventricular-valve opening). **B**. Four-chamber view in the same fetus in atrial flutter showing dilated right atrium and pericardial effusion (arrow). LA = left atrium; LV = left ventricle; RV = right ventricle; RA = right atrium. *(From Simpson LL, Marx GR. Diagnosis and treatment of structural fetal cardiac abnormality and dysrhythmia.* Semin Perinatol. *1994;18:215-227.)*

to be higher because a significant proportion of them can be intermittent or resolve spontaneously (Reed, 1989; Simpson and Marx, 1994). The most common and clinically significant tachyarrhythmias identified in utero are supraventricular tachycardia and atrial flutter.

SONOGRAPHIC FINDINGS

Ultrasound evaluation should include a complete fetal survey and a survey of the cardiac anatomy to confirm absence of structural malformations. The incidence of abnormal cardiac anatomy varies with the type of arrhythmia. The fetus should also be examined for evidence of hydrops as defined by fluid collections in the pericardium, the pleural spaces, ascites, or skin edema. Amniotic fluid may also be increased. An increase in fetal cardiac size or wall thickness may be an indication of abnormal cardiac hemodynamics (Reed, 1989).

Echocardiography, including M-mode assessment and Doppler analysis, is an important tool in the diagnosis and evaluation of fetal dysrhythmias (Kleinman et al., 1980; De Vore et al., 1983; Silverman et al., 1985). The atrial and corresponding ventricular activity can be viewed by two-dimensional echocardiography and the rates determined by placement of the M-mode cursor perpendicular to the atrial and ventricular walls. M-mode echocardiography can also be used to identify pericardial effusions and to measure wall thickness, chamber size, and fractional shortening (see Figures 41-1 and 41-2). Doppler evaluation of atrioventricular and semilunar valve flows can be used to time the ventricular contractions (Strasburger et al., 1986). The hemodynamic effects of a dysrhythmia are assessed by determining the size and function of the four chambers, the magnitude of the semilunar and atrioventricular flow-velocity integrals, and the presence of mitral or tricuspid regurgitation or nonimmune hydrops fetalis. Color flow mapping may also be used to identify flow disturbances. The approach to the ultrasound evaluation of arrhythmias is summarized in Table 41-1.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of fetal tachyarrhythmias includes benign isolated extrasystoles and more significant dysrhythmias such as atrial flutter and supraventricular tachycardia. M-mode echocardiography is useful in differentiating these conditions, as described above.

ANTENATAL NATURAL HISTORY

Premature atrial and ventricular contractions are considered to be benign and do not require treatment. However, it has

Table 41-1

Evaluation of Arrhythmias

Type of Study	Findings
Two-dimensional ultrasound examination	Anatomy Chamber dilatation Hydrops
M-mode	Type of arrhythmia Pericardial effusion Hypertrophy/dilatation
Doppler	Flow disturbances (regurgitation) Volume flow
Color flow	Flow disturbances

From Reed KL. Fetal arrhythmias: etiology, diagnosis, pathophysiology, and treatment. Semin Perinatol. *1989;13:294-304.*

been reported that a sustained tachyarrhythmia may subsequently develop in up to 1% of fetuses with premature beats (Kleinman, 1986).

The natural history of isolated in utero supraventricular tachycardia remains unclear. Although intermittent supraventricular tachycardia may be of no clinical significance, sustained supraventricular tachycardia may be life-threatening (Southall et al., 1980; Bergmans et al., 1985). Spontaneous resolution of supraventricular tachycardia has been reported (Newburger and Keane, 1979; Santulli, 1990). Complete resolution of protracted supraventricular tachycardia with subsequent normal fetal development has been observed (Simpson et al., 1997). In a small series of isolated fetal supraventricular tachycardia, hydrops developed in only one of nine cases managed conservatively without medical therapy (Simpson et al., 1997). Interestingly, the fetus in which signs of hydrops developed had intermittent supraventricular tachycardia at a rate of 200 bpm occurring less than 50% of the time. In the remaining eight fetuses in which hydrops did not develop, five had intermittent episodes of supraventricular tachycardia occurring less than 50% of the time and two had more sustained supraventricular tachycardia occurring between 50% and 75% of the time. Spontaneous resolution of the supraventricular tachycardia in these remaining eight fetuses occurred within 10 days of diagnosis, with no recurrence in the antepartum or newborn period. Antiarrhythmic agents were not administered to these eight mothers or their infants, who were all delivered at term. However, sustained supraventricular tachycardia can be associated with the development of congestive heart failure and hydrops and the potential for fetal death.

The presence of structural heart disease in association with fetal supraventricular tachycardia has been reported to have a poor outcome (Bergmans et al., 1985). However, a case of fetal supraventricular tachycardia and congenital heart disease has been observed in an infant, who is now 3 years old, without any recurrence of the dysrhythmia after surgery for a double inlet single left ventricle, subaortic stenosis, and coarctation of the aorta (Simpson et al., 1995).

Although rapid progression to fetal hydrops can occur with sustained supraventricular tachycardia of 24 to 48 hours' duration, signs of cardiac failure will not develop in all fetuses (Newburger and Keane, 1979; Kleinman et al., 1985a). In approximately 25% of cases, there seems to be no associated hemodynamic compromise. However, 55% to 60% of fetuses with supraventricular tachycardia will have evidence of cardiac decompensation in utero or during the newborn period (Newburger and Keane, 1979; Bergmans et al., 1985). At the time of diagnosis of supraventricular tachycardia, Kleinman (1986) detected hydrops fetalis in 16 of 18 cases. Fortunately, even in the presence of cardiac failure, supraventricular tachycardia has a favorable prognosis (Kleinman, 1986). In utero medical treatment can result in conversion to normal sinus rhythm within 48 hours (Sarno et al., 1989). Conversion to sinus rhythm seems to occur more easily in the absence of fetal hydrops (Kleinman et al., 1985a). It has also been shown that because of impaired placental transfer of antiarrhythmic agents, fetuses with hydrops could require 2 to 3 weeks of therapy before converting to normal sinus rhythm (Maxwell et al., 1988). Atrial flutter seems to have a poor in utero prognosis, with two of three fetuses with atrial flutter and associated hydrops dying in one series (Kleinman, 1986; Simpson and Marx, 1994).

MANAGEMENT OF PREGNANCY

The typical presentation of fetal tachyarrhythmia involves the auscultation of a rapid fetal heart rate in an asymptomatic woman at a routine prenatal visit. Such a finding should prompt a thorough prenatal evaluation, including a detailed ultrasound examination for fetal anatomy, growth, and biophysical status, in addition to an echocardiogram with M-mode and Doppler evaluation to characterize the arrhythmia fully and evaluate its impact on myocardial function. The latter studies are generally performed in consultation with a pediatric cardiologist. The finding of structural cardiac abnormalities in 5% to 10% of cases of supraventricular tachycardia reaffirms the need for careful anatomic assessment of the fetal heart (Beall and Paul, 1986; Reed, 1989).

In the absence of additional structural cardiac malformation, it is well accepted that in utero medical therapy or delivery, or both, is appropriate in cases of fetal supraventricular tachycardia with evidence of hemodynamic compromise. Gestational age is a significant factor in deciding appropriate intervention. In one series, use of digoxin alone or digoxin with verapamil or propranolol achieved in utero control in 13 of 14 cases of supraventricular tachycardia with associated hydrops (Kleinman et al., 1985b). Higher doses of digoxin are often necessary to achieve therapeutic levels because of the variable absorption, large volume of distribution, and rapid clearance associated with pregnancy. Conversion to sinus rhythm seems to occur more easily in the absence of fetal hydrops (Kleinman et al., 1985a). This may be because of impaired placental transfer of antiarrhythmic agents in hydropic fetuses (Maxwell et al., 1988). In a retrospective study of 11 cases of supraventricular tachycardia and 4 cases of atrial flutter with hydrops, a median of 12.5 days was required for in utero conversion to sinus rhythm, as compared with a median of 3 days in the absence of hydrops (van Engelen et al., 1994). In this series, indications were that flecainide was more effective than digoxin in achieving rhythm control. Oudijk retrospectively reviewed the charts of 21 patients treated with sotalol during the prenatal period (Oudijk et al., 2000). Ten patients had fetal supraventricular tachycardia, 10 had atrial flutter, and 1 had ventricular tachycardia. Hydrops was present in 9 cases. In the supraventricular tachycardia group, sinus rhythm was established in 6/10 of cases. In the atrial flutter group, sinus rhythm was established in 8/10 patients. The mortality rate was 19% (4/21 patients; 3 with supraventricular tachycardia and 1 with atrial flutter).

Two patients (2/17; 12%) who converted to sinus rythm in utero were diagnosed with adverse neurological outcomes postnatally. The authors suggested that sotolol may cause a proarrhythmic event in the fetus that may contribute to the high mortality rate in this study. The authors also recommend that sotalol be reserved for cases of fetal atrial flutter or refractory cases of supraventricular tachycardia.

We recommend digoxin for first-line therapy of isolated fetal tachyarrhythmia, with procainamide, flecainide, and sotolol reserved for second-line treatment when delivery is not desirable because of gestational age and when conversion to normal sinus rhythm with digoxin has been unsuccessful. It is important to note that both flecainide and sotolol have been associated with a risk for fetal death (Oudijk et al., 2000, 2002; Pradhan et al., 2006). Amiodarone has been used in refractory cases with good results but must be used with caution due to the fact that it has been associated with fetal hypothyroidism (Pradhan et al., 2006).

Successful in utero conversion from supraventricular tachycardia to atrial flutter with a variable ventricular response after maternal administration of digoxin has been described (Simpson et al., 1995). Atrial flutter has been found to be more difficult to treat successfully in utero, and this is partly responsible for the reported poor prognosis associated with this dysrhythmia (Simpson and Marx, 1994). In one series, antiarrhythmics were effective for in utero control of supraventricular tachycardia in 88% of cases, as compared with 66% of cases of atrial flutter (van Engelen et al., 1994). Although second-line antiarrhythmic agents may be tried, elective preterm delivery may be necessary in cases of supraventricular tachycardia alternating with atrial flutter that are refractory to digoxin. On the basis of the adverse outcomes reported in the literature, we recommend that atrial flutter with or without hydrops be promptly treated with an antiarrhythmic if delivery is not a reasonable option because of gestational age (Simpson et al., 1995).

In contrast, in the absence of hydrops or hemodynamic compromise, conservative management without medical therapy may be a reasonable option for fetuses with supraventricular tachycardia. Spontaneous resolution of protracted supraventricular tachycardia with subsequent normal fetal development has been observed (Stewart et al., 1983; Bergmans et al., 1985; Simpson et al., 1997). A review of the literature has identified seven cases of supraventricular tachycardia that converted to normal sinus rhythm spontaneously during parturition, with no recurrences after delivery (Bergmans et al., 1985). It is postulated that vagal stimulation during delivery slows conduction through the atrioventricular node, resulting in conversion to normal sinus rhythm.

A close follow-up of cases of isolated fetal supraventricular tachycardia without hydrops is warranted because of the potential for hydrops if conservative management without medical therapy is undertaken. Initially, daily assessments with ultrasound and fetal echocardiography are necessary. The interval between fetal evaluations can be extended, and resolution of the supraventricular tachycardia has been documented with individualization of follow-up thereafter. This regimen requires a reliable and compliant patient. If frequent evaluations are not possible or if compliance is questionable, medical therapy with antiarrhythmics is more appropriate.

When supraventricular tachycardia is diagnosed, the perinatologist and pediatric cardiologist together formulate a treatment plan (Simpson and Marx, 1994). Initially the fetus is assessed by the perinatologist for any signs of biophysical compromise. A detailed sonographic examination to determine fetal growth, development, and biophysical status is performed, with careful examination for the presence of pericardial, pleural, or abdominal fluid. The pediatric cardiologist then confirms the atrial and ventricular rate of contraction, atrial and ventricular size and function, and the presence and magnitude of atrioventricular valve regurgitation. Aortic and pulmonary flow-velocity integrals are determined during episodes of tachycardia and episodes of normal sinus rhythm. Immediate medical therapy is undertaken if there are signs of hemodynamic compromise, fetal distress, or hydrops fetalis. In all other cases, the mother is admitted to hospital and the fetus is monitored for 24 hours to determine the duration of the dysrhythmia. Expectant management without immediate medical therapy is considered if there are no signs of compromise, if the fetal tachycardia is not sustained, and if the patient is compliant (Simpson and Marx, 1994).

When fetal supraventricular tachycardia is persistent despite digoxin, and the gestational age precludes delivery, an additional antiarrhythmic drug should be tried. Procainamide, flecainide, quinidine, verapamil, propranolol, sotolol, and amiodarone have all been given for fetal tachyarrhythmias, with variable success (Bergmans et al., 1985; Kleinman et al., 1985b; Wladimiroff and Stewart, 1985; Oudijk et al., 2000). Unlike digoxin, however, these drugs can be associated with significant toxicity to the mother and fetus. Both procainamide and quinidine have the potential for proarrhythmic effects in the fetus and gastrointestinal toxicity in the mother (Kleinman et al., 1985a). Verapamil has been associated with cardiac decompensation and sudden fetal demise (Epstein et al., 1985; Owen et al., 1988). Intrauterine growth restriction and subsequent neonatal bradycardia and hypoglycemia have been observed with the use of propranolol (Gladstone et al., 1975; Rubin, 1981). Amiodarone can be considered for more protracted dysrhythmias, but both maternal and fetal thyroid dysfunction are potential complications. At our institution, flecainide or procainamide are most commonly used as the second-line treatment when delivery is not desirable. Procainamide can be administered orally or intravenously to the mother, and serum levels can be closely monitored. Procainamide has a short half-life, which is an important characteristic if maternal or fetal toxicity is experienced. Delivery is planned at term when conversion to normal sinus rhythm is successful, or sooner if conversion fails to occur and there is evidence of cardiac decompensation or fetal compromise.

When the diagnosis of fetal tachyarrhythmia is first made at term, medical therapy may be used in order

to facilitate a trial of labor and possible vaginal delivery (Silverman et al., 1985). Vaginal delivery should be possible in most cases; however, when conversion to normal sinus rhythm is unsuccessful or hydrops is present, delivery by cesarean section may be more appropriate. Intrapartum fetal monitoring may not be reliable with supraventricular tachycardia, and the fetus with hydrops may not tolerate labor. Intermittent sonographic surveillance of fetal well-being may be necessary in such cases.

FETAL INTERVENTION

For fetuses with evidence of hemodynamic compromise or hydrops prior to term, treatment of the rhythm disturbance is accomplished by administering antiarrhythmic medications to the mother. This approach is described in detail in the section for management of pregnancy. Maternal administration of digoxin, flecainide, procainamide, quinidine, and verapamil has been successfully used.

If an adequate trial of maternal medical therapy fails despite appropriate drug levels and time for effect, direct fetal therapy may be considered. This may be achieved by direct intravenous infusion of digoxin or amiodarone into the umbilical vein. Amiodarone may be helpful in this regard due to its prolonged duration of action.

In very rare cases, direct fetal intramuscular injection of medications may be possible, but this approach should be considered less optimal than direct fetal intravascular infusion (Weiner and Thompson, 1988; Hallak et al., 1991). Direct fetal therapy should be reserved for the preterm fetus that has evidence of heart failure and has not responded to maternally administered therapy. In one case, supraventricular tachycardia at 24 weeks of gestation was successfully controlled with direct fetal therapy after more traditional transplacental therapy with digoxin, verapamil, and procainamide had failed (Weiner and Thompson, 1988). In this case report, the fetus received 70 μg of digoxin in three divided doses administered intramuscularly over a period of 24 hours. In a further case, a 25-week-old fetus with severe hydrops fetalis secondary to supraventricular tachycardia was successfully treated with fetal intramuscular injections of digoxin together with maternal digoxin (Hallak et al., 1991). Fetal umbilical blood sampling had revealed poor placental transfer of digoxin even after 2 weeks of therapeutic maternal levels.

TREATMENT OF THE NEWBORN

Because 50% of infants have a relapse of tachycardia after birth, it is important to assess the neonatal rate with an electrocardiogram (van Engelen et al., 1994). Neonatal echocardiography should also be performed to confirm the absence of structural cardiac malformation and to evaluate cardiac function. Cardioversion, transvenous atrial overdrive pacing, or antiarrhythmic drugs have been used postnatally to convert the heart rate of infants who have tachycardia at birth to normal sinus rhythm (van Engelen et al., 1994). In the absence of hemodynamic instability, it is reasonable to either observe neonates closely without medical therapy, or begin prophylactic medical therapy for up to 1 year.

SURGICAL TREATMENT

No surgical treatments for tachyarrhythmias have been described.

LONG-TERM OUTCOME

In a group of 51 cases presenting with fetal tachycardia, 50% of all surviving infants had a relapse of tachycardia after birth (van Engelen et al., 1994). Relapse appeared to be more common in those with atrial flutter; 60% of infants with fetal atrial flutter had a relapse, as compared with 42% of infants with fetal supraventricular tachycardia. In the group of 33 infants with supraventricular tachycardia, a re-entry mechanism could be seen on the electrocardiogram in eight cases: four with Wolff–Parkinson–White syndrome and four with permanent junctional reciprocating tachycardias. At 1 month of age, 78% of the patients with a history of fetal supraventricular tachycardia or atrial flutter were receiving anti-arrhythmic drugs, usually digoxin, and sometimes in combination with propranolol, verapamil, or flecainide either for recurrent tachycardia or as prophylaxis. At 3 years of age, 14% were taking antiarrhythmic drugs (van Engelen et al., 1994). Of the three patients who were still receiving medications, one had Wolff–Parkinson–White syndrome and two had permanent junctional reciprocating tachycardia. The need for drug therapy seems to diminish as childhood advances, with re-entry tachycardia proving to be the most therapy-resistant form before and after birth as well as during later childhood.

Adverse neurological outcome has been associated with successful in utero treatment of fetal dysrhythmias (Oudijk et al., 2000). For example, in a series by Oudijk where patients were treated with transplacental sotolol two patients (2/17; 12%) who had converted to sinus rhythm in utero were diagnosed with adverse neurological outcomes postnatally. Both of these cases had been complicated by hydrops.

GENETICS AND RECURRENCE RISK

We are unaware of any reported cases of a recurrence of fetal arrhythmias in subsequent pregnancies. An exception is Wolff–Parkinson–White syndrome, which involves

paroxysmal supraventricular tachycardia and has a well-documented familial occurrence (Harnischfeger, 1959).

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42 CHAPTER Bradyarrhythmias

Key Points

- The most common fetal bradyarrhythmia diagnosed prenatally is congenital complete heart block (CHB), usually occurring in association with circulating maternal anti-Ro or anti-La antibodies, but also occurring together with structural fetal cardiac malformation.
- Sonographic diagnosis of complete heart block (CHB) is made using M-mode echocardiography, demonstrating complete dissociation between atrial and ventricular rates; varying degrees of cardiac failure and hydrops may also be present.
- Immune-mediated CHB usually leads to permanent damage to the fetal cardiac conduction system, and controversy exists as to whether subsequent prenatal therapy by maternal administration of corticosteroids will have any meaningful benefit.
- Other options for prenatal therapy include maternal betamimetic administration, although its role is generally limited by maternal side effects; additionally experimental approaches to fetal cardiac pacing have also been described in cases with very poor prognosis.
- While vaginal delivery is possible with appropriate intensive fetal surveillance, for practical reasons, most such fetuses are delivered elective by cesarean; delivery should occur in a tertiary care facility with appropriate pediatric cardiology backup available.

CONDITION

The diagnosis of fetal arrhythmias has become increasingly common as echocardiographic evaluation of the fetal heart has improved and been pursued earlier in gestation. Two-dimensional echocardiography can distinguish normal from disordered cardiac anatomy as early as 16 weeks of gestation (Kleinman et al., 1980; Allan et al., 1983, 1984a). Similarly, fetal arrhythmias can be accurately characterized with the addition of M-mode echocardiography (Allan et al., 1983; Devore et al., 1983). Although the vast majority of fetal arrhythmias reported are either extrasystoles (75%) or tachyarrhythmias (15%), fetuses with bradyarrhythmia due to complete heart block (CHB) account for 9% of all cases (Kleinman and Evans, unpublished data, 1988). CHB is seen in association with severe congenital heart disease in up to 53% of cases (Schmidt et al., 1991). In this setting the prognosis is poor, with a survival rate of less than 15% (Shenker, 1979; Teteris et al., 1979; Allan et al., 1983; Crawford et al., 1985; Cameron et al., 1989). However, CHB complicates structural congenital heart disease in only 0.4% to 0.9% of the cases (Camm and Bexton, 1984; Olah and Gee, 1993). CHB is observed with normal cardiac anatomy in up to 50% of cases (Kleinman and Evans, unpublished data, 1988). CHB with normal cardiac anatomy is usually associated with transplacental passage of maternal antibodies, anti-SSA or anti-SSB (anti-Ro or anti-La), in mothers with connective-tissue diseases (McCue et al., 1977; Scott et al., 1983; Litsey et al., 1985; Taylor et al., 1988).

The most common form of congenital heart block seen in the fetus is third-degree, or complete, atrioventricular (AV) block. First-degree AV block is the prolongation of the P–R interval and is difficult to detect prenatally. Second-degree AV block occurs either as a progressive lengthening of the P–R interval, with resulting dropped beats (Wenckebach phenomenon), or as a fixed P–R interval with a ratio of transmission of atrial beats to ventricular beats of 2:1, 3:1, 4:1, etc. Third-degree AV block occurs when there is complete dissociation of atrial and ventricular rates with no transmission of atrial beats to the ventricles.

Antibodies to soluble ribonuclear proteins, anti-Ro (Sjögren syndrome antigen-A, SS-A) and anti-La (Sjögren

syndrome antigen-B, SS-B) have been demonstrated in the serum of affected fetuses and their mothers (Franco et al., 1981; Kephart et al., 1981; Miyagowa et al., 1981). CHB in fetuses with structurally normal hearts is almost uniformly associated with the presence of anti-Ro or anti-La antibodies. Anti-Ro and anti-La antibodies have been demonstrated to bind to fetal heart conduction tissue (Deng et al., 1987; Harsfield et al., 1991). The pathophysiology of CHB involves the transplacental passage of maternal autoantibody, anti-Ro, which binds to an antigen in the fetal heart conduction system with consequent inflammation and fibrosis. The fetal and neonatal heart contains the body's highest concentration of Ro antigen (Wolin and Steitz, 1984; Harley et al., 1985; Deng et al., 1987). IgG deposits have been demonstrated in the cardiac tissues of affected infants (Litsey et al., 1985; Lee et al., 1987). Studies in vitro, using anti-Ro and anti-La antibodies, have demonstrated that anti-Ro antibodies selectively bind to newborn myocardium but not to adult myocardium and that this binding inhibits repolarization (Alexander et al., 1992).

Although it is thought that anti-Ro and anti-La antibodies play an important role in the pathogenesis of fetal CHB, some authors have suggested that there must be a cofactor (Taylor et al., 1988). The mothers of infants with CHB almost always have anti-Ro and anti-La antibodies. Fetal CHB, however, develops in only 1% to 2% of anti-Ro/anti-La antibody positive mothers, and usually occurs between 20 and 24 weeks' gestation. Since the majority of mothers with these antibodies have normal pregnancies, this implies that a second factor is necessary for the development of CHB. It has been suggested that viral infections may initiate immune damage by influencing antigenic expression. Ro and La ribonucleoproteins may become immunogenic by forming complexes with viral genomes (Venables et al., 1983). Interestingly, an increased frequency of antibodies to cytomegalovirus has been observed in mothers of babies with CHB (Peckham et al., 1983; Taylor et al., 1988).

In cases in which maternal anti-Ro/anti-La antibodies are not responsible for CHB, prolonged QT syndrome or viral infection may be responsible (Peckham et al., 1983).

The presence or absence of subendocardial fibroelastosis should be noted in cases of CHB. This is an echogenic appearance to the inner lining of the cardiac chambers, most often affecting the ventricles but also can affect the atria. This is thought to be due to subendocardial ischemia and is usually a sign of more severe myocardial injury, which without treatment is associated with a poor prognosis (Jaeggi et al., 2004).

INCIDENCE

CHB during fetal life is uncommon, with an incidence of approximately 1 in 20,000 to 1 in 25,000 livebirths (McHenry and Coyler, 1969; Michaelson and Engle, 1972; Gochberg, 1984). However, because many fetuses with CHB die in utero, the true incidence of fetal CHB is likely to be somewhat higher than this.

SONOGRAPHIC FINDINGS

The most common reason for referral for evaluation for fetal CHB is the detection of a slow or irregular heart rate on routine obstetric examination (Schmidt et al., 1991). The median gestational age at referral for fetal CHB is 26 weeks, but may range from 17 to 38 weeks (Schmidt et al., 1991). More than half of fetuses with CHB will have associated structural heart disease, making assessment of fetal cardiac anatomy essential. The diagnosis of CHB can be confirmed sonographically by demonstrating atrial and ventricular rate discrepancies. If detected early, type 1 or 2 second-degree AV block may be observed. M-mode examination may be particularly useful to independently confirm atrial and ventricular rates (Crowley et al., 1983). It is also important to sonographically assess myocardial function, as immune complex deposition and fetal inflammatory reaction may result in myocarditis and significant myocardial dysfunction.

A complete fetal survey should be performed, with special attention paid to the presence or absence of hydrops, as indicated by pericardial or pleural effusions, ascites, or skin edema. Echocardiographic assessment should include measurement of ventricular escape rate and atrial rate. An atrial rate of less than 120 beats per minute (bpm) should raise the possibility of a missed structural heart defect. In addition, assessment of stroke volume, left and right ventricular ejection fraction, combined ventricular output, and the presence and severity (or absence) of AV valvular insufficiency should be noted (Takomiya et al., 1989; Veille et al., 1990). Valvular insufficiency can be diagnosed by Doppler echocardiography. Peak systolic flow velocities in the ascending aorta and diastolic umbilical flow velocities should be assessed as indirect indicators of cardiac output, and should be measured as a basis for comparison for serial echocardiographic assessment.

Doppler ultrasound assessment of the umbilical artery has been used to estimate impedance to flow in the placental circulation. However, because calculations depend on the time taken for the velocity of flow to decay in diastole, the prolonged diastolic component in CHB limits the value of this technique (Olah et al., 1991; Olah and Gee, 1993). Complete absence or reversal of flow during diastole in CHB, however, has the same clinical significance as in cases in which the heart rate is normal (Olah et al., 1991). This form of sonographic assessment is thought to be particularly useful in CHB because of its association with anti-Ro antibodies and antibodies in connective-tissue disease, such as systemic lupus erythematosus, in which placental infarction and immunoglobulin deposition are frequently encountered (Guzman et al., 1987; Veille et al., 1990). Increases in placental resistance may be sufficient to precipitate cardiac decompensation, even

in the absence of further slowing in the ventricular escape rate.

Growth restriction may occur as a result of fetal CHB. Therefore, serial measurements of biparietal diameter, abdominal circumference, and long bones should be performed at bimonthly intervals to assess fetal growth.

Measurement of the cardiothoracic ratio should also be performed by two-dimensional echocardiography (Paladini et al., 1990). An increase in the cardiothoracic index beyond the normal range may assist in predicting the extent of lung compression and possible pulmonary hypoplasia, as well as the severity of cardiac failure as indicated by cardiac enlargement (Olah and Gee, 1993).

DIFFERENTIAL DIAGNOSIS

When evaluating a fetus with bradycardia, the differential diagnosis includes heart block as a complication of structural heart disease, heart block in a structurally normal heart (most often due to transplacental passage of maternal antibodies in connective tissue disease), and sinus bradycardia in a premorbid fetus. The most common structural defects seen in association with CHB are listed in Table 42-1. Although pregnant women with connective tissue disease are at significantly increased risk for having a fetus with CHB, only 50% of fetuses with bradycardia are born to women with a history of collagen vascular disease (Petri et al., 1989; McCauliffe, 1995). Fetal CHB may be the first manifestation of maternal collagen vascular disease.

A fetus diagnosed early in the development of heart block may present with irregular heart rhythm due to second-degree AV block. This may occur either as partial progressive AV block, (the Wenckebach phenomenon), or as second-degree AV block in which the P–R interval is relatively fixed and the ratio of transmission may be 2:1, 3:1, or 4:1, etc. Schmidt et al. (1991) have observed progression from normal sinus rhythm to second-degree block to CHB.

Table 42-1

Structural Heart Defects Most Commonly Associated with Fetal Complete Heart Block

Left atrial isomerism
Transposition of the great arteries
Atrioventricular septal defect
Pulmonic atresia
Anomalous pulmonary venous connection
Double outlet right ventricle
Atrioventricular discordance
Absent right atrioventricular connection
Double inlet ventricle
Right atrial isomerism
Pulmonic stenosis

ANTENATAL NATURAL HISTORY

While bradycardia is well tolerated by most fetuses, nonimmune hydrops will develop in up to 25% as a result of cardiac decompensation (Kleinman et al., 1982; Stewart et al., 1983; Holzgreve and Golbus, 1984; Crowley et al., 1985; Carpenter et al., 1986; Machado et al., 1988). In 90% of cases associated with a structurally normal heart, the infant is born with neonatal lupus erythematosus (McCauliffe, 1995).

Fetal CHB usually presents during the second trimester in the setting of a structurally normal heart. Although fetal CHB has been diagnosed as early as 17 weeks, the mean gestational age at presentation is closer to 26 weeks (Schmidt et al., 1991). There is some evidence to suggest that a progressive rise in transplacental passage of immunoglobulin occurs after 22 weeks' gestation, which correlates with progressive immune-mediated injury to the fetal conduction system (Stiehm, 1975).

The majority of the fetuses with CHB tolerate the slower ventricular rate relatively well and progress to term without incident. However, in 15% to 25% of fetuses with CHB nonimmune hydrops will develop and the fetus will die in utero or shortly after delivery. In a multicenter review, Schmidt et al. (1991) found that fetuses with structurally normal hearts and CHB with ventricular rates of less than 55 bpm had only a 14% survival rate. The presence of nonimmune hydrops was a poor prognostic feature, with only a 15% survival rate. Similarly, when CHB complicated structural heart disease, the survival was only 14%. The development of AV valve incompetence is also a harbinger of fetal cardiac decompensation and nonimmune hydrops (Schmidt et al., 1991). AV valve incompetence appears to be due to distortion at the valve rings by progressive ventricular dilation with the slow ventricular rate. In the fetal-sheep model of CHB, slower ventricular rates cause progressive diastolic distention of the ventricles distorting the AV valve rings, resulting in regurgitation (Crombleholme et al., 1991). The AV valve incompetence can be immediately reversed by increasing the ventricular rate by pacing the heart, which reduces the diastolic ventricular distention. AV valve incompetence tends to precede the development of nonimmune hydrops because it results in venous hypertension and passive hepatic congestion, leading to pericardial and pleural effusions, ascites, and anasarca.

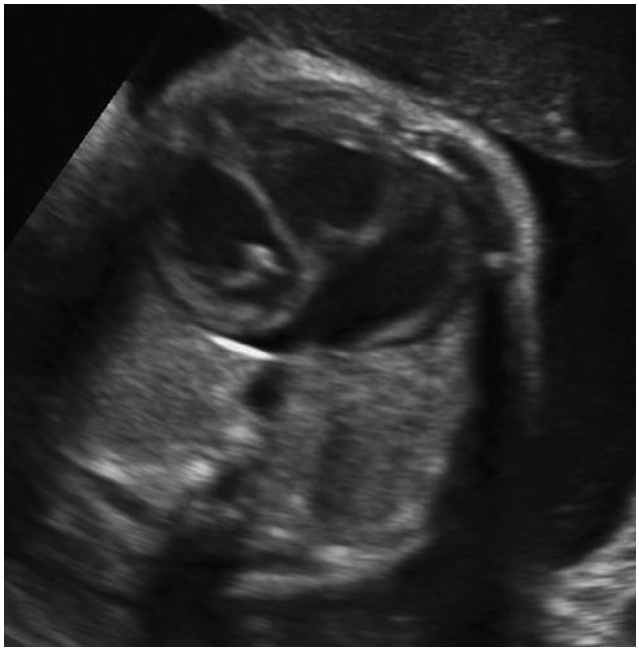

Figure 42-1 Four-chamber view of the heart in a fetus with complete heart block due to transplacental passage of SSA antibodies in a mother with systemic lupus erythematosis. The atrial rate was 135 beats per minute with a ventricular response rate of 54 beats per minute. There is evidence of endocardial fibroelastosis (EFE) in this heart most notably in the papillary muscle and in the interventricular septum.

In addition to progressive destruction of the fetal conduction system by an inflammatory response to maternal autoantibody deposition, a generalized myocarditis may also be seen in fetal CHB. In these cases, antibody deposition occurs throughout the heart, and the inflammatory reaction results in progressive myocardial decompensation. Subendocardial fibroelastosis may result, which can be an indicator of end-stage myocardial injury. These may appear as echogenic papillary muscles or areas of subendocardial myocardium in the ventricle or atria (Figure 42-1).

MANAGEMENT OF PREGNANCY

A woman with no previous history of collagen vascular disease who presents carrying a fetus with CHB should have a formal rheumatologic evaluation. On close questioning, such women often report dry eyes/mouth or arthralgias, which suggest collagen vascular disease (McCauliffe, 1995). The fetus should undergo a complete anatomic sonographic survey, including Doppler waveform studies of umbilical arterial diastolic flow. Echocardiography should be performed, not only to exclude structural heart disease, but also to confirm AV dissociation and document the atrial and ventricular rates. In addition, assessment of ventricular contractility, presence or absence of increased myocardial echogenicity suggestive of subendocardial fibroelastosis, AV valve incompetence, and stroke volume should be noted and serve as a baseline for comparison with future studies.

The diagnosis of immune-mediated fetal heart block should be treated by maternal steroid administration. During the third trimester there may be progressive slowing of ventricular rate, and increased frequency of surveillance is indicated in fetuses with ventricular rates of less than 65 bpm. Heart rates less than 60 bpm may prompt a twice-weekly ultrasound examination to detect AV valve incompetence or early signs of nonimmune hydrops. Similarly, serial echocardiography is indicated to detect subtle changes in contractility, stroke volume, myocardial echogenicity, and onset of AV valve incompetence. Diastolic flow in the umbilical arteries is also a useful marker to follow because it indicates impedance to flow in the placental circulation. Increased resistance due to deposition of immune complexes in the placental bed may precipitate heart failure. Because of the progressive dilation of heart chambers, cardiothoracic ratios may be useful indicators of possible pulmonary hypoplasia. Because of the lack of heart rate variability, standard nonstress tests are not helpful.

The indications for delivery in fetal CHB include obvious signs of deteriorating cardiac status, with the subsequent development of nonimmune hydrops. The mode of delivery in fetal CHB is controversial. If the fetus is being delivered for signs of cardiac decompensation, the stress of vaginal delivery may cause further hemodynamic compromise (Paladini et al., 1990). In addition, detection of nonreassuring fetal heart rate status in the setting of fetal CHB is very difficult. Some authors have delivered noncompromised fetuses with CHB vaginally, using continuous heart rate monitoring and fetal blood sampling during labor (Olah and Gee, 1993). Some authors have advocated continuous monitoring of ventricular rate by scalp electrodes, atrial rate by external transducers, or fetal pulse oximetry by scalp probes or transcutaneous pCO_2 (Todras et al., 1989; Chan et al., 1990a, 1990b). Other authors have suggested continuous intrapartum echocardiography.

While such intensive surveillance is possible, we recommend cesarean delivery for any fetus at more than 30 weeks' gestation with CHB and evidence of hemodynamic compromise, manifested by nonimmune hydrops, a ventricular rate of less than 55 bpm, AV valve insufficiency, or poor contractility. In fetuses in which CHB is well tolerated, vaginal delivery may be considered, but only if appropriate intrapartum monitoring is available. Delivery should be performed at a center with pediatric cardiologists and surgeons who are available for placement of either temporary transvenous or epicardial pacing leads.

FETAL INTERVENTION

Numerous antenatal treatments, both medical and surgical, have been proposed in the management of the fetus with CHB. The medical therapies are divided into those intended

to minimize the immunologic injury to the fetal heart and those geared toward increasing the ventricular rate.

Controversy exists over the prenatal treatment of CHB. The form of treatment used most often is administration of steroids to the mother to limit the fetal inflammatory response (Barclay et al., 1987; Bunyan et al., 1987; Fox and Hawkins, 1990; Jaeggi et al., 2004). Dexamethasone is preferred over prednisone. Because of the fear of adverse side effects due to steroids, such as maternal insulin resistance, lowered resistance to infection, and poor wound healing, some authors have recommended against prophylactic treatment for anti-Ro antibody positive mothers. However, once antibody-mediated damage to the fetal conduction system has occurred, it is permanent. Because myocardial injury is likely permanent at the time of presentation with CHB, it has been argued that there is minimal role for steroid therapy once that stage has been reached.

Jaeggi et al. published a protocol for the management of prenatally diagnosed CHB without structural heart disease (Figure 42-2). This report included 37 patients treated by this approach divided into two groups based on year of diagnosis. Patients received maternal dexamethasone or maternal betamimetics. The survival of the earlier group treated from 1990 to 1996 was 80% at birth and 47% to 1 year of life. In contrast, the more recent group of patients treated between 1997 and 2003 had a survival to birth and 1 year of 95% ($p < 0.01$). The use of the glucocorticoid dexamethasone appeared to be the primary reason for this improved survival. Among these mothers receiving dexamethasone, the survival was 90% versus 46% without dexamethasone.

This group therefore recommended maternal dexamethasone administration (4–8 mg/d) and with betamimetics (ritodrine 30–60 mg/d or salbutamol 10 mg/d) for cases in which ventricular response rate is below 55 bpm or in which there is evidence of abnormal ventricular function. In the dexamethasone-treated mother, adverse effects attributed to steroid included oligohydramnios (19%), and one mother developed hypertension. It is unclear whether the addition of betamimetics to dexamethasone conferred any additional benefit. It is possible that in this setting betamimetics either prevented further decrease in heart rate or improved myocardial function. The QT interval should be assessed in all patients prior to starting betamimetics and should be avoided in prolonged QT syndrome. Betamimetics may alter ventricular depolarization and dramatically lengthen QTc that may trigger cardiac events. The use of magnetocardiography may be useful in the diagnosis of prolonged QT syndrome and assist management of CHB (Hosono et al., 2001).

Betamimetic agents, such as terbutaline, ritodrine, and isoproterenol have been used in attempts to accelerate the fetal heart rate (Carpenter et al., 1986; Martin et al., 1988; Schmidt et al., 1991; Jaeggi et al., 2004). The responses to these agents have been variable, and no definite benefit has been proven (Crowley et al., 1985; Carpenter et al., 1986; Machado et al., 1988). In addition, doses sufficient to cause an increase in fetal ventricular rate are often poorly tolerated by the mother.

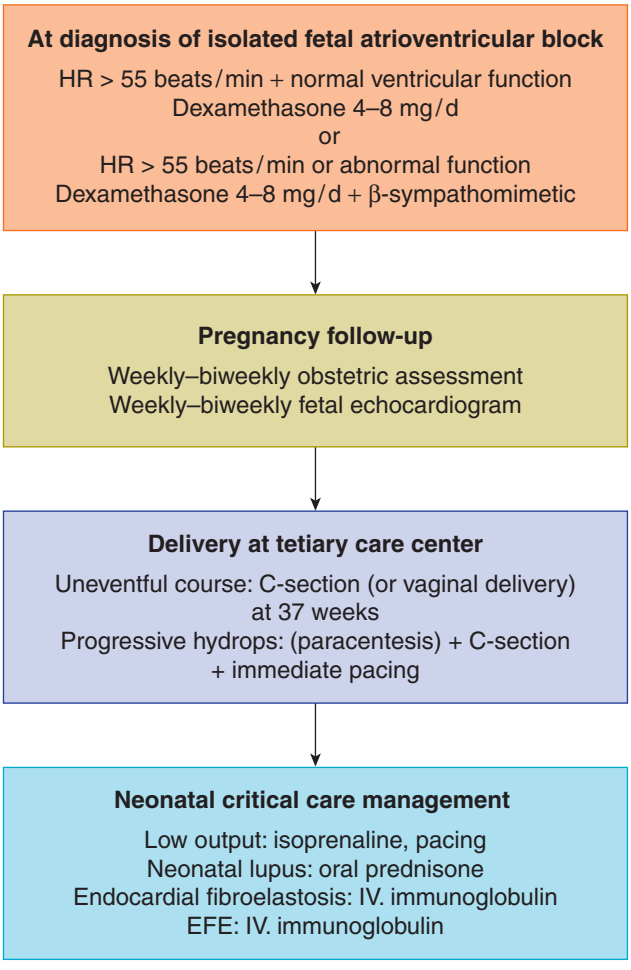

Figure 42-2 Suggested protocol for the management of prenatally diagnosed complete heart block without structural heart disease.

The use of intravenous immunoglobulin (IVIG) in fetal CHB has been described. IVIG is thought to bind circulating anti-Ro antibody in the maternal circulation to prevent transplacental passage, by increasing immune clearance of the antibody. It may also downregulate anti-Ro antibody production. Limited data are available to support this intervention.

Plasmapheresis has also been recommended to limit cardiac damage once pericardial effusion, heart enlargement, or conduction disturbance develops (Bunyan et al., 1987). However, plasmapheresis cannot reverse fetal CHB once it is established (Heurman and Golezewski, 1985). Bunyan et al. (1988) have suggested that plasmapheresis be used prior to 20 weeks' gestation, before increased antibody passage occurs across the placenta. This requires plasmapheresis three times a week, in addition to steroid treatment. The use of plasmapheresis is based on the idea of removing maternal anti-Ro antibody and decreasing transplacental passage, although damage to the fetal conduction system might not

be reversed using this regimen. None of these immunologic strategies has any proven efficacy in preventing or reversing the consequences of fetal CHB due to anti-Ro antibodies.

Early cesarean delivery for temporary pacemaker placement has been associated with a mortality rate that approaches 80% (Kleinman and Downerstein, 1985; Martin et al., 1988). The lack of effective medical treatment for the fetus with CHB and evidence of cardiac decompensation and poor outcome with early delivery have prompted some groups to attempt pacing the fetal heart in utero (Carpenter et al., 1986; Crombleholme et al., 1989, 1990, 1991; Harrison et al., 1993). While technically successful in individual human and animal model cases, such intervention is still considered experimental.

In order for fetal cardiac pacing to be effective, appropriate case selection is essential. Fetuses without hydrops do not need cardiac pacing. Fetuses with advanced hydrops are unlikely to benefit from cardiac pacing. However, a fetus with CHB with ventricular escape rates of less than 50 bpm despite corticosteroid and betamimetic therapy is at especially high risk. These fetuses should be followed closely for development of early signs of hydrops, such as pericardial or pleural effusion or AV valve insufficiency, which usually precedes hydrops. These fetuses are at high risk, and may be candidates for fetal cardiac pacemaker placement. Open fetal surgery for fetal CHB may be preferable because a percutaneously placed pacing lead may become dislodged, cause cardiac tamponade, chorioamnionitis, or cord enlargement. The contraindications to open fetal surgery for pacemaker placement include uterine irritability, maternal illness, structural fetal heart disease, massive hydrops, or poor ventricular function that is sometimes associated with subendocardial fibroelastosis. It may be reasonable for corticosteroids to be administered to the pregnant woman for fetuses with CHB to minimize ongoing immune-mediated myocardial cardiac injury. While the injury to the fetal conduction system is permanent and irreversible, it is possible that progressive myocarditis may be averted by maternal steroid treatment. Except for one anecdotal case, there are no data to support the use of plasmapheresis in fetal CHB.

TREATMENT OF THE NEWBORN

Neonatal lupus erythematosus (NLE) is a misnomer, as these newborns do not have systemic lupus erythematosus, but a constellation of clinical disorders associated with, and probably in part caused by, autoantibodies that are passively acquired by the fetus transplacentally (McCauliffe, 1995). The majority of newborns with NLE exhibit cutaneous or cardiac disease (Table 42-2).

In the absence of structural heart disease, the newborn with congenital CHB has NLE, which is associated with a distinctive skin rash of erythematous round eruptions due to antibody disposition on basal keratinocytes (McCauliffe, 1995). This rash may be increased by light exposure, especially phototherapy for hyperbilirubinemia. Parents are advised to keep affected infants out of direct sunlight for the first 6 months of life, after which the NLE resolves. In addition to cardiac and dermatologic manifestations, NLE may present with thrombocytopenia or anemia, as well as hepatosplenomegaly, hepatitis or cholestasis, aseptic meningitis, myopathy, or myasthenia (McCauliffe, 1995).

In the delivery room, an isoproterenol drip should be initiated as soon as intravenous access is secure. Corticosteroids may be administered to prevent ongoing myocardial injury. Some neonatologists have performed exchange transfusions to eliminate circulating maternal antibody, but no data are available to support its use. Cardiac pacing is the definitive treatment. If the child is unstable or delivered for cardiac decompensation, a transvenous or transthoracic temporary pacing lead should be placed. This may not be possible in a premature infant, in whom a left anterior thoracotomy for placement of temporary epicardial pacing leads should be performed until the infant is sufficiently large to undergo

Table 42-2

Clinical Manifestations of Neonatal Lupus Erythematosus

System	Description	Presentation
Cutaneous	Erythematous round, oval, and annular patches	Weeks to months after delivery. Resolves after 6 months, occasional residual pigmentation
Cardiac	Complete heart block, myocarditis, congestive heart failure	Usually third trimester, but as early as 17 weeks, invisible heart block
Hematologic	Thrombocytopenia, anemia, leukopenia	At birth, usually self-limited
Hepatic	Hepatomegaly, hepatitis, cholestasis	At birth, usually self-limited

permanent placement of a cardiac pacemaker. If the fetus is hydropic, delivered for cardiac decompensation, or has a ventricular rate less than 55 bpm, some form of cardiac pacemaker should be placed urgently. The degree of heart block is permanent and if the heart is decompensating, medical therapy such as isoproterenol is unlikely to prevent progressive deterioration.

LONG-TERM OUTCOME

The mortality rate for infants presenting in the newborn period with CHB is at least 25%. In a long-term follow-up study Vetter and Rashkind (1983) documented 90% survival after the neonatal period. Most deaths were due to pacemaker failure. These children need to be followed for the later development of rheumatologic disease. McCauliffe (1995) described seven patients with congenital CHB who went on to develop collagen vascular diseases, either systemic lupus erythematosus or Sjögren syndrome. Whether this is due to NLE is unknown. More likely, this represents familial predisposition or inheritance of an HLA type associated with collagen vascular disease.

GENETICS AND RECURRENCE RISK

There is no known genetic predisposition for the development of fetal CHB. The woman who has previously had a fetus with NLE is at greatest risk for recurrence. The manifestations of NLE tend to be the same in subsequent pregnancies. Petri et al. (1989) found that mothers of infants with NLE manifested by CHB had a 64% chance of a subsequent fetus being similarly affected. However, McCune et al. (1987) found only a 25% recurrence of CHB.

Women with a history of an autoimmune disorder and anti-Ro antibodies constitute the next highest risk category. Ramsey-Goldman et al. (1986) found that only 8% of infants born to mothers with SLE who had anti-Ro antibodies were affected by NLE. Among mothers with SLE but no anti-Ro antibodies, the incidence of NLE was only 0.6%. Normal women, or those with ill-defined symptoms who produce anti-Ro antibodies, are probably at even lower risk. Unfortunately, this latter category accounts for 50% of cases of NLE, which are impossible to identify before the fetus or newborn is symptomatic (Petri et al., 1989; McCauliffe, 1995).

Olah and Gee (1993) have defined four known risk factors: a previous child with CHB, a high titer of anti-Ro antibody (>1:16), presence of anti-La antibody in addition to anti-Ro antibody, and maternal HLA-DR3.

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43 CHAPTER Atrial Septal Defects

Key Points

- Atrial septal defects are relatively common congential cardiac malformations, but are difficult to diagnose prenatally due to problems differentiating the normal patent foramen ovale from an anatomic defect of the septum.
- Many cases close spontaneously within 2 years of life, while persistence of a large defect, especially with evidence of right ventricular overload, is an indication for elective closure.
- Open surgical approaches to closure have been replaced in most cases with minimally invasive transcatheter occlusion techniques.
- While the medium-term outcome of such transcatheter occlusion techniques appears favorable, it will likely be some time before sufficient data are available to confirm long-term safety and efficacy.

CONDITION

Atrial septal defect (ASD) refers to a congenital malformation in the development of the interatrial septum. In embryonic life, the interatrial septum begins as a septum primum, growing from the atrial walls to the endocardial cushions, which contains a temporary opening known as the foramen primum (Romero et al., 1988). Subsequently, a septum secundum grows on the right side of the septum primum and contains a normal opening known as the foramen ovale. The lower part of the septum primum forms a flap valve for this foramen ovale. Soon after birth, increased left atrial pressure closes this flap, normally resulting in complete closure of the foramen ovale within 2 years of life (Kerut et al., 2006).

Three different types of ASDs are possible, depending on the location within the heart (Romero et al., 1988). An inlet ASD is located near the entrance of the superior vena cava; a secundum ASD occurs in the body of the interatrial septum; a primum or outlet ASD is located near the atrioventricular junction and usually behaves similarly to an AV canal defect (see Chapter 45). Secundum ASDs typically occur because of absence of the foramen ovale flap valve. ASDs usually cause no hemodynamic effects in utero because of the normal right-to-left shunting of blood across the patent foramen ovale. If an ASD persists after birth it may allow for a left-to-right shunt, which can result in congestive heart failure or pulmonary hypertension.

INCIDENCE

Because of the difficulties in differentiating ASDs from asymptomatic patency of the foramen ovale, the precise incidence of ASD in neonatal life is difficult to establish. A patent foramen ovale may be present in up to 30% of normal adults (Kerut et al., 2006). ASDs comprise 7.5% of all congenital cardiac malformations (Ferencz et al., 1987). In one population series, the incidence of ASD was 6 in 10,000 total births (Mitchell et al., 1971).

SONOGRAPHIC FINDINGS

Prenatal sonographic diagnosis of ASD is problematic because the differentiation between a normal patent foramen ovale and true ASD may be difficult. The foramen ovale normally increases in size linearly with advancing gestational age (Phillipos et al., 1994). Large defects of the septum secundum are visualized as dropout of echoes at the level of the interatrial septum (Romero et al., 1988). If an apical four-chamber view is used it may be difficult to confirm an intact interatrial septum. For adequate visualization, the ultrasound probe should be perpendicular to the septum, which can be achieved through the use of a subcostal approach to the four-chamber view (Romero et al., 1988).

The accuracy of sonographic screening for prenatal detection of ASD is poor. In a series of 7459 fetuses who were screened at 18 weeks of gestation, there were 10 ASDs, none of which were identified prenatally (Tegnander et al., 1995). In another series, only 5% of the 761 ASDs that were present in a single large population were detected prenatally (Montana et al., 1996).

DIFFERENTIAL DIAGNOSIS

The main differential diagnosis to consider following the prenatal diagnosis of an ASD is the possibility of a normal patent foramen ovale.

ANTENATAL NATURAL HISTORY

In the majority of cases, an isolated ASD will not cause any significant hemodynamic compromise in utero because of the normal right-to-left shunting of blood across the patent foramen ovale. It is also possible for ASDs to close spontaneously in utero, although the exact frequency of this occurrence is unclear because the accuracy of prenatal diagnosis of isolated ASD is so poor.

MANAGEMENT OF PREGNANCY

Following prenatal diagnosis of an ASD, a careful sonographic fetal anatomy survey is recommended to exclude additional complex cardiac malformations. A sonographic search for extracardiac malformations should also be performed. Fetal echocardiography should be performed by an appropriately trained specialist to confirm the diagnosis and to exclude other cardiac malformations. Invasive fetal testing for karyotype analysis is recommended following the prenatal diagnosis of ASD because the incidence of chromosomal abnormalities may be up to 10% (Ferencz et al., 1987). Referral for prenatal consultation with a pediatric cardiologist is also recommended.

If expectant management is desired, sonographic surveillance to confirm appropriate fetal growth and to evaluate for the development of fetal hydrops is recommended, although the chances of significant hemodynamic disturbances occurring in utero are extremely low with isolated ASD. Although delivery need not necessarily occur at a tertiary care center if the ASD is isolated and uncomplicated, arrangements should be in place for a prompt careful examination of the infant soon after delivery and for referral to a pediatric cardiologist during the newborn period. There is no indication to alter the timing or method of delivery based on the prenatal diagnosis of isolated ASD.

FETAL INTERVENTION

No fetal intervention has been described for the prenatal management of an isolated ASD.

TREATMENT OF THE NEWBORN

Almost all infants with isolated ASD are asymptomatic at the time of delivery and do not require any alteration to usual neonatal care or resuscitation practices. A careful physical examination is mandatory to confirm hemodynamic stability immediately following delivery and again during the neonatal period. Consultation with a pediatric cardiologist should be obtained promptly and echocardiography performed to confirm the prenatal diagnosis and to rule out additional cardiac malformations. Confirmation of a significant patent foramen ovale is generally performed using transthoracic echocardiography. Injection of bacteriostatic saline containing benzyl alcohol can be performed, and the appearance of contrast bubbles in the left heart within three cardiac cycles confirms the diagnosis. Appearance of contrast after more than three cardiac cycles is not consistent with ASD or patent foramen ovale, as the contrast will likely have already passed through the pulmonary circulation (Kerut et al., 2006). It should be noted that physiological size and functional significance of an ASD are not directly correlated. It is important also to evaluate for the presence of an atrial septal aneurysm, as its presence together with a patent foramen ovale puts the patient at significantly higher risk for cryptogenic stroke (Overell et al., 2000).

SURGICAL TREATMENT

Most infants with an isolated ASD will remain completely asymptomatic during the first decade of life. Initially, there is a fall in pulmonary vascular resistance at the time of birth, which leads to left-to-right shunting of blood across the ASD. However, because of the distensibility of the ventricles during infancy, this shunt leads to progressive distention of the right ventricle rather than a sudden increase in pulmonary blood flow. In general, this situation persists throughout the second decade of life, at which time pulmonary artery blood flow increases significantly, leading to symptoms of right heart failure. In addition, as pulmonary flow increases, pulmonary vascular resistance can increase again, eventually leading to Eisenmenger syndrome, which results from cyanosis due to right-to-left shunting of blood.

The rate of spontaneous closure of isolated ASDs is 22% for infants younger than 1 year, 33% for children aged 1 to 2 years, and 3% for children older than 4 years (Cockerham et al., 1983). Because of the risks of heart failure and pulmonary hypertension, it has been recommended that

children with significant ASDs that persist beyond 4 years of age undergo elective surgical closure of the defect (Cockerham et al., 1983). Surgical repair is generally performed on cardiopulmonary bypass, through a median sternotomy incision, and by the use of pericardium or prosthetic material to close the defect (Merrill and Bender, 1985). Other open surgical approaches include right thoracotomy and submammary incisions, the latter being cosmetically preferable. The operative mortality rate for this procedure is currently less than 1% (Ward, 1994).

More recently however, transcatheter approaches for closure of ASDs have been perfected to the extent that in many centers, open surgical correction has been replaced for all but the largest ASDs. The great advantage of these approaches is the lack of open incisions and the ability to avoid cardiopulmonary bypass and stopping the heart. While there is controversy between interventional pediatric cardiologists and cardiac surgeons on the criteria to select between open surgical and transcatheter approaches to ASD closure, it is generally considered acceptable to rely on transcatheter devices if at least 5 mm of rim around the ASD is present (Holzer and Hijazi, 2004). With the latest transcatheter septal occlusion devices, 100% closure rates 1 month postoperatively are expected (Patel and Hijazi, 2005).

Because of the limitations of most of the studies of the natural history of isolated ASD, it has also been argued that only children with symptomatic ASDs should be offered surgical repair (Ward, 1994). There are virtually no good data on the natural history of asymptomatic children with ASDs because almost none of these children will have a diagnosis, so it is difficult to warrant routine surgical repair in the asymptomatic state. In addition, ASDs diagnosed prenatally may represent yet another patient group with a completely different natural history during childhood.

LONG-TERM OUTCOME

The long-term outcome following surgical repair for isolated ASD is excellent, with a 92%, 25-year actuarial survival (Morris and Menashe, 1991). It is possible that right ventricular enlargement and arrhythmias may persist postoperatively, but the long-term consequences of these conditions are unclear (Merrill and Bender, 1985). Almost all patients have a normal life span and a normal level of activity following surgical repair of ASD.

Long-term outcome results following transcatheter septal occlusion appear reassuring, although there have been sporadic reports of erosion of the device into the adjacent ascending aorta (Patel and Hijazi, 2005). The other major long-term adverse event with these minimally invasive devices is thrombus formation, which may occur in 2% to 7% of cases 6 months postoperatively (Krumsdorf et al., 2004; Patel and Hijazi, 2005).

GENETICS AND RECURRENCE RISK

Almost all cases of ASD are sporadic in occurrence. However, there is some evidence of familial occurrence, with siblings of women with a patent foramen ovale being more likely to also have patent foramen ovale (Arquizan et al., 2001). The recurrence risk if one previous sibling has an ASD is 2.5%; this increases to 8% if two previous siblings were affected (Nora and Nora, 1988). If the mother has an ASD, the recurrence risk for offspring is 4%; the recurrence risk is only 1.5% if the father has an ASD (Nora and Nora, 1988).

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Ventricular Septal Defects

44 CHAPTER

Key Points

- Ventricular septal defects are the most common congential cardiac malformations, and often occur as part of more complex abnormalities, such as tetralogy of Fallot or transposition.
- Prenatal diagnosis should be straightforward using a long axis view of the ventricles, followed by a short axis sweep from apex to base.
- Many isolated small VSDs, especially of the muscular type, will close spontaneously in utero, or in infancy.
- Significant VSDs that contribute to failure to thrive, or those associated with increased pulmonary vascular flow, should be surgically repaired by 6 months of age.
- Recent advances in minimally invasive transcatheter septal occlusion devices hold great promise as an alternative to open surgical repair with cardiopulmonary bypass.

CONDITION

Ventricular septal defect (VSD) refers to a congenital malformation in the development of the interventricular septum. VSDs can occur in the muscular or membranous portions of the septum. Muscular VSDs may be further subdivided into inlet, trabecular, or infundibular defects (Soto et al., 1980; Minette and Sahn, 2006). VSDs may also be classified as being either subvalvular or muscular (Capelli et al., 1983). Subvalvular VSDs are directly related to the atrioventricular or semilunar valves, without interposed muscle between the defect and the valve cusps. Such subvalvular defects may be further subclassified as inlet, subtricuspid, subaortic, subpulmonary, or double-committed subarterial, in which the defect is below the pulmonary and aortic valves. Muscular VSDs are bordered on all sides by muscle and are not directly related to the valves. Such defects may be further subclassified as being apical, central, or outlet in location. Most of these VSD types can be defined by echocardiography, although it is important to realize that small muscular defects can be missed by sonography during both the prenatal and the postnatal periods (Capelli et al., 1983).

VSDs usually cause no hemodynamic effects in utero because of the similarity in pressures between the right and left sides of the heart during prenatal life. Most VSDs are also asymptomatic immediately following birth. If the VSD persists after birth, it may allow for the development of a left-to-right shunt, which can result in congestive heart failure or pulmonary hypertension.

INCIDENCE

VSDs are the most common single congenital cardiac malformation, accounting for 26% of all structural cardiac abnormalities (Ferencz et al., 1987). In an earlier population series, the incidence of VSD was 2 in 10,000 total births (Mitchell et al., 1971). However, with the increasing use of prenatal and neonatal echocardiography, the birth incidence of VSDs seems to be much higher than previously suggested (Minette and Sahn, 2006). In one series, 5% of all newborns were found to have an isolated muscular VSD (Roguin et al., 1995). The most accurate estimate of birth prevalence of VSD is 3.5 per 1000 livebirths (Hoffman and Kaplan, 2002). In addition, VSDs are frequently found in association with other cardiac malformations, such as tetralogy of Fallot (see Chapter 52) and transposition of the great arteries (see Chapter 55).

SONOGRAPHIC FINDINGS

As with an ASD, prenatal sonographic diagnosis of a VSD can be difficult because it relies on visualization of dropout

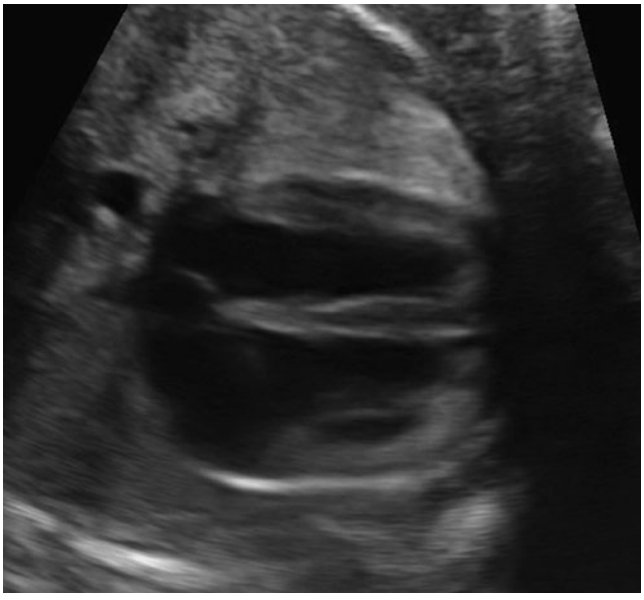

Figure 44-1 Long-axis view demonstrating intact ventricular septum.

of echoes at the level of the interventricular septum, which is best achieved using a subcostal approach to the four-chamber view. In order to confirm an intact interventricular septum, the septum should also be visualized by means of a long-axis view of the left and right ventricles, together with an apex-to-base sweep along the short axis of the heart (Figures 44-1 to 44-3) (Romero et al., 1988). Small membranous VSDs are still commonly missed on prenatal sonography, despite adequate views of all parts of the interventricular septum. In addition, artifactual areas of hypoechogenicity in the septum during the apical four-chamber view may give the false impression of a VSD; therefore a true VSD is confirmed only when it is

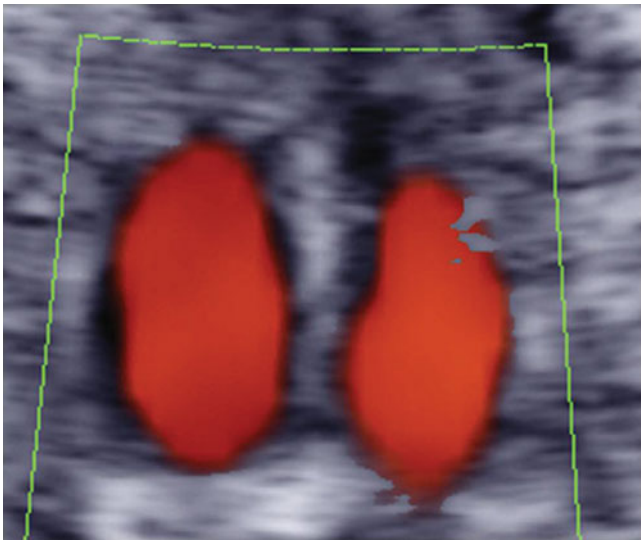

Figure 44-2 Axial image with color Doppler showing forward flow across the atrioventricular valves with an intact interventricular septum.

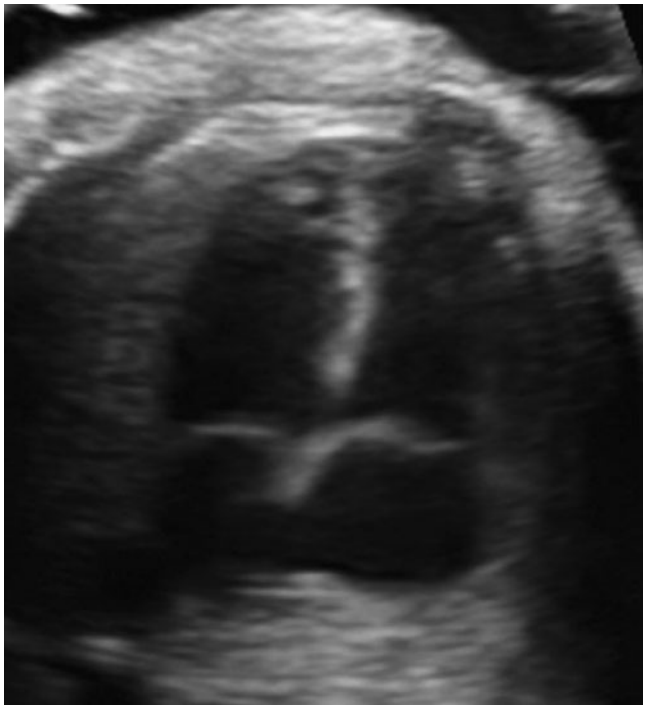

Figure 44-3 Axial image demonstrating a membranous ventricular septal defect.

visible in at least two different planes (Romero et al., 1988). Color Doppler sonography may also be used to demonstrate flow across the area of defect (Figure 44-4) (Sanders et al., 1996).

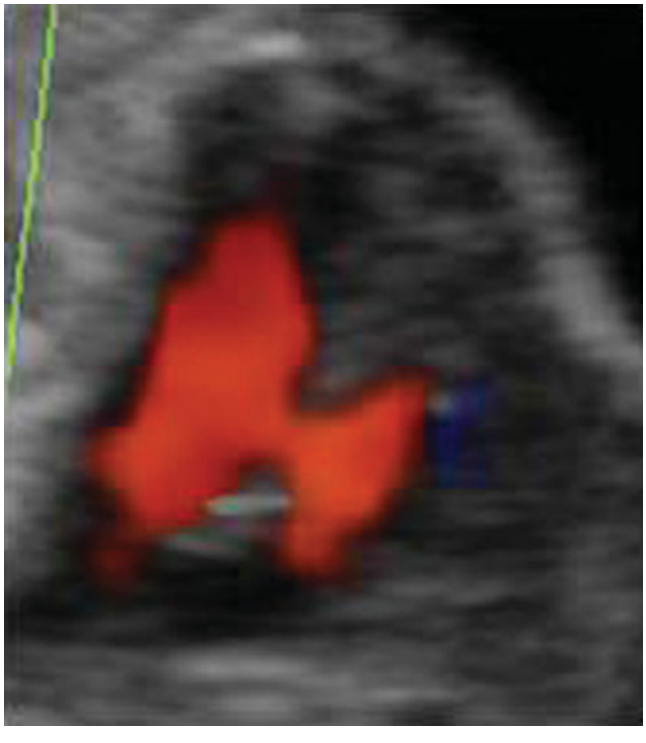

Figure 44-4 Axial image with color Doppler demonstrating forward flow across the atrioventricular valves and flow across a ventricular septal defect.

The accuracy of prenatal sonographic screening for VSDs is poor. In a series of 7459 fetuses that were screened at 18 weeks of gestation, there were 53 VSDs, none of which were identified prenatally (Tegnander et al., 1995). In another series, only 5% of the 486 VSDs present in a single large population were detected prenatally (Montana et al., 1996). The accuracy of targeted fetal echocardiography for prenatal detection of isolated VSDs is also poor. In one series of targeted fetal echocardiograms, only 4 (31%) of 13 ASDs or VSDs were correctly identified (Benacerraf et al., 1987). In another series of fetal echocardiograms, there were 29 VSDs, 19 (66%) of which were correctly identified; the vast majority of these were associated with other more complex cardiac malformations (Crawford et al., 1988). In one further series, only 11 (44%) of 25 isolated VSDs were correctly identified prenatally, with small and moderate-sized VSDs the most likely to be missed (Kirk et al., 1997).

DIFFERENTIAL DIAGNOSIS

As with ASD, it is important to consider a normal interventricular septum in all cases following the prenatal diagnosis of VSD because false-positive diagnoses are possible, especially if the septum is visualized by means of an apical four-chamber view. Other diagnoses to consider include the presence of additional, more complex cardiac malformations that may involve a VSD, such as tetralogy of Fallot, transposition of the great arteries, double outlet right ventricle, and tricupsid atresia.

ANTENATAL NATURAL HISTORY

As with ASDs, almost all isolated VSDs cause no significant hemodynamic compromise in utero; the pressures in both ventricles are similar, so shunting of blood between ventricles is not a problem. Many isolated VSDs, especially small muscular types, close spontaneously, either in utero or soon after birth (Nir et al., 1994). Muscular VSDs may close as a result of muscular occlusion, while membranous VSDs may close by tricuspid valve aneurysm formation (Minette and Sahn, 2006). In one series, 26 (74%) of 35 isolated VSDs diagnosed prenatally closed spontaneously before birth, and there was no correlation between the size of the defect and probability of closure (Orie et al., 1994). In another series, 89% of all muscular VSDs were asymptomatic and resulted in spontaneous closure within 1 to 10 months of neonatal life (Roguin et al., 1995). However, because prenatal diagnosis of VSDs is so poor, it is possible that VSDs successfully diagnosed in utero may be larger and may represent a group that has a more unfavorable prognosis.

In a series of 14 fetuses with VSDs diagnosed prenatally, 6 (43%) were terminated, 2 (14%) died in utero, 1 (7%) died postnatally, and 5 (36%) survived (Smythe et al., 1992). In another series of 19 fetuses with VSDs diagnosed prenatally, 1 (5%) died in utero, 10 (53%) died postnatally, and 8 (42%) survived (Sharland et al., 1990).

MANAGEMENT OF PREGNANCY

Following prenatal diagnosis of a VSD, a careful sonographic fetal anatomy survey is recommended to exclude additional complex cardiac malformations, such as tetralogy of Fallot, transposition of the great arteries, or double outlet right ventricle. Although most VSDs diagnosed after birth are isolated, the majority of prenatally diagnosed VSDs occur in association with more complex cardiac malformations (Crawford et al., 1988). A sonographic search for extracardiac malformations should also be performed. Fetal echocardiography should be performed by an appropriately trained specialist to confirm the diagnosis and to exclude other cardiac malformations.

Invasive fetal testing for karyotype analysis is recommended following the prenatal diagnosis of VSD because the incidence of chromosomal abnormalities may be up to 18%, although in one series of 7 prenatally diagnosed VSDs, 5 (71%) were associated with aneuploidy (Ferencz et al., 1987; Paladini et al., 1993). Referral for prenatal consultation with a pediatric cardiologist is also recommended.

Elective termination of pregnancy may be considered by some patients, especially if the VSD is part of a more complex cardiac malformation. However, the chances of spontaneous closure, both in utero and postnatally, should be emphasized before a decision on terminating the pregnancy is made. If expectant management is desired, sonographic surveillance to confirm appropriate fetal growth and to evaluate for the development of fetal hydrops is recommended, although the chances of significant hemodynamic disturbances occurring in utero are extremely low with isolated VSD.

Even though delivery need not necessarily occur at a tertiary care center if the VSD is isolated and uncomplicated, arrangements should be in place for a prompt, careful examination of the infant soon after delivery and for referral to a pediatric cardiologist during the early newborn period. If there is a suspicion that the VSD may be large and may become clinically significant soon after birth, consideration should be given to delivery in a tertiary care center. There is no indication to alter the timing or method of delivery based on the prenatal diagnosis of isolated VSD.

FETAL INTERVENTION

No fetal intervention has been described for the prenatal management of isolated VSD.

TREATMENT OF THE NEWBORN

Most infants with isolated VSD are asymptomatic at the time of delivery and do not require any alteration to usual neonatal

care or resuscitation practices. A careful physical examination is mandatory to confirm hemodynamic stability immediately following delivery and again during the neonatal period. Consultation with a pediatric cardiologist should be obtained promptly and echocardiography performed to confirm the prenatal diagnosis and to rule out additional cardiac malformations. More recently, three-dimensional echocardiography has been used successfully to quantify the left-to-right shunt, which aids in assessing the severity and prognosis (Ishii et al., 2001). If required, subsequent cardiac catheterization can be used to measure pulmonary vascular resistance and shunt volume, as well as confirming cardiac anatomy in complex cases.

Infants with large, membranous VSDs tend to become progressively more symptomatic during the first months of life as the pulmonary vascular resistance falls and left-to-right shunting increases. This can lead to right ventricular failure, which may require digoxin, fluid restriction, and diuretics. The use of hydralazine to achieve afterload reduction may also decrease the left-to-right shunt. As pulmonary vascular congestion worsens, lung compliance decreases, and such infants have difficulty feeding, which may require caloric supplementation or tube feedings.

SURGICAL TREATMENT

The majority of isolated VSDs tend to close spontaneously, and therefore the most common indication for surgical repair of a VSD is failure of medical treatment in a symptomatic patient. Other indications for surgical repair include pulmonary hypertension, aortic insufficiency, recurrent respiratory infections, persistent failure to thrive, and prior bacterial endocarditis. Most infants who become symptomatic from a VSD tend to demonstrate congestive heart failure at 1 to 2 months of life. If growth failure cannot be improved by medical therapy by 6 months of age, surgical repair should be considered (Ohye and Bove, 2001). If optimal medical treatment fails to relieve symptoms, definitive primary surgical repair should be performed. The repair is usually done by means of cardiopulmonary bypass, through a right atrial approach and the use of a Dacron patch to close the defect (Merrill and Bender, 1985). Operative mortality currently should be less than 5%.

Controversy exists about whether all asymptomatic VSDs should be surgically repaired. In one series of 141 patients with restrictive VSDs, elective surgical repair was performed, with no operative mortality, and the authors concluded that the accepted indications for VSD closure should be expanded (Backer et al., 1993). However, given that there is a 50% chance that a small VSD will close spontaneously by 5 years of age and an 80% chance that it will close by adolescence, it is difficult to recommend elective surgical repair in childhood for small asymptomatic VSDs (Waldman, 1993). Other indications for surgery may include infundibular VSDs, increased pulmonary vascular flow, or multiple "Swiss cheese" type defects refractory to medical therapy, in which case a palliative pulmonary artery band may be required (Minette and Sahn, 2006).

As with atrial septal defect repair, more recent trends are toward catheter device closure, thereby avoiding cardiopulmonary bypass. While currently considered investigational, early studies of transcatheter techniques, (such as the Amplatzer VSD occluder), have suggested 96% VSD closure success at 6 months, with a serious adverse event rate of 9% (Patel and Hijazi, 2005; Fu et al., 2006).

LONG-TERM OUTCOME

The long-term outcome following surgical repair for isolated VSD is also excellent, with an 86%, 25-year actuarial survival (Morris and Menashe, 1991). The risk of bacterial endocarditis remains significant following surgical repair of VSD, although it is twice as likely to occur before VSD closure than subsequently (Waldman, 1993). Other long-term problems include heart block, in 3% of cases, which may require pacemaker placement (Minette and Sahn, 2006). The majority of patients have a normal life span and normal level of activity following surgical repair of VSD.

GENETICS AND RECURRENCE RISK

While almost all cases of VSD are sporadic in occurrence, VSDs can be seen as part of a range of genetic conditions, including chromosomal disorders (such as trisomy 21 or DiGeorge syndrome), and single-gene disorders (such as Holt–Oram syndrome). In such cases, the recurrence risk is related to the underlying genetic abnormality. The recurrence risk if one previous sibling has a VSD is 3%; this increases to 10% if two previous siblings were affected (Nora and Nora, 1988). If the mother has a VSD, the recurrence risk for offspring is 6% to 10%; the recurrence risk is only 2% if the father has a VSD (Nora and Nora, 1988).

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Atrioventricular Canal Defect

45 CHAPTER

Key Points

- Atrioventricular (AV) canal defect is the most common form of congenital heart disease detected prenatally and usually involves both a lower atrial and an upper ventricular septal defect, together with a common AV valve orifice.
- In 70% of cases there will be additional cardiac malformations, and in the majority of isolated cases additional chromosomal abnormality will be diagnosed, most commonly trisomy 21.
- Prenatal diagnosis of complete AV canal defect should be straightforward, by failure to visualize the normal crux on a four-chamber cardiac view.
- Management of pregnancy includes detailed echocardiographic and general fetal anatomic evaluation, amniocentesis, and planned delivery with complete pediatric cardiology backup.
- Overall prognosis is variable as prenatally diagnosed AV canal defects represent a heterogenous group.

CONDITION

Atrioventricular (AV) canal defect is also known as an AV septal defect, common AV canal, endocardial cushion defect, ostium primum atrial septal defect, or persistent ostium atrioventriculare commune. Complete AV canal defect consists of an unrestrictive atrial septal defect, an unrestrictive ventricular septal defect, and a single common AV valve. It occurs because of failure of development of the endocardial cushion during embryogenesis and persistence of the primitive single AV canal beyond 6 weeks of gestation. Although the AV canal defect may involve a wide spectrum of abnormalities of the atrial and ventricular septa and the AV valves, the complete form with associated AV valve regurgitation is the one that most commonly presents during the neonatal period (Chin et al., 1982).

AV canal defects can be partial or complete. With a partial AV canal defect, there are two separate AV orifices, with communication between two atria or between the left ventricle and the right atrium. While the right AV valve is usually normal, the left valve usually has three leaflets (Becker and Anderson, 1981). With a complete AV canal defect, there is a defect in the inferior portion of the atrial septum and the superior portion of the ventricular septum, together with a single AV valve orifice, which usually has five valve leaflets. The anterior and posterior valve leaflets are inserted on the anterior and posterior surfaces of the ventricular septum, respectively; the degree of bridging of the anterior leaflet across the ventricular septum determines the type of defect (Rastelli et al., 1966). For type A complete AV canal defects, the anterior leaflet does not bridge the ventricular septum and is attached on both sides of the septum by chordae tendineae (Silverman et al., 1986). For type B complete AV canal defects, the anterior leaflet somewhat bridges the ventricular septum and is attached to the right ventricle by an anomalous papillary muscle. For type C complete AV canal defects, the anterior leaflet is not attached to the septum, and completely bridges it, being attached at either side by papillary muscles. Type A is commonly seen in trisomy 21, and type C is commonly seen with atrial isomerism (Mann et al., 2004).

INCIDENCE

Complete AV canal defect accounts for 1% to 5% of all cases of congenital heart disease (Rowe et al., 1981). It is the most common cardiac defect detected prenatally. In one series of 357 cases of congenital heart disease 13% were AV canal defects, almost 70% of which were of the complete type (Fontana and Edwards, 1962). In a series of 49 AV canal defects from a single center, 88% were of the complete type and 12% were partial (Allan, 1999). Familial clustering of AV canal defects has also been described (Tennant et al., 1984; Disegni et al., 1985). Review of population-based series of congenital heart disease suggests that the incidence of AV canal defect is 0.3 per 1000 livebirths (Hoffman and Kaplan, 2002).

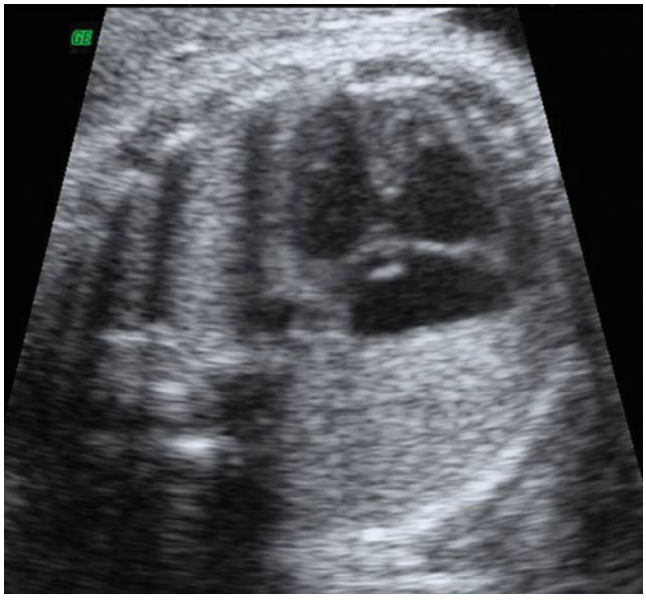

Figure 45-1 Axial image demonstrating defect in the crux of the fetal heart consistent with an atrioventricular canal defect.

SONOGRAPHIC FINDINGS

Prenatal diagnosis of a complete AV canal defect is relatively straightforward, because a large defect or hole is easily visualized at the crux of the heart during diastole on the four-chamber view (Figure 45-1). This hole represents the defects in the inferior portion of the atrial septum, the superior portion of the ventricular septum, and the single AV valve orifice. In the normal four-chamber view of the heart, the tricuspid valve inserts more apically than the mitral valve, leading to an offset appearance at the crux of the heart. With an AV canal defect, this offset appearance may be lost, with both valves forming a straight line across the crux of the heart when closed (Figure 45-2).

Because the defect can be large, the cardiac conduction apparatus is frequently abnormal, resulting in an increased frequency of bradyarrhythmias. In one series, 11 of 29 fetuses with AV canal defects also had complete heart block (Machado et al., 1988). In addition, all 11 of these fetuses also demonstrated features of the heterotaxy syndrome (see Chapter 56). Prenatal echocardiography should focus on the structure of the AV valve. The presence of a common leaflet at the level of the AV valve is suggestive of complete AV canal defect, while in its partial form the only abnormality may be a small defect in the inferior portion of the atrial septum (Romero et al., 1988).

Color and pulsed Doppler echocardiography may demonstrate turbulent systolic flow on the atrial side of the common AV valve because of significant valvular regurgitation (Barber and Chin, 1990). The presence of significant valvular regurgitation can be quantified, and when present throughout systole, it may be predictive of hydrops fetalis (Gembruch et al., 1991). In contrast, valvular regurgitation confined to early systole is not associated with hydrops and may be an indicator of improved prognosis.

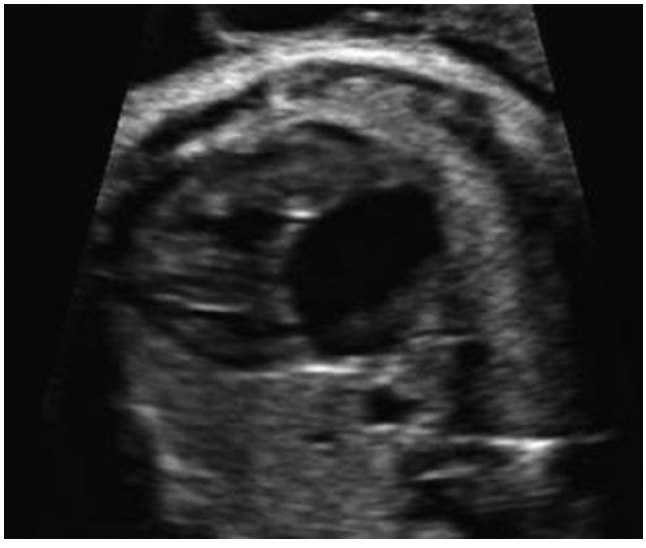

Figure 45-2 Axial image through the fetal heart with an atrioventricular canal defect demonstrating the abnormal positioning of the AV valves.

Prenatal sonography should also focus on excluding other abnormalities, such as malformations associated with aneuploidies or additional cardiac malformations. Sonographic markers associated with aneuploidy should be specifically sought, as approximately 50% of cases of AV canal defects have a chromosomal abnormality, the majority of which are due to trisomy 21 or 8p deletion (Machado et al., 1988). Additional cardiac malformations may be present in more than 70% of cases, such as tetralogy of Fallot, coarctation, pulmonary stenosis, and double outlet right ventricle (Machado et al., 1988). In a series of 49 cases of AV canal defect from a single center, 31 (63%) had additional cardiac malformations, typically heterotaxia or isomerism, but also including hypoplastic left ventricle and tetralogy (Allan, 1999). In the Baltimore–Washington infant study, 336 children were identified with an endocardial cushion defect. Of these, 76% were identified as having a syndromic diagnosis (78% of these had trisomy 21) (Carmi et al., 1992). A more recent review of 301 cases of AV canal defect from a single center in London demonstrated that approximately 50% with known karyotype had aneuploidy, with the vast majority (80%) of these being trisomy 21, and others including trisomy 18, trisomy 13 (Huggon et al., 2000). In this series, 155 of 301 (52%) had normal atrial arrangement and no other evidence of additional cardiac abnormalities, while 40 of 301 (13%) had significant extracardiac abnormalities (Huggon et al., 2000). Chromosomal abnormality appears to be much more likely in the setting of AV canal defect with normal atrial connections.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for complete AV canal defects includes a large atrial or ventricular septal defect, or a single ventricle (Barber and Chin, 1990). While complete AV canal defects can usually be easily distinguished from these lesions by prenatal echocardiography, differentiation from partial AV canal defects may be more problematic. Genetic considerations in the differential diagnosis include trisomy 21 (see Chapter 131), heterotaxy (Ivemark syndrome; see Chapter 56), Ellis–van Creveld syndrome (see Chapter 94), Holt–Oram syndrome, and CHARGE association.

ANTENATAL NATURAL HISTORY

Few data are available on the antenatal natural history of isolated complete AV canal defects and none are available for partial forms of this condition. In one series, 3 of 36 (8%) cases with AV canal defect that were managed expectantly resulted in spontaneous intrauterine demise (Allan, 1999). In another series of 301 cases of AV canal defect from a single center, 19 of 123 (15%) expectantly managed cases ended with spontaneous intrauterine demise (Huggon et al., 2000). If chromosomal abnormalities are also present, the rate of intrauterine loss is significantly increased. The worst antenatal prognosis seems to be associated with complete forms of the AV canal defect, in which there is also significant regurgitation across the common AV valve, as well as cases with bradycardia (Huggon et al., 2000). Such cases are mostly associated with hydrops fetalis (Gembruch et al., 1991). The partial forms of the AV canal defect tend to present clinically after 1 month of postnatal life because volume overload does not occur until pulmonary vascular resistance has dropped significantly (Chin et al., 1982).

MANAGEMENT OF PREGNANCY

If an AV canal defect is suspected on prenatal sonographic studies, a referral to a pediatric cardiologist or other specialist skilled in fetal echocardiography is recommended. Careful sonographic imaging to assess for the presence of additional cardiac malformations is also recommended. Because of the strong correlation between AV canal defects and trisomy 21, all patients should be offered prenatal karyotype evaluation, typically by means of amniocentesis. Prenatal consultation with a pediatric cardiac team, (including cardiology, cardiothoracic surgery, and neonatology), may also be helpful for planning immediate neonatal intervention.

Early delivery is not recommended because a low birth weight carries a less favorable prognosis for neonatal cardiac surgery as compared with a higher birth weight. Delivery should take place under controlled circumstances at a tertiary care center with an on-site pediatric cardiology team immediately available. The mode of delivery should be dictated by obstetric indications. However, the presence of hydrops may make vaginal delivery problematic because of soft-tissue dystocia. Weighing the benefits of cesarean delivery to avoid dystocia against the very poor prognosis for infants with hydrops secondary to structural cardiac malformations represents a difficult choice.

FETAL INTERVENTION

No fetal intervention has been described for prenatally diagnosed cases of AV canal defect.

TREATMENT OF THE NEWBORN

Some infants with partial AV canal defect are detected during the newborn period but the majority are asymptomatic at birth. The presence of a complete AV canal defect usually results in symptoms at birth, such as a heart murmur. In other infants with complete AV canal, tachycardia, tachypnea, and failure to thrive develop during early infancy. The development of clinical symptoms prior to 3 months of age may be delayed because pulmonary vascular resistance remains high, which limits left-to-right shunting. If symptomatic presentation occurs prior to 3 months it is usually due to the presence of severe valvular regurgitation or additional cardiac malformations. Infants presenting with these symptoms need appropriate medical and surgical intervention to avoid the development of significant pulmonary hypertension. Left untreated, infants with complete AV canal defects have a 50% chance of survival beyond 6 months, and only a 30% chance of survival beyond 1 year (Berger et al., 1978).

Initial medical treatment of the newborn with a complete AV canal defect includes cardiorespiratory support and complete cardiac work-up, including electrocardiography. The administration of digoxin to enhance myocardial contractility and diuretics to optimize preload is recommended (Barber and Chin, 1990). Appropriate caloric supplementation is also recommended to make up for the high metabolic state associated with an intracardiac shunt and pulmonary edema. Two-dimensional echocardiography with pulsed and color Doppler studies should be performed soon after birth to confirm the cardiac malformation and to assess the morphology of the valve leaflets. With careful echocardiographic evaluation and optimal visualization of cardiac anatomy, cardiac catheterization and angiography may be avoided (Zellers et al., 1994).

SURGICAL TREATMENT

Primary surgical repair of complete AV canal defect is usually performed electively between 3 and 6 months of age, or earlier if significant symptoms are present (Sand and Pacifico, 1990). Delay beyond this time may expose the infant to significant risk for the development of pulmonary hypertension and eventually Eisenmenger syndrome. Correction of partial AV canal defects is performed electively during the first few years of life.

Primary repair of AV canal defects is facilitated by the establishment of cardiopulmonary bypass. Repair usually involves closure of the atrial septal defect with a patch of pericardium, closure of the interventricular defect with a Dacron patch, and attachment of the common AV valve leaflets to this patch. Care must be taken to avoid surgical injury to the AV node or bundle of His to prevent surgically induced complete heart block. The use of a double-patch technique may produce less distortion of the valve, although it may be possible to achieve similar results using a single patch and ventricular distention (Santos et al., 1986). The precise details of surgical repair, especially if additional cardiac malformations are present, are beyond the scope of this textbook but are easily available in the literature (Capouya and Laks, 1991).

Poor prognostic factors for the surgical repair of AV canal defects include the presence of significant valvular regurgitation, poor overall functional capability, ventricular hypoplasia, presence of a ventricular septal defect, accessory valve orifice, or additional cardiac malformations (Studer et al., 1982). Unbalanced AV canal defect, in which the AV valve sits more over one ventricle with relative hypoplasia of the other ventricle, represents a much higher risk surgical scenario that may require a single ventricle repair (Cohen and Spray, 2005). Mortality directly related to surgery is approximately 0.6% for partial and 2% for complete AV canal defects (Kirklin et al., 1986; Sand and Pacifico, 1990). In another more recent series, overall operative mortality was 3.6% for complete AV canal defects (Tweddell et al., 1996). Higher operative mortality rates described in other series (up to 30%) may reflect different surgical techniques in earlier eras or the presence of additional complex cardiac malformations (Clapp et al., 1987).

LONG-TERM OUTCOME

Surgical series suggest that long-term survival after repair of AV canal defects is excellent. Almost 90% of survivors can be expected to be normally functioning at long-term follow-up, and survival at 12 years after surgery is approximately 85% (Sand and Pacifico, 1990). Valve failure occurs in 10% of cases following repair, which may necessitate valve replacement. Long-term follow-up in a series of 334 cases of surgical repair of partial AV canal defect demonstrated 94% and 87% 5-year and 20-year actuarial survival (El-Najdawi et al., 2000).

However, there seems to be some discrepancy with regard to the long-term survival rates reported by series including prenatally diagnosed AV canal defects and series including only postnatal surgical cases. In a study of 301 AV canal defect cases from London, only 57 (19%) children were still alive at 4 years of age (Huggon et al., 2000). Postnatal surgical series are likely favorably biased as they tend to only include uncomplicated cases, and those suitable for biventricular repair.

Controversy exists about whether the presence of trisomy 21 affects survival after surgical repair of AV canal defects. Caution is necessary in comparing outcomes following repair in infants with and without trisomy 21, as most infants with trisomy 21 tend to have complete AV canal defects and an earlier tendency for pulmonary hypertension

to develop as compared with chromosomally normal infants with AV canal defects. In one series comparing 47 cases of complete AV canal defects in chromosomally normal infants with 12 cases in infants with trisomy 21, there was a trend toward higher mortality in the trisomy 21 group (Morris et al., 1992). However, in a larger series comparing 94 infants with trisomy 21 with 127 chromosomally normal infants with AV canal defects, trisomy 21 was not found to be an independent risk factor for adverse outcome, after controlling for disease severity (Rizzoli et al., 1992). In another series, infants with AV canal defects and trisomy 21 did even better than chromosomally normal infants with AV canal defects (Vet and Ottenkamp, 1989). In view of these findings, most pediatric cardiology centers do not treat infants with AV canal defects and trisomy 21 differently than the way they treat chromosomally normal infants.

GENETICS AND RECURRENCE RISK

A strong correlation exists between the presence of AV canal defects and chromosomal abnormalities, particularly trisomy 21 and 8p deletion. If trisomy 21 is also present, the recurrence risk is related more to the aneuploidy than to the structural cardiac defect. Familial clustering of isolated AV canal defects has also been described, which suggests the possibility of a single-gene defect (Tennant et al., 1984; Disegni et al., 1985). The recurrence risk of AV canal defects in siblings of those affected ranges from 1.5% to 8.7% (Sanchez-Cascos, 1978). In general, with one affected child, we quote a recurrence risk of 3%, and with two affected children we quote a recurrence risk of 10% (Nora and Nora, 1988). The recurrence risk in offspring of chromosomally normal parents with AV canal defects is approximately 10% (Emanuel et al., 1983). This risk is higher when the mother has an AV canal defect as compared to when the father is affected.

In a large study of 103 individuals with isolated AV canal defect, Digilio et al. (1993) found 4 of 111 siblings to be similarly affected (3.6%), 4 of 206 parents affected (1.9%), and 5 of 644 uncles and aunts affected (0.8%). None of the grandparents were affected. Prenatal diagnosis in a subsequent pregnancy is by fetal echocardiography.

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46

CHAPTER

Ebstein Anomaly

Key Points

- Ebstein anomaly is a malformation of the tricuspid valve, causing tricuspid insufficiency and atrialization of a significant portion of the right ventricle.
- When it progresses it can be associated with right ventricular outflow tract obstruction and arrhythmias.
- It is rarely associated with extracardiac malformations or fetal aneuploidy.
- Prognosis for prenatally diagnosed cases is much worse than for those diagnosed later in childhood, with less than 50% of cases surviving to 5 years of age.
- Pregnancy management rarely needs to be altered significantly, other than to arrange for prompt referral for postnatal cardiac evaluation and likely surgical repair, either by means of valve repair or replacement.

CONDITION

Congenital downward displacement of the septal and posterior leaflets of the tricuspid valve is known as Ebstein anomaly. This downward displacement is associated with valvular dysplasia, resulting in tricuspid insufficiency (Schiebler et al., 1968). The displaced septal and posterior leaflets become adherent to the right ventricular walls, which may also be dysplastic. This results in division of the right ventricle into two segments, a proximal atrialized portion that forms a common enlarged chamber with the right atrium and a distal functional right ventricular chamber (Attenhofer Jost et al., 2007). Significant right atrial enlargement is common, and atrial septal defects or patent foramen ovale is commonly seen during neonatal life (Attenhofer Jost et al., 2007). Other cardiac malformations coexist with Ebstein anomaly in approximately one-third of cases (Celermajer et al., 1994). The most common additional malformations are pulmonary stenosis, pulmonary atresia with intact ventricular septum, ventricular septal defect, mitral-valve prolapse, aortic coarctation, patent ductus arteriosus, and right ventricular hypoplasia. Rarer coexisting malformations include tetralogy of Fallot, atrioventricular septal defect, aortic atresia, mitral dysplasia, and left ventricular diverticulum (Celermajer et al., 1994).

INCIDENCE

The incidence of Ebstein anomaly in the general population is approximately 1 in 10,000 livebirths (Hoffman and Kaplan, 2002). It accounts for 0.3% to 0.6% of congenital heart defects in children and occurs equally in males and females (Rao, 1990).

First trimester maternal lithium ingestion has been implicated in the occurrence of Ebstein anomaly for more than 20 years. Based on data from an international registry of mothers exposed to lithium during pregnancy it was suggested that the risk of Ebstein anomaly was 400 times greater

in lithium-exposed infants than in the general population (Weinstein, 1976). From the registry of 225 infants born to women treated with lithium during the first trimester, there was an 8% incidence of all cardiac malformations and a 2.7% incidence specifically of Ebstein anomaly.

Subsequent controlled studies have suggested that the actual risk of Ebstein anomaly is considerably less than originally estimated from population registries. A total of two cohort studies and four case–control studies did not demonstrate as high a risk of Ebstein anomaly as was suggested from population registries, although the precise magnitude of the risk of Ebstein anomaly following first trimester lithium exposure is unclear (Cohen et al., 1994). It was estimated that first trimester lithium exposure is associated with a 4% to 12% incidence of congenital anomalies, as compared with a general population risk of from 2% to 4%.

SONOGRAPHIC FINDINGS

Prenatally, Ebstein anomaly is suggested by an abnormal four-chamber cardiac view, in which the right atrium appears grossly enlarged (Figure 46-1) and the tricuspid valve is displaced downward toward the apex and below the level of the atrioventricular junction. Dysplasia of the valve appears as abnormal thickening, nodularity, and irregularity of the leaflets. The right ventricular wall may become dysplastic and appear thin (Roberson and Silverman, 1989). Pulsed and color Doppler evaluation may also demonstrate significant tricuspid regurgitation. As tricuspid regurgitation worsens, congestive heart failure may develop, leading to cardiac enlargement and eventually hydrops. On prenatal sonography, supraventricular tachycardia may also be noted in association with Ebstein anomaly (Sharf et al., 1983), and accessory conduction pathways resulting in Wolff–Parkinson–White syndrome may be common.

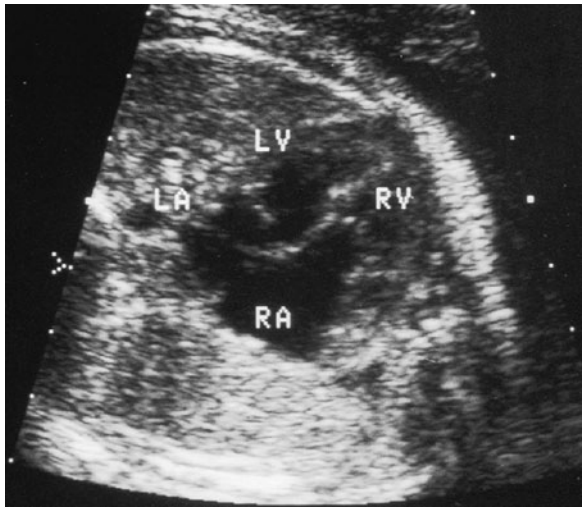

Figure 46-1 Antenatal four-chamber view of a fetal heart, demonstrating abnormally enlarged right atrium (RA) and downward displacement of tricuspid valve toward an abnormally small right ventricle. LA = left atrium; LV = left ventricle; RV = right ventricle.

Ebstein anomaly has been graded in severity based on the volume of the right ventricle and degree of restriction of the anterior leaflet of the triscupid valve. With type A, the volume of the right ventricle is adequate; type B involves a significant amount of atrialization of the right ventricle but with no restriction in movement of the anterior triscupid leaflet; type C involves severe restriction in movement of the anterior tricuspid leaflet, with obstruction of the right ventricular outflow tract; type D demonstrates almost complete atrialization of the right ventricle (Carpentier et al., 1988). Another system for grading severity involves calculation of the ratio of the area of the right atrium plus atrialized right ventricle to the functional right ventricle area (Celermajer et al., 1994).

Prenatal sonographic diagnosis of Ebstein anomaly is accurate. In one series of 17 fetuses diagnosed prenatally with Ebstein anomaly, the diagnosis was confirmed postnatally in 15, either by autopsy, surgery, or neonatal imaging (Hornberger et al., 1991). In another series of 19 cases of prenatally identified tricuspid abnormalities, 6 of 10 cases of Ebstein anomaly were correctly diagnosed by fetal echocardiography; the remaining 4 were incorrectly described prenatally as valvular dysplasia without displacement (Oberhoffer et al., 1992).

DIFFERENTIAL DIAGNOSIS

The sonographic detection of right atrial enlargement should prompt a search for abnormalities of the tricuspid and pulmonary valves. The differential diagnosis of Ebstein anomaly includes isolated tricuspid valve dysplasia without significant downward displacement of valve leaflets. In its most severe form, such valve dysplasia may represent an unguarded tricuspid valve orifice. In each of these conditions, significant tricuspid regurgitation and cardiomegaly will most likely be present, but only in Ebstein anomaly will there be an abnormally located insertion site for the valve. However, the differentiation between Ebstein anomaly and tricuspid dysplasia is largely academic; both conditions can present clinically with heart failure and additional cardiac malformations (Sharland et al., 1991).

Echocardiography should easily distinguish pulmonary stenosis, anatomic pulmonary atresia, tricuspid atresia, transposition of the great vessels, Uhl anomaly, and tetralogy of Fallot from Ebstein anomaly (Rao, 1990). With pulmonary stenosis or atresia, significant right ventricular hypertrophy should be visible, together with a small pulmonary artery. Functional pulmonary atresia with diminished pulmonary flow may occur secondary to Ebstein anomaly, tricuspid dysplasia, and tricuspid insufficiency; these may be difficult to differentiate without neonatal imaging (Rao, 1990). In cases of tricuspid atresia, marked right atrial enlargement will be present, but forward flow across the site of the tricuspid valve

will not be present. Uhl anomaly involves severe hypoplasia of the myocardium of the right ventricle, which may present with right atrial enlargement but with the tricuspid valve in a normal position (Benson et al., 1995).

ANTENATAL NATURAL HISTORY

Infants with Ebstein anomaly diagnosed in utero have a significantly worse prognosis as compared with patients diagnosed later in childhood (Celermajer et al., 1994). In one series of 16 cases of Ebstein anomaly diagnosed prenatally, 11 were managed expectantly, 4 of which resulted in intrauterine death (Sharland et al., 1991). Another 6 infants died within 3 months of birth, with only 1 infant surviving. All of 6 fetuses with Ebstein anomaly followed sequentially with ultrasound examination had significant increases in cardiac size, as measured by cardiothoracic ratio, as pregnancy progressed (Sharland et al., 1991).

In a further series of 17 fetuses diagnosed prenatally with Ebstein anomaly, 14 were managed expectantly, and in this group there were 6 intrauterine deaths, 5 early neonatal deaths, and only 3 survivors (Hornberger et al., 1991). Eight of the 17 fetuses had pulmonary hypoplasia, and hydrops developed in 3. Therefore, the prognosis in prenatally diagnosed Ebstein anomaly is poor: one-third die in utero and only one-tenth survive the neonatal period.

MANAGEMENT OF PREGNANCY

If the diagnosis of Ebstein anomaly is suspected after prenatal ultrasonography, the patient should be referred to a tertiary care center for careful sonographic evaluation of fetal anatomy to exclude additional noncardiac malformations and fetal echocardiography to confirm the diagnosis. However, no obvious pattern of extracardiac malformations has been described in association with Ebstein anomaly, and karyotypic abnormalities are rare (Siebert et al., 1989). In one series of 16 infants with Ebstein anomaly no karyotypic abnormalities were found (Ferencz et al., 1987). In another series of 16 fetuses with Ebstein anomaly, one case of Down syndrome was found (Roberson and Silverman, 1989), and a further series of 17 fetuses with Ebstein anomaly included 1 fetus with trisomy 13 (Hornberger et al., 1991). Prenatal consultation with a pediatric cardiologist is recommended. If the diagnosis is made prior to fetal viability, termination of pregnancy may be offered because of the significant neonatal mortality and surgical morbidity.

Following prenatal diagnosis, serial evaluation with obstetric ultrasonography is recommended to confirm adequate fetal growth and to exclude the development of congestive heart failure. If hydrops develops, the option of early delivery may be considered; however, it is unclear that this will alter the expected high mortality rate (Romero et al., 1988). In the absence of hydrops there is no indication to alter obstetric management, including timing and route of delivery. Delivery should occur in a tertiary care center, with the immediate availability of appropriately trained neonatologists, pediatric cardiologists, and pediatric cardiothoracic surgeons.

FETAL INTERVENTION

No fetal intervention has been described following the prenatal diagnosis of Ebstein anomaly.

TREATMENT OF THE NEWBORN

Many cases of Ebstein anomaly are completely asymptomatic and do not present until adolescence. Such postnatally diagnosed cases commonly present with cyanosis, right-sided heart failure, arrhythmias, or sudden cardiac death (Attenhofer Jost et al., 2007). By contrast, most cases diagnosed prenatally tend to have tricuspid regurgitation and cardiomegaly, which usually results in the development of congestive heart failure during the newborn period. Infants with Ebstein anomaly diagnosed in utero have a significantly worse overall prognosis as compared with patients diagnosed later in childhood (Radford et al., 1985).

Careful evaluation by a pediatric cardiologist is recommended during the immediate newborn period, including echocardiography, to confirm the diagnosis and to exclude the presence of additional cardiac malformations. Electrocardiography typically reveals evidence of right atrial enlargement, right bundle-branch block, and possibly first-degree atrioventricular block (Attenhofer Jost et al., 2007). For patients with arrhythmias such as Wolff–Parkinson–White syndrome, electrophysiologic mapping may also be required to localize any accessory conduction pathways. Clinical improvement of cyanosis is likely in many cases during the initial newborn period as pulmonary vascular resistance falls, thereby reducing right-to-left shunting of blood.

If severe hypoxemia is also present, infusion of prostaglandin E_1 to maintain patency of the ductus arteriosus may also improve pulmonary vascular flow. This requirement for prostaglandin infusion usually decreases as pulmonary vascular resistance continues to fall following delivery (Rao, 1990). Treatment with diuretics and digoxin may also be needed if congestive heart failure is present, and lidocaine or procainamide may be needed if arrhythmias develop. If tachyarrhythmias are present, radiofrequency ablation of accessory pathways may be performed.

SURGICAL TREATMENT

Indications for surgical repair of Ebstein anomaly are unclear but include the presence of New York Heart Association functional class III or IV disease, severe or progressive cyanosis,

paradoxical emboli, right ventricular outflow tract obstruction, progressive cardiac enlargement, and development of atrial arrhythmias due to the presence of accessory conduction pathways (Danielson et al., 1992; Dearani et al., 2006; Attenhoffer Jost et al., 2007). Sudden death postoperatively can occur secondary to ventricular arrhythmias. Preoperative electrophysiologic studies, with prophylactic lidocaine therapy followed by procainamide for 3 months, are recommended to reduce this complication (Danielson et al., 1992). Permanent pacing may be necessary in a small percentage of patients (4%) (Attenhoffer Jost et al., 2007).

Surgical technique for Ebstein anomaly involves repairing the tricuspid valve, which should be possible in many cases (Danielson et al., 1992). In one series of 540 consecutive operations for Ebstein anomaly at a single center, 34% of patients had a valve reconstruction procedure, while 66% underwent valve replacement (Attenhofer Joet et al., 2007). Following median sternotomy and cardiopulmonary bypass, redundant right atrial tissue is excised and a patch closure of any atrial septal defect is performed. The portion of the right ventricle is plicated, and an annuloplasty is performed to narrow the tricuspid annulus, allowing the single anterior leaflet to function as a monocuspid valve. If the tricuspid valve cannot be repaired, complete valve replacement is performed. Corrections of associated anomalies are also made, such as relief of pulmonary stenosis and ablation of accessory conduction pathways (Danielson et al., 1992).

In one large study from a single center, 189 patients with Ebstein anomaly underwent surgical repair (Danielson et al., 1992). There was a 7.3% incidence of early death within 30 days in the group who underwent valvuloplasty and a 5.8% incidence of early death in the group who underwent complete valve replacement.

Another approach to the surgical repair of Ebstein anomaly involves vertical plication of the right ventricle with reimplantation of the tricuspid valve leaflets (Quaegebeur et al., 1991). In a series of 10 patients treated with this technique, 9 demonstrated significant clinical improvement and 8 showed diminished tricuspid regurgitation on echocardiography. One patient continued to have significant tricuspid regurgitation and required prosthetic valve replacement. All 10 patients in this series survived (Quaegebeur et al., 1991).

LONG-TERM OUTCOME

The long-term outcome for Ebstein anomaly depends on the timing of clinical presentation and diagnosis. Patients diagnosed during the fetal and early neonatal periods almost always have severe disease, with tricuspid regurgitation and significant cardiomegaly. Up to 50% of infants diagnosed with Ebstein anomaly during the neonatal period die within the first year of life (Rowe et al., 1981). Approximately 20% to 40% of neonates do not survive past 1 month, and less than 50% are alive at 5 years (Celermajer et al., 1992; McElhinney et al., 2005).

In a series of 189 patients with Ebstein anomaly managed surgically, there were 10 late deaths, 4 of which were presumed secondary to arrhythmias and 3 of which were secondary to congestive cardiac failure (Danielson et al., 1992). More than 90% of survivors were in New York Heart Association functional class I or II, and 9 affected adult women had a total of 12 successful pregnancies. Four (3.6%) of the patients treated by valvuloplasty required subsequent tricuspid valve replacement, in one case 14 years after the initial surgical repair. In another series of 191 patients with repair of the abnormal tricuspid valve, the mean survival rate at 20 years was 82% (Carpentier et al., 1988).

In another series of 220 cases of Ebstein anomaly, actuarial survival was 67% at 1 year and 59% at 10 years of age (Celermajer et al., 1994). Significant predictors of death included severe tricuspid regurgitation at presentation, diagnosis in utero, and right ventricular outflow tract obstruction. Of 155 survivors overall, 83% remained in New York Heart Association functional class I, and 67% required no ongoing medical therapy.

Long-term data allowing comparison of outcome for tricuspid valve repair versus valve replacement are now available. In one series of 294 patients followed up for 12 years postoperatively, there was no significant difference in freedom-from-operation rates between valve repair versus valve replacement patients (Kiziltan et al., 1998; Attenhoffer Jost et al., 2007). It appears as if valve repair is preferable for neonatal patients, while valve replacement may be a better option for adult therapy (Chen et al., 2004; Attenhoffer Jost et al., 2007).

GENETICS AND RECURRENCE RISK

Ebstein anomaly usually occurs as an isolated lesion or together with an additional cardiac malformation. It does not seem to occur with karyotypic abnormalities or as part of a recognizable genetic syndrome or association. Although most cases are sporadic, there have been several familial reports, including occurrence in two sisters born to consanguineous Sri Lankan parents (Gueron et al., 1966; Donegan et al., 1968; McIntosh et al., 1992). Estimates of recurrence risk suggest a 1% rate of recurrence if one previous sibling has been affected and a 3% rate of recurrence if two siblings have been affected (Nora and Nora, 1988).

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47 CHAPTER Hypoplastic Right Ventricle

Key Points

- Hypoplastic right ventricle is considerably rarer than hypoplastic left heart syndrome.
- It is a complex cardiac malformation with a wide spectrum of presentations, the most serious of which frequently results in a single-ventricle functionality.
- Prenatal sonographic features include pulmonary atresia with an intact ventricular septum, varying degrees of tricuspid atresia and tricuspid regurgitation, and varying degrees of hypoplasia of the right ventricular walls.

Key Points (cont.)

- Neonates will be ductal-dependent and therefore delivery should be carefully coordinated in a center that can provide immediate pediatric cardiology intervention, prostaglandin infusion to maintain a patent ductus arteriosus, and ability to provide prompt catheter-based interventions such as pulmonary valvotomy, ductus arteriosus stenting, and balloon atrial septostomy.
- Optimal management is individualized between catheter-based approaches that allow blood flow from right to left sides of the heart, together with open surgical systemic-pulmonary shunting.
- Long-term outcome depends on whether a biventricular or univentricular repair is achieved.

CONDITION

Hypoplastic right ventricle (HRV) is also known as pulmonary atresia with intact ventricular septum (PA:IVS). The normally formed right ventricle becomes hypoplastic, in association with pulmonary atresia, and occasionally tricuspid atresia. The competence of the tricuspid valve determines the size of the right ventricle, with type I HRV being associated with a competent valve and small ventricle and type II HRV being associated with an incompetent valve and normal or large right ventricle (Romero et al., 1988). Another classification system is based on the degree of severity of right ventricular hypoplasia (Alwi, 2006). Group A patients have only mild right ventricular hypoplasia, with a well-developed infundibulum, beyond which the pulmonary arterial outflow tract is atretic. Group C patients have severe right ventricular hypoplasia, with an atretic infundibulum. Group B patients have a moderately HRV, but may have a reasonably well-developed infundibulum. Patients in Group C tend to have poor prognosis with long-term outcome being dependent on a single-ventricle repair.

In the setting of right ventricular hypoplasia, blood flows from the right to the left atria through the foramen ovale, and the left ventricle supplies both systemic and pulmonary circulations, the latter by retrograde flow through the ductus arteriosus. Additional cardiac malformations that may coexist include atrial and ventricular septal defects and transposition of the great vessels. Additionally, coronary arterial anatomy is frequently abnormal, and there may be varying degrees of tricuspid regurgitation or Ebstein malformation (see Chapter 46) (Daubney et al., 2002).

INCIDENCE

HRV is extremely rare, accounting for less than 3% of all cases of congenital heart disease diagnosed during the first year of life (Fyler et al., 1980). The overall population incidence is likely to be 1 to 2 per 10,000 livebirths (Hoffman and Kaplan, 2002). In another series, the livebirth prevalence was estimated at 4.1 per 100,000 livebirths (Daubney et al., 1998).

SONOGRAPHIC FINDINGS

Prenatal diagnosis of HRV is relatively straightforward if there is a significant disproportion in size between the two ventricular cavities (Figure 47-1) (McGahan et al., 1991). However, if the right ventricle is normal in size (due to an incompetent tricuspid valve) prenatal diagnosis may be extremely difficult and may depend on identification of isolated pulmonary atresia (Romero et al., 1988). While the right ventricular cavity is usually very small, the right ventricular wall is often hypertrophied (Grundy et al., 1987). Although adequate visualization of the right ventricular outflow tract may be difficult, Doppler echocardiography may demonstrate absence

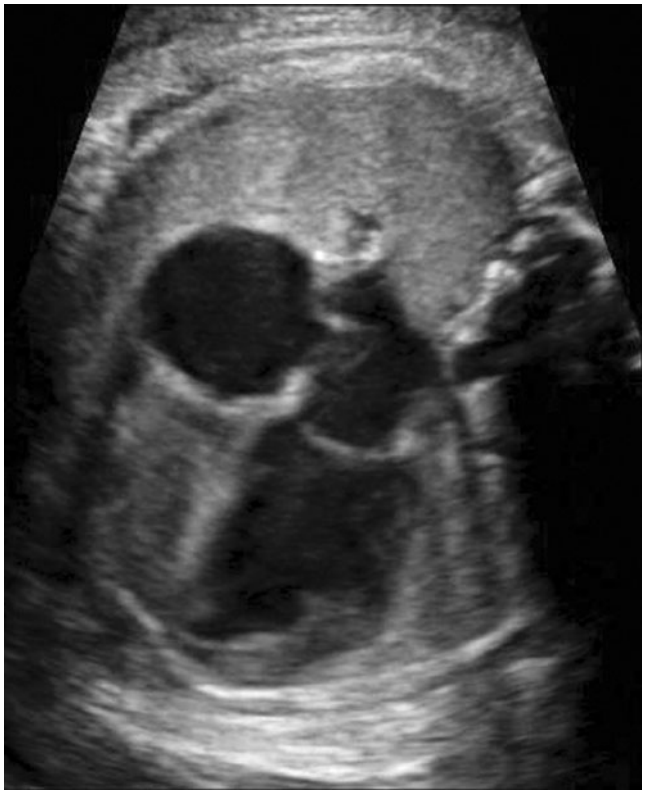

Figure 47-1 Axial image demonstrating ventricular disproportion with hypoplastic right ventricle.

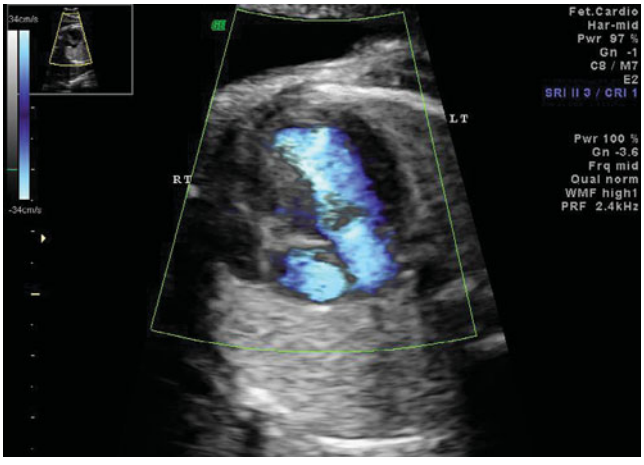

Figure 47-2 Power Doppler showing lack of filling of the hypoplastic right ventricle.

of flow across the pulmonary valve (Figure 47-2). As with hypoplastic left heart syndrome (see Chapter 48), the diagnosis of HRV may not be clear at an initial second trimester ultrasound examination, but instead may evolve over time so that true hypoplasia may not be visible until late in the third trimester (Hornberger et al., 1996). At fetal echocardiography, detailed evaluation of tricuspid valve annulus size, ratio of right to left ventricular size, and presence or absence of tricuspid regurgitation are essential.

DIFFERENTIAL DIAGNOSIS

When only one ventricle is clearly visible during fetal echocardiography, the differential diagnosis is similar to that for hypoplastic left heart syndrome and includes right-sided cardiac masses, pulmonary stenosis, and univentricular heart. Doppler echocardiography may be helpful in demonstrating absence of antegrade flow through the pulmonary valve, therefore confirming the presence of complete pulmonary atresia.

ANTENATAL NATURAL HISTORY

Congestive heart failure can often develop in utero with HRV because of significant tricuspid regurgitation. In one series of 28 cases of prenatally diagnosed pulmonary atresia with intact ventricular septum, antenatal predictors of poor outcome included a small tricuspid valve annulus (<5 cm) after 30 weeks' gestation, a ratio of right to left ventricular length or width of less than 0.5, and absence of tricuspid regurgitation (Peterson et al., 2006). Growth of the fetal tricuspid valve during gestation, and calculation of tricuspid valve z scores may also be useful for predicting outcome and which infants will ultimately survive with a biventricular anatomy (Salvin et al., 2006).

FETAL INTERVENTION

No fetal intervention has been described for the management of HRV.

MANAGEMENT OF PREGNANCY

Following the prenatal diagnosis of HRV, a careful sonographic fetal anatomy survey is recommended to exclude additional cardiac and extracardiac malformations. Fetal echocardiography should be performed by an appropriately trained specialist to confirm the diagnosis and to exclude other cardiac malformations. Particular attention should be paid to morphology of the tricuspid and pulmonary valves, and growth of the tricuspid valve should be monitored throughout gestation. It is unclear if invasive fetal testing for karyotype analysis is needed, because in one series of 48 cases of tricuspid or pulmonary atresia there were no chromosomal abnormalities (Ferencz et al., 1987). There may be a higher prevalence of chromosomal abnormalities in fetuses with prenatally diagnosed right ventricular hypoplasia, although minimal data are available to confirm the need for karyotype analysis.

Referral for prenatal consultation with a pediatric cardiologist and cardiothoracic surgeon is also recommended. If the diagnosis is made prior to fetal viability, termination of pregnancy may be offered because of the significant neonatal mortality and surgical morbidity. If expectant management is desired, sonographic surveillance to confirm appropriate fetal growth and to evaluate for the development of fetal hydrops is recommended. If fetal hydrops occurs, the prognosis deteriorates further, and the optimal management of such pregnancies is uncertain. In the absence of tricuspid regurgitation, or if the tricuspid valve is small, prognosis worsens with likely outcome being a single-ventricle repair (Peterson et al., 2006; Salvin et al., 2006). Delivery should occur at a tertiary care center, with the immediate availability of a neonatologist, pediatric cardiologist, and cardiothoracic surgeon. There is no indication to alter the timing or method of delivery based on the prenatal diagnosis of HRV.

TREATMENT OF THE NEWBORN

The infant should be transported to a neonatal intensive care unit, and prostaglandin E_1 infusion should be started as soon as possible to maintain blood flow across the ductus arteriosus. Care should be taken with the administration of supplemental oxygen to an infant with HRV, so as to avoid significant reduction in pulmonary vascular resistance, which may decrease the amount of blood shunted across the ductus arteriosus. Consultation with a pediatric cardiologist should be obtained promptly, and echocardiography should be performed to confirm the prenatal diagnosis and to exclude additional

cardiac malformations. Echocardiography should document patency of the ductus, size of the right ventricular cavity, and size of the tricuspid annulus. If inadequate atrial communication is present, balloon atrial septostomy may be considered to maximize cardiac output during the initial treatment phase. Consultation with a pediatric cardiothoracic surgeon should be obtained to decide on timing and method of surgical intervention.

Initial management of infants with pulmonary atresia and intact ventricular septum has moved toward prompt intervention with catheter-based therapies to allow blood flow from the right to the left sides of the heart (McLean and Pearl, 2006). Pulmonary valvotomy (laser assisted) and balloon pulmonary valvuloplasty are becoming increasingly common for the initial management of select patients (Mi et al., 2005).

SURGICAL TREATMENT

The choice of surgical procedure for right ventricular hypoplasia depends on the size of the tricuspid valve, the severity of outflow tract/infundibular atresia, and the presence of right ventricular-dependent coronary circulation. Because of the significant anatomic variation between patients, there is no agreement on a single best surgical approach to right ventricular hypoplasia. Management should be individualized for each infant depending on size and function of the right ventricle as well as on the presence of other abnormalities.

Group A patients, in which right ventricular hypoplasia is mild and membranous pulmonary atresia is present, are usually managed primarily with a catheter-based approach such as laser-assisted valvotomy and balloon pulmonary valvuloplasty (Mi et al., 2005; Alwi, 2006). In contrast, Group C patients, in which ventricular hypoplasia is severe and the infundibulum is almost completely atretic, are not candidates for the more conservative catheter-based approaches. Such patients will also likely have major right ventricular-coronary arterial connections and should be managed as a univentricular heart. These infants are ductal-dependent, may require prolonged prostaglandin infusion, and will likely need an initial systemic-pulmonary shunt during the neonatal period (Alwi, 2006). Options in such cases may include patent ductus arteriosus (PDA) stenting or modified Blalock–Taussig (BT) shunt (Armstrong, 1995). While further surgical intervention is uncommon for patients in Group A, most patients in Group C with severe hypoplasia will require multiple further interventions.

Patients with moderate right ventricular hypoplasia, (Group B), generally have individualized surgical intervention depending on the degree of infundibular hypoplasia and extent of right ventricular-coronary arterial connections. Such patients may do well with pulmonary valvotomy (laser assisted or radiofrequency), together with stenting of the PDA and balloon atrial septostomy (Alwi, 2006).

Depending on the anatomic variation with right ventricular hypoplasia, the operative mortality may range from 27% to 50% (DeLeval et al., 1982). In one series of 25 neonates with pulmonary atresia with intact ventricular septum, initial catheter-based intervention occurred at a mean of 3 days of life, but the majority of these required subsequent open surgical intervention within further 8 days (McLean and Pearl, 2006).

LONG-TERM OUTCOME

Data on long-term outcome following surgery for HRV are conflicting. In one series of 17 infants who were treated with both pulmonary valvotomy and systemic-pulmonary shunt, the long-term survival rate was 53% (Moulton et al., 1979). In another series of 60 patients with HRV, 5-year actuarial survival was only 36% (DeLeval et al., 1982). However, more recent data are more encouraging. In a series of 106 pateints with pulmonary atresia and intact ventricular septum managed at a single center in Los Angeles from 1982 to 2001, the 10-year actuarial survival was 86% (Odim et al., 2006). Over half of these patients underwent a biventricular repair, with initial severity of the ventricular hypoplasia being the best predictor for such a good outcome.

GENETICS AND RECURRENCE RISK

HRV occurs in a sporadic pattern. No recurrence risk data are available for counseling parents with a previously affected infant.

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48 CHAPTER Hypoplastic Left Ventricle

Key Points

- Hypoplastic left heart syndrome (HLHS) is a spectrum of disorders involving aortic atresia with or without mitral atresia or stenosis.
- The condition may be diagnosed as severe ventricular hypoplasia before 20 weeks' gestation, or it may evolve from aortic stenosis to HLHS during the second half of pregnancy.
- Prenatal diagnosis of classic HLHS is straightforward as the ventricular disproportion is obvious, leading to prenatal detection rates as high as 85%.
- Delivery needs to be carefully planned to optimize the availability of pediatric specialists, and will include immediate prostaglandin infusion and referral to cardiothoracic surgeons for initial palliation.
- Surgical management includes a choice between traditional three-stage Norwood procedure leading ultimately to a single ventricle repair, versus hybrid palliation involving open surgical and interventional catheterization until cardiac transplantation is available.

CONDITION

Hypoplastic left heart syndrome (HLHS) represents a spectrum of abnormalities in which there is underdevelopment of the left-sided cardiac structures, such as the left ventricle, the mitral valve, and aortic valve, such that the systemic circulation cannot be adequately supported (Rychik, 2005). Classic HLHS involves both aortic valve atresia, and either atresia or stenosis of the mitral valve (Simpson, 2000).

The spectrum of malformations can include congenital hypoplasia of the left ventricular wall, atresia of the aortic and/or mitral valves, and coarctation or hypoplasia of the aortic arch. Critical aortic stenosis can evolve into HLHS (see Chapter 50), and unbalanced atrioventricular canal defects (see Chapter 45) in which the left ventricle is quite underdeveloped and can also behave similar to HLHS (Simpson, 2000). Each of the components of HLHS may occur with varying degrees of severity, ranging from aortic stenosis with a small left ventricle to complete aortic and mitral atresia with a slit-like left ventricular remnant. Hypoplastic left ventricle and mitral atresia may also occur without aortic atresia, but such an anomaly is rare (Kiel, 1990). The cause of HLHS is unknown, but it may be due to abnormal intracardiac streaming during weeks 5 to 8 of embryonic life

(Harh et al., 1973). HLHS may also evolve during prenatal life from isolated severe aortic stenosis (see Chapter 50), which may result in decreased right-to-left shunting between the atria, and subsequent hypoplasia of the left ventricle (Sharland et al., 1991).

Postnatally, left-to-right shunting occurs in the newborn, returning oxygenated blood from the pulmonary veins through a patent foramen ovale into the right atrium. The right ventricle provides both pulmonary and systemic circulations, the latter through a patent ductus arteriosus with retrograde flow to the aortic arch and coronary vessels. The mitral valve is hypoplastic; the tricuspid valve is often large and regurgitant. The aortic outflow tract may end blindly below the coronary arteries, and the aortic valve and arch may be hypoplastic. Associated cardiac anomalies are common with HLHS. Other associated cardiac anomalies include ventricular septal defect, aortic-arch interruption, and transposition of the great vessels (Kiel, 1990). Central nervous system abnormalities have also been described in association with HLHS, including microcephaly, holoprosencephaly, and agenesis of the corpus callosum (Sanders et al., 1996).

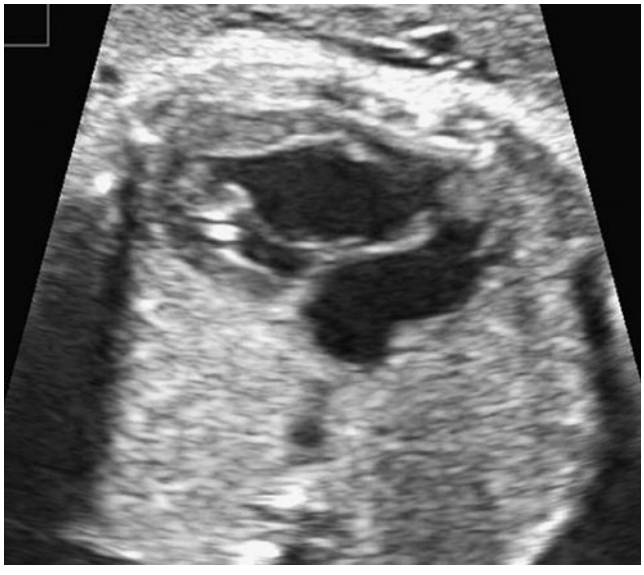

Figure 48-1 Axial image through fetal chest demonstrating ventricular disproportion and small left ventricle consistent with hypoplastic left heart syndrome.

INCIDENCE

HLHS accounts for up to 9% of all cases of congenital heart disease, with an incidence of 1 to 2 per 10,000 livebirths (Kiel, 1990; Hoffman and Kaplan, 2002). Twice as many males as females may be affected.

SONOGRAPHIC FINDINGS

HLHS is generally easy to detect prenatally by means of the standard four-chamber cardiac view. This should demonstrate an inequality in ventricle size, with the left ventricular cavity often appearing as a small remnant to the left of the right ventricle (Figure 48-1) (Silverman et al., 1984). The left ventricular wall may be hypocontractile or immobile and may also appear echogenic (Kluckow et al., 1993). The apex of the left ventricle will usually end more proximally than the right ventricular apex, and the ventricular cavity may be in a globular shape rather than in the normal elliptical shape. The right ventricular cavity is often enlarged, and the left atrium is usually small, with left-to-right bowing of the interatrial septum (Sanders et al., 1996). The aortic outflow tract may be atretic, with hypoplasia of the ascending aorta. However, the aortic arch and descending aorta should be visible because of retrograde filling through the ductus arteriosus. Doppler echocardiography may also be helpful in demonstrating a lack of antegrade flow into the left ventricle, abnormal flow through the foramen ovale, and retrograde flow in the ascending aorta (Figure 48-2) (Blake et al., 1991).

Even though these findings should be detectable at 18 to 20 weeks of gestation, it is possible that isolated aortic stenosis (see Chapter 50) may evolve over time into HLHS, so that the typical features of HLHS may not become visible until the late second trimester or the third trimester (Sharland et al., 1991). The detection rate of prenatal ultrasonography for HLHS is unclear in the general population, with only 28% of all cases of HLHS being detected prenatally in one series (Montana et al., 1996). However, as sonographer experience has improved over the past decades, it is likely that a much higher prenatal detection rate is now possible. In another population-based study from Australia, 66 of 78 cases (85%) of HLHS were correctly diagnosed antenatally (Chew et al., 2007). Additionally,

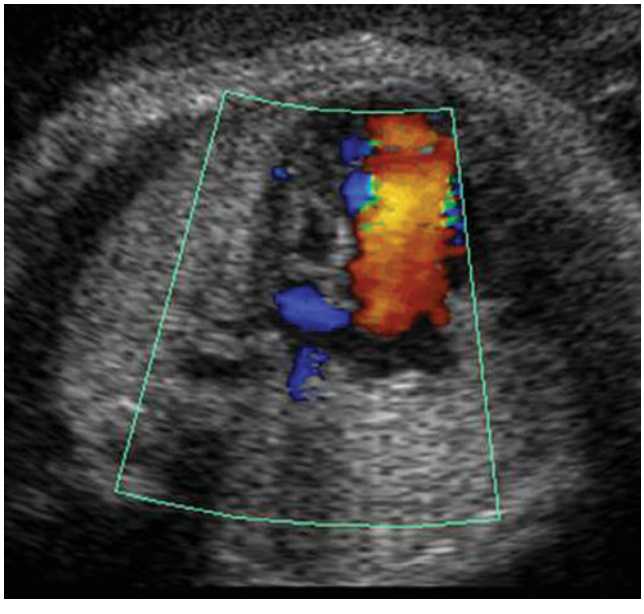

Figure 48-2 Axial image with color Doppler demonstrating absence of forward flow across mitral valve consistent with hypoplastic left heart syndrome.

the positive predictive value of prenatal ultrasonography for HLHS is high, with up to 95% of cases of prenatally diagnosed HLHS confirmed on postnatal examination (Chang et al., 1991).

DIFFERENTIAL DIAGNOSIS

Other conditions that should be included in the differential diagnosis of HLHS include left-sided cardiac masses, aortic stenosis, and univentricular heart (Sanders et al., 1996). Large cardiac masses, such as rhabdomyomas (see Chapter 58), may completely obliterate the left ventricular cavity, thus mimicking the sonographic appearance of HLHS. However, normal ventricular dimensions will be present, and Doppler echocardiography should demonstrate normal flow through the mitral and aortic valves. Severe aortic stenosis may be difficult to differentiate from HLHS because complete obliteration of the left ventricle may occur as the stenosis worsens (see Chapter 50). It is possible that aortic stenosis in early fetal life may progress to hypoplastic left ventricle as gestation advances (Sharland et al., 1991; Wilkins-Haug et al., 2005). Differentiation should be possible based on Doppler echocardiography demonstrating antegrade flow in the ascending aorta with aortic stenosis, as compared with retrograde flow in HLHS. Univentricular heart is a condition in which the entire atrioventricular junction is connected to a single ventricle. There is little agreement on the precise definition of univentricular heart, which makes prenatal differentiation difficult.

ANTENATAL NATURAL HISTORY

HLHS may evolve in utero from critical aortic stenosis (Sharland et al., 1991; Kluckow et al., 1993; Wilkins-Haug et al., 2005). The precise antenatal natural history of HLHS is therefore very variable. This malformation has several degrees of severity, ranging from critical aortic stenosis with normal left ventricular size to complete atresia of the aortic and mitral valves with near absence of the left ventricle. Previously, because of the lack of adequate pediatric surgical intervention, the vast majority of cases diagnosed prior to 24 weeks of gestation resulted in termination of pregnancy. In a series of 77 cases of HLHS diagnosed prior to 24 weeks, 72 resulted in termination of the pregnancy (Allan et al., 1991). However, as pediatric surgical management options have improved over the last 20 years and as the potential for in utero intervention has appeared, it is likely that the voluntary pregnancy termination rate may be significantly less in contemporary practice.

Expectant management of prenatally diagnosed HLHS is associated with a poor prognosis. In one series of 20 cases of prenatally diagnosed HLHS, 9 pregnancies were terminated (Blake et al., 1991). Four of the 11 expectantly managed pregnancies resulted in intrauterine fetal death, 7 resulted in livebirths, and 5 of these 7 infants died within 1 week of birth. Intrauterine congestive heart failure may occur with HLHS because of right ventricular overload. In another series, nonimmune hydrops developed in 4 of 20 cases of prenatally diagnosed HLHS. Only one of these cases resulted in a liveborn infant, following administration of digoxin to the mother (Blake et al., 1991).

When classic HLHS is diagnosed before 24 weeks' gestation, little in utero change is likely to occur to the already extremely hypoplastic left ventricle. However, in cases in which aortic outflow tract restriction is diagnosed before 24 weeks' gestation, it is possible that the left ventricle may not yet be hypoplastic, and this may evolve over subsequent months in utero (Wilkins-Haug et al., 2005). The rate of growth of left ventricular dimensions may be quite slow, and there may be limited growth of aortic and mitral valves. Additionally, reversed flow across the foramen ovale (from left to right) and retrograde flow in the aortic arch are predictors of subsequent severe HLHS that will unlikely support systemic circulation in postnatal life (Hornberger et al., 1996; Wilkins-Haug et al., 2005).

FETAL INTERVENTION

The only fetal intervention that has been described for HLHS is in utero balloon dilation for critical aortic stenosis (see Chapter 50), but if the stenosis has progressed to the development of HLHS it is unlikely that such an intervention will be of any benefit. Recently, attempts have been made to identify fetuses with hallmarks of potential HLHS at a sufficiently early gestational age to warrant in utero intervention in an attempt to optimize postnatal outcome. Prevention of in utero evolution of HLHS such that a biventricular repair is possible would represent a significant step forward in our management of this condition. The largest series of such interventions, by means of in utero balloon dilation of the aortic valve, is from the Children's Hospital, Boston. In a series of 20 cases operated on at a mean gestational age of 24 weeks, technical success was achieved in 14, and of these 9 resulted in either fetal loss or subsequent development of classic HLHS (Tworetzky et al., 2004). Overall, only 5 of the original 20 cases resulted in postnatal survival with a two-ventricle circulation. This study underlines the challenges in prenatal selection of cases in which the natural history can be modified. Currently, in utero balloon aortic dilation should be considered an unproven experimental intervention for the prevention of HLHS.

MANAGEMENT OF PREGNANCY

Following prenatal diagnosis of HLHS, a careful sonographic fetal anatomy survey is recommended to exclude additional

cardiac and extracardiac malformations. This evaluation should include a search for sonographic markers of Turner syndrome and trisomies 13, 18, and 21. Invasive fetal testing for karyotype analysis is recommended because of the association between HLHS and chromosomal abnormalities. Chromosomal abnormalities were found in 2 of 85 cases of HLHS in infants in one study (Ferencz et al., 1987) and in 9 of 83 cases in a later study, including trisomies 13, 18, and 21 (Natowicz et al., 1988). In a series of 20 cases of HLHS diagnosed prenatally, 1 fetus also had trisomy 13 and 2 had Turner syndrome (Blake et al., 1991). The incidence of karyotypic abnormalities is likely dependent on the exact form of HLHS diagnosed, as there appears to be a higher incidence in the setting of coarctation or unbalanced atrioventricular canal defect, compared with isolated aortic stenosis (Simpson, 2000). A detailed sonographic survey of the fetal anatomy should be performed to exclude extracardiac abnormalities, and fetal echocardiography should be performed by an appropriately trained specialist to confirm the diagnosis. Referral for prenatal consultation with a pediatric cardiologist and cardiothoracic surgeon is also recommended.

If the diagnosis is made prior to fetal viability, termination of pregnancy may be offered because of the significant neonatal mortality and surgical morbidity. If expectant management is desired, sonographic surveillance to confirm appropriate fetal growth and to evaluate for the development of fetal hydrops is recommended. If fetal hydrops occurs, the prognosis deteriorates further and the optimal management of such pregnancies is uncertain. Delivery should occur at a tertiary care center, with the immediate availability of a neonatologist, pediatric cardiologist, and cardiothoracic surgeon. There is no indication to alter the timing or method of delivery based on the prenatal diagnosis of HLHS. In one series of 13 cases of HLHS, all spontaneous or induced labors resulted in normal vaginal deliveries and there was only one case of an abnormal fetal heart rate pattern (Jackson et al., 1991). Routine labor management therefore does not need to be modified when the fetus has HLHS.

TREATMENT OF THE NEWBORN

All infants with HLHS will die soon after birth without surgical intervention. For many years the options for surgery were limited and, when available, the outcome from surgical intervention was very poor. Because of this poor prognosis, comfort care without aggressive resuscitation efforts was a common method of treatment for infants with HLHS. The provision of comfort measures only has been challenged recently as more centers become skilled in surgical palliation of HLHS and as survival from such surgery has improved (O'Kelly and Bove, 1997). Decisions regarding the aggressiveness of treatment for newborns with HLHS should be made during the antenatal period, and, depending on the results from the local pediatric cardiothoracic surgery center, such decisions should include options for surgical intervention and provision of only comfort care (Thwaites, 1997; Simpson, 2000).

Following delivery of an infant with HLHS, supplemental oxygen should be administered judiciously so as to avoid significant reduction in pulmonary vascular resistance, which may decrease the amount of blood shunted across the ductus arteriosus. The infant should be transported to a neonatal intensive care unit, and prostaglandin E_1 infusion should be started as soon as feasible to maintain patency of the ductus arteriosus. Other supportive measures that are essential include correction of metabolic acidosis and use of inotropic agents, such as dopamine, to maintain adequate cardiac output. If inadequate atrial communication is present, efforts to maximize cardiac output by balloon atrial septostomy may be considered during the initial resuscitative efforts (Kiel, 1990; Theilen and Shekerdemian, 2005).

Postnatal consultation with a pediatric cardiologist should be obtained promptly, and echocardiography should be performed to confirm the prenatal diagnosis and to exclude additional cardiac malformations. Echocardiography should document patency of the ductus, presence of coarctation, size of an atrial septal defect, and presence of significant tricuspid regurgitation (Sanders et al., 1996). Consultation with a pediatric cardiothoracic surgeon should then be obtained to decide on timing and method of surgical intervention.

SURGICAL TREATMENT

All infants with HLHS will require surgical intervention to permit postnatal survival. Contraindications to surgery include a decision by parents to receive comfort care only or the presence of significant hemodynamic instability, such as severe hypoperfusion, metabolic acidosis, or coagulopathy. These conditions should be aggressively corrected prior to surgical intervention. Two surgical choices are present for infants with HLHS: the Norwood three-stage procedure and neonatal cardiac transplantation.

The Norwood procedure is a complex operation, the precise surgical details of which are beyond the scope of this chapter (Simpson, 2000; Rychik, 2005; Alsoufi et al., 2007). Stage 1 is usually performed within the first week of life. It involves connecting the systemic circulation to the pulmonary circulation to maintain adequate pulmonary flow, together with an atrial septectomy to allow adequate mixing of pulmonary venous and systemic venous blood flows. Stage 2 is performed at 6 months of age. It involves connecting the superior vena cava to the pulmonary arteries in an effort to reduce ventricular volume overload. The final stage 3 procedure is performed at 2 years of age, and involves connecting the inferior vena cava to the pulmonary arteries, further reducing ventricular volume overload. Ultimately, this staged Norwood palliation treatment results in systemic venous return passing directly to the pulmonary arteries;

oxygenated pulmonary venous blood is then returned to the single ventricle and is pumped around the body through a reconstructed aortic arch (Simpson, 2000; Alsoufi et al., 2007).

Stage 1 is performed as soon as possible after birth and after initial medical stabilization. While pulmonary blood flow is generally controlled by a modified Blalock–Taussig shunt (which anastomoses the subclavian to the pulmonary arteries), more recent modifications have suggested use of a direct conduit from the right ventricle to the pulmonary artery (Ohye et al., 2007). It is unclear at this stage whether this so-called Sano modification to the stage 1 procedure is preferential to the more traditional modified Blalock–Taussig shunt.

The results for the Norwood procedure are variable, depending on the institution, operator experience, and modifications to the procedure to account for anatomic variations. The greatest surgical mortality seems to be related to the first stage of the Norwood procedure, with recent surgical mortality rates typically exceeding 70% for this first stage (Alsoufi et al., 2007). While interim mortality remains significant, once survivors become candidates for the second stage of the Norwood procedure, prognosis improves significantly. For example, among 23 patients who completed the second stage of the Norwood procedure, there was only 1 death, and among 12 patients who completed the third stage there was 1 further death (Kern et al., 1997). In one of the largest series from a single center, 120 of 158 patients survived the first stage of surgery, 103 of 106 patients subsequently survived the second stage, and 53 of 62 survived the final stage of the Norwood procedure (Bove and Lloyd, 1996).

It is now recognized that a major contributor to operative mortality and surgical morbidity is the requirement for cardiopulmonary bypass to complete the Norwood procedures. An alternative management has recently evolved that is known as the "hybrid" strategy, which avoids the need for cardiopulmonary bypass. This uses a combination of more limited surgery together with interventional catheterization to achieve HLHS palliation until a suitable donor heart for transplantation is obtained. With this approach, both pulmonary arteries are banded to control pulmonary blood flow, a stent is placed in the ductus arteriosus, and an atrial septal defect is created (Alsoufi et al., 2007). Initial results have suggested results comparable to those with the traditional Norwood procedure.

The alternative surgical management for HLHS is neonatal cardiac transplantation. As discussed above, this option will almost certainly require an initial interventional procedure to stent the ductus arteriosus or to enlarge the interatrial communication as a palliative step until a suitable donor heart is found. In a large series of cardiac transplantations as a primary treatment for HLHS, 176 infants were listed for transplantation, 34 of whom (19%) died during the waiting period (Razzouk et al., 1996). Of the 142 infants who underwent successful transplantation in this series, the median age at surgery was 26 days and there was a 9% operative mortality rate. Overall, transplant waiting list mortality is approximately 20% to 25%, and operative mortality is approximately 10% (Alsoufi et al., 2007).

LONG-TERM OUTCOME

The long-term outcome for infants with HLHS has improved in recent years, with the modifications to the original Norwood procedure as described above. In one series of 53 infants operated on from 1990 to 1996 the 5-year actuarial survival was 61% (Kern et al., 1997). In one of the largest series of Norwood procedures from a single center, 5-year actuarial survival was 58% from an initial cohort of 158 infants (Bove and Lloyd, 1996). The 5-year actuarial survival for primary neonatal cardiac transplantation was 76% from another initial cohort of 176 infants with HLHS (Razzouk et al., 1996). However, in this cohort, half of these late deaths were due to organ rejection, and approximately 4% required retransplantation. Although long-term outcome may appear better after transplantation compared with the Norwood procedure, this is tempered by the short supply of suitable neonatal donor hearts and the long-term need for medications to manage organ rejection.

Both survival and long-term outcome data for infants with HLHS should include neurodevelopmental information and quality-of-life outcomes. In one series of 11 survivors of staged repair of HLHS, 64% had major developmental disabilities (Rogers et al., 1995). Conversely, in another series of 14 survivors of pediatric heart transplantation for HLHS or cardiomyopathy, only 1 had a significant neurologic deficit (Lynch et al., 1994). More data are needed to adequately assess the long-term neurologic and quality-of-life outcome for infants following surgical management of HLHS. However, as modifications to palliation improve, including options that avoid cardiopulmonary bypass (such as the "hybrid" strategy, it is likely that neurologic deficits can be minimized. The majority of HLHS survivors will demonstrate long-term exercise intolerance, up to 50% will have arrhythmias, and there is a 10% ongoing risk of thromboembolism (Rychik, 2005). Overall incidence of neurocognitive disabilities, ranging from learning difficulties to attention deficit hyperactivity disorder, may range from 10% to 70% (Rychik, 2005).

GENETICS AND RECURRENCE RISK

The inheritance pattern for HLHS is not clear, and in the majority of cases it occurs sporadically. HLHS has been reported as an autosomal recessive condition, which would imply a recurrence risk as high as 25% (Shokeir, 1971; Grobman and Pergament, 1996). Other reports suggest HLHS is inherited in a polygenic pattern, with a recurrence risk of only 2% if one previous sibling was affected (Brownell and Shokeir, 1976). The recurrence risk increases to 6% if two previous siblings have been affected by HLHS (Nora and Nora, 1988). In

another series, a recurrence risk of 13.5% has been quoted for HLHS (Boughman et al., 1987). It is possible that different subsets of HLHS may have different patterns of inheritance, which may explain the wide range of recurrence risks quoted for HLHS (Brenner et al., 1989). If a chromosome abnormality is documented, the recurrence risks are related to the chromosomal findings.

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49 CHAPTER Pulmonary Stenosis and Atresia

Key Points

- Pulmonary stenosis and atresia refer to congenital narrowing or complete occlusion of the right ventricular outflow tract respectively.
- It may occur in isolation or as part of Williams or Noonan syndrome, or secondary to teratogenic exposure such as congenital rubella syndrome.
- Prenatal diagnosis relies upon identification of asymmetry in ventricular size, right atrial enlargement, thickening of the pulmonary valve and Doppler abnormalities across the pulmonary valve.
- Obstetric management generally does not need to be changed following this diagnosis, although in cases of critical pulmonary stenosis or atresia, delivery should occur in a controlled manner in a center with pediatric cardiology backup and ability to provide prostaglandin infusion.
- Neonatal management depends on the pressure gradient across the pulmonary valve, with invasive intervention reserved generally for those cases with pressure gradients greater than 30 to 50 mm Hg.
- While open surgical valvotomy or valve replacement represents definitive treatment, contemporary management is moving toward percutaneous approaches using balloon valvuloplasty and valve replacement.

CONDITION

The term *pulmonary stenosis* refers to narrowing of the right ventricular outflow tract; *pulmonary atresia* implies complete occlusion of the right ventricular outflow tract. Pulmonary atresia, when associated with an intact ventricular septum, is also considered as a hypoplastic right ventricle and is described in detail in Chapter 47. Pulmonary atresia with coexistent ventricular septal defect is generally considered part of the spectrum of tetralogy of Fallot and is described in detail in Chapter 52. Pulmonary stenosis usually results from fusion of the three cusps of the pulmonary valve. Other causes of pulmonary stenosis include narrowing of the infundibular portion of the right ventricular outflow tract, hypoplasia of the pulmonary artery, or pulmonary valve dysplasia, in which the valve leaflets are thickened and immobile. Pulmonary artery hypoplasia and supravalvar pulmonary stenosis may occur in association with Williams syndrome or with congenital rubella or toxoplasmosis (Gutgesell, 1990; Rhodes et al., 2008). Supravalvar pulmonary valve stenosis may also occur in association with Noonan syndrome, which has a phenotype similar to Turner syndrome, but a normal karyotype (Mendez and Opitz, 1985; Rhodes et al., 2008). Approximately 60% of cases of Noonan syndrome will have a dysplastic pulmonary valve (Bashore, 2007).

Pulmonary stenosis may lead to right ventricular hypertrophy, a decrease in right ventricular chamber size, and poststenotic dilation of the pulmonary artery (Romero et al., 1988). Poststenotic dilation of the pulmonary artery is rarely present in utero and usually takes several months of neonatal life to develop (Gutgesell, 1990). In cases of critical pulmonary stenosis, hypoplasia of the right ventricular cavity may occur together with hypertrophy of the ventricular wall and dilation of the right atrium. In such cases, neonates usually have an interatrial communication through either a patent foramen ovale or a secundum atrial septal defect. Other associated cardiac defects that may be seen with pulmonary stenosis include ventricular septal defect, total anomalous pulmonary venous return, and aortic stenosis (Romero et al., 1988).

Congenital pulmonary stenosis may be subdivided into three anatomical types: (1) a dome-shaped pulmonary valve with a narrow opening but preservation of mobile valve leaflets, (2) a dysplastic thickened pulmonary valve with a narrow outflow tract, and (3) a unicuspid or bicuspid

pulmonary valve (Bashore, 2007). Differentiation of these types by prenatal sonography is quite limited.

INCIDENCE

Pulmonary stenosis is a relatively common congenital cardiac defect, and in many mild forms the diagnosis may not be made until late in childhood. The incidence of congenital pulmonary stenosis is approximately 1 in 1500 livebirths, while pulmonary atresia occurs in approximately 1 in 10,000 livebirths (Hoffman and Kaplan, 2002). Pulmonary stenosis may account for 5% to 10% of all pediatric cardiology patients at tertiary care centers (Gutgesell, 1990).

SONOGRAPHIC FINDINGS

Prenatal sonographic features of congenital pulmonary stenosis include decreased size of the right ventricular chamber, thickening of the right ventricular walls, right atrial enlargement, increased diameter of the pulmonary artery, thickening of the pulmonary valve, and incomplete valvular opening (Figure 49-1). However, several of these features may be extremely difficult, if not impossible, to demonstrate reliably with two-dimensional echocardiography in the fetus. Duplex and color flow Doppler sonography may be used in the prenatal diagnosis of pulmonary stenosis to demonstrate poststenotic turbulence of flow in the pulmonary artery as well as significant tricuspid regurgitation. The demonstration of reversed flow across the ductus arteriosus is also suggestive of severe pulmonary stenosis or atresia and in one study was found in all seven fetuses with this prenatal diagnosis (Mielke et al., 1997).

The ability of routine prenatal sonography to detect pulmonary stenosis or atresia in unselected populations seems limited. In the largest study evaluating the prenatal detection rates for various congenital cardiac malformations, only 9 of 180 cases of pulmonary stenosis or atresia were detected prenatally (Montana et al., 1996). In another series of 11,984 fetuses examined by prenatal sonography, there were 19 cases of pulmonary stenosis or atresia of varying severity, only two of which were detected prenatally (Tegnander et al., 1995). However, if the diagnosis of pulmonary stenosis or atresia is made by targeted prenatal sonography, it appears to be accurate, with all seven cases in one series confirmed on postnatal examination (Mielke et al., 1997). In another series of 12 cases of prenatally diagnosed pulmonary stenosis or atresia, the four-chamber view was abnormal in all cases, and 10 of the 12 cases were confirmed on postnatal examination (Hornberger et al., 1994). Another problem in prenatal diagnosis of pulmonary stenosis is the possibility of late appearance of the typical sonographic features, which may lead to the diagnosis being missed during a second trimester survey of fetal anatomy (Todros et al., 1988).

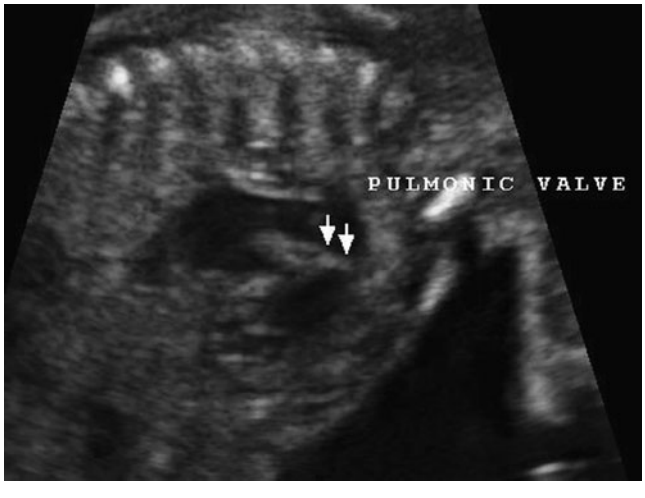

Figure 49-1 Short axis view of the right ventricular outflow tract demonstrating a thickened pulmonic valve and post stenotic dilation of the pulmonary artery in a fetus with pulmonic stenosis.

DIFFERENTIAL DIAGNOSIS

Differentiation of pulmonary stenosis from pulmonary atresia through the use of prenatal sonography is difficult, with the only reliable feature allowing differentiation being the presence of antegrade pulmonary blood flow in pulmonary stenosis. In cases of pulmonary stenosis without documented antegrade pulmonary flow, it may be impossible to differentiate prenatally between stenosis and atresia (Hornberger et al., 1994). Tetralogy of Fallot should be considered in the differential diagnosis of all cases of pulmonary stenosis or atresia. Hypertrophy of the right ventricular walls is almost always present in both isolated pulmonary stenosis and tetralogy of Fallot. The presence of a ventricular septal defect and an overriding aorta, together with the sonographic features of pulmonary stenosis should be sufficient to lead to the diagnosis of tetralogy of Fallot (see Chapter 52). Pulmonary atresia with intact ventricular septum should be considered as part of hypoplastic right ventricle (see Chapter 47).

ANTENATAL NATURAL HISTORY

Pulmonary stenosis may evolve in utero, leading to hypoplasia of the right ventricle or to worsening tricuspid regurgitation and congestive heart failure or hydrops (Romero et al., 1988). Few data are available describing the antenatal natural history of pulmonary stenosis or atresia. In a series of 222 cases of prenatally diagnosed cardiac malformations that were managed expectantly, there were 4 cases of pulmonary stenosis and 9 cases of pulmonary atresia (Sharland et al., 1990). All 4 fetuses with pulmonary stenosis survived through the neonatal period. However, 2 of the 9 fetuses with pulmonary atresia died in utero, and 2 more died during the neonatal period. In another series of 3 fetuses with pulmonary stenosis and

3 with pulmonary atresia managed expectantly, 1 fetus with pulmonary atresia died in utero (Smythe et al., 1992).

MANAGEMENT OF PREGNANCY

Following prenatal diagnosis of pulmonary stenosis or atresia, careful assessment of the remainder of the fetal anatomy is recommended to rule out associated cardiac and noncardiac malformations. Fetal echocardiography should be performed by an appropriately trained specialist to confirm the prenatal diagnosis and to exclude additional cardiac malformations such as ventricular septal defect, total anomalous pulmonary venous return, and aortic stenosis. Referral for prenatal consultation with a pediatric cardiologist and neonatologist is recommended.

Invasive testing to evaluate the fetal karyotype is generally recommended for most cases of prenatally diagnosed cardiac malformations, although the incidence of chromosomal abnormalities with isolated pulmonary stenosis or atresia is low. In 1 series of 105 infants with pulmonary stenosis there was only 1 abnormal karyotype (Ferencz et al., 1987). In another series of 7 fetuses with pulmonary stenosis or atresia, 1 fetus had a balanced translocation that was also present in the mother (Mielke et al., 1997). In a further series of 3 fetuses with pulmonary atresia and ventricular septal defect, 1 fetus had trisomy 13 (Paladini et al., 1996). Additionally, pulmonary stenosis is found in only a small percentage of cases with the DiGeorge 22q11 deletion (Bashore, 2007).

Following confirmation of diagnosis, termination of pregnancy may be considered for eligible patients. For expectantly managed patients, the fetus should be monitored with serial ultrasound examinations to confirm appropriate fetal growth and to detect early signs of hydrops. There is no reason to alter timing or mode of delivery based on a prenatal diagnosis of isolated pulmonary stenosis; therefore, in these cases the delivery plan should be for standard obstetric indications. Delivery of fetuses with critical pulmonary stenosis or pulmonary atresia should occur at a tertiary care center, with the immediate availability of a neonatologist and pediatric cardiologist.

FETAL INTERVENTION

Unlike aortic stenosis (see Chapter 50), no fetal intervention has been described following the prenatal diagnosis of pulmonary stenosis or atresia.

TREATMENT OF THE NEWBORN

Most infants with mild-to-moderate pulmonary stenosis are asymptomatic during the newborn period. Those with severe stenosis or atresia present with congestive heart failure, cyanosis, and severe hypoxia (Figure 49-2). If critical pulmonary stenosis or pulmonary atresia has been diagnosed during the antenatal period, maintenance of a patent ductus arteriosus may be achieved by starting a prostaglandin E_1 infusion and limiting oxygen supplementation to maintain reasonably normal perfusion. Immediately following delivery the neonate should be evaluated by a pediatric cardiologist. Echocardiography should be performed to confirm the diagnosis, assess the severity of stenosis, and rule out additional cardiac malformations. Medical stabilization may require the use of diuretics and digoxin.

Newborns with critical pulmonary stenosis may be treated with right-sided cardiac catheterization and balloon pulmonary valvuloplasty. By positioning a balloon across the

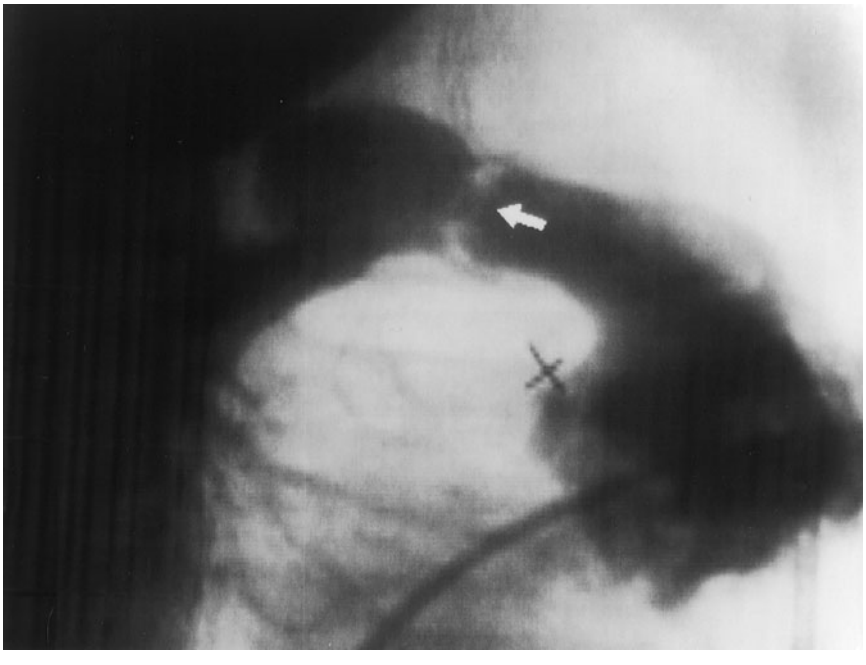

Figure 49-2 Lateral projection of a right ventricular angiogram in a symptomatic 1-day-old newborn with severe pulmonary valve stenosis. Arrow indicates the narrowed valve. (*Courtesy of Ziyad Hijazi, MD.*)

pulmonary valve and inflating to 100 lb per square inch (psi) for 10 seconds, a significant decrease in pressure gradient across the valve can be achieved (Lababidi, 1990). In a series of 23 infants with pulmonary stenosis good short- and medium-term relief of stenosis was achieved (Sullivan et al., 1985). In that series of 23 infants and children with pulmonary stenosis, repeat pulmonary-valve dilation was required on only four occasions. However, there are insufficient data to determine precisely which infants are treated best by balloon valvuloplasty and which infants will require surgical valvotomy.

Decisions on intervention for pulmonary stenosis depend on the gradient across the pulmonary valve. The latest recommendations from the American College of Cardiology/American Heart Association Task Force suggest that the vast majority of cases with a gradient of <30 mm Hg do not require any intervention (Bonow et al., 1998; Bashore, 2007).

SURGICAL TREATMENT

Surgical approaches to critical pulmonary stenosis include transarterial pulmonary valvotomy, closed transventricular pulmonary valvotomy, and open pulmonary valvotomy using cardiopulmonary bypass. The need for surgical treatment of pulmonary stenosis depends on the pressure gradient across the pulmonary valve. With gradients of less than 25 mm Hg, 5% of children require surgery; 20% of those with gradients of 25 to 49 mm Hg and 76% of those with gradients of 50 to 79 mm Hg require surgical treatment (Hayes et al., 1993). Catheter-based approaches using a percutaneous balloon valvuloplasty have also evolved such that this is now considered by many to be a viable alternative to open surgical valvotomy (Bashore, 2007).

The most commonly performed surgical procedure is a closed transventricular pulmonary valvotomy, with or without a modified Blalock–Taussig shunt from the subclavian to the pulmonary artery (Coles and Trusler, 1990). Following thoracotomy or sternotomy, a stab incision is made in the right ventricular wall and a valvulotome, or Hegar dilator, is inserted to open the pulmonary valve. In one series of 16 infants younger than 3 months of age who had critical pulmonary stenosis, 14 survived following closed transventricular valvotomy, and all survivors demonstrated clinical improvement (Srinivasan et al., 1982).

Presence of a dysplastic pulmonary valve, or significant pulmonary insufficiency, usually requires complete pulmonary valve replacement. Replacement is typically with a bioprosthetic valve or pulmonary homograft, rather than a mechanical valve (Bashore, 2007).

LONG-TERM OUTCOME

Late results after treatment of pulmonary stenosis seem favorable. Estimates of 25-year actuarial survival range from 90% to 95% (Morris and Menashe, 1991; Hayes et al., 1993). In a series of 14 infants who survived closed transventricular pulmonary valvotomy for critical pulmonary stenosis, 2 required repeat surgery with 1 needing open valvotomy for restenosis and 1 needing closure of a secundum atrial septal defect (Srinivasan et al., 1982). It seems that in the majority of patients, adequate growth of the right ventricle and pulmonary annulus occurs following surgical repair. If the infundibular portion of the right ventricular outflow tract is hypoplastic on initial evaluation, the requirement for late reoperation to repair residual stenosis increases significantly and may be as high as 50% at 10 years postoperatively (Coles and Trusler, 1990).

Comparison of balloon valvuloplasty versus open surgical valvotomy for pulmonary stenosis suggests similar long-term outcome, with perhaps higher rates of pulmonary insufficiency among the surgical group (Peterson et al., 2003; Bashore, 2007). Pulmonary valve replacement is now also possible as a percutaneous catheter-based technique, raising the possibility of hybrid approaches in the treatment of congenital heart disease in which interventional cardiologists and cardiothoracic surgeons jointly repair a range of defects (Holzer and Hijazi, 2004).

GENETICS AND RECURRENCE RISK

Pulmonary stenosis may occur as part of Williams syndrome, which may also involve supravalvular aortic stenosis, developmental delay, and unusual facies. Williams syndrome is due to the deletion of one copy of the elastin gene on chromosome 7. Pulmonary stenosis may also occur as part of Noonan syndrome. Noonan syndrome is autosomal dominant and appears to be associated with mutations in the *PTPN11* gene in 45% to 60% of cases (Tartaglia et al., 2002). At least one case report describing familial clustering of cases of pulmonary stenosis has also been reported (Manetti et al., 1990). Without a history suggestive of a mendelian or chromosomal disorder, the recurrence risk for a couple with one previously affected child having another child with pulmonary stenosis is 2% but is increased to 6% if two previous children have been affected (Nora and Nora, 1988). The chance of having an affected infant if the mother has pulmonary stenosis is 4% to 6.5%, but if the father is affected, it is only 2% (Nora and Nora, 1988).

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50 CHAPTER Aortic Stenosis

Key Points

- Prenatal diagnosis of aortic stenosis is unreliable.
- Aortic stenosis should be suspected whenever there is asymmetry of the cardiac ventricles including either left ventricular enlargement or left ventricular hypoplasia.
- Evaluation with serial fetal echocardiography should include consideration of coarctation of the aorta and the possibility of progression to hypoplastic left heart syndrome.
- In utero balloon dilation of the aortic valve has been described but is of questionable value.
- While pediatric balloon valvuloplasty is very successful, the high rate of reintervention required suggests that definitive surgical repair leads to best long-term outcome.

CONDITION

Aortic stenosis is the congenital obstruction of the left ventricular outflow tract of the heart. Stenosis can occur at, above, or below the aortic valve (Becker and Anderson, 1981). Subvalvular aortic stenosis can be either fixed or dynamic. Fixed aortic stenosis is due to the presence of a discrete membranous diaphragm or a diffuse fibromuscular ring below the valve. Dynamic subvalvular aortic stenosis demonstrates a constantly changing pressure gradient across the valve and is most commonly due to muscular thickening of the septum. This form of subvalvular aortic stenosis is often called "asymmetric septal hypertrophy" (ASH), "idiopathic hypertrophic subaortic stenosis" (IHSS), or "hypertrophic obstructive cardiomyopathy" (HOCM). A transient form of dynamic subvalvular aortic stenosis has also been described, secondary to fetal hyperglycemia (Gutgesell et al., 1976).

Valvular aortic stenosis occurs secondary to abnormalities of the cusps of the aortic valve. Congenital unicuspid or bicuspid aortic valves may be stenotic at birth or they may become stenotic later in adult life. Other causes of valvular aortic stenosis include dysplastic or thickened cusps and fusion of the commissures that separate the cusps.

Supravalvular aortic stenosis can occur secondary to a localized narrowing of the ascending aorta, the presence of a membrane just superior to the origin of the coronary arteries, or a diffuse narrowing of the aortic arch and great arteries. Because the obstruction occurs above the origin of the coronary arteries at the sinuses of Valsalva, the coronary arteries are also exposed to the elevated left ventricular pressures.

With all types of congenital aortic stenosis, if the stenosis becomes severe, secondary endocardial fibroelastosis can occur, leading to thickening of the endocardium and subsequent mitral insufficiency or cardiomyopathy. Aortic stenosis diagnosed early in gestation may evolve over time into hypoplastic left heart syndrome (Sharland et al., 1991).

INCIDENCE

The overall incidence of congenital heart disease is 4 in 1000 to 10 in 1000 livebirths (Hoffman, 1990). Aortic stenosis accounts for 3% to 6% of all congenital cardiovascular malformations, although it makes up 1% to 3% of all cardiac lesions in newborns presenting with significant cardiac defects (Rowe et al., 1981; Kitchener et al., 1993). It occurs up to four times more commonly in males than in females, although this sex predominance may be less marked in newborn populations. Overall, aortic stenosis has an incidence of 3.5 in 10,000 livebirths, while congenital bicuspid aortic valve may be as common as 1 in 100 livebirths.

SONOGRAPHIC FINDINGS

Prenatal diagnosis of aortic stenosis is unreliable. Because supravalvular and subvalvular forms of aortic stenosis are usually not clinically apparent during the newborn period, prenatal diagnosis of these conditions is rarely successful. Prenatal sonographic features suspicious for aortic stenosis include enlargement or hypoplasia of the left ventricle. However, it is important to realize that left ventricular size can also be normal despite the presence of significant aortic stenosis. The right ventricle is also usually dilated with critical aortic stenosis, as blood flow is redistributed to the right ventricle and through the ductus arteriosus. In addition, critical aortic stenosis is usually associated with poststenotic aortic root dilation.

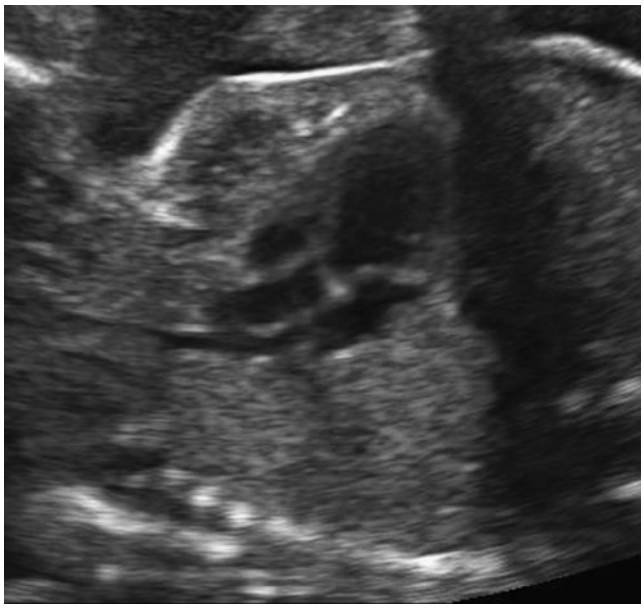

Figure 50-1 Long-axis view of the left ventricular outflow tract demonstrating a thickened and echogenic aortic valve consistent with aortic stenosis.

Incomplete opening of the aortic valve and increased aortic turbulence on Doppler echocardiography are both sonographic signs consistent with aortic stenosis during the newborn period (Figures 50-1 and 50-2), but prenatal

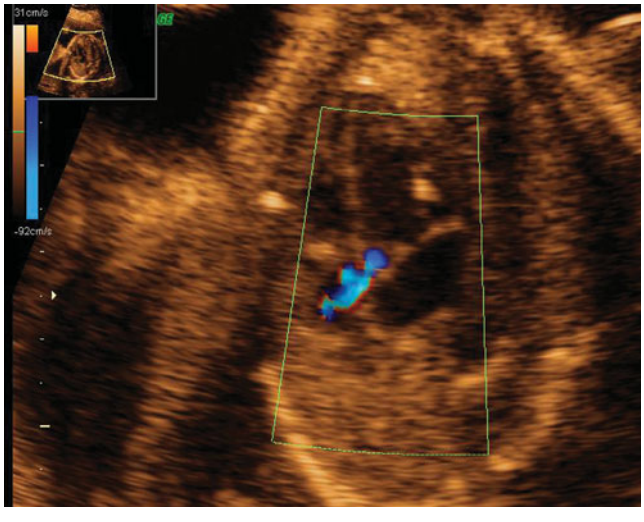

Figure 50-2 Color Doppler demonstrating high-velocity flow through the narrow aortic valve in a fetus with aortic stenosis.

visualization of these signs is extremely difficult because of the small size of the fetal aortic root. Prenatal diagnosis of a significant pressure drop (more than 50 mm Hg) across the valve is also suggestive of aortic stenosis (Jouk and Rambaud, 1991). Prenatal visualization of abnormal thickening of the interventricular septum in aortic stenosis has been documented (Stewart et al., 1986). In severe cases of congenital aortic stenosis, antenatal Doppler studies may demonstrate significant mitral regurgitation. Aortic stenosis may also be the underlying cause of some cases of hydrops fetalis or intrauterine growth restriction, and therefore aortic stenosis should be considered during the sonographic assessment of these conditions.

DIFFERENTIAL DIAGNOSIS

The main alternatives that must be considered in the prenatal diagnosis of aortic stenosis include primary cardiomyopathy (see Chapter 57) and hypoplastic left heart (see Chapter 48) (Huhta et al., 1987). In addition, coarctation of the aorta must be considered, but the prenatal diagnosis of this condition is also very limited (see Chapter 51). Unlike aortic stenosis, primary cardiomyopathy is usually associated with a normal aortic valve and no evidence of poststenotic dilation. Such primary cardiomyopathies may be secondary to endocardial fibroelastosis, viral or bacterial myocarditis, or some glycogen storage diseases.

Hypoplastic left heart syndrome is usually associated with both mitral- and aortic-valve atresia. In addition, the hypoplastic left ventricle may be globular in shape, rather than ellipsoid, which can be demonstrated on a four-chamber cardiac view by the left ventricle failing to reach the apex of the heart. In some cases, differentiation of aortic stenosis from hypoplastic left heart syndrome can be difficult because the enlarged right ventricle seen with aortic stenosis may make the left ventricle appear small or even hypoplastic. Other features that aid in differentiating aortic stenosis from hypoplastic left heart syndrome include failure of growth in left ventricular, aortic, or mitral dimensions on serial examinations, as well as severe restriction of interatrial shunting in cases of hypoplastic left heart syndrome (McCaffrey and Sherman, 1997). Of note, aortic stenosis and hypoplastic left heart syndrome are now considered part of a clinical spectrum with many cases of early fetal aortic stenosis evolving as gestation advances into the classic hypoplastic left heart syndrome. Therefore, attempts to differentiate between these two clinical conditions in utero may be purely academic (Hornberger et al., 1995).

ANTENATAL NATURAL HISTORY

The antenatal natural history of congenital aortic stenosis can be quite varied, with almost all cases of subvalvular and supravalvular aortic stenosis resulting in no fetal compromise, while critical valvular aortic stenosis can lead to intrauterine growth restriction, hydrops fetalis, and severe hemodynamic compromise during the early newborn period. The presence of hydrops with a structural cardiac malformation is usually considered an ominous finding.

Left ventricular pressure overload may lead to ventricular enlargement, relative coronary hypoperfusion, subendocardial ischemia, and consequently, significant impairment of cardiac function. This can result in severe metabolic acidosis, leading to death in a significant number of cases, either before or soon after birth (Sharland et al., 1991). Sustained elevated left ventricular pressure secondary to outflow tract obstruction can also lead to the intrauterine development of endocardial fibroelastosis and subsequent cardiomyopathy, which also increases the mortality rate for congenital aortic stenosis. In cases of aortic stenosis diagnosed prenatally, left ventricular volume and aortic root dimensions tend to fall off from the normal percentiles as gestation progresses, and this information may be useful in predicting the appropriate form of repair during the newborn period (Simpson and Sharland, 1997).

In one series of 30 cases of prenatally diagnosed left ventricular dysfunction, an initial appearance of aortic stenosis evolved over time into complete hypoplastic left heart syndrome in five cases (Sharland et al., 1991). There may be a spectrum of diseases in the fetus, involving primary left ventricular endocardial fibroelastosis, critical aortic stenosis, and hypoplastic left heart syndrome. Therefore, if screening takes place early enough, an initial clinical presentation of aortic stenosis may evolve over time into hypoplastic left heart syndrome (Sharland et al., 1991). For this reason, it is important to evaluate the appearance of the fetal heart whenever obstetric ultrasound examinations are performed in gestation.

MANAGEMENT OF PREGNANCY

Following the prenatal diagnosis of aortic stenosis, careful assessment of the remainder of the fetal anatomy is mandatory to rule out associated cardiac and noncardiac abnormalities. A referral for prenatal consultation with a pediatric cardiologist and neonatologist is recommended. Fetal echocardiography should be performed by an appropriately trained specialist if it has not already been done, as associated defects that may also be present include coarctation of the aorta, ventricular septal defect, and endocardial fibroelastosis. Karyotyping is also recommended because of the association between aortic stenosis and chromosomal abnormalities such as Turner syndrome. The fetus should be monitored with serial ultrasound examinations to detect early signs of congestive heart failure or hydrops fetalis. If hydrops develops, the prognosis is usually poor, although there are insufficient data at present to recommend changes in obstetric management. While it may be reasonable to offer early delivery in the setting of aortic stenosis with hydrops, it is as yet unclear if such an intervention will

change the already poor fetal prognosis. As described in the section on fetal intervention, there has been growing interest in balloon dilation of the aortic valve in utero in an attempt to improve the in utero natural history of this condition.

In the absence of hydrops, continued sonographic surveillance is recommended, followed by delivery for standard obstetric reasons in a tertiary care facility, with the immediate availability of a pediatric cardiologist and cardiothoracic surgeon. Although some pediatric specialists have recommended elective cesarean delivery in the presence of critical aortic stenosis (Robertson et al., 1989), there are insufficient data at present to support routine cesarean delivery in this setting.

FETAL INTERVENTION

Because of the high neonatal mortality rate associated with critical aortic stenosis, invasive attempts have been made in utero to correct the underlying valve abnormality. In one case report, a 16-gauge needle was placed transabdominally at 27 weeks of gestation and then inserted through the apex of the fetal heart, followed by a balloon catheter, which was threaded through the left ventricle into the ascending aorta (Lopes et al., 1996). Inflation of the balloon reportedly improved flow through the aortic valve, resulting in sonographic resolution of hydrops. The fetus was delivered by cesarean section but died from recurrent ventricular fibrillation soon after birth. In another case report, in utero balloon dilation for aortic stenosis was technically successful in one of two fetuses, but did not affect fetal outcome (Maxwell et al., 1991). One survivor has been described following in utero balloon dilation of a stenotic aortic valve (Allan et al., 1995).

The largest series of fetal aortic balloon valvuloplasties described to date has been from the Children's Hospital of Boston. In 20 fetuses with severe aortic stenosis and left ventricular dysfunction ranging from 21 to 29 weeks' gestation, technically successful aortic valve dilation was achieved in 14 cases (70%) (Tworetzky et al., 2004). Balloon insufflation with an oversized balloon seemed to provide more reliable degree of aortic regurgitation, with the goal being to improve left ventricular blood flow, thereby allowing the left ventricle to grow (Marshall et al., 2005). In their most recently updated series of 26 attempted valvuloplasties, 4 of 21 (19%) liveborn infants maintained a two-ventricle circulation postnatally (Marshall et al., 2005). It is, of course, uncertain whether these four cases would have had a two-ventricle repair postnatally if they were managed expectantly. Of note, in almost 50% of their cases maternal laparotomy was required to optimize fetal positioning following failed percutaneous access to the apex of the fetal heart.

The criteria to select appropriate fetal candidates for in utero intervention are not yet clear, although the presence of endocardial fibroelastosis may contraindicate intervention. The Boston group has suggested that cases of fetal aortic stenosis in which significant left ventricular dysfunction is present in the second trimester and in which retrograde flow is noted in the transverse aortic arch may be the best candidates for consideration for intervention as such fetuses almost invariably progress to hypoplastic left heart syndrome (Makikallio et al., 2006). The ethical challenges with this approach are also significant as potential morbidity to the mother needs to be balanced against an experimental procedure in which perhaps only 20% of fetuses gain significant benefit. Fetal intervention by means of in utero balloon dilation should therefore be considered experimental at this time, and should be limited to situations in which nondirective counseling is provided by a number of independent specialists in this area.

In addition to balloon dilation, the only other form of in utero intervention described for aortic stenosis is digoxin therapy for the mother, which was reported in two cases of hydrops fetalis secondary to severe aortic stenosis, followed by postnatal balloon valvuloplasty (Bitar et al., 1997).

TREATMENT OF THE NEWBORN

The initial treatment of newborns with congenital aortic stenosis involves diagnosing the severity of the condition followed by medical stabilization. Postnatal echocardiography should be performed promptly to confirm the diagnosis, establish its severity, and rule out other associated cardiac malformations. Echocardiography with Doppler studies should be sufficient to obtain this information without having to perform cardiac catheterization (Figure 50-3) (Huhta et al., 1987).

Medical management of aortic stenosis centers around stabilizing the infant while awaiting surgical intervention. Supplemental oxygen therapy, with or without mechanical

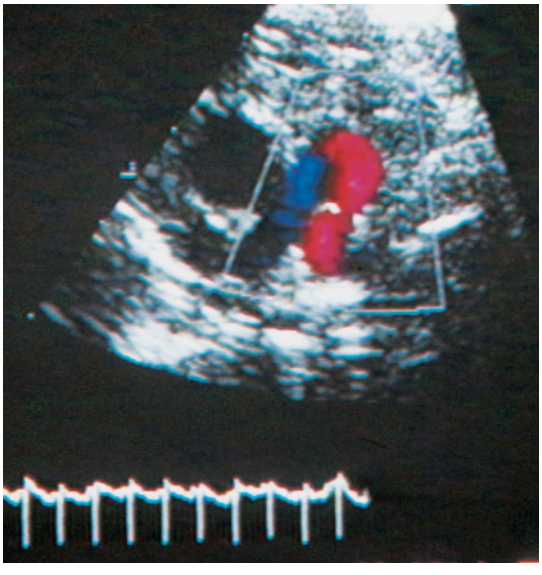

Figure 50-3 Color Doppler studies in a newborn with aortic stenosis, pulmonic atresia, and intact ventricular septum.

ventilation, correction of metabolic acidosis, maintenance of normal hematocrit, inotropic support with digoxin, and cautious use of diuretics to alleviate pulmonary edema are all recommended (Kiel, 1990). Prostaglandin E_1 infusion is recommended to maintain patency of the ductus arteriosus and improve tissue perfusion (Leoni et al., 1984). Balloon valvuloplasty via the umbilical artery may be useful as either a palliative procedure until definitive surgical repair takes place or as the primary repair procedure (Kiel, 1990).

Definitive therapeutic options for the repair of critical aortic stenosis include biventricular repair, univentricular repair, or cardiac transplantation. Biventricular repair involves aortic valvulotomy (either open surgical or percutaneous balloon approaches). Univentricular repair is by means of a Norwood-type surgical procedure (anastomosis of the main pulmonary artery to the aorta followed later by creation of an atriopulmonary connection). Often within hours or days of birth the physician must decide which of these therapeutic options to follow. The presence of multiple small left heart structures may suggest improved survival following a Norwood-type repair rather than a valvulotomy (Rhodes et al., 1991). Aortic valvulotomy may yield better results when the aortic root measures 5 mm or greater (Turley et al., 1990).

SURGICAL TREATMENT

Aortic valvulotomy is indicated when congestive heart failure is present or when the valve area is less than 0.5 cm^2 per square meter. Valvulotomy can be successfully performed via a closed, percutaneous approach, using a no. 5 Cook balloon catheter, which avoids the need for open surgery and cardiopulmonary bypass (Lababidi et al., 1984). In one series of 87 cases, balloon dilation of aortic stenosis is highly successful with a 98% technical success rate of reducing the pressure gradient across the valve being described (Pedra et al., 2004). However, repeat intervention may be required in more than 40% of these cases, with many requiring reintervention within 6 months of the original balloon dilation.

Alternatively, an open surgical approach can be performed with the aid of hypothermia and cardiopulmonary bypass. This approach involves making of commissural incisions in the stenotic valve, relieving stenosis but avoiding aortic incompetence. The disadvantage of this surgical approach is the need for cardiopulmonary bypass, which can significantly add to the morbidity for an already critically ill infant (Beeman and Hammon, 1990). An alternative surgical approach involves closed valvulotomy through a median sternotomy with insertion of a valvulotome through a left ventricular stab wound. The Norwood-type surgical repair is described in more detail in the chapter on hypoplastic left ventricle (see Chapter 48). More detailed description of surgical techniques for repair of congenital aortic stenosis is beyond the scope of this textbook, but is readily available in the literature (Gaynor and Elliott, 1993).

Operative mortality for aortic stenosis typically occurs within 48 hours of surgery. The operative mortality rate for corrective surgery has been given as 1.9% for valuvar stenosis, 6% for fixed subvalvular stenosis, and 5.5% for dynamic subvalvular stenosis (Jones et al., 1982). An overall operative mortality of 9% to 18% has been quoted for valvulotomy in cases of severe neonatal aortic stenosis (Messina et al., 1984; Gildein et al., 1996).

LONG-TERM OUTCOME

Without treatment, almost all clinically significant cases of congenital aortic stenosis result in death. Even when aortic stenosis is mild at presentation, it may become progressive, eventually requiring surgery (Kitchener et al., 1993). Later complications after repair include aortic incompetence or regurgitation and bacterial endocarditis. The long-term mortality rate from aortic stenosis is 23% during the first year of life and falls to 1.2% during the first two decades, 3% in the third, 3.5% in the fourth, 6% in the fifth, and 8.5% in the sixth decade of life (Campbell, 1968). In a more recent series, survival was 90% at age 10 years and 73% at age 25 years (Elkins et al., 1997). Twenty-five-year survival for aortic stenosis is 76% (Morris and Menashe, 1991).

Long-term outcomes described from a series of 87 balloon valvuloplasties demonstrated freedom from reintervention in 86% at 1 year, 67% at 5 years, and 46% at 12 years (Pedra et al., 2004). Approximately 50% to 70% of neonates who had surgical correction of aortic stenosis had satisfactory results when evaluated 5 to 14 years postoperatively (Jones et al., 1982). Almost one-third of patients will require repeat aortic valve repair within 15 to 20 years of the original operation (Beeman and Hammon, 1990; Gaynor et al., 1995). In another series, there was a 28% reoperation rate after a median duration of 8.7 years (Kitchener et al., 1993). A further 5% of patients may require a third operation later in childhood for aortic valve stenosis (Wheller et al., 1988). Sudden deaths comprise more than one-third of all late cardiac deaths for aortic stenosis (Morris and Menashe, 1991). One of the longest follow-up series of aggressive management of congenital aortic stenosis followed 88 cases and reported a 76% 12-year reoperation-free survival (Erentug et al., 2005).

GENETICS AND RECURRENCE RISK

Between 5% and 8% of all cases of congenital heart disease involve a chromosomal abnormality, usually trisomy 21, and therefore the recurrence risk is that of the chromosomal defect itself (Hoffman, 1990). Only a minority of cases of congenital heart disease (approximately 3%) are inherited in a classical Mendelian pattern. The dynamic form of subvalvular aortic stenosis (IHSS or HOCM) is most often inherited in an autosomal dominant pattern. Subvalvular aortic stenosis

may also occur as part of Turner and Noonan syndromes. Noonan syndrome is inherited as an autosomal dominant gene, and Turner syndrome is most commonly sporadic. Isolated supravalvular aortic stenosis may be inherited in an autosomal dominant pattern. Supravalvular aortic stenosis may also occur as part of Williams syndrome, together with developmental delay and an unusual facies. Williams syndrome is due to the deletion of one copy of the elastin gene and may be diagnosed using a fluorescence in situ hybridization probe that maps to the elastin gene on chromosome 7.

Without a history suggestive of a Mendelian or chromosomal disorder, the recurrence risk for a couple with one previously affected child with aortic stenosis is 2%. If there have been two affected children, the risk is 6%. Interestingly, the chance of having an affected infant if the mother has aortic stenosis is 13% to 18%, but if the father is affected, it is only 3% (Nora and Nora, 1988).

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51 CHAPTER Coarctation of the Aorta

Key Points

- Coarctation of the aorta refers to a congenital narrowing of the aorta and is relatively common, accounting for 7% of cases of congenital heart disease.
- Prenatal diagnosis is generally possible following the discovery of asymmetry of the ventricles and outflow tracts.
- There is a strong association with chromosomal abnormalities, particularly Turner syndrome, as well as other cardiac and extracardiac malformations.
- Prenatal diagnosis is critical, as it leads to significantly improved neonatal morbidity and mortality.
- Following prenatal diagnosis, the infant should be delivered under controlled circumstances with prompt pediatric cardiology backup and the ability to start a prostaglandin infusion.
- Definitive therapy in infancy involves surgical correction by means of aortic resection and end-to-end anastomosis, although there is a growing role for catheter-based therapy with a combination of balloon dilation and stent placement.

CONDITION

Coarctation of the aorta refers to narrowing of a segment of the aorta along the aortic arch, usually near the origin of the ductus arteriosus (Figure 51-1A and 51-1B). The narrowed segment of the aorta can be of any length and can be preductal, juxtaductal, or postductal in location. The area of narrowing can be caused by a discrete soft tissue shelf, or can be due to hypoplasia of a segment of the arch, leading to complete aortic arch interruption. Previously, coarctation was divided into infantile and adult forms. The infantile form classically occurred in a preductal location, was associated with other cardiac malformations, and was more likely to be associated with neonatal congestive heart failure. The adult form classically occurred in juxtaductal or postductal locations and was associated with a better prognosis. This distinction now seems to be imprecise and is of little relevance, with both forms of coarctation presenting at various ages.

The pathogenesis of coarctation is unclear. It may be due to a developmental defect of the aortic arch, possibly because of failure of connection of the fourth and sixth branchial arches to the descending aorta. Another possible mechanism is the development of abnormal blood flow patterns in utero, leading to decreased aortic-arch flow and increased flow in the pulmonary artery and ductus arteriosus. The consequence of this imbalance in flow may be the development of relative hypoplasia of the aortic arch. A third possible mechanism for the pathogenesis of coarctation is the presence of aberrant ductal tissue in the arch, leading to narrowing of the aortic arch after closure of the ductus (Whitley and Perry, 1990).

Associated cardiac malformations are present in up to 90% of cases of coarctation, including bicuspid aortic valve, aortic stenosis (see Chapter 50) or insufficiency, septal defects (see Chapters 43 and 44), transposition of the great vessels (see Chapter 55), double outlet right ventricle (see Chapter 53), postnatal patent ductus arteriosus, and truncus arteriosus (see Chapter 54) (Romero et al., 1988). In one series of 68 cases of prenatally diagnosed coarctation of the aorta, 43% had a ventricular septal defect, and 15% had a bicuspid aortic valve (Paladini et al., 2004). Additional noncardiac malformations are present in 40% of cases (Paladini et al., 2004). A strong association exists between Turner syndrome and coarctation, with 10% of Turner syndrome patients being affected (see Chapter 134). Overall, 35% of cases of aortic coarctation will have an abnormal karyotype (Paladini et al., 2004).

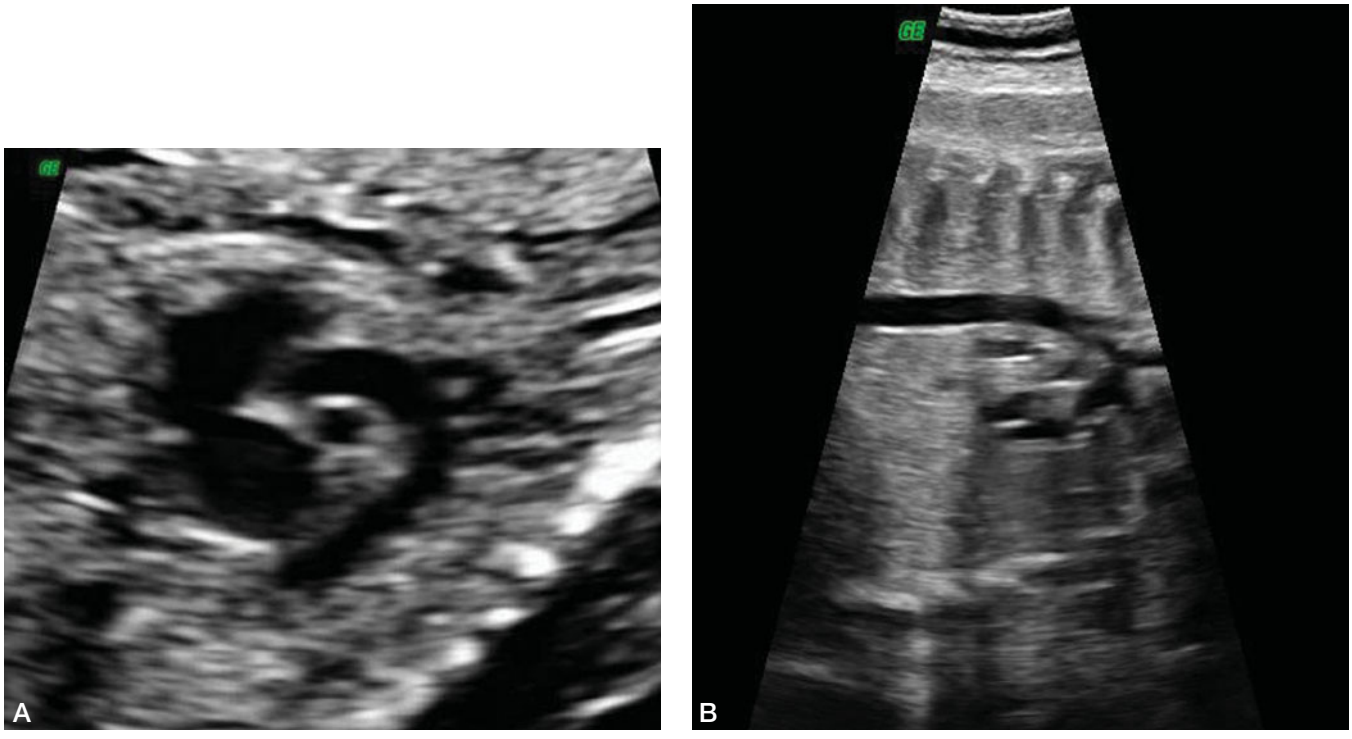

Figure 51-1 **A.** Parasagittal image of a normal aortic arch; **B.** Parasagittal view of the aortic arch demonstrating narrowing in the distal portion of the transverse arch consistent with coarctation of the aorta.

INCIDENCE

Coarctation of the aorta is present in approximately 2.5 per 1000, or 4 per 10,000, livebirths (Hoffman and Kaplan, 2002). While there is a significant male preponderance for coarctation in the entire population, there appears to be an equal incidence in both genders at birth. Coarctation accounts for up to 8% of all cases of congenital heart disease.

SONOGRAPHIC FINDINGS

Prenatal diagnosis of coarctation of the aorta using ultrasound examination is controversial. Some believe that it cannot be reliably diagnosed prenatally because in most cases the hemodynamic complications depend on closure of the ductus. Although it is true that coarctation of the aorta can be entirely a postnatal event, several series of prenatally diagnosed cases of coarctation have been documented (Allan et al., 1988; Sharland et al., 1994). However, in a population-based study of prenatal diagnosis of congenital heart disease from Australia, correct identification of coarctation prenatally was possible in only 26% of cases (Chew et al., 2007). This study ranked coarctation as the second most difficult form of congenital heart disease to accurately diagnose prenatally, after simple transposition of the great arteries (see Chapter 55).

An increased nuchal translucency measurement may be an early marker for aortic coarctation (Moselhi and Thilaganathan, 1996). Pathologic examination of fetuses with increased nuchal translucency thickness has demonstrated a high prevalence of cardiac defects and abnormalities of the great arteries. This has been shown in both trisomic and chromosomally normal fetuses (Hyett et al., 1995, 1996). In fetuses with trisomy 21, the aortic valve and ascending aorta are wider than in normal fetuses, while the aortic isthmus is narrower. In chromosomally normal fetuses, the aorta is narrowed at both the level of the isthmus and immediately above the aortic valve.

Later in gestation, prenatal visualization of a shelf or discrete area of narrowing in the aortic arch is extremely difficult. However, if there is complete hypoplasia or arch interruption, Doppler evaluation may demonstrate a disturbance of flow (Figure 51-2). Prestenotic or poststenotic dilation of the aortic arch may also be present. Growth curves for the transverse aortic arch at various gestational ages have been published, with the suggestion that cases of coarctation are associated with measurements at or below the third percentile (Hornberger et al., 1992). However, no data are available on the reliability or sensitivity of these techniques for the prenatal diagnosis of coarctation.

Relative enlargement of the right ventricle and pulmonary artery, when compared with the left ventricle and aorta, may be more easily detectable signs consistent with coarctation. The combination of ventricular disproportion and great vessel disproportion probably represents a more sensitive marker for coarctation (Rosenthal, 2005). In one series of prenatally diagnosed dilation of the right ventricle

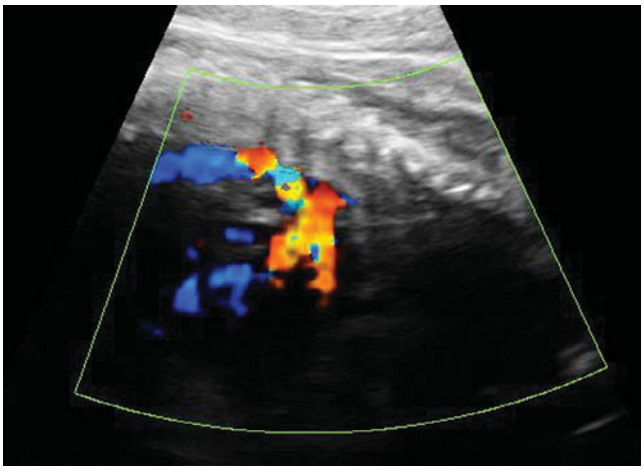

Figure 51-2 Color Doppler image of the same fetus showing turbulent flow in distal portion of the transverse aortic arch.

and pulmonary artery, 18 of 24 fetuses had coarctation (Allan et al., 1988). Doppler visualization of reduced aortic blood flow was present in most cases of coarctation, but was also present in some normal fetuses. Discrepancy in the size of the ventricles, caused by relative hypoplasia of the left heart structures, has a poor positive predictive value for coarctation, with the false-positive rate being higher after 34 weeks of gestation (Brown et al., 1997). Overall, 62% of cases of coarctation may have ventricular discrepancy recognizable on fetal echocardiograms. The higher false-positive rate at later gestational ages may be due to the normal relative increase in right heart size as gestation advances (Sharland and Allan, 1992). At present, no prenatal sonographic signs—taken either individually or in combination—can reliably distinguish true cases of coarctation from false-positive results (Sharland et al., 1994).

DIFFERENTIAL DIAGNOSIS

The main differential diagnosis for isolated coarctation of the aorta diagnosed prenatally is pulmonic stenosis, which may also present with a dilated right ventricle. However, in cases of pulmonic stenosis the pulmonary artery is small or hypoplastic as compared with the typical dilation of the pulmonary arterial dilation seen with coarctation. Other cardiac malformations commonly coexist with coarctation, so their presence cannot exclude coarctation.

ANTENATAL NATURAL HISTORY

The antenatal course of fetuses with coarctation of the aorta is usually benign, since the presence of an open ductus arteriosus carries blood supply from the heart to the aorta. However, in cases of severe coarctation or arch hypoplasia, progressive dilation of the right ventricle may result in right ventricular hypertrophy. The antenatal course may also be influenced by the presence of additional cardiac and noncardiac malformations, which frequently coexist with coarctation. As pregnancy advances, it is possible that isolated coarctation initially caused by a discrete shelf in early gestation may progress into complete arch hypoplasia (Allan et al., 1984). The prognosis for an individual fetus may therefore change as pregnancy progresses and the arch abnormality evolves. Congestive heart failure may occur early during the newborn period following closure of the ductus, especially in infants with an intact ventricular septum.

In one series of 68 cases of prenatally diagnosed coarctation of the aorta, the only independent predictor of poor outcome was the coexistence of fetal growth restriction (Paladini et al., 2004). It appears as if prenatal diagnosis of aortic coarctation confers a significant advantage on the infant. In one series of 10 cases of prenatally diagnosed cases of aortic coarctation, which were compared with 22 cases in which the diagnosis was not made until postnatal life, there was a significant improvement in neonatal mortality and morbidity amongst prenatally diagnosed cases (Franklin et al., 2002).

MANAGEMENT OF PREGNANCY

If the diagnosis of coarctation is suspected on obstetric ultrasound evaluation, fetal echocardiography should be performed by an appropriately trained specialist to confirm the diagnosis and to evaluate for the presence of additional cardiac malformations. In addition, careful sonographic evaluation should be performed for other noncardiac abnormalities, such as diaphragmatic hernia or sonographic signs of Turner or DiGeorge syndrome. Because of the significant association (up to 35%) with chromosomal abnormalities, karyotype evaluation should be offered, including fluorescence in situ hybridization analysis for chromosome 22 deletions (Paladini et al., 2004). Pediatric cardiology and neonatology consultations should also be arranged to facilitate neonatal treatment.

Serial ultrasound evaluation during pregnancy is recommended because the appearance and severity of the coarctation may change as pregnancy advances. Progressive obstruction will be evidenced by increasing right ventricular dilation with hypertrophy and possibly congestive cardiac failure. Additionally, the development of fetal growth restriction may be an independent marker for poor prognosis (Paladini et al., 2004). It is rare for coarctation to require early delivery, as the presence of an open ductus during intrauterine life usually delays significant hemodynamic disturbances until after birth. Because there is no absolute indication for cesarean delivery with coarctation, the mode of delivery should be dictated by standard obstetric circumstances. Delivery should occur at a tertiary care center, with the immediate availability of a pediatric cardiologist.

FETAL INTERVENTION

No fetal intervention has been described for isolated coarctation of the aorta.

TREATMENT OF NEWBORN

Immediate neonatal resuscitation is essential in the management of significant aortic coarctation. This is evidenced by the significantly higher morbidity and mortality amongst cases of aortic coarctation in which the correct diagnosis is not made prenatally (Franklin et al., 2002). Medical stability depends on the presence of continued patency of the ductus arteriosus with a right-to-left shunt supporting systemic perfusion. Because hyperventilation and supplemental oxygen therapy reduce pulmonary vascular resistance, these interventions may reduce the right-to-left shunt, thereby reducing systemic perfusion. Supplemental oxygen therapy should therefore be avoided unless absolutely necessary and, when used, should be limited to 40% to 60% maximum fractional inspired oxygen (Fio_2).

Prostaglandin E_1 infusion should be started to maintain patency of the ductus in severe cases of aortic coarctation. This will improve perfusion of the lower body, increase urinary output, and improve metabolic acidosis (Whitley and Perry, 1990). Prostaglandin E_1 infusion has been shown to improve surgical survival in left-sided obstructive congenital cardiac disease (Leoni et al., 1984). Diuresis and inotropic support with dopamine or dobutamine may be necessary if severe congestive cardiac failure develops.

Additional treatment of the newborn includes complete echocardiographic evaluation to confirm the diagnosis, to evaluate the severity of the coarctation, and to exclude any additional coexisting cardiac malformations. The involvement of a pediatric cardiologist and pediatric cardiac surgeon is essential.

The definitive neonatal treatment of coarctation is primary surgical repair. Balloon angioplasty has been advocated as an alternative to surgical repair, but it is associated with increased risks of restenosis at the site of coarctation. In one randomized comparison of balloon dilation with surgical repair of coarctation, subsequent aortic aneurysm occurred in none of those undergoing surgery, compared with 20% of those having balloon dilation (Shaddy et al., 1993). Long-term follow-up of these cases also revealed that significantly more of the patients who underwent surgery were symptom-free compared to those having balloon dilation (Cowley et al., 2005). In addition, since most cases of coarctation presenting during the newborn period are complex, or demonstrate aortic hypoplasia, balloon angioplasty is often not possible (Whitley and Perry, 1990). Isolated coarctation that is not symptomatic may be managed expectantly, with close surveillance of Doppler gradients across the area of narrowing or examination of the femoral pulse.

More recently, the development of endovascular stents appears to have improved the success of catheter-based interventions for coarctation. Balloon dilation of the area of coarctation need not be as extensive if a stent can be subsequently placed. This has resulted in balloon dilation and stent placement taking a more prominent first-line role for aortic coarctation in some centers, especially after the first year of life (Rosenthal, 2005; Wong et al., 2008).

SURGICAL TREATMENT

Surgical repair of symptomatic isolated coarctation of the aorta is generally delayed until at least 6 months of age, unless there is complete interruption of the aortic arch, which requires urgent correction (Beeman and Hammon, 1990). The presence of poor peripheral perfusion or congestive heart failure refractory to initial medical therapy may prompt earlier primary surgical repair. The timing of surgery also depends on the diagnosis of additional cardiac malformations, with the presence of a coexisting ventricular septal defect often considered an indication for immediate operation.

The most common surgical procedure used to repair isolated coarctation of the aorta is resection with an end-to-end anastomosis (Rosenthal, 2005; Abbruzzese and Aidala, 2007). Alternative surgical approaches include subclavian flap aortoplasty, and patching with a Dacron or pericardial patch (Beeman and Hammon, 1990; Rosenthal, 2005). These approaches are generally performed through a left thoracotomy. The main complications associated with patch repairs and subclavian flap aortoplasty are aneurysm formations at the flap site and weakening of the left arm with subclavian steal symptoms, respectively. For cases of aortic arch interruption, direct end-to-end anastomosis of the two aortic ends is performed using an endogenous vessel or graft.

Operative mortality for primary repair of isolated coarctation is less than 5% and probably approaches zero (Beeman and Hammon, 1990; Rosenthal, 2005). Mortality increases with the presence of additional complex cardiac malformations and the presence of medical complications such as congestive heart failure, metabolic acidosis, and prolonged preoperative ventilation.

LONG-TERM OUTCOME

Long-term survival after coarctation of the aorta depends on the presence of additional cardiac malformations. For isolated coarctation, 92% of patients are alive 15 years after repair, as compared with 81% with coexisting ventricular septal defect; 41% are alive at 3 years with more complex cardiac malformations (Kirklin and Barratt-Boyes, 1986). Survival 25 years after repair has been estimated at 79% of affected individuals (Morris and Menashe, 1991). Restenosis at the site of coarctation repair may occur in up to 50% of cases, depending on

the type of correction (Beekman et al., 1981). However, some centers have reported extremely low rates of recurrence of the coarctation following subclavian flap aortoplasty (Moulton et al., 1984). Aortic stenosis may also occur in up to 7% of cases following repair in infancy (Kirklin and Barratt-Boyes, 1986). Additionally, as many as 70% of survivors face long-term problems with chronic hypertension (Rosenthal, 2005). Other long-term problems include aortic dilation, dissection and rupture, which may occur in up to 16% of survivors (Oliver et al., 2004).

GENETICS AND RECURRENCE RISK

There is a strong association between Turner syndrome (45,X) and coarctation of the aorta, with 10% of patients with this syndrome also having coarctation. The occurrence of Turner syndrome is generally sporadic (see Chapter 134). In addition, coarctation has been described as part of the DiGeorge sequence (see Chapter 139). Inheritance patterns for most cases of coarctation of the aorta are considered polygenic. Estimates of recurrence risk for children with one parent diagnosed with coarctation range from 2.7% to 4.4%. The recurrence risk for siblings of an affected child is 2% (Nora and Nora, 1988; Whitley and Perry, 1990). The recurrence risk if two siblings are affected is 6% (Nora and Nora, 1988). At least one familial cluster of coarctation of the aorta, possibly consistent with autosomal dominant inheritance, has also been described (Gerboni et al., 1993). In this family, four members of three generations had mild or severe coarctation of the aorta, either isolated or in association with other congenital heart defects. Prenatal diagnosis was successfully performed in this family using fetal echocardiography, which at 26 weeks of gestation demonstrated severe narrowing of the aortic isthmus and hypoplastic left heart.

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52 CHAPTER

Tetralogy of Fallot

Key Points

- Tetralogy of Fallot is a complex congenital cardiac malformation consisting of varying degrees of right ventricular outflow tract obstruction, ventricular septal defect, overriding aorta and right ventricular hypertrophy (although the latter is generally not present in fetal life).
- Prenatal diagnosis generally requires careful evaluation of cardiac outflow tracts, including discontinuity between ventricular septum and aortic outflow, as well as a relatively small pulmonary outflow.
- Testing for fetal karyotype and 22q11 deletion is recommended.
- Infants should be delivered in a controlled setting with ability to provide prostaglandin infusion and prompt pediatric cardiology availability.
- While initial palliation with a systemic-to-pulmonary arterial shunt may be required, many centers today perform definitive complete surgical correction within the first 6 months of life.

CONDITION

Tetralogy of Fallot is a cardiac malformation comprising ventricular septal defect (VSD), right ventricular outflow tract obstruction, aorta overriding the interventricular septum, and right ventricular hypertrophy. This malformation presumably occurs because of unequal division of the conotruncus or incorrect alignment of the ascending aorta during embryogenesis (Romero et al., 1988). A wide spectrum of severity exists for this condition, ranging from mild right ventricular outflow tract obstruction to complete pulmonary atresia, and aortic override ranging from minimal to 75% (Pinsky and Arciniegas, 1990). In addition, the hypoplasia may involve simply the infundibulum of the right ventricle or it may also involve the pulmonary valve or pulmonary arteries. Tetralogy may therefore also include pulmonary stenosis, pulmonary atresia or absent pulmonary valve, with this degree of right ventricular tract obstruction determining the amount of right-to-left shunting and cyanosis in infancy (Bashore, 2007). Approximately 3% to 6% of all cases of tetralogy will present with absent pulmonary valve (Shinebourne et al., 2006). The VSD is most often in a superior or perimembranous location, and it is usually large and nonrestrictive. The diameter of the aortic root is generally inversely proportional to that of the pulmonary artery, so that in cases of pulmonary atresia the aorta is very wide, with more than 50% committed to the right ventricle (Graham and Gutgesell, 1990).

In general, tetralogy of Fallot does not cause significant intrauterine hemodynamic compromise for the fetus because of similarities in the pressure between the systemic and pulmonary circulations. Right ventricular hypertrophy is therefore usually not seen until after birth. In cases of tetralogy with complete absence of the pulmonary valve, significant regurgitation may cause congestive cardiac failure in utero and ultimately, hydrops (Romero et al., 1988). Following birth, the closure of the ductus arteriosus, together with the narrowed right ventricular outflow tract, results in development of a significant right-to-left shunt. This leads to blood flow bypassing the pulmonary bed, resulting in hypoxemia in the systemic circulation. Because the right ventricular outflow-tract obstruction is fixed, the degree of right-to-left shunt is almost entirely dependent on the systemic vascular resistance (Graham and Gutgesell, 1990). In times of low systemic resistance, such as during exercise, fever, or following feeding, the right-to-left shunt becomes more pronounced, which leads to cyanotic spells in the child. These can be treated by knee–chest positioning and by the use of peripheral vasoconstrictors.

Additional abnormalities that may coexist with tetralogy of Fallot include chromosomal abnormalities (such as trisomies 13, 18, and 21), syndromes (such as velocardiofacial), and associations (such as CHARGE and VATER)

(Sanders et al., 1996). In one series, 3 of 6 cases (50%) of prenatally diagnosed tetralogy were associated with trisomy 18 (Crawford et al., 1988). In another series of prenatally diagnosed cardiac malformations, 3 of the 18 fetuses (17%) with tetralogy and known karyotype had trisomy 13 (Paladini et al., 1996). In a series of 138 liveborn infants with tetralogy, 17 (12%) had chromosomal abnormalities (Ferencz et al., 1987).

INCIDENCE

Tetralogy of Fallot is one of the most common congenital cardiac malformations, occurring in approximately 2 to 3 per 10,000 livebirths (Hoffman and Kaplan, 2002). It accounts for 5% to 10% of congenital cardiac defects diagnosed in liveborn infants (Fyler et al., 1980; Ferencz et al., 1987).

SONOGRAPHIC FINDINGS

Because right ventricular hypertrophy does not generally develop in utero and visualization of fetal right ventricular outflow tract obstruction is difficult, the prenatal diagnosis of tetralogy of Fallot relies on the demonstration of the aortic outflow tract overriding a VSD at the interventricular septum (Figures 52-1 and 52-2) (Romero et al., 1988). The demonstration of a VSD with overriding aorta may be performed as early as 14 weeks of gestation with the aid of transvaginal sonography (Bronshtein et al., 1990). Because of the difficulties in visualizing small perimembranous VSDs with prenatal sonography, the diagnosis of tetralogy may be missed on a standard four-chamber view of the heart. This emphasizes the importance of careful visualization of the cardiac outflow tracts during prenatal sonography (Shinebourne et al., 2006). In one series of 22 fetuses with tetralogy, the four-chamber view was abnormal in only 1 case (Paladini et al., 1996). The VSD is best imaged by a demonstration of discontinuity between the interventricular septum and the aortic outflow tract in the left parasternal long-axis view rather than by a standard four-chamber cardiac view (DeVore et al., 1988). Color Doppler sonography may also be helpful in demonstrating flow from the right ventricle, across the VSD, and into a dilated aortic root (Anderson et al., 1994).

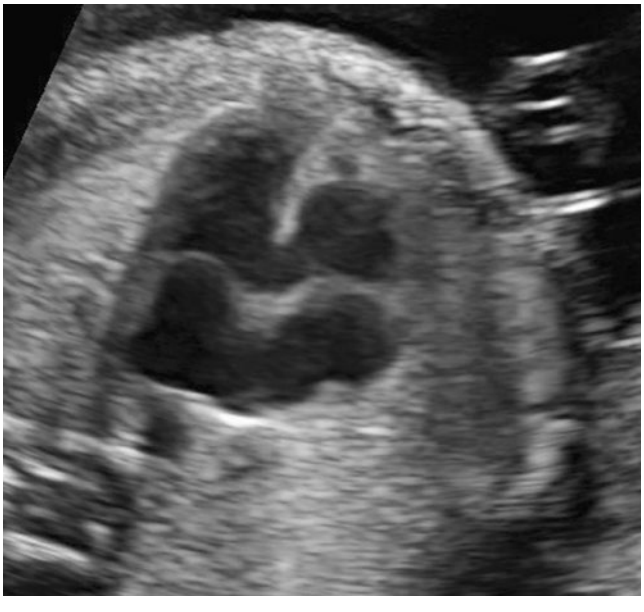

Figure 52-1 Four-chamber view demonstrating a ventricular septal defect in a fetus with tetralogy of Fallot.

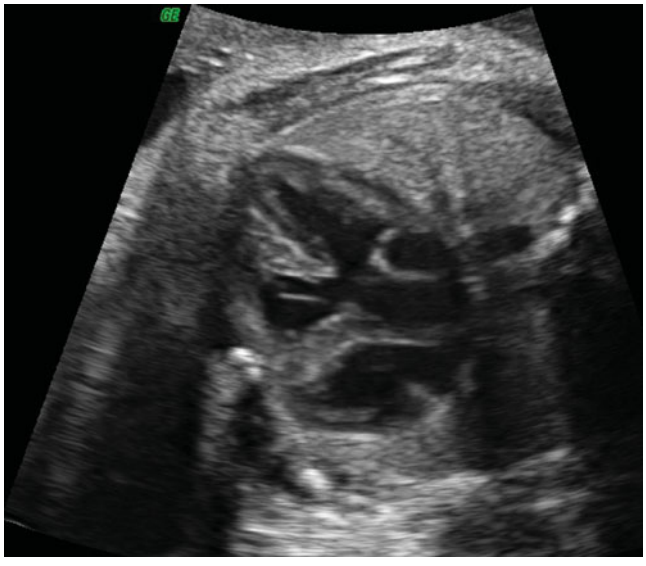

Figure 52-2 Axial image through the chest of a fetus with tetralogy of Fallot. Note the aorta overriding the ventricular septal defect.

Additional features that may assist in the prenatal diagnosis of tetralogy include the right ventricle being slightly larger than the left, a relatively small pulmonary artery (Figure 52-3), a dilated aortic root, and axis deviation (Sanders et al., 1996). In fetuses with tetralogy, the aortic-root diameter is increased as compared with other biometric parameters, such as the biventricular diameter (DeVore et al., 1988). However, the presence of a normal pulmonary artery:aorta ratio does not exclude tetralogy; in many cases the pulmonary artery narrowing may not become apparent until late in gestation (Lee et al., 1995). In some cases of tetralogy with absence of the pulmonary valve, the pulmonary outflow tract may even appear massively dilated (Liang et al., 1997). Polyhydramnios may also be present in cases of tetralogy with absent pulmonary valve, as the massively dilated pulmonary artery may cause tracheobronchial and esophageal compression that lead to impaired fetal swallowing and an increase in amniotic fluid volume (Callan and Kan, 1991).

The usefulness of screening ultrasonography for prenatal detection of tetralogy is unclear. In one study, 13 of the 20 cases (65%) of tetralogy were detected prenatally when careful screening obstetric sonography was performed

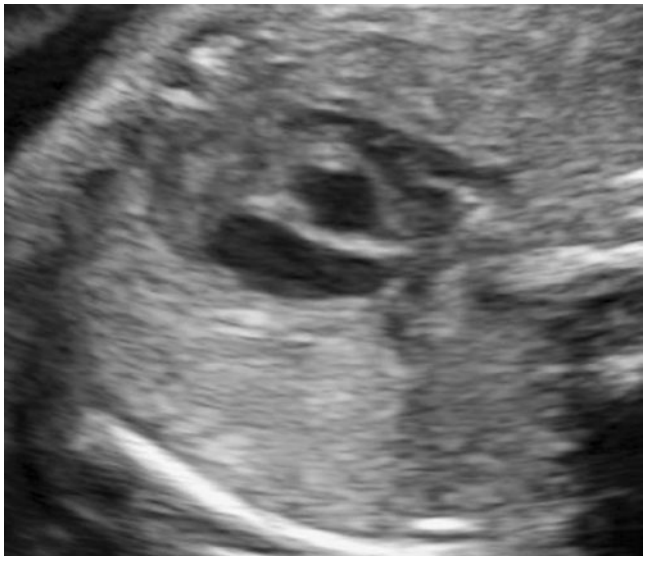

Figure 52-3 Narrow right ventricular outflow tract in a fetus with tetralogy of Fallot.

(Kirk et al., 1997). By contrast, in another study only 9 of 66 cases (14%) of tetralogy were detected using fetal echocardiography (Montana et al., 1996). In a population-based screening study from Australia, the prenatal detection rate for tetralogy was 43% (Chew et al., 2007).

DIFFERENTIAL DIAGNOSIS

Cardiac malformations that should be included in the differential diagnosis of tetralogy of Fallot include pulmonary atresia with a VSD (see Chapter 49), truncus arteriosus (see Chapter 54), and double outlet right ventricle (see Chapter 53). Doppler echocardiography may be helpful in confirming the presence of pulmonary atresia as opposed to narrowing of the right ventricular outflow tract, which is more typically seen with tetralogy. The differentiation of truncus arteriosus from tetralogy with coexisting pulmonary atresia is very difficult, with both having almost identical antenatal sonographic appearances. Visualization of more than three leaflets in a truncal valve may help differentiate these two conditions (see Chapter 54). It may be necessary to base differentiation of tetralogy from some cases of double outlet right ventricle solely on the relative area of the aortic outflow tract that arises from the right ventricle (see Chapter 53).

ANTENATAL NATURAL HISTORY

In general, since the pressures in the pulmonary and systemic circulations are similar, tetralogy of Fallot does not cause intrauterine hemodynamic instability. Given that right- and left-sided afterloads are similar, ventricular hypertrophy generally does not occur in the prenatal period (Shinebourne et al., 2006). An exception would be tetralogy with absent pulmonary valve, in which significant regurgitation may lead to hydrops (Romero et al., 1988). In addition, if a major chromosomal abnormality is also present, such as trisomy 13 or 18, there will be a considerably increased risk of intrauterine death. As a general rule, the antenatal natural history of isolated tetralogy of Fallot is relatively uneventful. However, there have been reports of progression of the degree of pulmonary stenosis associated with tetralogy as gestation progresses, which would suggest that fetuses diagnosed with tetralogy should be followed serially as pregnancy continues (Hornberger et al., 1995).

In one series of 22 cases of prenatally diagnosed tetralogy of Fallot, 9 pregnancies (41%) were terminated, no cases resulted in intrauterine death, 6 infants (27%) died during the neonatal period, and 7 infants (32%) survived (Paladini et al., 1996). In another series of 11 cases of prenatally diagnosed tetralogy, 2 pregnancies (18%) were terminated, no cases resulted in intrauterine death, 6 infants (55%) died during the postnatal period, and 3 infants (27%) survived (Smythe et al., 1992).

MANAGEMENT OF PREGNANCY

Following prenatal diagnosis of tetralogy of Fallot, a careful fetal echocardiogram is recommended to exclude additional complex cardiac malformations, such as absence of the pulmonary valve, which is seen in 3% to 6% of cases (Shinebourne et al., 2006). In addition, a detailed fetal anatomic survey is recommended to exclude extracardiac malformations. In particular, malformations associated with the major autosomal trisomies, DiGeorge syndrome (see Chapter 139), and VATER should be excluded (Sanders et al., 1996).

Invasive fetal testing for karyotype analysis is recommended following the prenatal diagnosis of tetralogy, because in reported series the incidence of chromosomal abnormalities ranges from 12% to 50% (Ferencz et al., 1987; Crawford et al., 1988). If a karyotype is performed, additional fluorescence in situ hybridization (FISH) studies for chromosome 22q11 microdeletions that comprise the DiGeorge syndrome (see Chapter 139) should also be performed (Trainer et al., 1996). Referrals for prenatal consultation with a pediatric cardiologist and cardiothoracic surgeon are also recommended.

If the diagnosis is made before fetal viability, termination of pregnancy may be offered because of the neonatal mortality and surgical morbidity associated with this condition. If expectant management is desired, sonographic surveillance to confirm appropriate fetal growth and to evaluate for the development of fetal hydrops is recommended, especially if additional cardiac malformations such as absence of the pulmonary valve are present. If fetal hydrops occurs, the prognosis is poor; the optimal management of such pregnancies is unknown. Delivery should occur at a tertiary care center,

with the immediate availability of a neonatologist, pediatric cardiologist, and cardiothoracic surgeon. There is no indication to alter the timing or method of delivery based on the prenatal diagnosis of tetralogy of Fallot.

FETAL INTERVENTION

No fetal intervention has been described for tetralogy of Fallot.

TREATMENT OF THE NEWBORN

Initial clinical presentation of neonates with tetralogy is quite variable. The presence of cyanosis in a newborn with tetralogy suggests that significant right ventricular outflow tract obstruction is present. In such cases, or if there is any other reason to suspect ductal dependence, prostaglandin E_1 infusion should be started to maintain patency of the ductus arteriosus. The infant should be transported to a neonatal intensive care unit as soon as possible.

Consultation with a pediatric cardiologist should be obtained promptly and echocardiography performed to confirm the prenatal diagnosis and to exclude additional cardiac malformations. The degree of pulmonary arterial obstruction should be assessed, which may require the use of cardiac catheterization. Cardiac catheterization is useful in delineating the anatomy of the coronary arteries, the degree of pulmonary artery narrowing, the anatomy of the pulmonary arterial branches and aorta, and the extent of the VSD (Graham and Gutgesell, 1990). Further medical management in the neonatal intensive care unit will include maintenance of adequate oxygenation and treatment of metabolic acidosis and congestive heart failure. If assisted ventilation, oxygen supplementation, and prostaglandin E_1 infusion cannot maintain adequate oxygenation, consultation with a pediatric cardiothoracic surgeon should be obtained to decide on timing and method of surgical intervention, such as a palliative shunt procedure or definitive repair (Sanders et al., 1996). Optimal age for complete surgical correction of tetralogy has been falling and is now considered to be between 3 and 12 months of age, but is individualized in all cases (Shinebourne et al., 2006).

Some neonates with tetralogy of Fallot do not have significant cyanosis, may have minimal right ventricular outflow tract obstruction, and may not be dependent on a patent ductus arteriosus. Such infants generally do not require prostaglandin E_1 infusion, provided they can maintain adequate oxygenation, even after spontaneous closure of the ductus arteriosus. In such cases, cyanosis may only be visible intermittently, for example after crying (Shinebourne et al., 2006). Eventually however, all children with tetralogy will present with "tet spells" as the degree of pulmonary vascular resistance increases leading to a significant right-to-left shunt. In such mild cases, cardiac catheterization can generally be delayed until 3 to 6 months of age, with surgical repair planned for soon after onset of symptoms or electively at 18 to 24 months of age (Pinsky and Arciniegas, 1990). However, in more than 70% of infants with tetralogy, symptoms sufficient to warrant surgical intervention develop within the first year of life (Castaneda and Jonas, 1990).

SURGICAL TREATMENT

Debate still exists on the timing of surgical repair for tetralogy of Fallot and the role of palliative shunting procedures prior to definitive correction. Infants with isolated tetralogy of Fallot and favorable anatomy generally receive complete primary repair soon after the onset of symptoms or within the first year of life. Infants with more complex tetralogy, such as hypoplasia of the pulmonary arteries or anomalous coronary arterial anatomy, are initially treated with a systemic-to-pulmonary shunt followed by final repair at 18 to 24 months of age (Pinsky and Arciniegas, 1990; Derby and Pizarro, 2005). As surgical techniques advance, the age at which complete primary repair is performed continues to decrease (Castaneda and Jonas, 1990).

Primary repair of tetralogy of Fallot requires cardiopulmonary bypass and a median sternotomy approach (Castaneda and Jonas, 1990). The infundibulum of the right ventricular outflow tract is incised, and the incision is carried up to the bifurcation of the pulmonary artery. Thickened or dysplastic pulmonary valve leaflets are usually excised. A Dacron patch is used to close the VSD and a patch of pericardium is used to augment the right ventricular outflow tract and pulmonary artery. If a patent foramen ovale or patent ductus arteriosus is present, these are also closed at this time. For the few patients who are not candidates for complete primary repair, the most commonly performed palliative procedure is a Blalock–Taussig systemic-to-pulmonary shunt, in which the subclavian artery is anastomosed to the pulmonary artery.

The operative mortality rate for primary repair of tetralogy of Fallot during infancy has improved, with mortality quoted as 14% in 1979 but subsequently improved to as low as 3% more recently (Tucker et al., 1979; Touati et al., 1990; Bashore, 2007). At one center, of 467 infants who underwent surgery for tetralogy of Fallot, there were only 16 (3.4%) early postoperative deaths (Pinsky and Arciniegas, 1990). In another series of 366 infants who had complete correction of tetralogy, one center reported an operative mortality rate of only 0.5% when using a 6- to 8-kg weight cutoff for surgical eligibility (Karl et al., 1992). Recent national outcome data from the United Kingdom suggests a 97% survival rate 1 year postoperatively (Shinebourne et al., 2006). Operative mortality now appears to be most affected by the presence of complex cardiac anatomy or an abnormal metabolic state, rather than infant age or weight (Castaneda and Jonas, 1990).

LONG-TERM OUTCOME

A study of the long-term outcome of 163 patients who survived complete repair of tetralogy of Fallot demonstrated a 90% 30-year actuarial survival rate, with 94% of survivors being in either New York Heart Association functional class I or II (Murphy et al., 1993). However, up to 12% of patients who survive surgical correction may have unsatisfactory results, and reoperation may be required for those with residual right ventricular outflow tract obstruction or residual VSD (Pinsky and Arciniegas, 1990). Other long-term complications include the development of pulmonary valve insufficiency and arrhythmias, possibly leading to sudden death.

GENETICS AND RECURRENCE RISK

Tetralogy of Fallot has been described with velocardiofacial syndrome, DiGeorge syndrome (see Chapter 139), and the VATER associations (Sanders et al., 1996). In addition, tetralogy has been described with trisomies 13, 18, and 21. Chromosome 22q11 microdeletions that are seen as part of the DiGeorge syndrome have been noted in many infants with tetralogy, being present in 21% of infants with tetralogy in one series (Trainer et al., 1996).

The recurrence risk for tetralogy of Fallot is 2.5% if one previous sibling has been affected and increases to 8% if two previous siblings have been affected (Nora and Nora, 1988). If the mother has tetralogy, the recurrence risk for her offspring is 2.5%. If the father is affected, the recurrence risk for his offspring is 1.5% (Nora and Nora, 1988).

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53 CHAPTER Double Outlet Right Ventricle

Key Points

- Double outlet right ventricle (DORV) is a complex cardiac malformation in which the majority of both pulmonary and aortic trunks arise from the right ventricle, typically coexisting with a VSD.
- While DORV represents a heterogeneous group of abnormalities with various classification systems, a combined anatomic-surgical classification system is now used as it predicts optimal surgical intervention.
- Prenatal diagnosis depends on accurate delineation of the outflow tract paths, including localizing the VSD.
- The majority of cases have associated cardiac malformations, abnormalities of organ situs, or chromosomal abnormalities.
- Because of the variable clinical presentation at birth, delivery should occur in controlled circumstances at a center with pediatric cardiology backup available, and the ability to begin a prostaglandin infusion.
- Definitive surgical correction should occur during the first year of life, with most cases achieving a biventricular repair using an intraventricular tunnel.

CONDITION

Double outlet right ventricle (DORV) refers to a congenital cardiac malformation in which most of the pulmonary artery and the aorta arise from the right ventricle, one subtype of which is known as the Taussig–Bing heart. Such an abnormality is generally compatible with life only when there is an additional malformation that allows blood flow from one side of the heart to the other, most commonly a ventricular septal defect (VSD).

Attempts have been made to define the malformation based on the relative area of each outflow tract arising from the right ventricle, with an anatomic threshold of 50% being used. The surgical definition of DORV requires that at least 90% of the area of the outflow tracts arise from the right ventricle. The most commonly used definition requires one great artery to arise fully over the right ventricle and at least 50% of the other great artery to also originate from the right ventricle (Aoki et al., 1994). Therefore, cases of tetralogy of Fallot (see Chapter 52) in which the majority of the aortic outflow tract arises from the right ventricle could also be defined as DORV. Such anomalies may arise because of arrest of normal rotation of the outflow tracts (Bostrom and Hutchins, 1988). DORV has also been classified based on the relationship of the outflow tracts. The most common is where the aortic outflow tract is situated posterior to the pulmonary outflow tract, each spiraling around the other as they exit the heart (Romero et al., 1988). The Taussig–Bing heart is a subtype of DORV in which the aortic outflow tract ascends posterior to the pulmonary outflow tract in a parallel fashion. In the third type of DORV, the aortic outflow tract ascends anterior to the pulmonary outflow tract in a parallel fashion. DORV may also be classified based on the location of the VSD, either subaortic or subpulmonary; in the Taussig–Bing heart the VSD is subpulmonary (Bashore, 2007).

Because of this confusion in classification of DORV anatomically, the Society of Thoracic Surgeons (STS) and the European Association of Cardiothoracic Surgery (EACTS) have agreed a new classification system based on clinical presentation and surgical management (Walters et al., 2000). The four types are: (1) VSD-type, (2) tetralogy of Fallot-type, (3) transposition of great arteries-type (Taussig–Bing), and (4) DORV with noncommitted VSD. Patients with a subaortic VSD present clinically very similar to tetralogy of Fallot (Bashore, 2007).

Additional cardiac malformations are almost always present, with the most common being a VSD. Other coexisting cardiac malformations include atrial septal defect, atrioventricular canal defect, pulmonary stenosis, coarctation of the aorta, and anomalous venous return. Noncardiac

malformations may also be present, including chromosomal abnormalities, such as trisomy 18 or 13, tracheoesophageal fistula, cardiosplenic syndrome, and orofacial clefting (Rowe et al., 1981; Wladimiroff et al., 1989; Kim et al., 2006).

INCIDENCE

DORV is rare and accounts for approximately 1% of all congenital cardiac malformations. However, this incidence may be higher if cases of tetralogy of Fallot that can also be defined as DORV are included. In one multicenter series, DORV accounted for 4.1% of all cases of prenatally diagnosed congenital heart disease (Paladini et al., 1996). The presence of pre-existing maternal diabetes mellitus seems to be a significant risk factor for the development of DORV, with an odds ratio of 21.3 (Ferencz et al., 1990). The incidence of DORV is approximately 1 to 2 per 10,000 livebirths (Hoffman and Kaplan, 2002).

SONOGRAPHIC FINDINGS

Definitive prenatal sonographic diagnosis of DORV is difficult, as successful prenatal diagnosis requires careful examination of both the four-chamber view and the outflow tracts. On the four-chamber view, a VSD is almost always present, either in a subpulmonary or a subaortic location. In DORV, both outflow tracts are visible arising from the right ventricle and are often in a side-by-side, or parallel position (Figures 53-1 to 53-3) (Stewart et al., 1985).

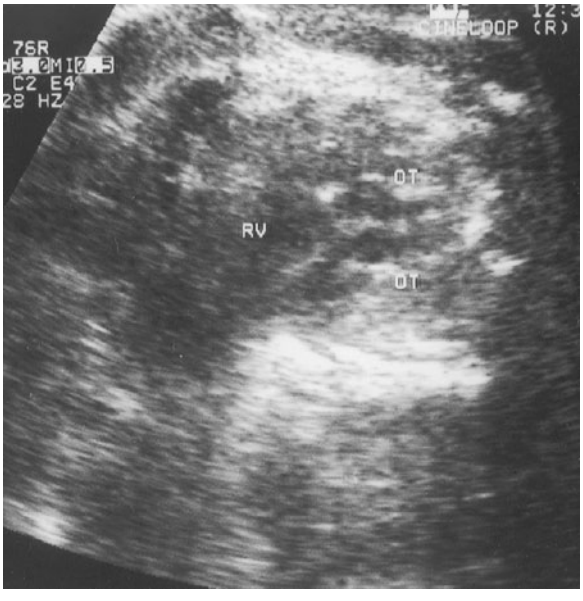

Figure 53-1 Prenatal sonographic image from a fetus with DORV, demonstrating parallel outflow tracts emanating from the right ventricle. RV = right ventricle; OT = outflow tract.

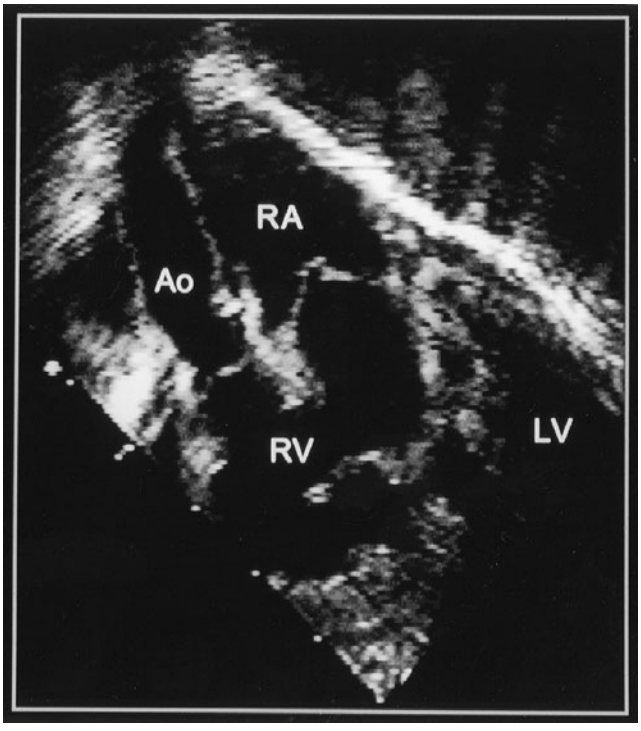

Figure 53-2 Subxiphoid long-axis transthoracic echocardiographic view of an infant with a variant of DORV. Both great vessels arise from the right ventricle in a side-by-side arrangement. RA = right atrium; LV = left ventricle; RV = right ventricle; Ao = aorta. (*Image courtesy of Dr. Jonathan Rhodes.*)

In one series of 24 fetuses with parallel outflow tracts, 7 were found to have transposition of the great arteries, while the remaining 17 had DORV (Allan, 1997). In that series, most of the mothers were referred for fetal echocardiography because of an initial abnormal four-chamber cardiac view. In another series, 13 cases of DORV were correctly diagnosed by fetal echocardiography, 5 of which had an abnormal four-chamber cardiac view (Paladini et al., 1996). A transverse three-vessel view through the upper fetal mediastinum, demonstrating the main pulmonary artery, ascending aorta, and superior vena cava, may also be helpful in diagnosing DORV (Yoo et al., 1997). In a population-based study from Australia, 54 of 73 (74%) cases of DORV were correctly identified prenatally (Chew et al., 2007). When DORV is suspected prenatally, the diagnosis will subsequently be proven correct in approximately 75% of cases (Gelehrter et al., 2007). It appears clear, therefore, that maximal prenatal detection of DORV requires careful visualization of both the four-chamber view and the cardiac outflow tracts.

DIFFERENTIAL DIAGNOSIS

Because DORV is almost always associated with additional cardiac malformations, a final diagnosis is often not possible until postnatal life. The prenatal sonographic appearance of DORV can be similar to that of tetralogy of Fallot (see Chapter 52) and transposition of the great arteries with a

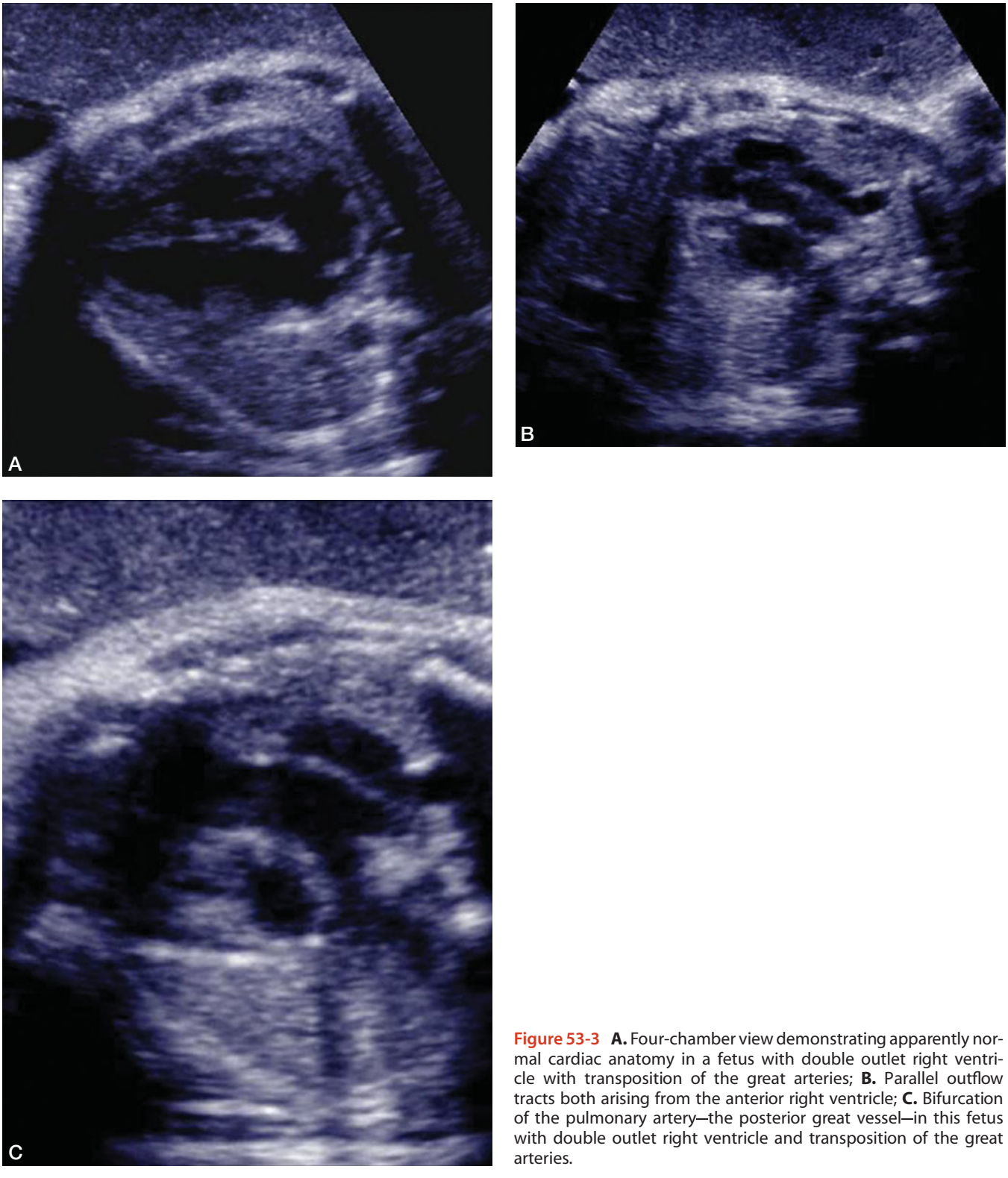

Figure 53-3 **A.** Four-chamber view demonstrating apparently normal cardiac anatomy in a fetus with double outlet right ventricle with transposition of the great arteries; **B.** Parallel outflow tracts both arising from the anterior right ventricle; **C.** Bifurcation of the pulmonary artery—the posterior great vessel—in this fetus with double outlet right ventricle and transposition of the great arteries.

coexisting VSD (see Chapter 55). Indeed, the differentiation of some cases of DORV and tetralogy of Fallot may be based solely on the relative area of the aortic outflow tract that arises from the right ventricle. The appearance of parallel great arteries, which is present in some subtypes of DORV, may aid in differentiation from tetralogy of Fallot, but does not help to differentiate from transposition of the great arteries.

ANTENATAL NATURAL HISTORY

The antenatal natural history of DORV depends on the presence and nature of any additional cardiac or extracardiac malformations. For isolated DORV with a VSD, in utero development should be normal, and should not lead to congestive

heart failure. In postnatal life, however, congestive heart failure may develop because the right ventricle provides both pulmonary and systemic circulation. In cases of DORV with pulmonary stenosis, in utero cardiac failure and hydrops may develop, but this is much more likely to occur during postnatal life as the ductus arteriosus closes.

In a series of 13 cases of DORV diagnosed prenatally, 7 resulted in elective termination of pregnancy, 3 in intrauterine fetal death, and 3 in liveborn neonates (Paladini et al., 1996). There were 5 cases of chromosomal abnormalities in this series, 4 of which were trisomy 18 and 1 trisomy 16. Of the 3 cases of intrauterine death, one fetus had extracardiac malformations in addition to trisomy 18. In a series of 24 fetuses with parallel great vessels, 17 of which had DORV, 22 had additional cardiac malformations, 8 had extracardiac anomalies, and 1 had trisomy 18 (Allan, 1997). This series resulted in 6 terminations of pregnancy, 1 intrauterine fetal death, and 17 liveborn neonates, 15 of whom required early surgical intervention. More recently, in a series of 19 cases of prenatally diagnosed DORV, 3 were terminated and the 16 remaining cases resulted in livebirths (Kim et al., 2006). Among the 14 cases in which postnatal follow-up was available, all but 1 had additional cardiac malformations, and 8 had extracardiac malformations (including 2 cases of aneuploidy).

MANAGEMENT OF PREGNANCY

Following prenatal sonographic detection of DORV, fetal echocardiography should be performed to confirm the diagnosis and assess for additional cardiac malformations. In addition, a careful sonographic evaluation of extracardiac fetal anatomy is required to exclude orofacial clefting, tracheoesophageal fistula, and cardiosplenic syndrome. In a series of 19 cases of prenatally diagnosed DORV there were 4 cases of atrial isomerism, one case of situs inversus, and one case of asplenia (Kim et al., 2006). Because up to 40% of cases of DORV will have a chromosomal abnormality, most commonly trisomies 18 and 13, fetal karyotyping should also be offered. Careful genetic counseling is required to provide parents with a complete set of options for management of the pregnancy. Prenatal consultations with a neonatologist, geneticist, pediatric cardiologist, and pediatric cardiac surgeon are recommended to ensure timely and appropriate treatment during the newborn period.

In the absence of hydrops, there is no indication to alter management of the pregnancy, timing of delivery, or mode of delivery. Serial sonographic assessment to confirm appropriate fetal growth and absence of hydrops is recommended. The optimal management of the fetus with congenital heart disease and secondary hydrops fetalis is unclear. Mortality in such cases is usually very high (Kleinman et al., 1982), and it is uncertain if either early delivery or cesarean delivery will change the outcome. Delivery should occur in a tertiary care center, with the immediate availability of a pediatric cardiologist and pediatric cardiac surgeon.

FETAL INTERVENTION

No data on fetal intervention for DORV are available.

TREATMENT OF NEWBORN

Initial care of the newborn with DORV depends on the presence of additional cardiac or extracardiac malformations. For example, if significant pulmonary stenosis is also present, a duct-dependent situation may exist, and the infant may benefit from prostaglandin infusion to maintain the patency of the ductus arteriosus (Allan, 1997). In addition, initial treatment requires prompt postnatal evaluation by a pediatric cardiologist, with echocardiography to confirm the prenatal diagnosis and to assess for the presence of additional cardiac malformations.

The presence of a VSD should be categorized according to the STS-EACTS classification described earlier as this system suggests the optimal surgical approach (Walters et al., 2000; Artrip et al., 2006). Coronary artery anatomy should be defined, and tricuspid to pulmonary valve annular distance should be measured, as these have implications for surgical repair (Sakata et al., 1988). The treatment of the newborn with DORV requires early surgical intervention, which today usually involves a single primary repair procedure rather than an initial palliative procedure (Tchervenkov et al., 1995).

SURGICAL TREATMENT

Contemporary data on operative mortality and reoperation rates suggest that repair of DORV should be performed early in infancy, thereby avoiding the need for additional palliation procedures (Aoki et al., 1994; Tchervenkov et al., 1995). The main principles behind surgical repair of DORV are to achieve an anatomic biventricular repair by connecting the left ventricle to the systemic circulation and to repair all associated cardiac lesions simultaneously (Tchervenkov et al., 1995; Walters et al., 2000).

Preoperative echocardiographic evaluation is crucial in planning the surgical approach to DORV. When the tricuspid to pulmonary valve annular distance is greater than the diameter of the aortic annulus, intraventricular rerouting is the surgical procedure of choice in the repair of DORV with a coexisting VSD, particularly if the VSD is subaortic in location (Aoki et al., 1994). With this procedure, an intraventricular tunnel is created to take blood flow directly from the VSD to the aortic outflow tract, while maintaining the pre-existing continuity of flow from the right ventricle to pulmonary outflow tract (Kirklin et al., 1964; Walters et al., 2000). A right ventricular outflow patch may be required to direct blood flow appropriately.

When the tricuspid to pulmonary valve annular distance is small, or if the anatomy otherwise prevents an intraventricular rerouting procedure, other surgical techniques are

performed, such as an arterial switch procedure, with blood flow taken directly from the VSD to the pulmonary outflow tract. If significant pulmonary stenosis is also present, or if coronary artery anatomy is abnormal, a conduit procedure may be needed, in which blood flow is directed from the VSD to the aortic outflow tract and a conduit is placed to channel blood flow from the right ventricle to the pulmonary artery (Rastelli-type procedure).

Immediate operative mortality following repair of DORV ranges from 8% to 11% (Aoki et al., 1994; Tchervenkov et al., 1995). Risk factors for early mortality include the presence of multiple VSDs, or aortic-arch obstruction (Kleinert et al., 1997). In a series of 50 cases of DORV with two viable ventricles, the vast majority (44 of 50, 88%) successfully underwent a biventricular repair, with surgery being performed at a median age of 9 months (Artrip et al., 2006). Surgical mortality was between 4% and 6% in this series.

LONG-TERM OUTCOME

Long-term survival following surgical repair of DORV has been estimated to be from 73% to 88% at 5 to 8 years (Serraf et al., 1991; Aoki et al., 1994; Tchervenkov et al., 1995). The incidence of reoperation ranges from 26% to 42% (Serraf et al., 1991; Aoki et al., 1994). Reasons for reoperation include subaortic stenosis, subpulmonary stenosis, and the presence of a significant residual VSD. In another series, the probability of survival, free from reoperation, was calculated as 65% at 10 years (Kleinert et al., 1997). The presence of a noncommitted VSD was a significant risk factor for reoperation, while the presence of a subaortic VSD was protective against reoperation (Aoki et al., 1994). In one series, 95% of long-term survivors had no restriction on physical activities and required no cardiac medications (Tchervenkov et al., 1995).

GENETICS AND RECURRENCE RISK

An association exists between DORV and both trisomies 13 and 18. The recurrence risk for these syndromes is extremely low, unless one parent is a balanced translocation carrier. In one consanguineous family, either tetralogy of Fallot or DORV with subaortic VSD and pulmonary stenosis were found in three of four offspring (Bindewald et al., 1994). This implies the existence of a rare autosomal recessive syndrome involving DORV.

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Truncus Arteriosus

54 CHAPTER

Key Points

- Truncus arteriosus is a rare form of congenital cardiac disease in which a single cardiac outflow tract gives rise to the pulmonary, coronary, and systemic circulations.
- Prenatal diagnosis relies upon failure to visualize three separate vessels in a transverse view through the upper mediastinum, and failure to visualize the normal branch pulmonary arteries and their origin from the right ventricle.
- Up to 40% of cases are associated with a 22q11 deletion and the DiGeorge syndrome, thereby making amniocentesis a crucial part of the prenatal diagnostic evaluation.
- While timing and mode of delivery do not need to be altered following the diagnosis, planned delivery in a tertiary care setting with appropriate pediatric cardiology backup is critical, as congestive cardiac failure can occur in the neonatal period.
- Early definitive surgical repair is recommended, typically by means of a homograft from the right ventricle to the pulmonary artery, with closure of a VSD.
- Long-term survival rates of 80% can be expected.

CONDITION

Truncus arteriosus (also known as common aorticopulmonary trunk, truncus arteriosus communis, and single-outlet heart) refers to a single large ventricular outflow tract arising from both right and left ventricles. This single large outflow tract, or truncus, gives rise to the coronary arteries, aorta, and pulmonary arteries.

In the original anatomic classification of Collett and Edwards (1949), four subtypes were described:

Type I demonstrates a single pulmonary trunk arising from the truncus, which then subdivides into right and left pulmonary arteries.
Type II demonstrates two pulmonary arteries arising directly from the posterior surface of the truncus.
Type III demonstrates two pulmonary arteries arising from the lateral aspects of the truncus.
Type IV demonstrates absent pulmonary arteries, but collateral arteries arising from the descending aorta supply the pulmonary vasculature.

Van Praagh and Van Praagh (1965) subsequently described a different classification system in which type A truncus is associated with a ventricular septal defect (VSD) and type B truncus is not associated with a VSD. Type A truncus is divided further into four subtypes, which closely resemble the classification of Collett and Edwards:

Type A1 demonstrates a partially separated pulmonary trunk.
Type A2 demonstrates two pulmonary arteries arising directly from the truncus.
Type A3 demonstrates a single pulmonary artery arising from the truncus together with further collaterals arising from the descending aorta.
Type A4 demonstrates significant arch anomalies in association with the truncus.

Additionally, The Society of Thoracic Surgeons has further modified the classification by combining Types A1 and A2 from the Van Praagh and Van Praagh classification system (Jacobs, 2000).

Almost 60% of cases of truncus are type I, based on the classification of Collett and Edwards, 35% are type II, 5% are type III, and a small minority are type IV (Bharati et al., 1974). In 65% of cases, the single truncus seems to arise predominantly from the right ventricle that may make differentiation from tetralogy of Fallot difficult. The truncus arises entirely from the right ventricle in 15% of cases, straddles the

ventricular septum equally in a further 15% of cases, and arises mostly from the left ventricle in less than 5% of cases (Bharati et al., 1974). The single valve within the truncus is known as the truncal valve, and it is tricuspid in more than 65% of cases, although the number of leaflets may range from one to six (Bashore, 2007). Truncal valve dysplasia is very common, although significant truncal stenosis is rare, occurring in only 5% of cases (Bharati et al., 1974). Truncal valve regurgitation may be common, occurring in up to 40% of cases (Di Donato et al., 1985).

Associated cardiac malformations are common with truncus arteriosus; a VSD is present in the vast majority of cases. Right-sided aortic arch, atrial septal defect, abnormal origin of brachiocephalic vessels, aortic coarctation, atrioventricular canal defect, mitral atresia, and abnormal cardiac situs have all been described in association with truncus (Bharati et al., 1974). Approximately 50% of patients will have a patent ductus arteriosus in childhood, and approximately 20% will have an interrupted aortic arch (Bashore, 2007). Extracardiac abnormalities include situs inversus, heterotaxy syndrome (see Chapter 56), DiGeorge syndrome (see Chapter 139), and genitourinary anomalies (Collett and Edwards, 1949; Bharati et al., 1974).

INCIDENCE

Truncus arteriosus is a rare form of congenital heart disease, accounting for only 1.5% of all severe cardiac malformations seen during infancy (Fyler et al., 1980). Its incidence is estimated to be 1 in 10,000 livebirths and may be slightly more frequent in females (Hoffman and Kaplan, 2002). Truncus arteriosus likely accounts for only 7% to 10% of prenatally diagnosed conotruncal malformations (Sivanandam et al., 2006). The incidence of truncus arteriosus may be increased 12-fold in the presence of pregestational diabetes mellitus in the mother (Ferencz et al., 1990).

SONOGRAPHIC FINDINGS

Prenatal diagnosis of truncus arteriosus is possible with obstetric sonography and targeted fetal echocardiography. Visualization of the outflow tracts should demonstrate a single large ventricular outflow tract, overriding a VSD (Romero et al., 1988) (Figures 54-1 and 54-2). The right ventricular outflow tract should be absent, and pulmonary arterial branches may be visible arising from the truncus or from the descending aorta. A distended coronary sinus may also be visible directly posterior to the left atrium (de Araujo et al., 1987). Diagnosis in utero may also be aided by the identification of additional anomalies, such as those involving the aortic arch, as well as by Doppler identification of truncal-valve regurgitation (Marasini et al., 1987). Truncus arteriosus may also lead to the development of congestive heart failure in utero, leading to the typical sonographic features of hydrops.

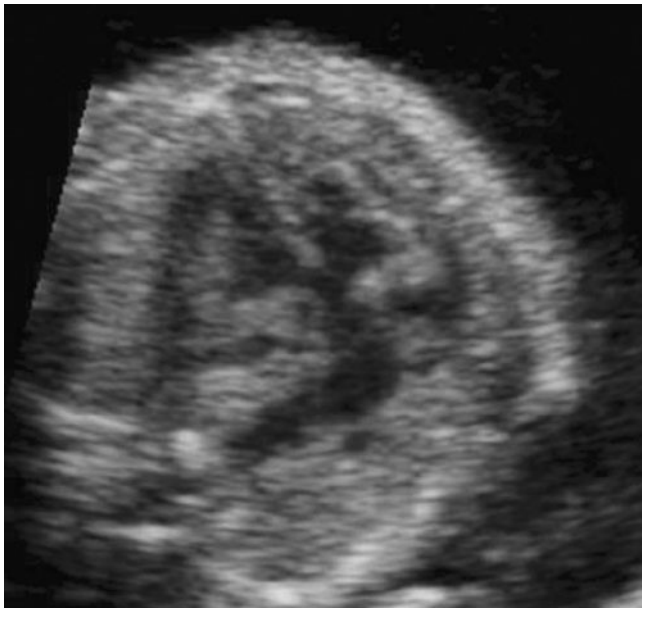

Figure 54-1 Axial image in a fetus with truncus arteriosus demonstrating a large single outflow tract overriding the intraventricular septum.

A transverse view through the upper fetal mediastinum, which normally contains the main pulmonary artery, ascending aorta, and superior vena cava, should demonstrate only two vessels in cases of truncus arteriosus (Yoo et al., 1997). The importance of visualization of the outflow tracts is evident from a series of six cases of prenatally diagnosed truncus arteriosus in which only two of the six cases were detected

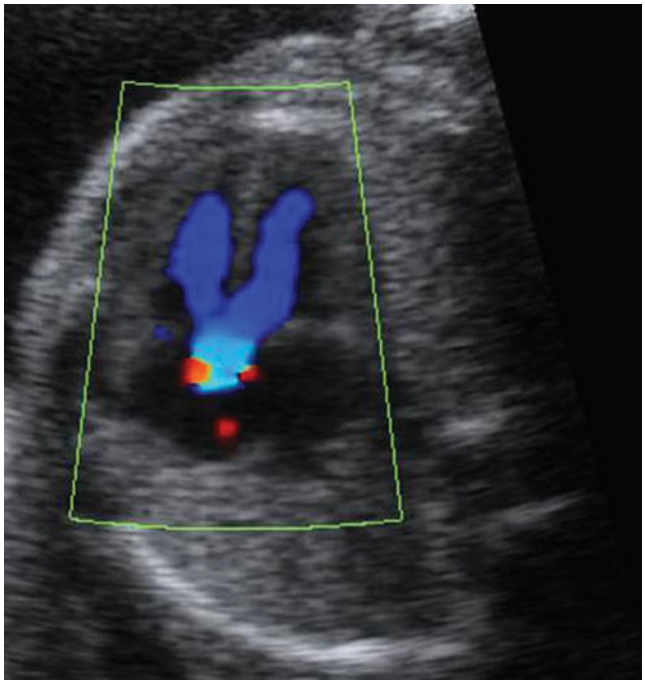

Figure 54-2 Color Doppler demonstrating presence of single large outflow tract consistent with a diagnosis of truncus arteriosus.

with the four-chamber cardiac view (Paladini et al., 1996). The remaining four cases were detected using a combination of four-chamber and outflow tract views.

In the hands of experienced fetal medicine and pediatric cardiology specialists, accurate prenatal diagnosis of the relationship of the arterial outflow tracts is possible. In a series of 113 consecutive fetuses with conotruncal malformations, including 8 cases of truncus arteriosus, the great arterial spatial relationship was correctly identified in 92% (Sivanandam et al., 2006). In an Australian population database study of prenatal detection of congenital heart defects, 18 of 27 cases (67%) of truncus arteriosus were successfully identified prenatally (Chew et al., 2007).

DIFFERENTIAL DIAGNOSIS

Differentiation between truncus arteriosus and tetralogy of Fallot (see Chapter 52) with coexisting pulmonary atresia may be extremely difficult because both have virtually identical sonographic appearances. Visualization of pulmonary arteries arising from the back of the truncus and the presence of more than three leaflets in the truncal valve may aid in the correct diagnosis (Houston et al., 1981). Truncus arteriosus may also be difficult to differentiate from aorticopulmonary window, in which the clinical features of truncus are present, but without a VSD and with a normal pulmonary valve (Riggs and Paul, 1982; Graham and Gutgesell, 1990).

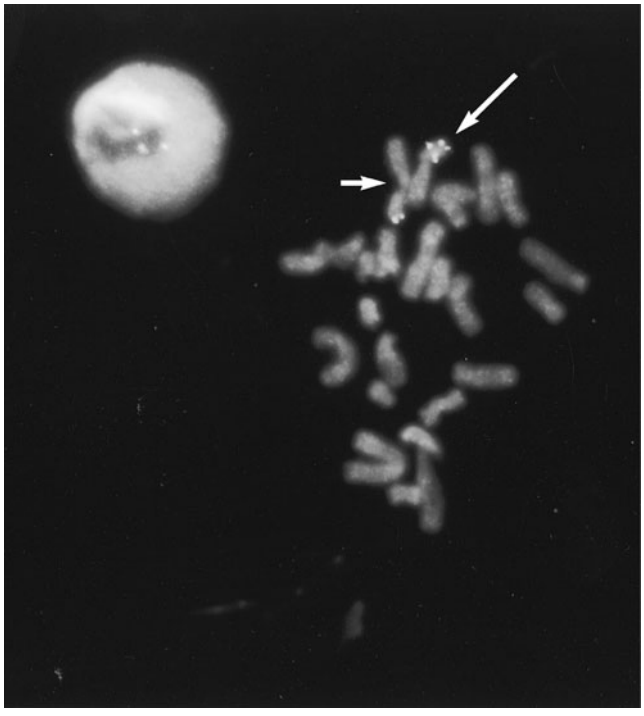

Figure 54-3 Fluorescence in situ hybridization studies using a DNA probe specific to DiGeorge region. The long arrow indicates chromosome 22 with distal flanking marker and presence of DiGeorge probe. The short arrow indicates the other chromosome 22 with distal flanking probe but absent DiGeorge probe. This is diagnostic for a microdeletion of chromosome 22. (*Courtesy of Janet Cowan.*)

ANTENATAL NATURAL HISTORY

Few reports of the antenatal natural history of truncus arteriosus are available. In one series of six cases diagnosed prenatally, three pregnancies were terminated, two cases resulted in neonatal death, and one fetus survived (Paladini et al., 1996). The antenatal development of hydrops is rare with truncus arteriosus, as the relatively high fetal pulmonary vascular resistance prevents the development of significant ventricular dysfunction. Immediately after delivery, however, the drop in pulmonary vascular resistance leads to significantly increased pulmonary flow, truncal valve insufficiency, and ventricular dysfunction. Development of congestive heart failure in utero is likely only if significant truncal-valve dysplasia and obstruction are present.

MANAGEMENT OF PREGNANCY

Once the diagnosis of truncus arteriosus is suspected on a prenatal sonographic image, referral to a tertiary care center is recommended for a thorough targeted sonographic evaluation as well as fetal echocardiography by an appropriately trained specialist. Prospective parents should meet with a pediatric cardiologist. Attention should be paid to the potential presence of additional cardiac malformations, as well as the possibility of heterotaxy syndrome (see Chapter 56). Invasive testing for prenatal karyotype is recommended. Although only a small number of fetuses with truncus arteriosus will be aneuploid (de Araujo et al., 1987; Ferencz et al., 1987; Paladini et al., 1996), there is a strong association between truncus arteriosus DiGeorge syndrome (see Chapter 139). DiGeorge syndrome can be diagnosed prenatally by use of a fluorescence in situ hybridization probe for chromosome 22q11 (Figure 54-3). All patients undergoing prenatal karyotyping should have fluorescence in situ hybridization studies for the 22q11 microdeletion. If a chromosome abnormality or DiGeorge syndrome is diagnosed, the prospective parents should meet with a medical geneticist.

After prenatal diagnosis, serial evaluation with obstetric ultrasonography is recommended to confirm adequate fetal growth and to exclude the development of congestive heart failure. Infants with this condition can deteriorate rapidly as pulmonary vascular resistance falls after birth. Therefore, delivery of the fetus with truncus arteriosus should occur at a tertiary care center, with the immediate availability of a neonatologist, pediatric cardiologist, and pediatric cardiothoracic surgeon. The timing and route of delivery should not be changed by the diagnosis of truncus arteriosus. The onset of spontaneous labor should be awaited, and cesarean delivery should be reserved for standard obstetric indications. It

is unclear if intervention with early or cesarean delivery is of any benefit when the diagnosis is complicated by the presence of hydrops. The prognosis in such cases is almost always poor, irrespective of obstetric interventions (Romero et al., 1988).

FETAL INTERVENTION

No fetal intervention has been described following the prenatal diagnosis of truncus arteriosus.

TREATMENT OF THE NEWBORN

Immediately following delivery, the newborn with truncus arteriosus should have an evaluation by a pediatric cardiologist, including an echocardiographic examination to confirm the diagnosis and to exclude the presence of additional cardiac malformations. If complete visualization of cardiac and major-vessel anatomy is not obtained with echocardiography, cardiac catheterization may be required, with particular attention paid to the branching pattern of the pulmonary arteries, the anatomy of the aorta, and the presence of truncal insufficiency (Graham and Gutgesell, 1990). More recently, cardiac magnetic resonance imaging is playing an important role in delineation of cardiac anatomy, and may enable cardiac catheterization to be minimized (Dorfman and Geva, 2006).

Newborn infants with truncus arteriosus may initially appear cyanotic at birth, but this usually improves as pulmonary blood flow increases (Qu, 2004). Progressive congestive heart failure may then occur soon after delivery because pulmonary vascular resistance falls, often as early as 1 or 2 weeks after birth. Coronary artery perfusion may also be compromised, which, in combination with increased postnatal myocardial oxygen demand, may predispose to subendocardial ischemia (Graham and Gutgesell, 1990). To treat congestive heart failure during the newborn period, aggressive medical therapy is required, including the use of diuretics and digoxin. Medical therapy is often inadequate to prevent further deterioration of cardiac failure in these patients. Early intervention with definitive surgical repair may be the only option to prevent worsening cardiac failure and also to prevent the development of pulmonary hypertension secondary to increased pulmonary flow. Delaying surgical repair may also lead to the development of chronic ventricular dysfunction secondary to volume overload, which may compromise later repair (Graham, 1982).

SURGICAL TREATMENT

Surgical palliation of truncus arteriosus by means of pulmonary artery banding in an effort to reduce pulmonary flow and prevent the development of irreversible pulmonary hypertension has yielded disappointing results. In one series of 15 cases of pulmonary artery banding for truncus arteriosus during infancy, the overall mortality rate was 73% with all but one death occurring soon after surgery (Singh et al., 1976). Early definitive surgical repair of truncus arteriosus now seems to be the treatment of choice (Graham and Gutgesell, 1990; Bashore, 2007). In one series of 153 cases of truncus arteriosus repair from 1986 to 2003, the median age at surgery was 35 days (Henaine et al., 2008).

The standard surgical procedure for repair of truncus arteriosus involves placing a homograft between the right ventricle and the pulmonary artery and closing the VSD. This leaves the left ventricle in continuity with the truncus leading to the aorta. Hospital mortality for this procedure has been quoted as almost 30%, although the reported series often span a long period, include patients with many complicating factors, and use a valveless conduit (Spicer et al., 1984; Di Donato et al., 1985). Today however, the procedure generally also uses a valved conduit, yielding much better results with hospital mortality rates ranging from 11% to 17% of cases (Ebert et al., 1984; Pearl et al., 1992). Increased mortality occurs if significant truncal valve insufficiency is present, and in such cases a truncal valve replacement or truncal valve repair is generally also performed (Elami et al., 1994). Other risk factors for early death include the presence of coronary-artery anomalies, interrupted aortic arch, and age greater than 100 days at repair (Hanley et al., 1993). In a series of infants with simple truncus arteriosus repaired within the first 100 days of life, the operative mortality was 0% (Hanley et al., 1993).

LONG-TERM OUTCOME

The long-term outcomes associated with truncus arteriosus repair appear good. In one recent series of 153 cases, the 6-month survival rate was 82% while the 18-year survival rate was 79% (Henaine et al., 2008). The most common long-term complication following surgical repair of truncus arteriosus is the requirement for replacement of the right ventricle–pulmonary artery conduit because of body growth or development of pseudointimal proliferation within the conduit. Conduit replacement may be required in up to 60% of long-term survivors (Ebert et al., 1984). Reoperation may be associated with a further 4% to 7% risk of mortality (Pearl et al., 1992). Late deaths following contemporary surgical repair are uncommon, with only 3 late deaths in a series of 89 hospital survivors following repair; 2 of these 3 deaths were unrelated to the underlying cardiac condition (Ebert et al., 1984). The quality of life following surgical repair appears to be excellent, with 97% of patients in one series being very functional (Di Donato et al., 1985).

GENETICS AND RECURRENCE RISK

Truncus arteriosus may occur as part of the spectrum of the DiGeorge sequence. In a series of 26 infants with truncus

arteriosus, a high prevalence of facial dysmorphism, aortic-arch abnormalities, and immunodeficiency possibly consistent with DiGeorge sequence was noted (Radford et al., 1988). Familial clustering of truncus arteriosus is rare, with one case report of the abnormality recurring in a subsequent pregnancy and one case report of dizygotic twins concordant for the abnormality (Lang et al., 1991; Ferry et al., 1994). Generalized estimates of recurrence risk suggest a 1% rate of recurrence if one previous sibling has been affected and 3% if two siblings have been affected (Nora and Nora, 1988). If chromosomal analysis was not performed prenatally, it should be performed postnatally with fluorescence in situ hybridization studies for a microdeletion of chromosome 22q11. A 22q11 microdeletion will be found in up to 40% of cases of truncus arteriosus (Momma et al., 1997; Goldmuntz et al., 1998; Goldmuntz, 2005). In some cases, the microdeletion is inherited from one of the parents, who may not have cardiac disease. Diagnosis of DiGeorge syndrome in an infant necessitates study of the parental karyotypes before accurate recurrence risk counseling can be given.

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55 CHAPTER

Transposition of Great Arteries

Key Points

- Transposition of the great arteries is a relatively rare congenital cardiac malformation that has potential to cause major morbidity and mortality in the neonatal period.
- Complete TGA results in separation of the systemic and pulmonary circulations, because of ventriculoarterial discordance, and leads to severe hypoxia in the early neonatal period.
- Corrected TGA has both atrioventricular and ventriculoarterial discordance, so that effectively pulmonary and systemic circulations are normal, thereby rarely resulting in pediatric morbidity.
- Prenatal diagnosis of complete TGA is achieved by noting a parallel path of the ventricular outflow tracts, with lack of the normal crossover of these vessels.
- Prenatal recognition of complete TGA is critical, as immediate pediatric cardiology intervention in the early neonatal period will be required.
- The surgical treatment of choice for complete TGA has changed from the atrial switch to the arterial switch procedure, and is associated with excellent long-term survival.

CONDITION

Transposition of the great arteries (TGA) may be either complete or corrected. Complete TGA is also known as d-transposition, simple transposition, or atrioventricular concordance with ventriculoarterial discordance. This anomaly probably occurs because of failure of the aorticopulmonary septum to follow a spiral course during embryogenesis, resulting in the aorta arising from the right ventricle and the pulmonary artery arising from the left ventricle (de la Cruz et al., 1981). Atrial septal defect (ASD) and ventricular septal defect (VSD) are commonly seen with complete TGA and may also be associated with pulmonary artery obstruction. This is a potentially critical abnormality because, without a persistent communication between right and lefts sides of the heart, both the systemic and pulmonary circulations will run in parallel thereby preventing adequate oxygenation. Complete TGA usually causes no significant hemodynamic compromise when the fetus is in utero, but rapid deterioration occurs soon after birth in those cases without sufficient mixing of the right- and left-sided circulations.

In a cohort of 130 neonates delivered with TGA, Jouannic et al. (2004) noted that 13 of 130 neonates (10%) with TGA had profound hypoxemia (defined as a $Pao_2 < 25$ mm Hg) and metabolic acidosis (pH < 7.15) in the first 30 minutes of life (Jouannic et al., 2004). Fortunately, concurrent cardiac structural anomalies such as VSDs may allow for communication between right and left sides of the heart to allow adequate mixing of blood. Even in infants with an intact ventricular septum, a nonrestrictive foramen ovale and patent ductus arteriosus may also allow for adequate mixing of systemic circulation and oxygenated venous return to avoid significant hypoxemia early in the neonatal course. However, neonates with an intact ventricular septum and either a restrictive foramen ovale or constricted ductus arteriosus may experience significant preoperative morbidity due to inadequate intracardiac mixing. In these cases, severe hypoxemia may necessitate immediate balloon atrioseptostomy in order to prevent end organ damage from ongoing hypoxemia.

In order to optimally plan for delivery and neonatal management, efforts have been directed at identifying fetal echocardiographic predictors of fetuses who will require emergent atrial septoplasty at the time of birth. Jouannic et al. (2004) retrospectively assessed the degree of antenatal restriction of the foramen ovale and/or constriction of the ductus arteriosus in 119 fetuses (mean GA ~ 36 weeks' gestation). Twenty-four of 119 (20%) fetuses were noted to

have at least one abnormal shunt on prenatal echocardiography, and 4 (3.4%) had restriction of both the foramen ovale and the ductus arteriosus. Although the specificity of prenatal echocardiography in predicting neonatal emergency was high (84%), the sensitivity was only 54% and the authors concluded that prenatal echocardiography cannot detect all fetuses that will require required immediate balloon atrioseptostomy as neonates (Jouannic et al., 2004).

By contrast, corrected TGA refers to the connection of the right atrium to the morphologic left ventricle, which connects to the pulmonary artery, while the left atrium connects to the morphologic right ventricle and then to the aorta. This anomaly is also known as l-transposition, or atrioventricular discordance with ventriculoarterial discordance. Because both right and left cardiac blood flow follow their intended paths from systemic to pulmonary and back to systemic circulations, this anomaly effectively cancels itself out (Romero et al., 1988). While the right atrium empties into the anatomic right ventricle, this ventricle is in fact the morphologic left ventricle with a transposed pulmonary artery as its outflow tract. Similarly the left atrium empties into the anatomic left ventricle, which is in fact the morphologic right ventricle, connected to a transposed aorta. Physiologically it might be expected that this anomaly would not lead to hemodynamic compromise; however, because of a frequent association with other abnormalities such as VSD, pulmonic stenosis, conduction defects, and atrioventricular valve abnormalities, significant neonatal morbidity and mortality may still occur.

INCIDENCE

Earlier studies suggested that TGA may account for up to 10% of all infants born with congenital cardiac defects, representing approximately 2 to 3 per 10,000 livebirths (Fyler et al., 1980; Hoffman and Kaplan, 2002). In a more recent birth defects registry from Australia covering 631,209 births from 1993 to 2002, there were 4897 cases of congenital heart disease, of which 47 were TGA (Chew et al., 2007). This represents a birth prevalence of 0.7 per 10,000 births, or 1% of all cases of congenital heart disease.

SONOGRAPHIC FINDINGS

Complete TGA is recognized on prenatal sonography by careful visualization of the cardiac outflow tracts. Sonographic diagnosis relies on the demonstration of parallel outflow tracts, with absence of the normal crossover (Morelli et al., 1996). The normal crossover of the pulmonary artery and aorta is not seen, and the outflow tracts appear to run parallel to each other. Each outflow tract should be followed to its branches to positively differentiate the pulmonary artery from the aorta (McGahan et al., 2007) (Figures 55-1 and 55-2). The pulmonary trunk should be visible arising from the posterior ventricle, bifurcating into the left and right pulmonary arteries and ductus arteriosus. The aorta is visible arising anterior to the pulmonary artery and connecting to the aortic arch with brachiocephalic vessels. One of the most reliable prenatal diagnostic signs of complete TGA is the visualization of a straight vessel arising from the left ventricle, and giving off lateral branches, which represents the pulmonary artery bifurcation (Vinals et al., 2006).

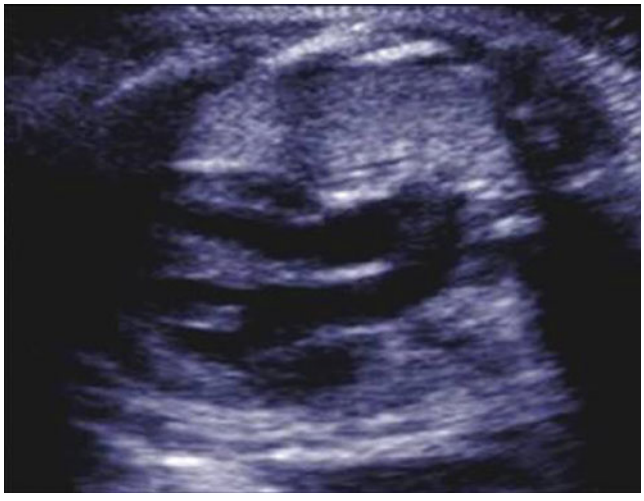

Figure 55-1 Sonographic image of a fetus with TGA demonstrating the parallel arrangement of the great arteries as they arise from the ventricles.

Prenatal sonographic diagnosis of corrected TGA is extremely difficult because the ventricular outflow tracts may appear to arise correctly from the anatomic right and left ventricles. In addition, the morphologic appearance of the anatomic left ventricle is more suggestive of a right ventricle, with a moderator band and triangular-shaped ventricular

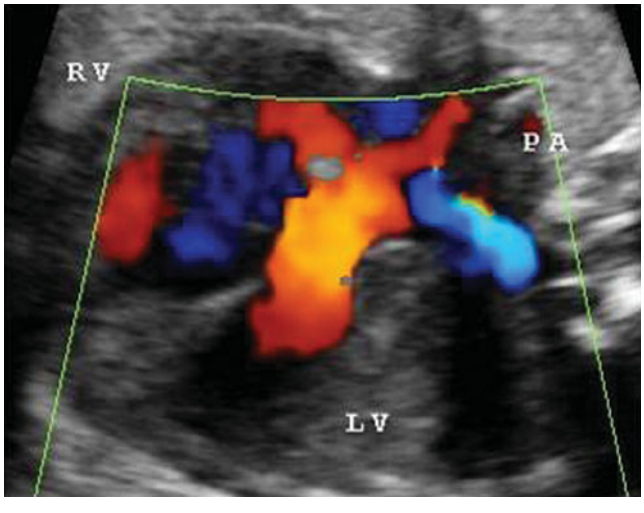

Figure 55-2 Color Doppler image in a fetus with transposition of the great arteries demonstrating the aorta arising from the anterior right ventricle and the pulmonary trunk from the left ventricle.

cavity. A normal left ventricular cavity should not demonstrate a moderator band and should be elliptical, rather than triangular, in shape.

Prenatal sonography is an important means of diagnosing or excluding additional coexisting cardiac malformations. VSD may be present in 50% of cases of TGA and, when found, is commonly accompanied by subvalvular pulmonic stenosis (Schiebler et al., 1961). As a result of interference with the conduction apparatus of the heart, arrhythmias are common, with complete heart block found in 4 of 21 fetuses with corrected TGA (Gembruch et al., 1989). Other cardiac malformations that may be detectable include ventricular hypoplasia and coarctation of the aorta (Santoro et al., 1997). The presence of situs inversus may also be found in the presence of corrected TGA (Abossolo et al., 1996). In a series of nine neonates with TGA, five were diagnosed prenatally and four of these five had complex cardiac malformations (McGahan et al., 2007). These complex cardiac malformations that were amenable to prenatal diagnosis included abnormal cardiac axis, abnormal ventricular size, and VSDs.

The precision of sonography as a tool in the prenatal diagnosis of TGA is unclear. In one series of screening sonograms of 11,894 fetuses, none of the 4 cases of TGA were detected prenatally (Tegnander et al., 1995). In another series of 50 infants operated on for TGA, 17 (34%) were successfully diagnosed prenatally through the use of obstetric sonography (Lupoglazoff et al., 1997). In addition, in another recent series of 111 congenital cardiac abnormalities, 5 of the 8 cases (63%) of TGA were detected on prenatal screening sonography (Kirk et al., 1997). In a review of all congenital cardiac malformations in one geographical area, only 5 of the 80 cases (6%) of TGA were detected prenatally (Montana et al., 1996).

It would appear that in the hands of expert sonologists in a referral population, the accurate prenatal detection of TGA is relatively high, but in general population screening, the vast majority of such cases go undiagnosed. This is supported by a review of all livebirths in Victoria, Australia, from 1993 to 2002, when only 17% of TGA cases were correctly identified prenatally (Chew et al., 2007). In fact, TGA was the least likely major congenital cardiac malformation to be diagnosed prenatally.

DIFFERENTIAL DIAGNOSIS

One of the most difficult congenital cardiac anomalies to differentiate from TGA is double outlet right ventricle, especially when TGA is accompanied by a VSD (Sanders et al., 1996). Careful attention should be paid to any potential straddling or overriding of atrioventricular valves. The Taussig–Bing heart, a variant of double outlet right ventricle in which the aortic and pulmonary outflow tracts ascend in a parallel fashion, may mimic the appearance of TGA (see Chapter 47).

ANTENATAL NATURAL HISTORY

In general, both complete and corrected forms of TGA are well tolerated by the fetus in utero because both ventricles pump into the systemic circulation. However, the presence of additional cardiac malformations, such as VSD or pulmonic stenosis, may alter the antenatal natural history, potentially leading to the development of congestive heart failure, or hydrops, in utero.

In a series of five fetuses with TGA diagnosed prenatally, one pregnancy was terminated, and the remaining five resulted in livebirths; two of these infants died during the neonatal period (Smythe et al., 1992). In another series evaluating the outcome of various prenatally diagnosed cardiac malformations, all three fetuses with TGA survived (Sharland et al., 1990). More recently, in 23 cases of prenatally diagnosed TGA, 6 pregnancies (26%) were terminated, 3 (13%) fetuses died in utero, 8 (35%) died during the neonatal period, and 6 (26%) survived (Paladini et al., 1996).

MANAGEMENT OF PREGNANCY

Following prenatal diagnosis of TGA, a careful sonographic fetal anatomy survey is recommended to exclude additional cardiac malformations, such as VSD, pulmonic stenosis, aortic coarctation, and arrhythmias. A sonographic search for extracardiac malformations should also be performed, although in general such abnormalities are rarely found with TGA. Fetal echocardiography should be performed by an appropriately trained specialist to confirm the diagnosis and to exclude other cardiac malformations. Invasive fetal testing for karyotype analysis is recommended following the prenatal diagnosis of most cardiac malformations, although the incidence of chromosomal abnormalities is likely to be very low. In one series of 23 cases of prenatally diagnosed TGA, chromosomal analysis was normal in the 21 cases in which karyotype was known (Paladini et al., 1996). Referral for prenatal consultation with a pediatric cardiologist and cardiothoracic surgeon is also recommended.

If the diagnosis of complete TGA is made prior to fetal viability, termination of pregnancy may be offered because of the significant neonatal mortality and surgical morbidity. If expectant management is desired, sonographic surveillance to confirm appropriate fetal growth and to evaluate for the development of fetal hydrops is recommended, especially if additional cardiac malformations such as VSD and pulmonic stenosis are present. If fetal hydrops occurs, the prognosis deteriorates further; the optimal management of such pregnancies is uncertain.

Delivery should occur at a tertiary care center, with the immediate availability of a neonatologist, pediatric cardiologist, and cardiothoracic surgeon. In an effort to identify fetuses that may require immediate balloon atrioseptostomy, predelivery echocardiography may be performed to assess for restriction of the foramen ovale and/or the ductus arteriosus.

For those fetuses noted to have restriction of either the foramen ovale and/or the ductus arteriosus, delivery plans should be discussed with neonatalogy and pediatric cardiology in order to facilitate timely intervention if emergent balloon atrial septostomy is needed.

FETAL INTERVENTION

No fetal intervention has been described for the obstetric or prenatal management of TGA.

TREATMENT OF THE NEWBORN

The condition of most infants with isolated complete TGA will deteriorate soon after birth, resulting in death, without surgical intervention. Indeed, complete TGA is one of the most common cyanotic defects seen in newborns, with cyanosis presenting within hours of life if the ventricular septum is intact (Warnes, 2006). Following delivery, care should be taken with the administration of supplemental oxygen so as to avoid significant reduction in pulmonary vascular resistance, which may decrease the amount of blood shunted across the ductus arteriosus. The infant should be transported to a neonatal intensive care unit and, if cyanosis is present, prostaglandin E_1 infusion should be started to maintain patency of the ductus arteriosus (Sommer et al., 2008).

Consultation with a pediatric cardiologist should be obtained promptly, and echocardiography should be performed to confirm the prenatal diagnosis and to determine the absence of additional cardiac malformations. Patency of both ventricular outflow tracts should be assessed, and the coronary-arterial anatomy should be mapped in preparation for surgical repair. When an intact ventricular septum exists and when inadequate atrial communication is present, balloon atrial septostomy may be needed during the initial resuscitation to maximize oxygenation of systemic blood (Graham and Gutgesell, 1990). Such balloon atrial septostomy may be performed either during cardiac catheterization or using echocardiographic guidance. This usually results in sufficient bidirectional shunting of blood to improve the systemic oxygen content. Occasionally, atrial septostomy is insufficient to improve systemic oxygenation, which may be secondary to inadequate atrial defect size, abnormal ventricular compliance, elevated pulmonary vascular resistance, or left ventricular outflow tract obstruction (Graham and Gutgesell, 1990). Consultation with a pediatric cardiothoracic surgeon should then be obtained to decide on the timing and method of surgical intervention, such as surgical atrial septostomy or arterial switch procedure.

Infants with TGA and a coexisting large VSD are usually stable initially, and then after a few weeks of life congestive heart failure occurs. These infants account for less than 25% of all cases of TGA. Such patients can usually be treated medically, with digoxin and diuretics, before surgical repair is considered. However, delay in surgical repair beyond the end of the third month of life may lead to the development of abnormal pulmonary vascular resistance, which occurs earlier in infants with TGA and VSD as compared with infants with left-to-right shunts without TGA (Graham and Gutgesell, 1990).

SURGICAL TREATMENT

Surgical repair is indicated for all infants with complete TGA and is generally best performed soon after birth, often within the first 2 weeks of life. Initial procedures, such as the Senning or the Mustard operation, were designed to physiologically correct cardiac blood flow through the use of the atrial septum or a baffle to redirect vena caval return to the left ventricle and pulmonary venous return to the right ventricle. However, such atrial repairs were associated with high operative mortality as well as significant late complications (Castaneda and Mayer, 1990). Such significant late complications included bradyarrhythmias and tachyarrhythmias (Warnes, 2006). Subsequently, an anatomic repair, known as the arterial switch procedure, has been devised, and involves dividing the pulmonary artery with reanastomosis to the right ventricular outflow tract, and dividing the aorta with reanastomosis to the left ventricular outflow tract. To be successful this procedure must be done early in neonatal life, before the left ventricle adapts to the lower pressure pulmonary circulation that would prevent it being able to subsequently support the systemic circulation.

Arterial switch repair is performed through a median sternotomy incision and with cardiopulmonary bypass (Castaneda and Mayer, 1990). The aorta is transected distal to the origin of the coronary arteries. The coronary arteries are then excised and transposed to the origin of the pulmonary artery from the left ventricle (Warnes, 2006). The pulmonary artery is then transected distal to this coronary artery connection but proximal to the bifurcation, and is reanastomosed to the original right ventricular outflow tract stump. Similarly, the aorta is reanastomosed to the left ventricular outflow tract stump. This results in complete anatomic repair of the great vessels and coronary arteries.

The operative mortality rate for the arterial switch repair is between 5% and 8%, with a 1-month survival of 84% (Kirklin et al., 1992; Qamar et al., 2007). Risk factors for perioperative death include the presence of multiple VSDs, anomalous coronary artery anatomy, additional cardiac malformations, and long aortic cross-clamp time. In another series of 432 arterial switch procedures performed in a single center at an average of 3 days of life, the operative mortality rate was 8%, with anomalous coronary artery anatomy being the only identified risk factor for early death (Serraf et al., 1993). A further series of 168 cases that underwent arterial switch suggested that weight less than 2.5 kg, premature gestational age at delivery, and more than 150 minutes of

cardiopulmonary bypass time as being associated with decreased hospital survival (Qamar et al., 2007). Complications of the arterial switch procedure include coronary stenosis that may lead to sudden death or myocardial infarction (Warnes, 2006; Sommer et al., 2008).

One other surgical approach that may be considered includes the Rastelli procedure, which is used when complete TGA coexists with a large VSD and pulmonary stenosis. The pulmonary valve is oversewn and a new valved conduit is placed between the right ventricle and the pulmonary artery (Warnes, 2006).

LONG-TERM OUTCOME

Overall long-term results for TGA suggest a 60% actuarial survival at 15 years of age (Morris and Menashe, 1991). Long-term results specifically for the atrial switch repair (Senning or Mustard procedures) suggest that up to 10% die while waiting for surgery, but of those operated on, 80% are alive after 20 years (Kirklin et al., 1990). There seems to be a progressive decline in the prevalence of normal sinus rhythm in these patients, which may account for sudden late deaths. Although atrial switch survivors can live normal active lives, exercise testing is generally subnormal (Kirklin et al., 1990).

Survival data on long-term outcome following the arterial switch repair is as readily available because of relatively short duration of use. Five-year survival following the arterial switch repair was 82% in one multicenter series, with almost all survivors in New York Heart Association functional class I (Kirklin et al., 1992). In a series of 168 arterial switch procedures, 3-year actuarial survival was 89% (Qamar et al., 2007). In one of the largest series of long-term follow-up of cases of arterial switch surgery, 224 patients were followed and revealed 83% survival at 15 years after surgery (Wong et al., 2008).

The long-term fate of the coronary arteries is unclear, as there may be significant kinking or compression following the arterial switch procedure. Surveillance with echocardiography and myocardial scintigraphy is therefore recommended for survivors to detect early ventricular ischemia (Kaplan and Allada, 1992). In one series of 58 children with coronary-artery surveillance following the arterial switch procedure, 8% had evidence of late coronary artery complications (Bonnet et al., 1996). Delayed repair of TGA may be associated with progressive impairment of cognitive function (Newburger et al., 1984).

GENETICS AND RECURRENCE RISK

Almost all cases of TGA occur as isolated cardiac malformations with normal karyotype (Paladini et al., 1996). Risk of recurrence has been estimated as 1.5% if 1 prior sibling has been affected, and this may increase to 5% with 2 prior affected siblings (Nora and Nora, 1988).

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56 CHAPTER

Heterotaxy Syndrome

Key Points

- Heterotaxy is an abnormality of formation of the left–right axis of the body.
- Heterotaxy refers to any arrangement that deviates from situs solitus or complete situs inversus.
- Left atrial isomerism or polysplenia syndrome usually has absent right-sided organs and bilaterally placed left-sided organs with multiple splenic masses along the greater curvature of the stomach.
- Right atrial isomerism or asplenia syndrome usually has bilaterally trilobed lungs, globular central lines, severe congenital heart defects, and absent spleen.
- Fetal echocardiography is indicated in all suspected cases of heterotaxy.
- Delivery in a tertiary care center is recommended.

CONDITION

Heterotaxy is defined as any arrangement of the body organs that deviates from complete situs solitus with levocardia and dextrocardiac loop (the normal arrangement) or from complete situs inversus with dextrocardia and a levocardiac loop.

During development there is a failure to form asymmetry along the left–right axis in the heterotaxy syndrome. In normal development, this asymmetry is first manifested at 2 to 23 days of gestation, with looping of the cardiac tube to the right (Gutgesell, 1990). During this same period, abdominal situs is determined (Chandra, 1974; Gray et al., 1994). The

270-degree counterclockwise rotation of the intestine about the axis of the superior mesenteric artery is completed by 10 weeks. Because looping of the cardiac tube and intestinal rotation both occur during the 4th week of gestation, defects of the cardiac situs are frequently associated with abnormal intestinal rotation. Because development of the heart is dependent on the formation of a normal left–right relationship, heterotaxy is associated with congenital heart disease in the majority of cases (Chandra, 1974; Gutgesell, 1990; Cohen et al., 2007).

There is a spectrum of defects in heterotaxy syndrome, varying from isolated levocardia with abdominal situs inversus or isolated dextrocardia with abdominal situs solitus to total absence of asymmetry along the left–right axis. The most significant forms of heterotaxy syndrome are seen in left isomerism (also known as the polysplenia syndrome) or right isomerism (also known as asplenia syndrome). The term *asplenia* originated from Ivemark's (1955) initial description of cardiac malformations associated with congenital asplenia. Moller et al. (1967) subsequently reported another syndrome, also with cardiac and visceral abnormalities, but because it was associated with multiple splenic masses, it was called "polysplenia syndrome."

Sapire et al. (1986) further described these syndromes in relation to anatomic features of the atria, such as right atrial isomerism (asplenia syndrome) and left atrial isomerism (polysplenia syndrome). This distinction was suggested because the anatomic features of the atria more reliably reflect the visceral abnormalities than does the spleen. Usually asplenia occurs in right atrial isomerism and polysplenia occurs in left atrial isomerism, but discrepancies have been reported (Caruso and Becher, 1979). In addition, each condition has been described with both the presence of a normal spleen (Laman et al., 1967; Landing et al., 1971) and normal cardiac anatomy (Peoples et al., 1983). Left atrial isomerism accounts for most cases of "polysplenia syndrome" (Moller et al., 1967; Van Mierop et al., 1972; Rose et al., 1975; Peoples et al., 1983). Polysplenia is usually manifested as multiple splenic masses along the greater curvature of the stomach. The combined weight of the splenic tissue is approximately equivalent to a normal spleen. Left atrial isomerism usually has absent right-sided organs and bilaterally placed left-sided organs. Left atrial isomerism is usually associated with less severe cardiac anomalies and better survival than right atrial isomerism (Peoples et al., 1983; Sapire et al., 1986).

Left Atrial Isomerism

The organs most involved in left atrial isomerism are the lungs, liver, heart, and intestines. The lungs are symmetric mirror images of the left lung with only two lobes. Each side has left-sided relationships between the pulmonary artery and the mainstem bronchi (Moller et al., 1967). The pulmonary artery courses over and behind the mainstem bronchus on both sides, as in a normal left lung. The bronchi branch in a pattern similar to the left tracheobronchial tree and there is no horizontal minor fissure on the right because there are only two lobes.

The liver usually is abnormal in shape and position and typically has a central globular appearance, as it is symmetric. The gallbladder may be midline, hypoplastic, or absent. In 10% of the cases, biliary anomalies can also be seen (Peoples et al., 1983). Several cases of biliary atresia have been reported in left atrial isomerism (Mayo et al., 1949; Teichberg et al., 1982).

The intestines demonstrate nonrotation or reverse rotation of the midgut loop. The initial 90-degree counterclockwise rotation occurs, but the final 180-degree rotation about the superior mesenteric artery does not occur. The result is that the small intestine is on the right side of the abdomen and the colon is on the left. In severe reverse rotation, the midgut rotates clockwise instead of counterclockwise. The result is that the duodenum lies inferior to the superior mesenteric artery and the transverse colon behind it. These rotational abnormalities are prone to proximal intestinal obstruction or midgut volvulus.

Cardiac anomalies in the left atrial isomerism can occur at every level of the heart (Moller et al., 1967; Van Mierop et al., 1972; Rose et al., 1975; Tommasi et al., 1981; Peoples et al., 1983). In 50% of the cases, there are bilateral venae cavae connecting to the superior posterior aspect of the ipsilateral atrium. In rare cases, a single superior vena cava (SVC) connects to the coronary sinus, but the coronary sinus is usually absent. In 65% of the cases, the intrahepatic inferior vena cava (IVC) is interrupted. The IVC above the renal veins connects to the azygous system. The hepatic veins connect directly to the floor of the atrium. Anomalous pulmonary venous return occurs in 40% of the patients (Ware et al., 2004). This is usually partial, with the veins from each lung entering the ipsilateral atrium on the opposite sides of the midline. The atria each show features of the left atrium with a long narrow atrial appendage. The atrial septum is usually absent, with an ostium primum defect in 65% of the cases.

Peoples et al. (1983) reviewed the ventricular anatomy of 127 cases of left atrial isomerism and found that in 38 the ventricular septum was intact, in 80 a ventricular septal defect (VSD) was present, and in 9 there was a univentricular heart. The VSD was either a form of endocardial cushion defect or a VSD in one of the typical locations. The atrioventricular connection is ambiguous through either a common or two-leaflet valve (Tommasi et al., 1981). In a univentricular heart, there is usually a double inlet ventricle to a chamber of right or left ventricular morphology.

The great vessels in the left atrial isomerism are concordant in 69% (Peoples et al., 1983). The remainder are equally divided between discordant atrioventricular connection and double outlet ventricle (usually of the right, but sometimes double outlet left ventricle can be seen). In 20% of the cases, the side of the aortic arch is opposite the side of the cardiac apex.

The pulmonary valve of the right ventricular outflow area is normal in 65% of the cases. In the remaining cases, the pulmonic valve is stenotic (20%) or atretic (10%) with isolated subpulmonic stenosis in the remainder. In the left side

of the heart, Peoples et al. (1983) found obstructive lesions in 22% of cases. These included valvular or subvalvular aortic stenosis (11 cases), coarctation of the aorta (7), hypoplastic left heart, hypoplastic left ventricle (6), mitral stenosis (3), and cor triatriatum (1).

Right Atrial Isomerism

The asplenia syndrome is now best described, in terms of the visceral asymmetry, as right atrial isomerism. Although most patients will lack a spleen, some patients will have a normal spleen or multiple spleens. These patients usually come to the attention of a pediatric cardiologist early in life, secondary to severe associated congenital heart disease. Although historically 90% of the patients with the asplenia syndrome died by 1 year of age, survival has significantly improved due to advances in cardiac diagnosis, the use of prostaglandin E_1 in duct-dependent lesions, and improvements in cardiac surgery (Ivemark, 1955; Van Mierop et al., 1972; Chang et al., 1993).

In right atrial isomerism, there are multiple visceral abnormalities that affect the heart, lungs, liver, and gastrointestinal tract. The lungs are both trilobed and the pulmonary arterial relationships with the tracheobronchial tree may be obscured by proximal pulmonary atresia. The lungs often derive significant blood flow from systemic vessels. The liver occupies a central position in the upper abdomen with the globular transverse lie.

Some take exception to the concept of atrial isomerism in heterotaxy (Van Praagh, 1985; Van Praagh and Van Praagh, 1990). Van Praagh has written that the concept of atrial isomerism is conceptually and anatomically flawed, as the atrial appendages are not mirror images of each other. The heart is organized initially as a cephalocaudally oriented blood vessel. In contrast to other viscera, in the heart left–right organization is not initially present in the embryo but is acquired later in development. This group suggested criteria to define the morphologic right atrium as one that receives: (1) all of the systemic veins, while a separate atrium receives all of the pulmonary veins; or (2) all of the systemic veins and some or all of the pulmonary veins, without losing a common atrium because a second atrium is present; or (3) the orifice of a normal coronary sinus. In contrast, the morphologically left atrium can be defined as the atrium that receives: (1) all or half of the pulmonary veins, but none of the systemic veins (except for a persistent SVC associated with an unroofed coronary sinus in cases with bilateral SVC); or (2) none of the pulmonary veins and none of the systemic veins. In addition, the left atrial appendage is usually smaller and more posterior than the right atrial appendage.

INCIDENCE

It is difficult to estimate the incidence of heterotaxy, because birth defect registries track each anomaly separately. A recent study with strict diagnostic criteria estimated the prevalence of heterotaxy to be 1 in 10,000 birth (Lin et al., 2000). The observed male-to-female ratio is 2 to 1. Overall, heterotaxy account for 3% of cases of congenital heart disease (Ware et al., 2004).

SONOGRAPHIC FINDINGS

Accurate prenatal diagnosis in heterotaxy is not only possible but offers the advantage of assisting postnatal management (Allan et al., 1994; Copel et al., 1997; Lin et al., 2002; Taketazu et al., 2006).

The determination of visceral situs may be quite challenging for the ultrasonographer. Often, abnormal cardiac situs and a structural defect are detected simultaneously, raising the suspicion of heterotaxy. Certain cardiac defects are more commonly associated with asplenia syndrome. These include total anomalous pulmonary venous return, VSD, single ventricle, transposition of the great arteries, and dextrocardia. In polysplenia, bilateral SVC, absent or interrupted IVC, anomalous pulmonary venous return, dextrocardia, atrioventricular septal defect, transposition of great arteries, and double outlet right ventricle are typical anomalies (Van Mierop et al., 1972). The sonographic findings that distinguish between polysplenia and asplenia are summarized in Table 56-1.

Detection of visceral situs can be difficult, as the liver may have a central position and the stomach bubble location may be right, left, or central (Figure 56-1). In the asplenia syndrome, the relationship between the IVC and aorta is helpful in diagnosing heterotaxy. Huhta et al. (1982) noted in newborns that in asplenia syndrome the descending aorta and the IVC run on the same side of the spine, either to the right or left. The aorta is usually positioned posterior to the IVC. This relationship is best appreciated in a transverse cross section of the fetal abdomen below the diaphragm (Figure 56-2). The IVC and aorta should then be followed proximally to the right atrium and descending thoracic aorta, respectively. The IVC is often interrupted in the polysplenia syndrome, with blood flow continued via communication though the azygos vein on either the left or right side of the spine. The aorta usually courses anterior to the spine in the midline. There is a good deal of overlap between these conditions, and identification of IVC and aorta on the same side of the spine has been described in both asplenia and polysplenia syndromes.

Echocardiographic assessment should attempt to identify the presence of right, left, or bilateral SVC and its connection to the atria. In bilateral SVCs, the left may connect to the coronary sinus or the left atrium. An attempt should be made to identify the pulmonary veins. In total anomalous pulmonary veins, if a venous connection is seen with situs ambiguous, then right atrial isomerism should be suspected. In contrast, partial anomalous venous connection to the right atrium suggests left atrial isomerism. In addition, the atrioventricular connection and ventriculoatrial connection should be determined.

Table 56-1

Prenatal Sonographic Findings in Heterotaxy Syndromes

Finding	Polysplenia	Asplenia
Sidedness	Left	Right
Spleen	Present (multiple)	Absent
Gallbladder	Absent	Present
Liver	Left or right side	Midline
Heart malformations	ASD, AVC, TGA, DORV	AVC, single ventricle, TGA, PS
Vena cava	Interrupted IVC Bilateral SVC	Same side as aorta Bilateral SVC
Anomalous pulmonary	70% of cases	100% of cases
Venous return		
Sex ratio	Equal in males and females	2 females : 1 male

KEY: ASD = atrial septal defect; AVC = atrioventricular canal defect; DORV = double outlet right ventricle; IVC = inferior vena cava; PS = pulmonic stenosis; SVC = superior vena cava; TGA = transportation of great arteries.

ANTENATAL NATURAL HISTORY

Little is known of the antenatal natural history of heterotaxy because it has been recognized prenatally only relatively recently (Berg et al., 2003; Cohen, 2006). Abnormal situs does not in itself pose adverse consequences for the fetus, with two notable exceptions. The prenatal as well as postnatal courses are thought to be determined primarily by the severity of the cardiac defect. Most structural heart defects associated with heterotaxy are well tolerated in utero. Because most cases of right atrial isomerism have pulmonary stenosis or atresia and total anomalous pulmonary venous return, they will usually need palliative treatment early in postnatal life (Masood et al., 1996; Wu et al., 1998). Patients with left atrial isomerism tend to have less complex cardiac anomalies and in general a better prognosis than patients with right atrial isomerism (Rose et al., 1975; Van Praagh et al., 1992). Exceptions to this are cases of left atrial isomerism associated with heart block, which result in nonimmune hydrops (Phoon et al., 1996).

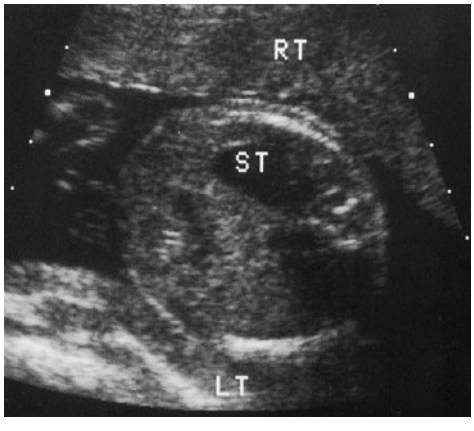

Figure 56-1 Antenatal sonographic image demonstrating the presence of the fetal stomach in the right upper quadrant.

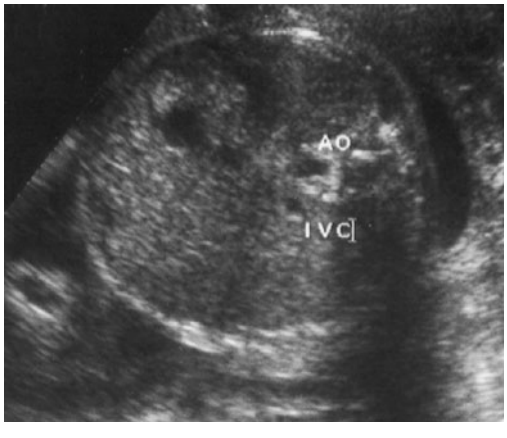

Figure 56-2 Transverse section through the abdomen of a fetus with total sinus inversus. The fetal right side is superior in this picture. Ao = aorta; IVC = inferior vena cava. (*Courtesy of Dr. Marjorie Treadwell.*)

Prenatal mortality in left atrial isomerism may be as high at 31% due to heart block and extracardiac pathology (Taketazu et al., 2006).

In cases in which heterotaxy results in intestinal malrotation, the risk of midgut volvulus exists. However, no case of prenatal midgut volvulus due to heterotaxy has been reported to date. The presence of biliary atresia or intestinal obstruction is more frequently identified in nonsurvivors (Taketazu et al., 2006). The presence of biliary atresia or other gastrointestinal malformations is associated with 2- and 2.5-fold increased risk of mortality, respectively (Gilljam et al., 2000).

MANAGEMENT OF PREGNANCY

In cases of suspected heterotaxy, obstetric management should include a detailed sonographic evaluation to delineate the situs and extent of visceral abnormalities. Fetal echocardiography should be performed in all cases to determine the nature and severity of associated cardiac defects. Chromosome abnormalities are associated with major congenital heart defects, but they are not typically associated with heterotaxy (Lin et al., 2000). Nonetheless, if a cardiovascular malformation is present with heterotaxy, amniocentesis is warranted. The prospective parents should meet with a medical geneticist to review the family history and discuss DNA mutation testing.

There is no indication for changing the mode or timing of delivery except for standard obstetrical indications. However, because of the potential for severe structural heart disease, referral for delivery in a tertiary care center with neonatologists, pediatric cardiologists, and pediatric cardiac surgeons available is recommended.

FETAL INTERVENTION

There is no fetal intervention for heterotaxy. However, in cases of left atrial isomerism, heart block may result in hydrops and fetal mortality. Complete heart block complicates as many as 15% of left isomerism cases (Taketazu et al., 2006). If caught early in the progression to hydrops, fetal cardiac pacemaker placement may be an option to salvage fetuses with correctable cardiac anomalies.

TREATMENT OF THE NEWBORN

Much of the initial treatment of the infant with heterotaxy will be dictated by the specific associated cardiac defect. The reader is referred to the individual chapters on structural heart disease (see Chapters 43–55). The newborn with heterotaxy should undergo plain abdominal radiography of the chest and abdomen to confirm the diagnosis of heterotaxy. Postnatal echocardiography should be performed to confirm prenatal

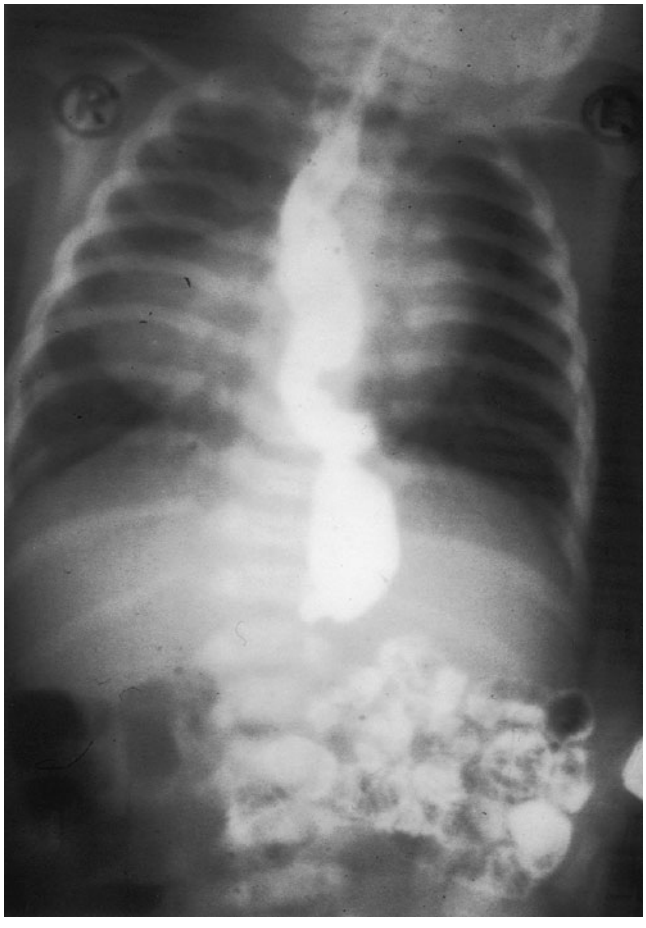

Figure 56-3 Postnatal contrast study in an infant with heterotaxy. Note that there is dextrocardia, vascular congestion, and situs ambiguous with the stomach lying centrally. The stomach is small and the liver fills the upper abdomen. (*Courtesy of Dr. Roy McCauley.*)

echocardiographic assessment and to define the anatomic defect. When the infant is stable for transport to the radiology suite, an upper gastrointestinal series and small-bowel follow-through should be performed to evaluate abnormalities in intestinal fixation that may predispose to midgut volvulus (Figure 56-3). In cases of asplenia, the newborn should be maintained on prophylactic penicillin and receive the pneumococcal vaccine.

LONG-TERM OUTCOME

The long-term outcome of children with heterotaxy is directly related to the severity of the associated cardiac anomaly and/or the presence of biliary atresia (Zhu et al., 2006).

GENETICS AND RECURRENCE RISK

There is evidence to support multiple patterns of inheritance of heterotaxy. Most cases of heterotaxy are single

occurrences in a family. Approximately 10% of infants with heterotaxy, however, have a family history of a close relative with congenital heart defects (Belmont et al., 2004). Analysis of the Baltimore-Washington Infant Study data from 1980 to 1989 suggests the potential importance of a positive family history of cardiac malformations (odds ratio 5.1; 95% CI, 2.0–12.9), maternal diabetes (odds ratio 5.5; 95% CI, 1.6–19.1), and parental cocaine use (odds ratio 3.7; 95% CI, 1.3–10.7) as risk factors for heterotaxy (Kuehl and Loffredo, 2003).

Heterotaxy occasionally occurs in families in a recurring pattern, suggestive of autosomal recessive, X-linked, or autosomal dominant inheritance. Alonso et al. (1995) reported six families with a pattern of recurrence suggestive of an autosomal dominant inheritance. Ferraro et al. (1997) studied a large family in which a gene for heterotaxy (*HTX-1*) was mapped to Xq26.2.

There is a growing body of evidence that supports the role of single-gene mutations in heterotaxy. The occurrence of families with X-linked inheritance has been demonstrated by linkage analysis (*HTX1*, Xq26.2) and confirmed by mutations in the gene *ZIC3*. *ZIC3* is a zinc finger protein that localizes to the nucleus with potential DNA binding activity. The 5 zinc finger motifs in *ZIC3* share sequence similarities with the *GL1* family of transcription factors. Mutations in *ZIC3* may result in absent or abnormal transcriptional activator function (Ware et al., 2004). There have been several reports of deletion nonsense, frameshift, and missense mutations in *ZIC3*. Some of these mutations have occurred in phenotypically normal subjects, and individuals with situs inversus without congenital heart defects, or with congenital heart defects such as hypoplastic left heart syndrome, which would not usually be considered in the spectrum of left–right patterning defects. Mutations in *ZIC3* account for 1% of all cases of heterotaxy (Belmont et al., 2004; Ware et al., 2004). Commercial DNA testing is available for *ZIC3* mutations. If consultation with a medical geneticist was not obtained prenatally, it should be obtained postnatally to take a complete family history, consider DNA testing options, and to discuss recurrence risk. Studies in model organisms suggest that more than 80 genes must function to develop normal asymmetric left–right organs (Zhu et al., 2006).

In the *Zic3*-deficient mouse, there is improper nodal expression (Purandare et al., 2002). The node is a transient midline structure that forms during gastrulation and is critical for decisions regarding laterality. In null mutations in *ActRIIB* and *Cryptic/EFG-CFC* there is a failure of *nodal* signaling and right atrial isomerism. Null mutations in *lefty-1* result in left isomerism due to failure of nodal signaling restricted to the left. Human mutations do not replicate exactly the mouse phenotype. For example, the phenotype of patients with mutations in *LEFTYA*, the human homolog of mouse *lefty-1* is not characterized as left or right patterning failure (Kosaki et al., 1999). There are numerous possible reasons that may account for discrepancies between murine and human phenotypes which include, but are not limited to, haploinsufficiency versus null mutations, deficiencies in *NODAL* functions between mouse and human alternative roles for *CRYPTIC* or *ACVR2B*, or differential role of modifier genes (Belmont et al., 2004). The differences between the mouse and human phenotypes highlight the complexities involved in left–right patterning at the level of signaling pathways and regulatory interaction, even when the mutations are the same.

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57 CHAPTER

Cardiomyopathy

Key Points

- Generally classified as dilated or hypertrophic cardiomyopathy.
- Incidence is 1.2 per 100,000. Higher in males due to X-linked conditions.
- Most common causes of hypertrophic cardiomyopathy are maternal diabetes, twin–twin transfusion, Noonan syndrome, inborn error of metabolism, and familial single-gene disorder.
- Most common causes of dilated cardiomyopathy are infection, endocardial fibroelastosis, dysrhythmia, carnitine deficiency, and familial single-gene disorder.
- Associated with high incidence of antenatal cardiac dysfunction and in utero mortality (except if due to maternal diabetes).
- Twenty percent of cases are familial. Obtain a family history and consider evaluating both parents.
- As many as 40% of cases require postnatal heart transplant.
- Increasing numbers of causative mutations in genes for sarcomeric and cytoskeletal proteins have been identified. Most are inherited as autosomal dominant disorders with variable penetrance.

CONDITION

Cardiomyopathy refers to cardiac hypertrophy manifested by an increased interventricular septal size and/or free ventricular wall size in the absence of an increased cardiac load, accompanied by decreased cardiac function and by ventricular dilation (Michels et al., 1992). More broadly, cardiomyopathy is defined as a disease of the myocardium characterized by the presence of systolic or diastolic dysfunction or abnormal myocardial structure (Schwartz et al., 1996). The condition is rarely observed during fetal life. Cardiomyopathy is generally classified as dilated or hypertrophic.

INCIDENCE

The incidence of fetal cardiomyopathy is not precisely known, but it is rare. In one study, dilated cardiomyopathy was present in approximately 2% of fetal cardiac abnormalities (Sivasankaran et al., 2005).

Relatively recently, two large-scale population-based cohort studies of cardiomyopathy in children were published. One was performed in Australia (Nugent et al., 2003) and one involved American children in New England and the Central Southwest (Lipshultz et al., 2003). In the Australian study, the incidence of cardiomyopathy was 1.24 per 100,000. Of these, 58.6% had dilated cardiomyopathy, 25.5% had hypertrophic cardiomyopathy, 9.2% had cardiomyopathy due to noncompaction of the left ventricle, and 2.5% of cases were restrictive. There was a large familial component (19.8% of cases). Indigenous children had a 2.67-fold relative risk of having the disease compared to nonindigenous children. The American study showed a similar incidence (1.13 per 100,000) and identified a peak incidence in the first year of life. In this study, 51% of cases were due to dilated cardiomyopathy, 42% to hypertrophic, 3% to restrictive, and 4% to unspecified. The American study noted a higher incidence in black children. Both studies documented a higher incidence in males, presumably due to the X-linked conditions that are associated with cardiomyopathy, such as Duchenne, Becker, and Barth syndromes.

SONOGRAPHIC FINDINGS

Relatively few reports of the prenatal diagnosis of fetal cardiomyopathy exist. One of the most comprehensive encompasses a 9-year retrospective review of fetuses studied in the Fetal Cardiac Program at the Hospital for Sick Children in Toronto (Pedra et al., 2002). This study reported on 55 affected fetuses. Evaluation included a complete two-dimensional study, spectral Doppler, and color flow mapping. The authors measured cardiothoracic ratio, left and right ventricular end-systolic and end-diastolic diameters, and wall thickness. Measurements in affected pregnancies were compared with values obtained in 55 normal fetuses. Ventricular systolic and diastolic function was assessed. Dilated cardiomyopathy was diagnosed in the presence of systolic dysfunction with or without significant chamber enlargement but without wall thickening. Hypertrophic cardiomyopathy was diagnosed when the ventricular wall thickness was $\geq$2 SD above the normal mean for gestational age, with or without ventricular systolic or diastolic dysfunction (Pedra et al., 2002).

Although the incidence of hypertrophic cardiomyopathy in the Pedra et al. (2002) study was higher than dilated cardiomyopathy, the numbers are affected by two reasonably common conditions, maternal diabetes and twin–twin transfusion syndrome (see Chapter 119). A significant body of literature exists on the fetal heart in the offspring of the diabetic mother. Gutgesell et al. (1980), studied 47 infants of diabetic mothers by echocardiography. In this study, 24 of the infants were clinically symptomatic. Five had marked septal hypertrophy with echocardiographic features that suggested left ventricular outflow obstruction. Five infants had hypertrophy of the right ventricular free wall. One symptomatic infant died from an unrelated bacterial infection. In the clinically asymptomatic infants, three were shown to have septal hypertrophy, two had right ventricular free wall hypertrophy and no patients had left ventricular outflow obstruction. None of the patients in the entire study had evidence of dilated or congestive cardiomyopathy, and all patients had resolution of their echocardiographic abnormalities during the first 6 months of life. This was the first report to suggest the use of echocardiography to follow cardiac changes occurring in infants of diabetic mothers. The alterations in the hearts of infants of diabetic mothers were shown to be due to an increased mass of myocardial nuclei and sarcoplasm, but they were self-limited.

Subsequently, fetuses in mothers who had well-controlled type I insulin-dependent diabetes were studied at 4-week intervals between 20 and 30 weeks of gestation by M-mode and Doppler echocardiographic studies (Rizzo et al., 1992). These investigators measured intraventricular septal thickness, left and right ventricular wall thickness, and the ratio between the peak velocities during the early passive ventricular filling and active atrial filling at the level of the atrioventricular valves. They also studied peak velocities and time to peak velocity at the level of the ascending aorta and pulmonary artery. The findings in the 14 fetuses of diabetic mothers were compared with those in 10 normal control fetuses. This study revealed that all indices investigated increased linearly with advancing gestation. The fetuses of the diabetic mothers showed an accelerated increase in cardiac size occurring during the late second trimester, manifested by progressive thickening of the intraventricular septum and ventricular walls. These investigators demonstrated that strict control of maternal diabetes did not prevent the accelerated fetal cardiac growth and abnormal development of cardiac function, which was mainly manifested by impaired diastolic function (Rizzo et al., 1992). The study was followed by a related report that compared fetal echocardiographic indices in fetuses of mothers with well-controlled insulin-dependent

diabetes to normal fetuses during the second and third trimester (Gandhi et al., 1995). An increase in right ventricular shortening fraction was associated with global cardiac enlargement, which did not adversely affect myocardial contractility. These authors hypothesized that metabolically stable maternal diabetes may be associated with a mild but definite myocardial hypertrophy that affects the growth of the ventricular and septal walls (Gandhi et al., 1995). The echocardiographic changes associated with maternal diabetes are not, strictly speaking, a cardiomyopathy, but rather a self-limited cardiac hypertrophy. Only in extremely rare cases does the maternal diabetes result in systolic or diastolic cardiac dysfunction, progressing to congenital heart failure.

Prenatal sonographic manifestations of familial hypertrophic cardiomyopathy are increasingly being appreciated. In one report, a 25-year-old primigravida was described with hypertrophic apical cardiomyopathy whose fetus had normal echocardiographic examinations at 19 and 21 weeks of gestation. At 27 weeks of gestation, two-dimensional and M-mode echocardiograms revealed a generalized fetal cardiac hypertrophy with a markedly thickened intraventricular septum. This was confirmed at 32 and 36 weeks of gestation but did not worsen throughout the rest of the pregnancy. The patient was studied postnatally and followed to age 15 months, when stable cardiac hypertrophy was observed (Stewart et al., 1986).

Genetic syndromes, such as Noonan syndrome, can present with hypertrophic cardiomyopathy. In one case report, a fetus with cystic hygroma and a normal karyotype, diagnosed postnatally with Noonan syndrome, was referred for fetal echocardiography at 23 weeks of gestation. A small primum atrial septal defect, increased echogenicity of the mitral valve, and modest hypertrophy of both ventricles were observed (Sonesson et al., 1992). In the same fetus, observed serially at 35 weeks of gestation, prominent hypertrophy of both ventricles was demonstrated. Retrospectively, these authors noted that the first sign of myocardial abnormality was observed in the diastolic filling of both ventricles. However, this may be a subtle finding, as all fetuses have different diastolic filling velocities compared with newborn infants.

In a retrospective review of six cases of fetal dilated cardiomyopathy, Schmidt et al. (1989) made a sonographic diagnosis by numerous approaches, including the four-chamber, long-axis, short-axis, and aortic-arch views. Prenatal sonographic imaging was complemented by M-mode echocardiography for better definition of the motion patterns of the atrioventricular and semilunar valves (Schmidt et al., 1989). This group defined the right and left ventricular fractional shortening (FS) index as:

$$FS = (EDD - ESD) \times 100/EDD,$$

where EDD is the end-diastolic diameter of the ventricle and ESD the end-systolic diameter of the ventricle. These investigators demonstrated that in five of the affected fetuses, the right ventricular FS index was less than 2 SD below the normal mean for gestational age, and in four, the left ventricular FS index was less than 2 SD below the normal mean. In addition, they observed significantly larger mean end-diastolic diameters. In affected fetuses, the FS decreased progressively during gestation while the chamber enlargement increased (Schmidt et al., 1989).

DIFFERENTIAL DIAGNOSIS

The most important consideration in the differential diagnosis is to determine whether the cardiomyopathy is dilated or hypertrophic (Table 57-1). In dilated cardiomyopathy, the ventricle is thin-walled and dilated; mitral and or tricuspid regurgitation is also present (Figures 57-1 and 57-2). In the study performed at the Hospital for Sick Children (Pedra et al., 2002) 22/55 fetuses had dilated cardiomyopathy and 33 had hypertrophic. The various causes of the dilated cardiomyopathy were endocardial fibroelastosis (6 cases), familial (5), cytomegalovirus infection (2), and idiopathic (9). The underlying diagnosis in the hypertrophic cases included: twin–twin transfusion (18 cases) (Figure 57-3), maternal diabetes (7), Noonan syndrome (2), alpha thalassemia (2), familial (1), and idiopathic (3).

The important potentially treatable conditions to be ruled out include dysrhythmias, infection, endocardial fibroelastosis due to maternal antibodies, and severe anemia (usually accompanied by hydrops fetalis). Viruses potentially involved in fetal cardiomyopathy include cytomegalovirus, group B Coxsackie, echovirus, rubella, and herpes (Boston et al., 1994). Carnitine deficiency, although not directly diagnosable prenatally, should be considered, because postnatal treatment exists.

Inborn errors of metabolism associated with infantile cardiomyopathy are listed in Table 57-2. These include storage disorders, such as Pompe disease (glycogen storage

Table 57-1

Differential Diagnosis of Fetal Cardiomyopathy

Hypertrophic
Maternal diabetes
Twin to twin transfusion
Noonan syndrome
Inborn error of metabolism
Familial single-gene disorder
Alpha thalassemia
Dilated
Infection (most commonly, cytomegalovirus)
Endocardial fibroelastosis
Dysrhythmia
Familial single-gene disorder
Carnitine deficiency

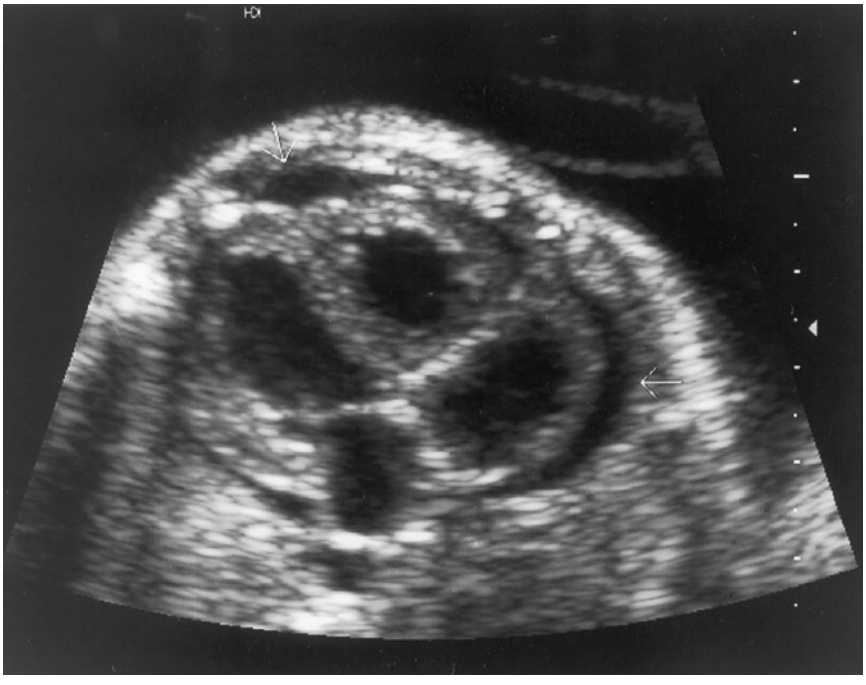

Figure 57-1 Antenatal four-chamber view of a fetal heart, demonstrating dilation of all four chambers. Arrows indicate the presence of a pericardial effusion.

disease, type II). This autosomal recessive condition results in symmetric massive hypertrophy of individual muscle fibers due to infiltration with glycogen. Pompe disease is diagnosed histochemically by the presence of vacuolar myopathy with positive periodic acid Schiff (PAS) staining and fiber reactivity for acid phosphatase. Frozen sections of liver reveal the absence of lysosomal acid α-glucosidase (Cottrill et al., 1987). For the sake of completeness, inborn errors of enzymes or transport proteins involved in mitochondrial β-oxidation of fatty acids are included in Table 57-2. Disorders of fatty acid oxidation are among the most common metabolic diseases known, with an incidence of 1 in 10,000 to 1 in 15,000 livebirths (Kelly and Strauss, 1994). However, they generally become apparent only during a fasting episode associated with infection and are unlikely to be recognized during fetal life.

Single-gene disorders associated with hypertrophic cardiomyopathy include neurofibromatosis, Friedreich ataxia, LEOPARD syndrome (lentigines, echocardiographic abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, restriction of growth, deafness), and Noonan syndrome (Schwartz et al., 1996). Of these, Noonan syndrome is the only one that has been described during fetal life (Battiste et al., 1977; Sonesson et al., 1992).

ANTENATAL NATURAL HISTORY

There is a high incidence of cardiac dysfunction and in utero mortality when fetal cardiomyopathy is observed, except in the setting of maternal diabetes. Pedra et al. (2002)

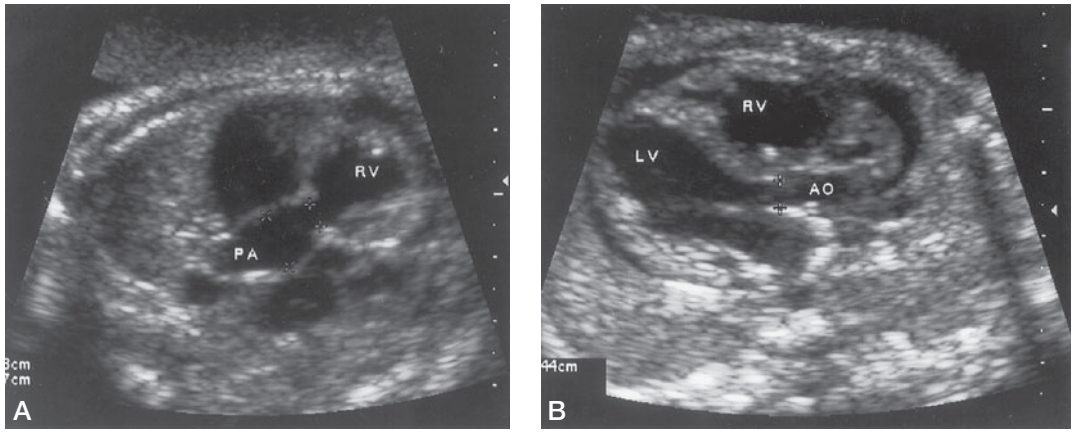

Figure 57-2 **A**. Antenatal sonographic image of same fetus shown in Figure 57-1, demonstrating significant dilation of the pulmonary outflow tract. **B**. Corresponding view of the left ventricular outflow tract, also showing dilation.

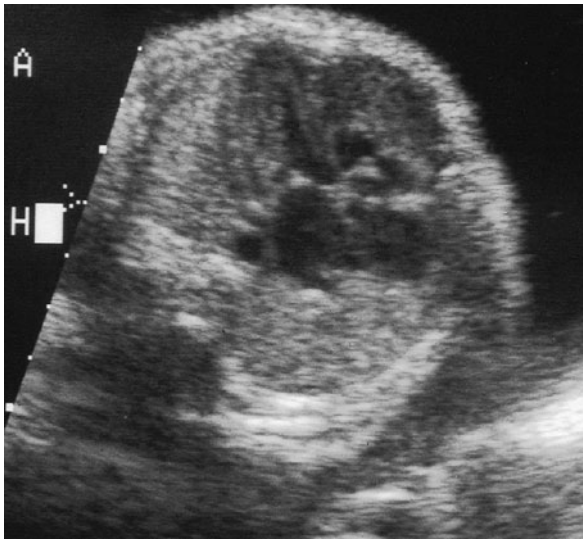

Figure 57-3 Antenatal four-chamber view of a fetal heart, demonstrating marked biventricular hypertrophy in a recipient of twin–twin transfusion.

demonstrated that systolic dysfunction was present in all cases of dilated cardiomyopathy and 15/33 cases of hypertrophic cardiomyopathy. Eight of the fetuses in their study were hydropic, and 23 had signs of early hydrops. The risk factors for mortality in utero included evidence of systolic or diastolic dysfunction, and significant atrioventricular valve dysfunction. Diastolic dysfunction was associated with the highest risk of mortality.

In another study, Sivasankaran et al. (2005) reported on outcome in 50 fetuses diagnosed with dilated cardiomyopathy. Two-thirds became hydropic at some point during gestation. Ten fetuses were terminated. Of the 40 remaining fetuses, only 25 survived to delivery, indicating a 37.5% mortality in utero.

MANAGEMENT OF PREGNANCY

Fetuses in which cardiomyopathy is suspected should be referred to a center capable of performing fetal echocardiography to rule out structural heart disease. Ideally, this center should be able to serially monitor the fetal cardiac function, including repeated measurement of the ventricular FS index and cardiac chambers, and rule out dysrhythmias such as supraventricular tachycardia and atrial flutter. It is important to rule out dysrhythmias, because they are treatable. If a high index of suspicion exists for an arrhythmia, 24-hour monitoring of the pregnant patient and fetus in the hospital is recommended. A targeted fetal sonographic study should be performed to identify any additional anomalies that could help in the diagnosis of a specific genetic syndrome. An attempt should be made to identify whether the mother has evidence of diabetes or infection. If the fetus has dilated cardiomyopathy, some centers screen maternal blood for the presence of anti-Ro (SS-A) and anti-La (SS-B) antibodies. If positive, the pregnant woman can be treated with oral dexamethasone.

It is important to obtain a complete family history, with specific questions directed toward sudden death in family members. Consideration should be given to performing echocardiography on both parents due to the high incidence of familial cases (Burkett and Hershberger, 2005).

Table 57-2

Metabolic Causes of Cardiomyopathy in Infancy

Storage Disorders
Glycogen storage disease, type II (Pompe disease)
Lysosomal glycogenosis without acid maltase deficiency
Glycogen storage disease, type III
Cardiac glycogenosis
GM1-gangliosidosis (β-galactosidase deficiency)
GM2-gangliosidosis (Sandhoff disease)
Ethanolaminosis
Familial steatosis
Inborn Errors of Fatty Acid Oxidation
Carnitine transport defect
Carnitine-acyl carnitine translocase defect
Carnitine palmitoyltransferase II defect
Long- and medium-chain acyl coenzyme A (COA) dehydrogenase deficiencies
Long-chain 3-hydroxyacyl-coA dehydrogenase deficiency
Inborn Errors of Mitochondrial Oxidative Phosphorylation
Lethal infantile cardiomyopathy
Benign infantile mitochondrial myopathy and cardiomyopathy
Maternally inherited myopathy and cardiomyopathy
Inherited cardiomyopathy with multiple deletions of mitochondrial DNA
Myoclonic epilepsy and ragged red fiber (MERRF) disease
Mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes (MELAS)
Kearns–Sayre syndrome

Modified from Kohlschütter A, Hausdorf G. Primary (genetic) cardiomyopathy in infancy. Pediatrics. *1986;145;454-459* and *Kelly DP, Strauss AW. Inherited cardiomyopathies.* N Engl J Med. *1994;330:913-919.*

FETAL INTERVENTION

If a dysrhythmia is diagnosed, medical treatment is indicated (see Chapters 41 and 42).

TREATMENT OF THE NEWBORN

Infants born after a fetal diagnosis of cardiomyopathy need to be delivered in a center capable of newborn resuscitation and aggressive cardiac management. Symptomatic infants may have respiratory distress and require mechanical ventilation with oxygen administration. A chest radiograph should be obtained to demonstrate cardiomegaly. An electrocardiogram should also be obtained. Infants with cardiomyopathy may have left ventricular hypertrophy with or without strain. If the electrocardiogram demonstrates giant QRS complexes in all leads with a shortened P–R interval, glycogen storage disorders may be considered (Kohlschütter and Hausdorf, 1986). A complete physical examination is indicated. Additional anomalies or dysmorphic facies may suggest a particular genetic disorder, such as Noonan syndrome. If inborn errors of metabolism are suspected, the infant should be evaluated for evidence of enlargement of the liver, spleen, or tongue, as well as clinical evidence of seizures, skeletal changes, or corneal opacities. Work-up should also include measurement of carnitine and acylcarnitine levels, as supplementation with carnitine will result in clinical improvement if a deficiency exists.

Further treatment for infants with dilated cardiomyopathy consists of administration of diuretics, together with digoxin and afterload reduction if pulmonary edema develops. Hypertrophic cardiomyopathy is treated with calcium-channel blockers and β-blockers to relax the heart. It is our experience that infants of mothers with diabetes almost never require treatment, even when their hypertrophic cardiomyopathy is severe.

SURGICAL TREATMENT

The only surgical treatment for severe dilated cardiomyopathy is heart transplantation, which may be needed in as many as 40% of cases (Lipshultz et al., 2003).

LONG-TERM OUTCOME

The postnatal natural history for 20 infants identified with cardiomyopathy during the first year of life has been described (Maron et al., 1982). Fourteen of the infants presented with a murmur that suggested evidence of outflow obstruction. For all these infants, the initial diagnosis was a suspected congenital cardiac malformation. Twelve of the 14 infants who presented with a murmur underwent cardiac catheterization, which demonstrated substantial left and right ventricular outflow tract obstruction, asymmetric hypertrophy of the ventricular septum relative to the left ventricular free wall, and a thickened interventricular septum. This study indicated that the onset of pulmonary edema during the first year of life was an unfavorable prognostic sign, as 9 of the 11 infants who developed this finding died. Several patients were treated with propranolol to decrease left ventricular outflow tract obstruction, but the authors expressed caution regarding the negative inotropic effect on ventricular contractility, and recommended administration of diuretics as a more conservative and safe regimen.

In Maron et al.'s report (1982), 6 of the 20 infants were documented to have a family history of dilated cardiomyopathy, as demonstrated by at least one of the parents having echocardiographic evidence of asymmetric septal hypertrophy. Although this report is over two decades old, it does emphasize that the familial and genetic contribution is probably greater than was originally appreciated.

In another report, the clinical course of 63 consecutive infants and children who presented with idiopathic dilated cardiomyopathy was described (Burch et al., 1994). The age at diagnosis was 1 day to 15 years (median, 12 months), with follow-up occurring through 1 day to 13 years of life (median, 19 months). The survival of this group from clinical presentation onward was 79% at 1 year after diagnosis and 61% at 5 years after diagnosis. Predictors of adverse outcome in this group included the presence of a mural thrombus, a left ventricular end-diastolic pressure of greater than 20 mm Hg, and an age at presentation of greater than 2 years. In 36 of the 63 patients, left ventricular echocardiography showed a decline or no improvement. Of these 36, 17 died, and 3 required cardiac transplantation. In 16 of 63 patients, partial improvement was noted; 3 patients in this group died. In the group whose left ventricular function returned to normal (11 of 63), all patients survived. These authors concluded that with no documentation of improvement in left ventricular echocardiographic dimensions or function, a poor prognosis exists, and these infants or children should be considered for cardiac transplantation.

GENETICS AND RECURRENCE RISK

Approximately 20% of cardiomyopathy cases are familial (Michels et al., 1992; Nugent et al., 2003; Burkett and Hershberger, 2005). The genetics of isolated cardiomyopathy are increasingly being explained at the molecular level. Some cases of familial dilated cardiomyopathy are inherited as autosomal recessive or X-linked (Berko and Swift, 1987) condition, but in the majority of families, the disease is inherited as an autosomal dominant disorder with age-related penetrance (Krajinovic et al., 1995). X-linked conditions associated with dilated cardiomyopathy include Duchenne and Becker muscular dystrophies, and Barth syndrome (dilated cardiomyopathy, cyclic neutropenia, and skeletal myopathy).

Much progress has ensued regarding the understanding of the molecular basis of the hypertrophic cardiomyopathies (Table 57-3). Approximately 50% of familial hypertrophic cardiomyopathies are due to mutations occurring in genes on chromosomes 1, 14, and 15, although other disease loci are known at chromosomes 11p13-q13, 7q3, and 9q13-q22 (Krajinovic et al., 1995; Watkins et al., 1995b). Approximately

Table 57-3

Major Genes and Gene Products Involved in Hereditary Cardiomyopathy

Hypertrophic (primarily involve sarcomeric problems)
Beta myosin heavy chain
Myosin-binding proteins
Troponin

Dilated (primarily involve cytoskeletal proteins)
Dystrophin (Duchenne and Becker syndromes; X-linked dilated cardiomyopathy)
Beta myosin heavy chain
Lamin
Taffazin (Barth syndrome)
Desmin
Actin
Titin

Genes Involved in Metabolic Processes
Phospholamban (calcium metabolism)
Adenosine monophosphate-activated protein kinase
Carnitine transporter
Fatty acid oxidation enzymes
Respiratory chain oxidative phosphorylation pathway

30% of cases of familial hypertrophic cardiomyopathy and some sporadic cases are due to missense mutations in the cardiac β-myosin heavy-chain gene on chromosome 14q11. All these mutations are single-nucleotide substitutions that result in a change of a single amino acid in the globular head or the head-rod junction of the myosin heavy-chain molecule. These mutations are not null alleles. They act as dominant-negative alleles, which means that they result in the production of an alternative molecule that impairs cross-bridge cycling and interferes with the assembly of the sarcomere (Watkins et al., 1995a). Approximately 15% of cases are due to mutations occurring in the cardiac troponin T gene on chromosome 1q3. These mutations are associated with a poor prognosis and a high incidence of sudden death before age 35 years (Watkins et al., 1995a). Approximately 3% of cases of familial hypertrophic cardiomyopathy are due to mutations in the α-tropomyosin gene on chromosome 15q2. All these loci are important in specifying genes for a sarcomeric contractile protein.

Because of the substantial progress being made in the molecular mapping of genes that affect families with cardiomyopathy, presymptomatic diagnosis is now possible, although only a few cases of prenatal diagnosis using DNA analysis have been published. In one family, a 24-year-old man was diagnosed with a cardiac β-myosin heavy-chain gene mutation following identification of his affected sister. At the time of his diagnosis, his partner was expecting a child. He asked for DNA testing on his daughter shortly after her birth. She was diagnosed as carrying the same mutation. An ethical debate ensued as to the wisdom of identifying a healthy newborn infant as a carrier of this gene mutation (Ryan et al., 1995). The parents very strongly wanted this information so that they would be able to redirect the child's lifestyle to avoid energetic activities and to ensure regular medical and cardiac surveillance. Physicians argued against this diagnosis because of the future stigmatization of the child with regard to employment, life insurance, and loans. In addition, the question has been raised as to whether the presence of the mutation is equivalent to having clinical evidence of the disease. For this condition, the presence of the responsible gene is necessary but not sufficient for the development of clinical symptoms of cardiomyopathy.

In a French family with a known R403L mutation in the beta myosin heavy-chain gene (*MYH7*), prenatal diagnosis was performed and demonstrated that the fetus was affected. The couple elected to terminate the pregnancy, as the phenotype in their particular family was severe and they already had one affected child (Charron et al., 2004). This family's experience is somewhat atypical. In another report, 22 couples with a family history of cardiomyopathy were seen in one center for prenatal genetic counseling. In 15/22 families the underlying molecular abnormality was known. During the counseling session autosomal dominant inheritance was explained, as well as the variability in the expression of the disease. In other words, *absence* of the gene mutation means that the child will not have cardiac disease, but *presence* of the gene mutation could mean anything from no symptoms to severe symptoms. Given this information, none of the couples counseled requested prenatal diagnosis (Charron et al., 2002).

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CHAPTER 58

Intracardiac Tumors

Key Points

- Intracardiac tumors are extremely rare in fetuses, occurring in 0.11% to 0.14% of fetal echocardiographic studies.
- Most fetal intracardiac tumors (60%–80%) are due to rhabdomyoma. Other causes (in order of decreasing frequency) are teratoma, fibroma, vascular tumors, and myxoma. If multiple tumors are present, the diagnosis is almost always rhabdomyoma.
- Sixty to ninety-five percent of cases of rhabdomyoma are due to tuberous sclerosis, an autosomal dominant disorder.
- Antenatal management includes evaluation of fetal cardiac function and determining if dysrhythmias are present.
- Hydrops and dysrhythmias are associated with in utero demise. Overall, there is a 66% survival rate for fetuses with intracardiac tumors.
- Genetic consultation, examination of parents and siblings, fetal brain MRI, and level II sonography are all indicated to rule in or rule out tuberous sclerosis.
- Delivery should occur at a tertiary center.
- Most tumors regress postnatally, but if surgical removal is necessary, the postoperative prognosis is excellent.
- Tuberous sclerosis is associated with relatively high rates of new mutation and gonadal mosaicism, so the affected fetus/neonate should undergo DNA testing to both confirm diagnosis and provide a definitive means of prenatal diagnosis in future pregnancies.

CONDITION

The most common intracardiac tumors found in fetuses, infants, and children are rhabdomyomas (Abushaban et al., 1993; Holley et al., 1995). Rhabdomyomas can involve the myocardium, endocardium, pericardium, papillary muscles, cardiac valves, and the pulmonary and aortic outflow tracts (Gava et al., 1990). Rhabdomyomas occur with equal frequency in the right and left ventricles. In 30% of cases, one or both atria are involved (Deeg et al., 1990).

Tuberous sclerosis is a neurocutaneous disorder resulting from hamartomatous growths that can occur in any organ. Interestingly, there is an age-related presentation of the lesions in different organs in tuberous sclerosis (Kwiatkowski and Short, 1994). Rhabdomyomas are primarily the fetal manifestation of tuberous sclerosis (Bader et al., 2003). The classic presentation of tuberous sclerosis, however, is later in life, when the hallmark findings are facial angiofibromas, seizures, and mental retardation.

INCIDENCE

Overall, intracardiac tumors are extremely rare in infants and children. In one series of children presenting to a pediatric cardiology referral unit, 0.08% had an intracardiac tumor as their referring symptom. Cardiac tumors are found in 0.0017% to 0.25% of pediatric autopsies (Groves et al., 1992). The most likely diagnosis for an intracardiac tumor is rhabdomyoma.

The incidence of intracardiac tumors has been estimated from antenatal sonographic studies. In a series of 794 congenital cardiac malformations derived from more than 10,000 fetal scans, 11 cardiac tumors were identified (0.11%) (Groves et al., 1992). Similar numbers were reported by Holley et al. (1995), who identified 19 fetuses with intracardiac tumors in ~14,000 fetal echocardiographic reports (=0.14%).

SONOGRAPHIC FINDINGS

In 1982, DeVore et al. was the first to describe an intracardiac tumor. A fetus was identified at 26 weeks of gestation with a dense, echogenic mass within the heart. On presentation, however, these authors were not sure whether the mass was extrinsic to the heart or within it. M-mode echocardiography demonstrated that the mass was in the heart. This fetus later became hydropic and died in utero. Subsequently there have been multiple reports of fetuses with large echogenic masses demonstrated clearly by prenatal sonography (Figure 58-1). In many of these cases, the mother was known to be affected with tuberous sclerosis. In other cases, the in utero demonstration of a rhabdomyoma prompted further assessment of both parents, with retrospective diagnosis of one of the parents with tuberous sclerosis.

A consistent theme among many of these case reports is that early sonographic examinations were negative for the presence of intracardiac tumors (Brackley et al., 1999). The tumors were found during the late second trimester but no earlier than 22 weeks of gestation. For example, Green et al. (1991) described a mother who was known to have tuberous sclerosis, who had undergone left nephrectomy for multiple angiomyolipomas of both kidneys, and who was known to have subependymal periventricular lesions by her computed tomographic (CT) scan. Sonographic examinations performed on her fetus at 13 and 16 weeks of gestation were completely normal. At 33 weeks, however, multiple solid cardiac

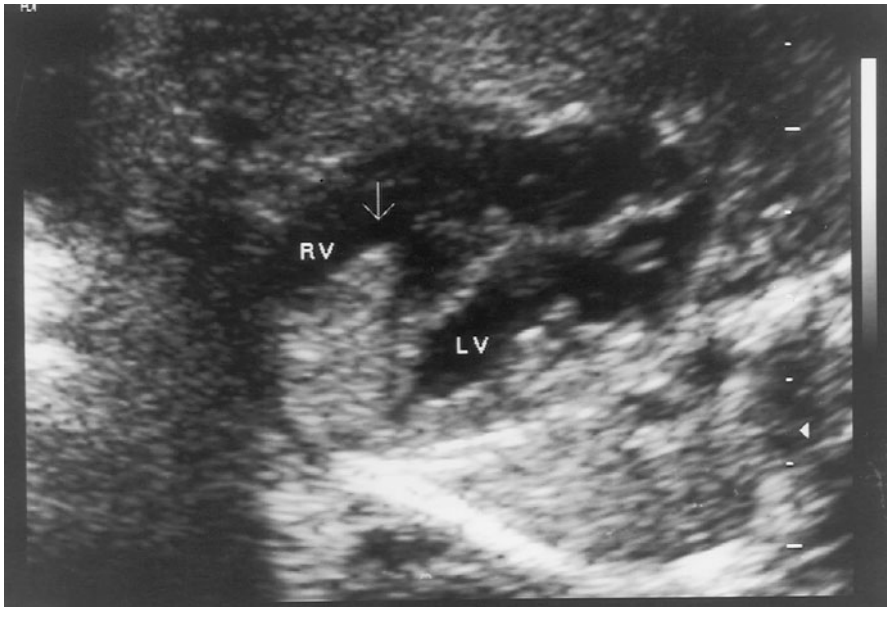

Figure 58-1 Antenatal sonographic image of a large intracardiac echogenic mass, which was postnatally diagnosed as a rhabdomyoma. Arrow indicates tip of mass; RV = right ventricle; LV = left ventricle.

tumors were noted in the left ventricle and intraventricular septum. The fetal central nervous system and renal examinations were within normal limits. In another case reported by Gava et al. (1990), cardiomegaly developed in a fetus with normal sonographic examinations at 10 and 23 weeks of gestation and an echodense mass in the wall of the right ventricle and right atrium at 31 weeks. Over the remaining course of pregnancy, new intracardiac tumors developed in this fetus. The mother, who was previously thought to be healthy, was subsequently diagnosed with a renal angiolipoma, consistent with a diagnosis of tuberous sclerosis.

With increasing prenatal sonographic experience in the diagnosis of intracardiac tumors, it is now clear that they do not become apparent until around 20 weeks of gestation. They undergo their maximal growth between 22 and 32 weeks of gestation and rarely grow after 35 weeks of gestation (Nir et al., 2001).

In fetuses identified with an intracardiac tumor, the following sonographic findings should be noted: the presence or absence of hydrops, whether the tumor is single or multiple, the morphology and characteristics of the intracardiac tumor(s), and the presence of or potential for obstruction of cardiac flow (Groves et al., 1992). The fetal cardiac rhythm should also be observed, as these fetuses are at particular risk for the development of dysrhythmias. Because of the multiple case reports documenting a normal sonographic examination during the first and early second trimesters, all women at high risk for a fetus with tuberous sclerosis (due to a positive family history) should have sequential sonographic examinations, beginning at 20 to 22 weeks of gestation (Journel et al., 1986; Gava et al., 1990; Green et al., 1991; Groves et al., 1992). Another potential intracardiac sonographic finding is diffuse ventricular myocardial thickening (Coates and McGahan, 1994).

Once an intracardiac tumor has been identified, a careful search should be undertaken for associated malformations. The associated findings most likely to occur in the setting of tuberous sclerosis include renal cysts and intracranial abnormalities, such as subependymal nodules (Chen et al., 2005a). Two fetuses have been described with tuberous sclerosis and agenesis of the corpus callosum (Barth et al., 1978; van Oppen et al., 1991). It is unclear whether this finding is related to tuberous sclerosis.

The fetal kidneys should be closely examined. Renal lesions are extremely common in older patients with tuberous sclerosis. For example, angiomyolipoma is found in 47% to 73% of affected patients (Blethyn et al., 1991). Renal cysts are found in 18% to 53% of adult patients with tuberous sclerosis, and both angiomyolipoma and renal cysts are found in 12% to 27% of patients with tuberous sclerosis (Blethyn et al., 1991). Thus, it would seem likely that some patients with tuberous sclerosis will present antenatally with renal cysts. In one case report, a fetus at 28 weeks of gestation was described with a large echogenic unilateral cystic kidney (Blethyn et al., 1991). Initially, this was considered to be consistent with the adult form of polycystic kidney disease or a renal hamartoma. Postnatally, seizures developed in this infant, who had an abnormal electroencephalogram. The definitive diagnosis of tuberous sclerosis was not made until 2 months of age, when calcified cortical tubers were demonstrated on cranial CT examination.

DIFFERENTIAL DIAGNOSIS

If multiple tumors are present, the diagnosis is rhabdomyoma until proven otherwise (Green et al., 1991). If a single intracardiac tumor is demonstrated, the diagnosis is still most likely to be rhabdomyoma, but other causes in decreasing order of frequency of occurrence in the perinatal period are teratoma, fibroma (Figure 58-2), vascular tumors, and myxoma. If the tumor is a rhabdomyoma there is a greater than 50% chance that the fetus has tuberous sclerosis (Table 58-1). Intracardiac myxoma is the most common tumor in adults, but it is extremely rare during the perinatal period (Chitayat et al., 1988). Characteristic findings of myxoma include its location in the left atrium and/or the interatrial septum (Gava et al., 1990). Rhabdomyomas have a characteristic echodense appearance on sonography. If a cyst is present within the mass, it is less likely to be rhabdomyoma. Extracardiac masses that can potentially mimic rhabdomyoma include bronchopulmonary sequestration (see Chapter 34) and congenital cystic adenomatoid malformation of the lung (see Chapter 35) (Calhoun et al., 1991). Fetal echocardiography is recommended to differentiate between intracardiac and extracardiac masses.

ANTENATAL NATURAL HISTORY

Groves et al. (1992) described the natural history of cardiac tumors in 11 cases that were referred because of hydrops ($n = 2$), a positive family history of tuberous sclerosis ($n = 2$), or detection of an intracardiac tumor on routine sonographic examination ($n = 7$). The gestational age at presentation was between 20 and 34 weeks of gestation. There was a high in utero mortality rate for these cases, which included spontaneous antenatal death in 4 of 7 cases (57%) continuing to term. Of the 8 cases that were terminated or died spontaneously, all had postmortem examination; in 7 the cardiac mass was rhabdomyoma, and in 1 the mass was a teratoma. The cases in which death occurred antenatally were caused by obstruction to intracardiac blood flow and secondary fetal hydrops. Autopsy revealed tricuspid-valve incompetence and pulmonary outflow obstruction as direct consequences of tumor growth (Groves et al., 1992). In a subsequent meta-analysis of 89 fetuses with intracardiac tumors, Isaacs (2004) demonstrated a 66% survival rate.

There has never been any evidence that the intracardiac tumors can or will regress during intrauterine life. Maternal hormones have been implicated in the development of these tumors (Chitayat et al., 1988). Postnatally, however, all tumors

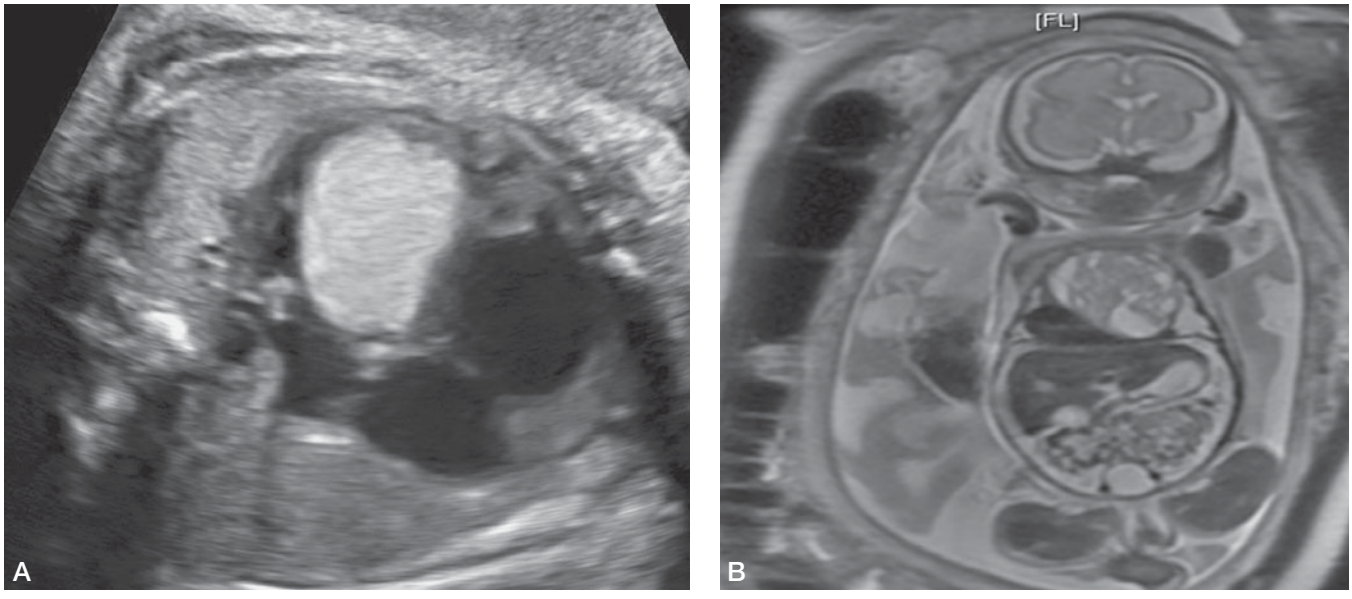

Figure 58-2 **A:** Antenatal sonographic image of a large intracardiac echogenic mass postnatally diagnosed as a fibroma; **B** shows the same mass on fetal MRI.

either stop growing or regress in size. In one report, 4 of 24 cases showed some regression of tumor growth postnatally and in 20 of these 24 cases the tumors completely regressed (Smythe et al., 1990).

Secondary consequences of intracardiac tumors include cardiac failure and dysrhythmias due to interruption of the conduction system (Chitayat et al., 1988). The dysrhythmias most commonly include supraventricular tachycardia, Wolff–Parkinson–White syndrome, atrial flutter and fibrillation, variable atrioventricular block, ectopic atrial tachycardias, premature extrasystoles, and ventricular tachycardia (Mehta, 1993). Two theories have been proposed to account

Table 58-1

Risk of Tuberous Sclerosis in Fetuses with Intracardiac Tumors

Publication	No. of Fetuses Studied	Gestational Age at Diagnosis (wk)	Percent with Single Tumor	Percent Diagnosed with Tuberous Sclerosis*	Notes
Holley et al. (1995)	19	21–38	52	52	
Geipel et al. (2001)	12	22–34	50	36	
D'Addario et al. (2002)	6	22–34	50	50	
Gamzu et al. (2002)	18	21–33	66	38	
Bader et al. (2003)	20	28 ± 6	10	79	All affected fetuses had multiple tumors
Tworetzky et al. (2003)	42	15–38	21	78	95% of fetuses with multiple tumors
Fesslova et al. (2004)	13	20–36	62	82	Brain MRI positive in 2 fetuses

** Based on clinical findings, not DNA testing.*

for the development of these dysrhythmias. One is that the tumors include an overgrowth of Purkinje cells, which may be capable of impulse conduction (Mehta, 1993). The more prevalent hypothesis is that the arrhythmias develop as a result of disruption of conduction tissue by tumor growth within the intraventricular septum (Groves et al., 1992). Intracardiac rhabdomyomas are composed of large muscle fibers that contain prominent vacuoles that histologically give them a spider web or honeycomb appearance (Thibault and Manuelidis, 1970; Ostör and Fortune, 1978).

In summary, the antenatal natural history of intracardiac tumors is compromised by the development of dysrhythmias, right or left ventricular outflow tract obstruction, valvular insufficiency, myocardial dysfunction due to tumor infiltration, hydrops, and death (Green et al., 1991).

MANAGEMENT OF PREGNANCY

There are two important considerations in the management of a fetus shown to have an intracardiac tumor. The first is to evaluate cardiac function with detailed echocardiography. Early delivery is indicated if there is a suggestion that the cardiac tumor is compromising cardiac function (Chitayat et al., 1988). Administration of digoxin to the mother is indicated if supraventricular tachycardia is the cause of the hydrops as opposed to outflow tract obstruction (Roach and Sparagana, 2004).

The second aspect of management is to evaluate the fetus for other signs and symptoms of tuberous sclerosis. A genetic counselor and/or medical geneticist should meet with the family to obtain a detailed three-generation pedigree and examine the parents and siblings for signs of tuberous sclerosis. Major and minor criteria for the diagnosis of tuberous sclerosis are listed in Table 58-2. Detailed fetal sonographic evaluation should be performed to look for renal cysts and cerebral abnormalities. A fetal MRI (Figure 58-3) may be helpful in evaluating for the presence of subependymal nodules (Chen et al., 2005a). A fetus identified with cardiac rhabdomyoma and renal cysts or subependymal nodules, independent of family history, has a presumptive clinical diagnosis of tuberous sclerosis. When a positive family history exists and a rhabdomyoma is found in the fetus, the fetus can also be presumptively diagnosed as affected. The question of

Table 58-2

Diagnostic Criteria for Tuberous Sclerosis

Major Features	Minor Features
Single or multiple rhabdomyoma in heart*	Multiple renal cysts*
Cortical tuber*	Bone cysts
Subependymal nodule	Multiple pits in dental enamel
Subependymal giant cell astrocytoma	Hamartomatous rectal polyps
Facial angiofibroma or forehead plaque	Cerebral white matter radial migration lines
Ungual or periungual fibroma	Gingival fibromas
Shagreen patch (connective tissue nevus)	Nonrenal hamartoma
Multiple retinal nodular hamartomas	Retinal achromic patch
Lymph angiomyomatosis	"Confetti" skin lesions
Renal angiomyolipoma	
Definite TS = Two major features or one major plus two minor features	
Probably TS = One major feature plus one minor feature	
Possible TS = One major feature or two or more minor features	

** Has been observed with prenatal imaging.*

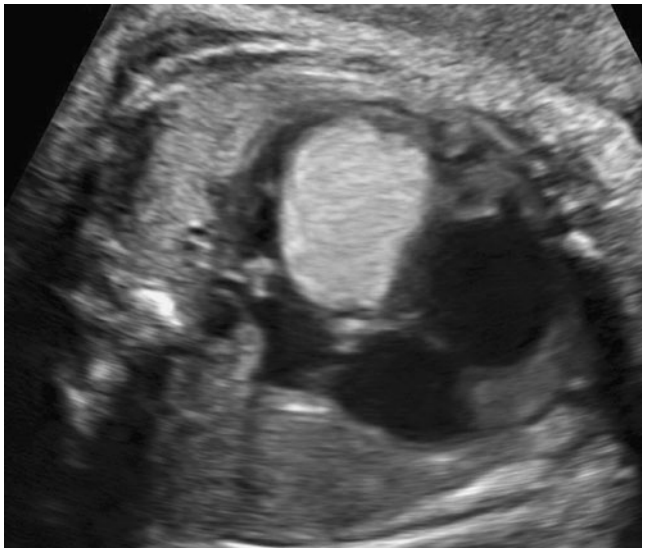

Figure 58-3 Coronal MRI of a fetus with a mass occupying the majority of the chest. Diagnosis was confirmed following fetal surgery as a pericardial teratoma.

termination of the pregnancy can be discussed with the family at this point.

Fetal karyotyping is not indicated for this condition. However, specific effort should be made to obtain DNA from fetal cells, either by amniocentesis or by collection of umbilical cord blood to identify a mutation in *TSC1* or *TSC2*.

FETAL INTERVENTION

There are no fetal interventions for rhabdomyoma indicated at present.

TREATMENT OF THE NEWBORN

The fetus with an intracardiac tumor should be delivered at a tertiary care center, and a neonatologist should be present at the delivery because of the risk of the development of dysrhythmias. Ideally, the infant should be delivered in a center where pediatric cardiologists are also available. In addition to a complete physical examination, the newborn should have a chest X-ray examination, electrocardiography, four-extremity blood pressure measurement, and postnatal echocardiography. Additional diagnostic studies should include postnatal renal sonography to look for the presence of renal cysts (Saguem et al., 1992). Medical genetics consultation should be sought.

Magnetic resonance imaging (MRI) is now considered to be superior to CT examination for the postnatal diagnosis of cortical tubers because MRI provides better soft tissue contrast without exposure to ionizing radiation. White matter tubers are readily identified within the white matter or cortical gyri. These tubers are sclerotic areas that exist throughout the cerebral hemispheres. They are the result of malformations of neuronal and glial elements characterized by decreased neurons and increased glia, and abnormal heterotopic cells (Truhan and Filipek, 1993). MRI has been used to demonstrate the presence of cortical, subcortical, and subependymal tumors in a 3-week-old infant (Christophe et al., 1989). These abnormalities were more completely and clearly seen on the T_1-weighted MR images as opposed to CT images.

Newborns with tuberous sclerosis are at risk for the development of seizures and infantile spasms, which may require anticonvulsant therapy. Children with tuberous sclerosis should be followed with MRI and renal ultrasound examination every 1 to 3 years.

SURGICAL TREATMENT

Surgical intervention should be restricted to cases with significant hemodynamic obstruction or life-threatening arrhythmias (Smythe et al., 1990). Because the natural history of these tumors is that they regress postnatally, a nonoperative approach with careful postnatal follow-up is recommended when possible.

In rare cases, however, surgery must be performed because the tumor affects hemodynamic function. In one review from the University of Padova, eight infants and children underwent operation for removal of an intracardiac tumor and were followed for more than a period of 17 years (Padalino et al., 2005). The diagnoses included myxoma ($n = 2$), fibroma ($n = 2$), rhabdomyoma ($n = 2$), vascular hematoma ($n = 1$), and teratoma ($n = 1$). Complete surgical excision of the cardiac mass was feasible in all but one patient, who underwent orthotopic heart transplantation. All eight children survived the operation, but one died 38 months post heart transplantation due to a cerebral malignancy. Surgical resection was definitive, safe, and effective for this group of patients.

LONG-TERM OUTCOME

Previous reports in the medical literature have emphasized a poor prognosis for fetuses or neonates affected with intracardiac rhabdomyomas. These include a reported 33% mortality rate during the first week of life and an 80% mortality rate during the first year of life (Green et al., 1991). Since approximately 60% of patients with tuberous sclerosis have asymptomatic rhabdomyomas, a better than reported prognosis likely exists. As stated earlier, the natural history of the rhabdomyomas is that they regress and that the cardiac volume increases, so the prognosis should be reasonably good (Webb et al., 1993). Infants in whom symptoms of hydrops or dysrhythmias developed antenatally have an increased risk of mortality.

Concerns regarding long-term outcome are mainly focused on the developmental and health consequences of tuberous sclerosis. The long-term outcome for patients with tuberous sclerosis is extremely variable and can range from completely normal intelligence to severe mental retardation. The prevalence of mental retardation in an unbiased sample of patients with tuberous sclerosis is 38% (Webb et al., 1993). Understandably, most parents are concerned about the risk for the development of seizures and mental retardation. For infants in whom seizures develop within the first year of life, there is a higher likelihood of mental retardation. It has been suggested that there is a correlation between the presence of cortical tubers and the severity of mental retardation (Kwiatkowski and Short, 1994). Other health consequences of tuberous sclerosis include renal angiomyolipomas, pulmonary lymphangiomyomas, seizure disorders, and multiple skin findings that could be considered a cosmetic issue.

GENETICS AND RECURRENCE RISK

The most likely cause for rhabdomyoma is tuberous sclerosis, which is inherited as a single-gene disorder with an autosomal dominant pattern of inheritance. Two-thirds of cases are the result of a new mutation. This means that one-third of the fetuses that present with cardiac rhabdomyoma have an affected parent. The penetrance for known cases of tuberous sclerosis is close to 100%, but one of the characteristics of this condition is that there is extraordinary variability in the expression of the phenotype (Roach and Sparagana, 2004). For example, an affected parent with normal intelligence can have an affected child with severe mental retardation. Although the inheritance pattern is classically described as autosomal dominant, several families have also been described with two affected children being born to normal parents. It is now appreciated that the incidence of somatic or gonadal mosaicism for a mutation in one of the tuberous sclerosis genes is as high as 10% (Verhoef et al., 1999).

If a fetal rhabdomyoma is documented in the setting of a negative family history, both parents should undergo a thorough clinical and radiologic examination for the diagnosis of tuberous sclerosis. The suggested work-up includes a dermatologic examination under ultraviolet light, MRI study of the brain, as well as renal sonography to look for the presence of angiomyolipomas or cysts (Roach et al., 1991).

There are two distinct genes involved in the causation of tuberous sclerosis, *TSC1* and *TSC2* (Jones et al., 1999). Approximately 30% of cases are caused by mutations in *TSC1*, which codes for a protein product called hamartin. *TSC1* is located on 9q34. The other 70% of cases are caused by a mutation in *TSC2*, which maps to chromosome 16 band p13.3 near the adult polycystic kidney disease gene. This gene product has been identified and named tuberin, a 198-kd protein of unknown function (European Chromosome 16 Tuberous Sclerosis Consortium, 1993). In general, *TSC2* mutations are associated with a more severe phenotype. Both hamartin and tuberin have been shown to be present in the tissues of a 19-week fetus affected with tuberous sclerosis (Wei et al., 2002). Hamartin and tuberin are thought to act together to regulate cell proliferation. Loss of heterozygosity due to a tuberin mutation was shown to be associated with a fetal rhabdomyoma, lending credence to the idea that *TSC1* and *TSC2* function as tumor-suppressor genes (Wei et al., 2002).

Prenatal diagnosis for this condition will likely be DNA-based. For families with a positive family history of tuberous sclerosis, DNA mutation studies should ideally be performed prior to contemplation of pregnancy. A comprehensive mutation analysis of the genes *TSC1* and *TSC2* was able to characterize mutations in 120 of 150 (80%) of cases studied (Jones et al., 1999). Mutation analysis of affected individuals' DNA must be performed prior to a subsequent pregnancy in order to facilitate DNA-based diagnosis of chorionic villi in the first trimester.

Chen et al. (2005b) described two different prenatally ascertained cases of rhabdomyoma in which mutation testing was performed using denaturing high-performance liquid chromatography (DHPLC) analysis and direct sequencing. In both cases pathogenic mutations in *TSC2* were identified. Note that the presence of a mutation in *TSC1* or *TSC2* confirms the clinical diagnosis of tuberous sclerosis, but the absence of a mutation does not rule it out.

For families that have not undergone mutation analysis, prenatal diagnosis for tuberous sclerosis consists of serial prenatal sonographic examinations. This has limitations, however, because definitive diagnosis can occur only during the late second trimester.

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Ectopia Cordis

59 CHAPTER

Key Points

- Ectopia cordis is a rare malformation in which the fetal heart is present in an extrathoracic location.
- It is easily diagnosable by fetal ultrasound, as early as 10 weeks of gestation.
- Detailed fetal echocardiography is recommended to confirm whether the internal cardiac anatomy is normal, as the prognosis is essentially lethal if associated cardiac malformations are present.
- Detailed general fetal sonographic anatomical evaluation and amniocentesis for fetal karyotype are recommended, because of reported associations with other malformations.
- If a patient chooses to continue the pregnancy and no other malformations are present, planned elective cesarean delivery at term, with immediate availability of neonatologists, pediatric surgeons and cardiac surgeons, is recommended.
- Postnatal survival has been rarely reported in cases in which no associated malformations are present.
- There have been no reported cases of recurrence of ectopia cordis.

CONDITION

Thoracic wall defects arise from failure of part or all of the sternum to develop. These defects may involve only the sternum or may be associated with more severe anomalies. The most striking of these is ectopia cordis. Ectopia cordis is defined as a portion or all of the heart being located in an extrathoracic position. Ravitch (1985) has classified sternal defects into three major groups: cleft sternum without associated anomalies, true ectopia cordis, and pentalogy of Cantrell (see Chapter 61) (Table 59-1).

Sternal defects are commonly associated with ectopia cordis. A spectrum of sternal defects also occurs without displacement of the heart (Skandalakis and Gray, 1994). In rare cases, segments of the sternum are absent. The xiphoid process is the sternal element most commonly absent. Byron (1948) reported a case in which only the manubrium remained. Martin and Helsworth (1962) reported a case of clavicles and upper ribs attached to an abnormally small manubrium separated from lower ribs attached to a sternum element. Complete absence of all sternal elements is rare, but has been reported, and can be successfully reconstructed (Asp and Sulamoa, 1961). In contrast to absent sternal elements, failure of sternal fusion may occur with wide separation of all sternal elements. This is most often seen with associated eventration of the heart. However, several cases have been reported with no herniation of thoracic viscera and intact skin covering the defect (Greenberg et al., 1991).

Superior sternal fusion occurs with a V- or U-shaped cleft in the upper sternum, with variable extension inferiorly even to the level of the xiphoid. Jewett et al. reported nine cases, all with skin-covered defects and structurally normal

Table 59-1

Ravitch's Classification of Sternal Clefts

Cleft sternum without associated anomalies V- or U-shaped clefts of the upper sternum involving manubrium and one or two sternebrae Lower sternum cleft with the xiphoid process united Entire sternum cleft
True ectopia cordis with varying degrees of cleft sternum with the heart outside the chest wall, usually internally malformed and with other malformations
Cantrell's pentalogy composed of the following anomalies: Cleft or absent distal sternum Crescenting ventral diaphragmatic defect Midline ventral abdominal defect or omphalocele Defect at the apical pericardium with communication with the peritoneal cavity Cardiac defects

From Ravitch MM. Congenital deformities of the chest wall and their operative correction. Philadelphia: WB Saunders; 1985:35.

hearts located within the chest cavity. Four of these cases had hemangiomas of the head and neck and a midline raphe indicating a midline fusion defect (Jewitt et al., 1962).

More than 200 cases of ectopia cordis have been reported in the literature (Skandalakis and Gray, 1994). Ravitch (1985) has classified ectopia cordis into four types based on the position of the heart: cervical (3%), thoracic (64%), thoracoabdominal ectopia (18%), and abdominal ectopia (15%). The heart was exposed in 40% of these cases or covered by a serous membrane (31%) or skin (27%) (Schao-Tsu, 1957).

It is important to distinguish true ectopia cordis from failure of sternal fusion in which the heart, though beating prominently beneath the skin-covered gap, is within the chest and is structurally normal. Many cases reported as thoracic ectopia, with intact skin, are more likely examples of isolated failure of sternal fusion.

"Thoracoabdominal ectopia cordis" is better known as the pentalogy of Cantrell and is in part a misnomer, given that the heart is not truly ectopic. In pentalogy of Cantrell the heart is abnormally sited with the apex oriented down, but is positioned within the chest and therefore not true ectopia cordis (see Chapter 61). Both cervical and abdominal ectopia cordis may occur without a sternal cleft. Abdominal ectopia cordis does not belong in this group of anomalies because the defect is diaphragmatic and does not involve the thorax or the anterior abdominal wall.

In true ectopia cordis, internal cardiac anomalies are generally the rule (Medina-Escobedo et al., 1991). Kanagasuntheram and Verzin (1962) suggested that the embryologic basis of ectopia cordis was excessive pericardial coelom formation and subsequent destruction of the transverse septum with rupture of the anterior body wall at 6 weeks of gestation. The frequency of major intrinsic cardiac defects in true ectopia cordis suggests that there may be a primary defect in the splanchnic mesoderm (Ravitch, 1985).

INCIDENCE

Ectopia cordis is extremely rare. The most common form is thoracic ectopia cordis. Only a handful of cases of cervical and abdominal ectopia cordis have been reported. Schao-Tsu (1957) cited figures for ectopia cordis as high as 5.5 in 1000 births at Tubingen and 0.4 in 1000 at Munich. Abbott (1936) found 8 cases in her series of 1000 congenital heart defects. However, most fetuses are lethally deformed and are either stillborn or have no prospect of extrauterine survival. Males tend to be affected more often than females with a ratio of 2.5:1.5 (Blatt and Zeldes, 1942).

SONOGRAPHIC FINDINGS

The first case of ectopic cordis diagnosed in utero by sonographic examination was reported in 1960 by Lumsden (1962) in a fetus near term. Advances in ultrasound examination since that time have allowed recognition of this anomaly as early as the first trimester, using transabdominal and transvaginal ultrasound (Flemming et al., 1991; Achiron et al., 1994; Sepulveda et al., 1994; Tongsong et al., 1999)

True thoracic ectopia cordis (Figure 59-1) is perhaps one of the most startling anomalies to be seen sonographically. The heart is seen entirely outside the thoracic cavity (Bianca et al., 2006). The apex of the heart is usually deviated anteriorly but may also be seen angled up toward the chin (Bennett et al., 1991). Color flow Doppler may be particularly useful in defining the location and anatomy of ectopia cordis (Figure 59-2). Transverse scanning through the fetal chest may allow the sternal defect to be visualized (Figure 59-3). Determining the intracardiac anatomy is of paramount importance in establishing a prognosis. Fetal echocardiography

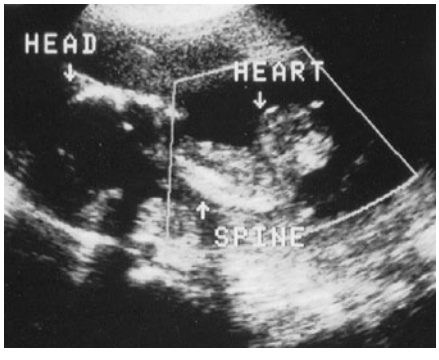

Figure 59-1 Ultrasound image of fetus at 18 weeks of gestation with thoracic ectopia cordis.

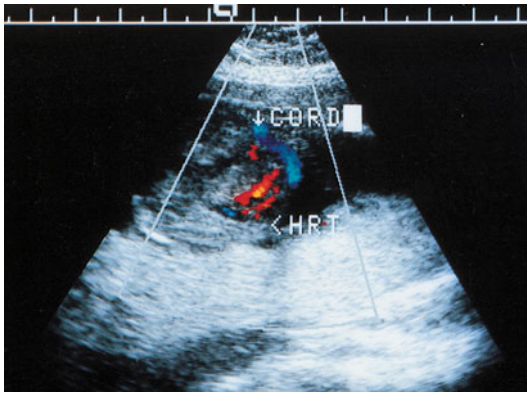

Figure 59-2 Color flow Doppler image of true thoracic ectopia cordis. This fetus was found to have severe associated intracardiac abnormalities and subsequently died in utero.

should be performed in any fetus diagnosed with ectopia cordis.

The cases of cervical and abdominal ectopia cordis are sufficiently rare that none have yet been diagnosed prenatally. The sonographic features of pentalogy of Cantrell (thoracoabdominal ectopia cordis) are covered in Chapter 61. In cases of thoracic ectopia cordis, the size and shape of the fetal chest should be carefully noted. Hypoplasia of the chest wall and lungs has been associated with ectopia cordis.

A careful search should be made for associated anomalies, especially midline defects. A broad range of anomalies have been reported in association with ectopia cordis (Leca et al., 1989; Diaz et al., 1992; Sharma et al., 2001) (see Table 59-2). Particular attention should be paid to possible associated cleft lip or palate. Jewitt et al. (1962) have reported an association between cleft sternum, ectopia cordis, and hemangiomas of the face and neck. Any soft tissue mass in the head and neck region should be scanned with color flow or power Doppler studies.

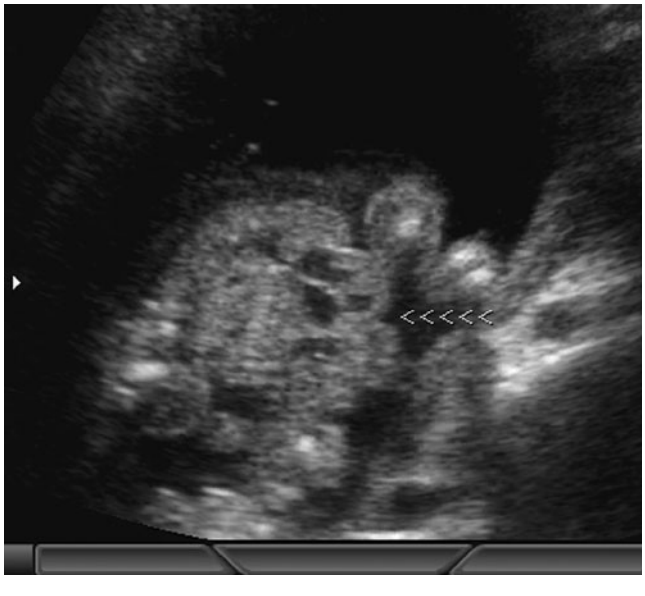

Figure 59-3 Ultrasound image of fetus at 20 weeks of gestation with small arrows pointing to apex of the fetal heart protruding through a sternal defect.

DIFFERENTIAL DIAGNOSIS

The unique appearance of true thoracic ectopia cordis is diagnostic. However, other manifestations of ectopia cordis have a differential diagnosis that may be difficult to sort out prenatally. The pentalogy of Cantrell can usually be diagnosed by the presence of epigastric hernia or marked diastasis of the rectus muscles (see Chapter 61). Complete sternal clefts can be covered with skin or have the heart exposed. In this anomaly, unlike ectopia cordis, the heart is completely within the chest cavity, and there are no associated intracardiac defects. Complete sternal clefts have an excellent prognosis. Similarly, in cases of cervical or abdominal ectopia cordis, the sonographic findings are so striking and pathognomonic that no differential diagnosis is required.

ANTENATAL NATURAL HISTORY

The antenatal natural history of ectopia cordis, similar to the postnatal history, depends on the presence or absence of associated intracardiac defects. Skandalakis and Gray (1994) found that of 138 patients for whom follow-up or survival records were available, 16.6% (23 of 138) were stillborn, and an additional 30% (42 of 138) died on the first day of life. These patients had ectopia cordis with severe intracardiac abnormalities. Abdominal ectopia cordis does not appear to be incompatible with life, but approximately one-third of patients will be stillborn or die on the first day of life because of severe congenital heart malformations. In general, survivors with ectopia cordis are fetuses without associated intracardiac defects. No stillborn infants had isolated ectopia cordis with normal intracardiac anatomy. However, even if a pregnancy goes to term and the infant is born alive, there has never been a long-term survivor who underwent successful reconstruction who had ectopia cordis associated with intracardiac defects. Watterson et al. (1992) reported a case of thoracic ectopia cordis with a double outlet right ventricle that was diagnosed prenatally. This prenatal diagnosis allowed planning of a single-stage reconstruction at birth. Although the procedure was technically successful, the infant died on the 12th postoperative day of sepsis.

MANAGEMENT OF PREGNANCY

Once a diagnosis of ectopia cordis is made, the pregnant patient should have a targeted ultrasound examination to establish the nature and extent of ectopia cordis and, most importantly, to establish the presence or absence of associated intracardiac defects. Similarly, a careful ultrasound

Table 59-2

Anomalies Associated with Ectopia Cordis

Craniofacial	Chest Wall	Intracardiac	Abdominal Wall and Diaphragmatic Defect	Others
Microcephaly	Cleft sternum	Pericardial defects	Omphalocele	Chromosomal anomalies
Hydrocephalus	Bifid sternum	Septal defects	Diastasis recti	Pulmonary hypoplasia
Cleft lip	Absent sternum	Outflow tract obstructions	Gastroschisis	Imperforate anus
Anencephaly	Xiphoid defect	Cardiac diverticuli	Diaphragmatic hernia	Rectovaginal fistula
Neural tube defect	Manubrial defect	Double outlet right ventricle		Amniotic band
	Defect of body or sternum	Anomalies of caval and pulmonary venous return		Dissociation complex
	Partial defect	Transposition of great arteries		Malrotation of bowel
	1/3 lower sternal defect	Aortic coarctation		Liver hemangioendothelioma
	2/3 lower sternal defect	Truncus arteriosus		

examination should be performed to exclude possible associated noncardiac anomalies and evaluate the thorax for signs of pulmonary hypoplasia. Invasive diagnosis of fetal karyotype by means of chorionic villus sampling or amniocentesis is recommended because of a reported association with fetal aneuploidy (Shaw et al., 2006; Yildirim et al., 2008).

Fetal echocardiography is an essential part of the evaluation of any fetus with ectopia cordis. The presence of intracardiac defects is an extremely poor prognostic indicator, and parents should be counseled appropriately.

In cases of ectopia cordis in which the family chooses to continue the pregnancy, serial ultrasound examinations are indicated to monitor fetal growth and well-being. The delivery should occur in a tertiary care setting in which pediatric surgeons, pediatric cardiac surgeons, and neonatologists are available. In most cases of ectopia cordis there is no skin covering the heart, and immediate surgical closure of the defect is necessary to prevent life-threatening infection.

Few reports are available on which to base recommendations for mode of delivery. In cases in which survival is not anticipated because of the presence of severe intracardiac anomalies, vaginal delivery without fetal monitoring is appropriate. In cases in which the cardiac anatomy is normal and full resuscitative efforts are planned, cesarean delivery is justified. The potential adverse effects on venous return to the extrathoracic heart and compromised cardiac output during labor and delivery appear to justify cesarean delivery in cases with normal cardiac anatomy.

FETAL INTERVENTION

There are no fetal interventions for ectopia cordis.

TREATMENT OF THE NEWBORN

The newborn with ectopia cordis should have a planned delivery with neonatologists and pediatric surgeons in attendance. Because the heart is exposed, a detailed examination of the newborn chest to assess sternal defects and prospects for skin coverage should be performed in the delivery room by the surgeon who will close the defect. The heart should be covered loosely with a nonadherent dressing such as gauze covered with petroleum jelly and then wrapped circumferentially with gauze and plastic wrap to minimize evaporative water loss. Immediately after the dressing is applied, the infant's blood pressure and perfusion should be assessed to ensure that the dressing is not restrictive. Plain posteroanterior and

lateral chest X-ray films should be obtained. Venous access should be obtained via the umbilical vein or peripherally and systemic antibiotics should be administered. An arterial line should be placed for continuous arterial pressure monitoring during attempted skin closure (Diaz, 1992). The infant should undergo a detailed physical examination as soon as possible to detect any additional anomalies missed by prenatal ultrasound examination. Postnatal echocardiography should be repeated prior to surgery to verify that the cardiac anatomy is normal.

The evaporative water loss in this defect may be substantial, and initial intravenous fluid administration should be at least 100 mL per kilogram of body weight per day and boluses of crystalloid or colloid administered as necessary. Antibiotics (ampicillin and gentamicin) should be started immediately.

SURGICAL TREATMENT

Reconstruction of ectopia cordis is undertaken in stages. The initial goal of surgery is to achieve skin coverage to protect the heart. This must be achieved without excessive compression or posterior displacement, which may compromise venous return and cardiac output. Successful repair in this defect has been achieved by the use of skin flaps (Dobell et al., 1982; Ravitch, 1985; Amato et al., 1995; Lije et al., 2006) and prosthetic material (Tachibana et al., 1989; Watanabe et al., 1992). In the second stage, a procedure may be performed to reposition the heart within the chest. This may be possible after the infant has been allowed to grow with reduction of the heart and prosthetic coverage over the cleft sternum. Glass and Fernbach (1987) reported the successful use of intrathoracic tissue expanders to create space for subsequent intrathoracic placement of the heart.

LONG-TERM OUTCOME

Although the prognosis is guarded for any fetus with ectopia cordis, long-term survival is possible for cases with normal internal cardiac anatomy. In fact, the first attempted repair of ectopia cordis by Lannelongue in 1988 was successful and he reported follow-up at 20 years of age. However, of 138 patients in whom follow-up or survival records are available, only 32 (23%) survived more than 1 month after birth. Seven of these are known to have reached maturity and 19 others survived infancy and were alive at the time their cases were reported (Skandalakis and Gray, 1994). The oldest reported survivor with ectopia cordis was 75 years old (Byron, 1948).

Among patients with thoracic ectopia cordis, 50% died within 1 day of life, most often from cardiac anomalies (Skandalakis and Gray, 1994). Only seven patients survived to maturity and most of these suffered from only partial ectopia cordis. The prognosis in cervical ectopia cordis is poor, with only two patients surviving to adulthood (Laliberte, 1918; Asp and Sulamoa, 1961). Abdominal ectopia cordis is not incompatible with life, as 10 of 17 patients who were followed have survived (Skandalakis and Gray, 1994). These patients had no intracardiac defects.

GENETICS AND RECURRENCE RISK

True ectopia cordis has not been associated with chromosomal abnormalities. There has not been a reported case of recurrence of ectopia cordis in a sibling.

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60 CHAPTER Body-Stalk Anomaly

Key Points

- Body-stalk anomaly is a sporadic disorder leading to severe deformations of the abdominal wall and spine.
- Prenatal diagnosis is generally straightforward with massive abdominoschisis, severe kyphoscoliosis, and relatively short umbilical cord being clearly visible.
- There is no indication to perform amniocentesis as almost all cases are karyotypically normal.
- The condition is considered uniformally fatal, although there has been at least one case report of a survivor following neonatal surgical closure of omphalocele.
- While there has been one report of recurrence in a subsequent pregnancy, the condition is generally considered to be sporadic.

CONDITION

Body-stalk anomaly is a severe abdominal wall defect that results from abnormalities in the development of the cephalic, caudal, and lateral embryonic body folds. This maldevelopment results in the absence or shortening of the umbilical cord with the abdominal organs lying outside the abdominal cavity and directly attached to the placenta (Shalev et al., 1995; Smrcek et al., 2003). Body-stalk anomaly was first described by Kermauner in 1906 in a newborn with an abdominal wall defect consisting of an amniotic sac that contained viscera; the anterior wall of the sac was directly attached to the placenta and there was no umbilical cord. Other than the references given in textbooks of pathology, body-stalk anomaly was not appreciated in the general obstetric literature until the report of Lockwood et al. in 1986.

After gastrulation, the embryo consists of a three-layered, flat, oval germinal disk. The rapid growth of the embryo, especially along the sagittal axis causes the germinal disk to curve. Through circumferential folding, the embryo becomes cylindrical. As a result of this process, the body of the embryo closes, the body stalk forms, and an intraembryonic coelom (peritoneal cavity) separates from an extraembryonic coelom (chorionic cavity) (Giacoia, 1992). The amniotic cavity, which is initially located dorsal to the germinal disk, grows rapidly and eventually encircles the fetus, obliterates the chorionic cavity, and envelops the umbilical cord. The abnormality in the folding process prevents this obliteration of the

chorionic cavity and formation of the umbilical cord. Without an umbilical cord, the fetus becomes directly attached to the placental chorionic plate. This body-stalk anomaly consists of a sac of amnion–mesoderm that contains the displaced abdominal organs (Giacoia, 1992).

Causes proposed for body-stalk defect include early amnion rupture with direct mechanical pressure and amniotic bands (see Chapter 99), vascular disruption of the early embryo, or an abnormality in the germinal disk that leads to the formation of an anomalous amniotic cavity (Van Allen et al., 1987). In the early amnion-rupture theory, the abdominal wall and spinal defects could be secondary to the passage of the lower half of the fetal body into the coelomic cavity through the defect in the amniotic sac. The fetus has no room to move and remains practically attached to the placenta. Limb amputations and encephalocele could be secondary to the entrapment of the fetal skull and/or limbs in the coelomic cavity (Daskalakis et al., 1997). Alternatively, early generalized compromise of embryonic blood flow could lead to a failure of closure of the ventral body wall and persistence of the coelomic cavity (Van Allen et al., 1987). This could also lead to a rupture of an unsupported amnion and formation of amniotic bands.

INCIDENCE

Body-stalk anomaly is the rarest and most severe of the abdominal wall defects. The incidence of body-stalk anomaly in a population of Scottish patients identified by abnormal maternal serum screening results was 1 in 14,273 (Mann et al., 1984). The incidence of body-stalk anomaly in a Hawaiian birth defects registry that encompassed the years 1986 to 1997 was 0.32 per 10,000 births (Forrester and Merz, 1999). Recently, an increased incidence of body-stalk anomaly was noted in a population of first trimester fetuses studied for nuchal translucency thickness. In this first trimester population, the incidence of body-stalk anomaly was between 10 in 4116 cases and 14 in 106,727 cases or 1 in 7500 fetuses (Daskalakis et al., 1997; Souka et al., 1998). Another series of 11 cases of limb–body wall complex suggested an incidence of 1 in 3000 (Luehr et al., 2002). Several case reports exist of body-stalk anomaly and limb–body wall complex in association with monozygotic twinning, triplet pregnancy, and with maternal cocaine abuse (Viscarello et al., 1992; Martinez et al., 1994; Smrcek et al., 2003).

SONOGRAPHIC FINDINGS

The criteria for the diagnosis of body-stalk anomaly in the first trimester include demonstration of abdominal organs in the extraembryonic coelom and a short umbilical cord with only two vessels (Ginsberg et al., 1997). The diagnosis may be more difficult to make during the second trimester than during the first because of the presence of severe oligohydramnios. During the second trimester, Goldstein et al. (1989) suggested that body-stalk anomaly should be strongly considered when there is a body wall defect, skeletal abnormalities, and the umbilical cord is absent or very rudimentary (Figures 60-1 and 60-2).

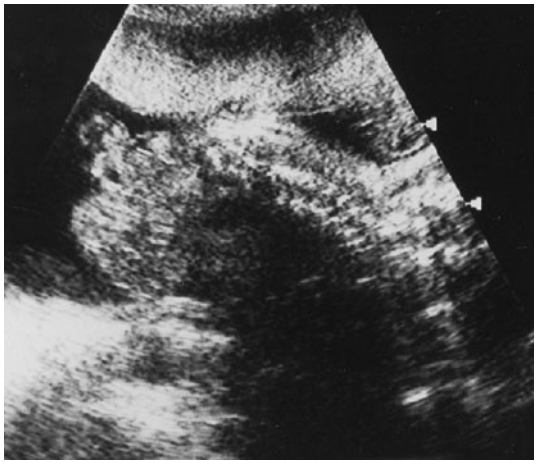

Figure 60-1 Longitudinal sonographic image of a fetus with body-stalk anomaly demonstrating severe kyphoscoliosis of the lower spine. *(From Takeuchi K, Fujita I, Nakajima K, Kitagaki S, Koketsu I. Body stalk anomaly: prenatal diagnosis.* Int J Gynecol Obstet. *1995;51:49-52.)*

In a multicenter project of screening for chromosomal defects by fetal nuchal translucency thickness and maternal age, 14 of 106,727 fetuses examined had a body-stalk anomaly (Daskalakis et al., 1997). During the first trimester, the ultrasonographic features observed included a major abdominal wall defect, severe kyphoscoliosis, and short umbilical cord. In all of the cases observed, the upper part of the fetal body was in the amniotic cavity and the lower part was in the coelomic cavity. The nuchal translucency thickness was above the 95th

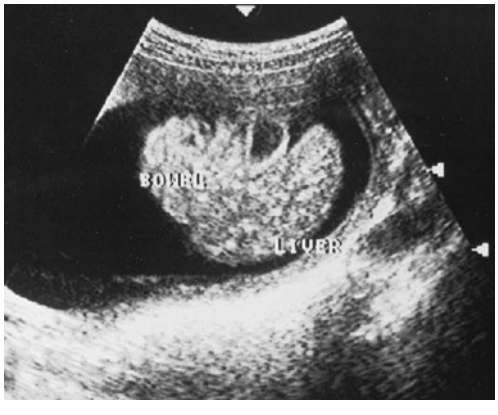

Figure 60-2 Coronal sonographic image of the fetus in Figure 60-1, with body-stalk anomaly demonstrated a 5- by-6-cm mass with a covering membrane that contained stomach, liver, and bowel. *(From Takeuchi K, Fujita I, Nakajima K, Kitagaki S, Koketsu I. Body stalk anomaly: prenatal diagnosis.* Int J Gynecol Obstet. *1995;51:49-52.)*

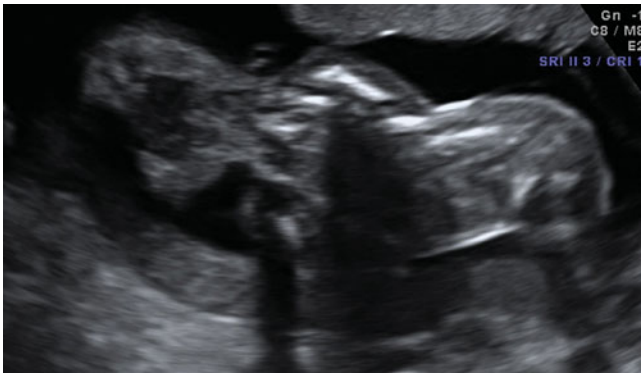

Figure 60-3 Sagittal view of a fetus with body-stalk anomaly at 18 weeks demonstrating severe kyphoscoliosis.

percentile in 10 of the 14 cases, but the fetal karyotype was normal in 12 of the 14 fetuses evaluated. These authors suggested that early amnion rupture before obliteration of the coelomic cavity is a possible cause of the syndrome (Daskalakis et al., 1997).

Multiple case reports have described the prenatal sonographic diagnosis of body-stalk anomaly (Lockwood et al., 1986; Jauniaux et al., 1990; Giacoia, 1992; Shalev et al., 1995; Takeuchi et al., 1995; Ginsberg et al., 1997). An additional helpful sonographic finding is the presence of scoliosis, which is observed in approximately 75% of cases (Ginsberg et al., 1997) (Figures 60-3 and 60-4). Scoliosis is thought to be due to the absence of thoracolumbar and paraspinal muscles on the ipsilateral side of the abdominal wall defect. In addition, it is thought that fetal hyperextension and direct attachment to the placenta, which limit fetal movement, result in skeletal anomalies.

A more recent series of 11 cases of body-stalk anomaly showed that the earliest prenatal diagnosis was at 11 weeks, but ranged from 11 to 21 weeks' gestation (Smrcek et al., 2003). Six of the fetuses presented with severe abdominoschisis, while the remaining five had thoracoabdominoschisis. Kyphoscoliosis was diagnosed prenatally in 9 of the 11 cases, and all had a short umbilical cord.

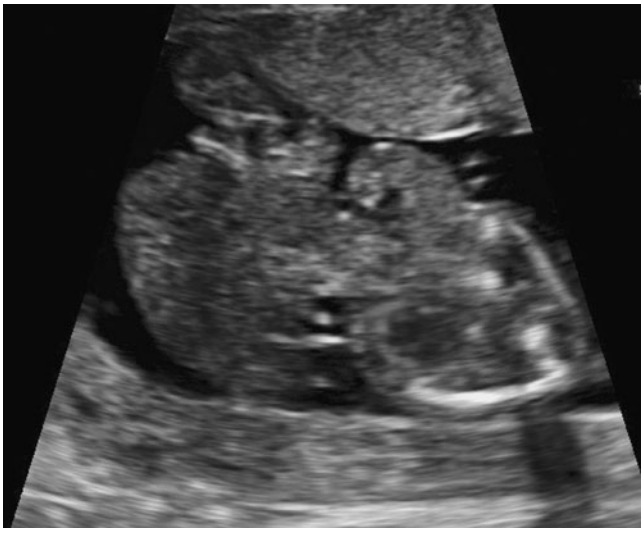

Figure 60-4 Transverse view of the same fetus with body-stalk anomaly at 18 weeks, as in Figure 60-3, demonstrating a massive abdominal wall defect with most of the intra-abdominal contents outside of the abdominal cavity.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for body-stalk anomaly includes isolated omphalocele, isolated gastroschisis, short umbilical cord syndrome (Miller et al., 1981), and limb–body wall complex. Some authors consider body-stalk anomaly to be a severe form of amniotic band syndrome (see Chapter 99) (Takeuchi et al., 1995). Amniotic bands are present in 40% of cases of body-stalk anomaly. In addition, some of the limb defects that can be associated with body-stalk anomaly can be attributed to amniotic bands.

Limb–body wall complex is included in the spectrum of defects seen in the early amnion-rupture sequence. Two phenotypes are thought to exist in limb–body wall complex. In the first one, craniofacial defects, amniotic bands, and/or adhesions are seen. In the second phenotype, urogenital abnormalities, anal atresia, abdominal placental attachment, and a persistent embryonic coelom are seen. The overlap between body-stalk anomaly, limb–body wall complex, and a severe form of amniotic band syndrome can be confusing. In a complete review of the limb–body wall complex, Van Allen et al. (1987) stated that the diagnosis of limb–body wall complex is based on the presence of two of three of the following: exencephaly or encephalocele with facial clefts, thoracoschisis and/or abdominoschisis, and a limb defect. In an evaluation of fetuses with limb–body wall complex, 24 of 25 cases studied by Van Allen et al. had associated internal structural defects. In 85% of these cases, there was evidence of persistence of the extraembryonic coelom by examination of the placenta. The abnormalities observed in this group of fetuses and data from experimental models support vascular disruption during 4 to 6 weeks of gestation as the cause for limb–body wall complex.

Martínez-Frías (1997) disagreed with Van Allen et al.'s definition of limb–body wall complex. He stated that an infant with encephalocele, facial clefts, and limb defects could be considered as having limb–body wall complex. Martínez-Frías has argued that the presence of abdominal wall defect with a variable spectrum of associated anomalies (with or without limb deficiencies) should be called body wall complex. He distinguished body wall complex from the amniotic band sequence without body wall defects, but included amniotic band sequence with body wall defects in the category of body wall complex.

Further adding to the confusion is that the epidemiology of body-stalk anomaly and limb–body wall complex is similar. Both malformations have been associated with cocaine abuse. Both conditions are associated with young maternal age, and inheritance is sporadic, with normal

karyotypes (Negishi et al., 1998). In a series of 11 cases of limb–body wall complex, 50% of patients reported use of cigarette, alcohol, and marijuana during pregnancy (Luehr et al., 2002).

With regard to sonographic diagnosis, it is helpful to remember that body-stalk anomaly is not associated with craniofacial or limb anomalies.

ANTENATAL NATURAL HISTORY

The discrepancy in the prevalence of body-stalk anomaly between 10 to 14 weeks of gestation and 17 to 19 weeks of gestation suggests that body-stalk anomaly is associated with a high incidence of spontaneous abortion early in the second trimester (Daskalakis et al., 1997).

The patterns of malformations associated with body-stalk anomaly depend on the degree of abnormal development of each of the four major embryonic folds. Associated anomalies observed in cases of body-stalk anomaly include colonic atresia, agenesis of the colon, intestinal atresia, cloacal exstrophy, vaginal atresia, agenesis of the uterus and gonads, absent external genitalia, hypoplastic kidneys, absent diaphragm, spina bifida, and dysplastic thorax.

Few data are available on the expectant management of body-stalk anomaly as the majority of cases result in elective pregnancy termination following prenatal diagnosis. In a series of prenatally diagnosed body-stalk anomaly, 10 of 11 cases resulted in pregnancy termination, with the one expectantly managed case being a monochorionic twin that resulted in early neonatal demise following delivery at 32 weeks' gestation (Smrcek et al., 2003).

MANAGEMENT OF PREGNANCY

If the diagnosis of body-stalk anomaly is suspected, the pregnant patient should be referred to a tertiary care center capable of detailed prenatal anatomic sonographic evaluation. The diagnosis of body-stalk anomaly is generally reliable when made prenatally. The major issue is to be certain that the sonographic abnormality observed is not isolated omphalocele or gastroschisis, which would carry a reasonably normal prognosis. If the diagnosis of body-stalk anomaly is certain, chromosomal analysis is not indicated, as almost all reported cases have been associated with a normal karyotype. In one series of 11 prenatally diagnosed cases, 10 of 11 had normal karyotype, with one having mosaic trisomy 2 (Smrcek et al., 2003). If the diagnosis of body-stalk anomaly is made, termination of pregnancy should be offered, as the condition is uniformly fatal in a newborn. A further complication of pregnancy is that abnormal fetal presentation is common and cesarean delivery may be indicated to allow delivery of an intact fetus. The short umbilical cord frequently results in abnormal presentation and lack of descent of the fetus into the pelvis during labor. Infants who are born alive with body-stalk anomaly die shortly after birth.

FETAL INTERVENTION

There are no fetal interventions indicated for body-stalk anomaly.

TREATMENT OF THE NEWBORN

In the rare setting of the limited postnatal survival of an affected newborn with body-stalk anomaly, only comfort care is indicated. The condition is almost uniformly fatal (Figure 60-5). One recent case report described the surgical management of a surviving fetus with body-stalk anomaly, in which surgical closure of the large omphalocele was successfully achieved (Kanamori et al., 2007). Such cases should be

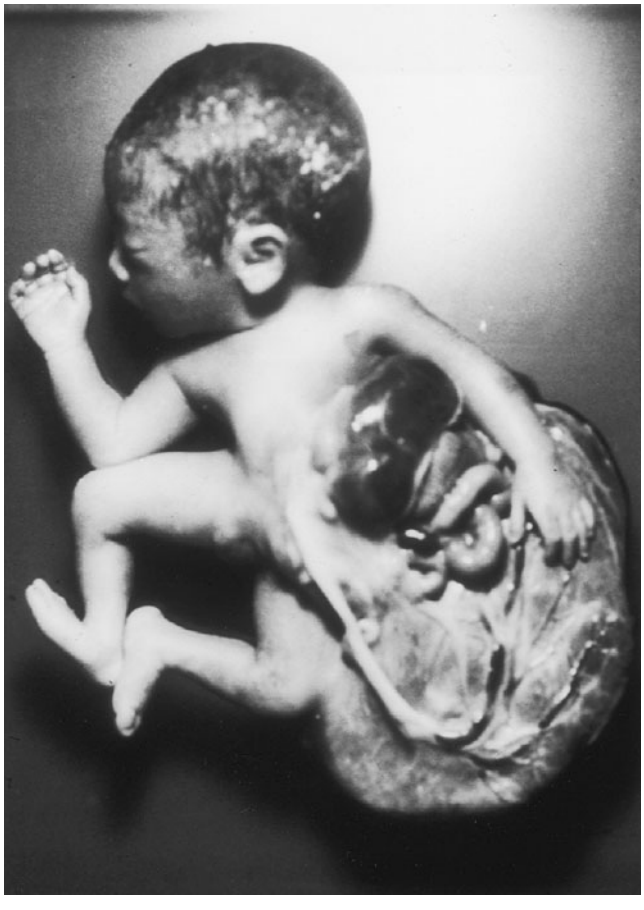

Figure 60-5 Postmortem photograph of the same fetus shown in Figures 60-1 and 60-2 demonstrating a large omphalocele in continuity with the placenta and a very short umbilical cord. *(From Takeuchi K, Fujita I, Nakajima K, Kitagaki S, Koketsu I. Body stalk anomaly: prenatal diagnosis.* Int J Gynecol Obstet. *1995;51:49-52.)*

considered exceptional; these cases typically have associated pulmonary hypoplasia and result in early neonatal demise.

SURGICAL TREATMENT

There are no surgical treatments indicated for body-stalk anomaly, although there has been one case report of a surviving infant following surgical closure of the large omphalocele (Kanamori et al., 2007).

LONG-TERM OUTCOME

In general, fetuses with body-stalk anomaly do not survive, and the condition should be considered a lethal anomaly. However, there is at least one case report of a surviving infant following surgical closure of omphalocele, but no long-term data are available yet regarding this infant (Kanamori et al., 2007).

GENETICS AND RECURRENCE RISK

All cases of body-stalk anomaly reported in the literature have been sporadic. The pregnant patient should be advised that there is unlikely to be an increased recurrence risk in subsequent pregnancies. In one series of 11 cases of limb–body wall complex, there was one patient who delivered two consecutive infants with the condition (Luehr et al., 2002). In addition, an increased incidence of body-stalk anomaly in monozygotic twins has been reported (Shih et al., 1996; Smrcek et al., 2003). This is probably due to an early embryonic cleavage disorder and is thought to represent a gradual transition from monoamniotic twins to conjoined twins. The development of body-stalk anomaly is therefore an intrinsic part of the twinning process and should not carry an increased recurrence risk.

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61 CHAPTER

Pentalogy of Cantrell

Key Points

- Pentalogy of Cantrell is defined by the association of five anomalies: (1) epigastric abdominal wall defect, (2) lower sternal defect, (3) defect in the anterior diaphragm, (4) defect in the epicardium, and (5) intracardiac defects.
- Can be associated with other midline ventral defects such as cleft lip and palate, exencephaly, and sirenomelia.
- Rare association thought to occur in only 1 in 65,000 to 200,000 births.
- Most common intracardiac defects include VSD, ASD, pulmonic stenosis, tetralogy of Fallot, and LV diverticulum.
- All the defects are amendable to repair yet outcomes in this condition have been generally poor.
- An X-linked pattern of inheritance has been suggested for ventral midline defects including pentalogy of Cantrell.

CONDITION

Pentalogy of Cantrell is an unusual form of abdominal wall defect that consists of five associated anomalies, including: (1) midline epigastric abdominal wall defect, (2) defect of the lower sternum, (3) deficiency of the anterior diaphragm, (4) defect in the diaphragmatic pericardium, and (5) intracardiac defects. This constellation of anomalies was first described by Cantrell et al. (1958), hence, the term pentalogy of Cantrell, although it has also been referred to as the Cantrell–Haller–Ravitch syndrome and peritoneal pericardial diaphragmatic hernia. Not every case will have all five factors and some cases may have associated anomalies, usually midline defects also such as cleft lip or palate, sirenomelia, exencephaly (Carmi and Boughman, 1992; Egan et al., 1993; Polat et al., 2005). Toyama suggested a classification scheme for pentalogy of Cantrell in which Class 1 included those cases in which the diagnosis was definite and all five defects were present. In Class 2, the diagnosis was probable with the presence of four defects including the pressure of intracardiac and ventral abdominal wall defects. In Class 3, there was incomplete expression and various combinations of defects including a sternal abnormality (Toyama, 1972). Although pentalogy of Cantrell has been used interchangeably with ectopia cordis, in their original description Cantrell et al. (1958) were careful to distinguish between these two anomalies (see Chapter 59).

Cantrell suggested that the defects in this syndrome fell into two groups by mechanism of embryologic development. In the first group, a developmental failure of mesoderm results in diaphragmatic, pericardial, and intracardiac defects. The diaphragmatic defect is a failure of the transverse septum to develop. The pericardial defect arises from the somatic mesoderm immediately adjacent to the region of the same layer from which the transverse septum develops. Defective development of one but not the other of these structures is possible only with highly specific loss of somatic mesoderm. This is rarely seen in pentalogy of Cantrell in which the diaphragmatic and pericardial defects occur together in most patients. The intracardiac lesions result from abnormal development of the epimyocardium, which is derived from the splanchnic mesoderm. While the resulting intracardiac defects vary, almost all include defects of the cardiac septa.

The second group of defects results from failure of the ventral migration of the periprimordial structures and includes the sternal defect and the epigastric omphalocele. All elements of the sternum are present, and the costocartilages connect with the cartilaginous plates, which represent the paired sternal anlagen with variable degrees of fusion. The sternal defect results not from an absence of sternal primordia but from the failure of paired sternal anlagen to complete migration. A similar failure of migration results in the abdominal wall defect. The normal layers of the ventral abdominal wall are present, but there is a lack of ventral

migration of the myotomes. These patients have structurally normal rectus abdominus muscles that correctly attach to the pubic symphysis, but deviate laterally as they run cephalad to insert into the costal margins at the midclavicular line. This lack of migration is thought to be due to a defective development of the paramedian mesoderm.

The heart in pentalogy of Cantrell is normally positioned within the chest. In contrast, ectopia cordis is characterized by abnormal position of the heart outside of the chest (see Chapter 59). This becomes confusing, as classification systems for ectopia cordis list three types: cervical, thoracic, and thoracoabdominal, which is the same as pentalogy of Cantrell. Ectopia cordis may encompass partial or complete sternal defects, and invariably includes intracardiac anomalies, but does not include the pericardial, diaphragmatic, and abdominal wall defects seen in the pentalogy of Cantrell. Kanagusuntheram and Verzin (1962) suggested that ectopia cordis occurs as a result of excessive pericardial coelom formation and subsequent destruction of the transverse septum with rupture of the anterior body wall at 6 weeks of gestation (Kanagusuntheram and Verzin, 1962). Ravitch (1986) has suggested that the high frequency of major intrinsic cardiac defects with true ectopia cordis indicates that there is a primary defect in the splanchnic mesoderm responsible for cardiac development.

The primitive thoracic wall consists of somatopleura covering the ventral wall of the pericardial cavity. The ectodermal layer of the somatopleura forms the skin, but the remainder of the components of the body wall derive from invading dorsal mesoderm during the 6th week of gestation. The sternum appears as two parallel condensations of mesenchyme, the lateral sternal bands. A median cranial condensation, the presternum, appears independently. The lateral sternal bands fuse with the presternum cranially and with the tips of the ribs laterally. During the 7th week, the sternal bands begin fusing at their cephalic end and proceed caudally and cease by the 9th or 10th week.

INCIDENCE

The pentalogy of Cantrell is a rare association of anomalies with fewer than 100 cases having been reported (Craigo et al., 1992; Jochems et al., 2004). Due to the rarity of this condition, its incidence is difficult to accurately estimate. The incidence of the syndrome has been suggested to range between 1:65,000 to 1:200,000 (Martin et al., 1992; Vazquez-Jimenez et al., 1998). Carmi et al. (1993) reported five cases of pentalogy of Cantrell ascertained through the Baltimore–Washington population-based study of infants with congenital cardiovascular malformations, and estimated a regional prevalence of 5.5 cases for 1 million liveborn infants. The prevalence in fetuses is unknown (Aber-Yousef et al., 1987). African Americans may be more predisposed to developing pentalogy of Cantrell (Kousseff et al., 1996). Males appear more at risk with an incidence 2.7 times that of females (Egan et al., 1993). There have been five cases of pentalogy of Cantrell occurring in twins (Baker et al., 1984; Ghidini et al., 1988; Carmi and Boughman, 1992).

SONOGRAPHIC FINDINGS

The most obvious feature of pentalogy of Cantrell is the epigastric omphalocele (Figure 61-1). There are reported cases with diastasis rectus without an omphalocele, which may be difficult to diagnose prenatally. The anterior diaphragmatic and pericardial defects are difficult, if not impossible, to discern sonographically. MRI may offer assistance in defining anterior diaphragmatic defects in some cases (Song and McLeary, 2000).

The three features of the pentalogy that may be most easily detected include the epigastric omphalocele, lower sternal defects, and intracardiac defects (Romero et al., 1988; Craigo et al., 1992).

Even if no other structural defects can be found, any fetus with an epigastric omphalocele should be evaluated for pentalogy of Cantrell, with particular attention paid to possible associated cardiac defects. The abdominal wall defect in pentalogy of Cantrell may vary from a very large omphalocele containing the stomach, liver, and apex of the heart to only widely displaced rectus abdominus muscles with skin covering the other defects and a ventral hernia.

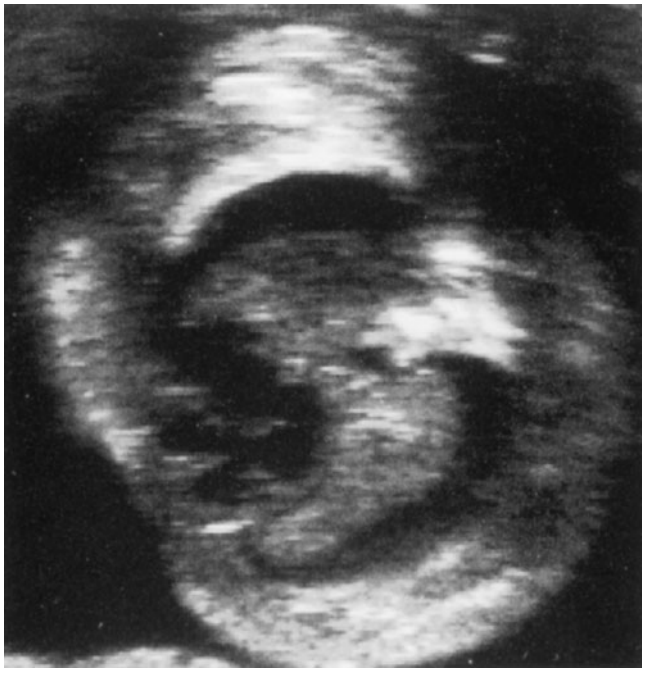

Figure 61-1 Prenatal sonographic image showing the transverse thoracic view of a fetus with pentalogy of Cantrell. The anterior chest wall defect—epigastric omphalocele with the heart in the cephalad portion of the defect—can be appreciated.

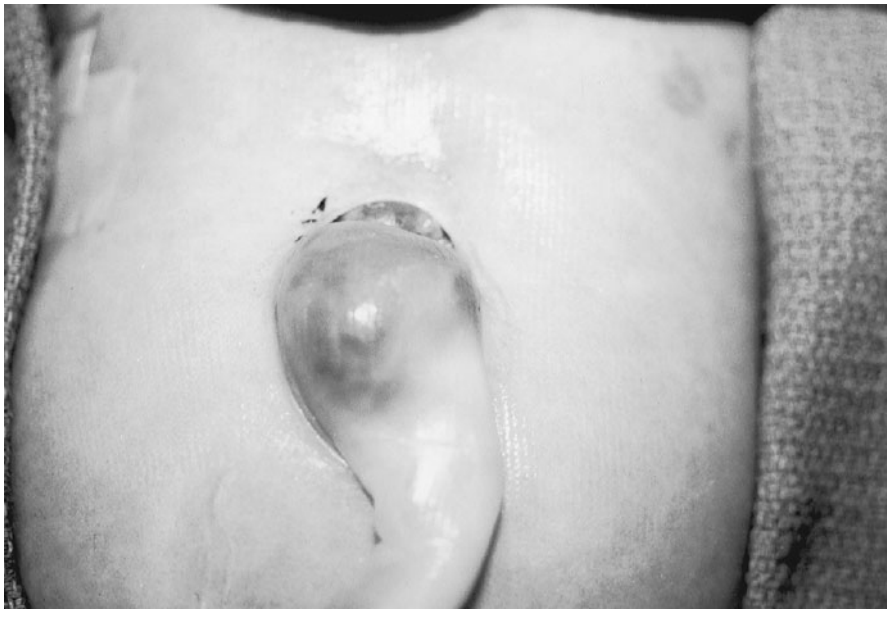

Figure 61-2 Postnatal appearance of the fetus in Figure 61-1. The epigastric omphalocele is apparent, with separation of the omphalocele membrane from the skin at the superior aspect of the abdominal wall defect. The heart can be seen in the space between the skin and separated omphalocele membrane.

The heart in the pentalogy of Cantrell is positioned within the fetal chest (Figure 61-2). If the heart is located outside the fetal chest, this indicates ectopia cordis (see Chapter 59). Even though positioned within the chest, there is a subtle shift in the cardiac axis in pentalogy of Cantrell. The heart is normally oriented horizontally, with the apex to the left. However, in this syndrome, the apex is oriented vertically, with the apex at the superior edge of the abdominal wall defect. Usually, but not invariably, the heart in the pentalogy of Cantrell has intracardiac anomalies. The most commonly observed is a ventricular septal defect (Table 61-1).

In addition to the five anomalies that constitute the pentalogy of Cantrell, other associated anomalies have been reported. Care should be taken to adequately visualize the fetal spine and hands, as vertebral and digital anomalies are often seen, including kyphoscoliosis and clinodactyly. Likewise, a detailed inspection of the fetal head and face should be performed to exclude potentially associated craniofacial anomalies, including encephalocele, cleft lip, microphthalmia, and low-set ears (Fox et al., 1988; Ghidini et al., 1988). In addition, a two-vessel cord, absent left lung, cloacal exstrophy, and fetal ascites have all been observed in cases of pentalogy of Cantrell (Toyama, 1972; Baker et al., 1984; Goncalves and Jeanty, 1994). Egan et al. (1993) have reported a case of pentalogy of Cantrell associated with sirenomelia in a monozygotic twin. They suggested that anterior midline ventral wall defects may be caused by either monozygotic twinning or vascular dysplasia. Similarly, a vascular steal phenomenon is thought to cause sirenomelia (see Chapter 86). They suggested that a common cause for these defects, that is, an alteration in vascular development, may be responsible. Carmi and Boughman (1992) found that three of their five patients had associated cleft lip with or without cleft palate. In a review of the literature on pentalogy of Cantrell and the various combinations of the anomalies within the spectrum, they suggested that pentalogy of Cantrell defines a specific midline ventral developmental field. Cleft lip with or without cleft palate and encephalocele tend to associate specifically with ventral midline anomalies within the spectrum of pentalogy of Cantrell. The authors speculated that these associations might be due either to previously observed tendencies or to specific occurrences of certain combinations of midline defects, or they may represent defined subunits of the midline developmental field (Carmi and Boughman, 1992; Martin et al., 1992).

Table 61-1

Intracardiac Anomalies in Pentalogy of Cantrell

	Percentage
Ventriculoseptal defect	37.5
Atrioseptal defect	20.0
Pulmonic stenosis	12.5
Tetrology of Fallot	7.5
Left ventricle diverticulum	7.5
Anomalous venous return (caval)	7.5
Tricuspid atresia	2.3
Truncus arteriosus	2.3
Anomalous venous return (pulmonary)	2.3

DIFFERENTIAL DIAGNOSIS

The differential diagnosis in pentalogy of Cantrell includes ectopia cordis, body-stalk anomaly, simple omphalocele, and amniotic band syndrome (see Chapters 59, 60, 62, and 100).

ANTENATAL NATURAL HISTORY

Our understanding of the antenatal natural history of pentalogy of Cantrell is limited not only by the rarity of this syndrome, but also by the few cases that have been diagnosed prenatally. According to one report, fewer than 90 cases have been reported (Craigo et al., 1992). If seen in isolation, none of the anomalies in pentalogy of Cantrell are associated with an adverse outcome or with in utero fetal death. Even the intracardiac anomalies most often seen in the pentalogy of Cantrell do not affect fetal survival. Ghidini et al. (1988) reported 10 cases from Yale in which there were no survivors. However, five of these pregnancies were terminated electively and the other five died postnatally. The authors did not distinguish between pentalogy of Cantrell and ectopia cordis, however. The prognosis for ectopia cordis, however, is quite different and significantly worse than for pentalogy of Cantrell. The overall prognosis in pentalogy of Cantrell is more closely correlated with the severity of the intracardiac defect and other associated anomalies not part of the pentalogy (Paidas et al., 1994).

MANAGEMENT OF PREGNANCY

An estimation of the size of the omphalocele and the contents of the omphalocele sac should be documented and care taken to ensure that the amnioperitoneal membrane is intact circumferentially. The orientation of the heart should be carefully noted and attempts should be made to discern the anterior diaphragmatic defect. A careful sonographic search for other potential associated anomalies should be performed. Chromosomal analysis, as in all cases of omphalocele, is strongly recommended. Given the complexity of this syndrome, it is useful to have the parents meet with several specialists who provide a team approach for comprehensive counseling. This team should include not only maternal–fetal medicine specialists but also a geneticist, a pediatric surgeon, a pediatric cardiologist, a neonatologist, and a pediatric cardiac surgeon. If a chromosomal abnormality or other significant anomaly is diagnosed, the parents should be counseled appropriately and termination may be offered. After a decision has been reached to continue the pregnancy, in the absence of such associated adverse prognostic indicators, attention should be focused on antepartum surveillance for preterm labor and the possibility of intrauterine growth restriction. Both of these complications can be seen in all forms of omphalocele, including the pentalogy of Cantrell. The rates of preterm delivery and intrauterine growth restriction have ranged from 26% to 65% and from 6% to 35%, respectively (Carpenter et al., 1984; Sermer et al., 1987; Lafferty et al., 1989; Sipes et al., 1990). In addition to surveillance for growth restriction and polyhydramnios, observation for occasional rupture of the omphalocele membrane is necessary, as it would expose the herniated viscera and require emergency surgery once the infant has been delivered.

Delivery of an infant with pentalogy of Cantrell is best managed in a tertiary care center that provides newborn medicine specialists as well as pediatric cardiologists and pediatric surgeons who can provide immediate postnatal care. The mode of delivery is not affected by the diagnosis of pentalogy of Cantrell. We currently recommend that omphaloceles, including pentalogy of Cantrell, be delivered vaginally and reserve cesarean section for routine obstetric indications. However, because severe giant omphalocele may predispose to dystocia, cesarean delivery may be indicated in cases of giant omphalocele.

FETAL INTERVENTION

There are no fetal interventions for pentalogy of Cantrell.

TREATMENT OF THE NEWBORN

Treatment of the newborn is the same as the treatment of any infant born with an intact omphalocele (see Chapter 62). The one confounding variable is the presence of the intracardiac defect. The most common of these is a ventricular septal defect, which does not change the treatment. In severe cases of tetralogy of Fallot, in which the baby may be cyanotic, treatment during the immediate postnatal period may be altered.

SURGICAL TREATMENT

Surgical reconstruction of an infant with pentalogy of Cantrell depends on several features. The timing of the surgery depends on whether or not the omphalocele membrane is intact, or if there is skin covering the defect (see Figure 61-2). Dehiscence of the omphalocele membrane from the abdominal wall requires emergency closure within the first few hours of life to prevent infectious complications. In the absence of such separation, it is prudent to perform a complete postnatal evaluation to confirm the presence of the complete pentalogy and to exclude other potential associated anomalies. Paramount among these is echocardiography to define the nature of the intracardiac defect. Once the infant has been adequately resuscitated and a complete evaluation performed, elective reconstruction may be undertaken. This is

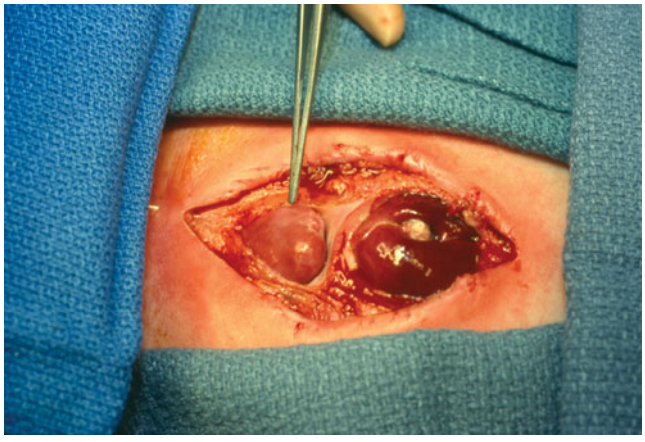

Figure 61-3 Operative repair of pentalogy of Cantrell. Four of the five defects can be seen in this photograph: (1) epigastric abdominal wall defect, (2) defect in anterior diaphragm, (3) defect in anterior pericardium, and (4) lower sternal defect. The intracardiac defect in this newborn was a ventricular septal defect, completing the pentalogy.

performed in a staged fashion, with the initial attention given to closure of the omphalocele, anterior diaphragmatic defect, and pericardial defects. The cardiac defects are repaired at a later date (Abdullah et al., 1993). The one exception to this is a left ventricular diverticulum, which may be readily excised at the time of the abdominal wall and sternal reconstruction. These small lesions may be a source of thrombus, focus for arrhythmia, or may rupture (Hamaoha et al., 1987; Tsujimoto and Takeshita, 2000; Halbertsma et al., 2002).

The omphalocele membrane is excised, which reveals the defect to include a common pericardial peritoneal cavity with the anterior diaphragmatic defect, and a lower sternal defect (see Figure 61-3). Because the rectus abdominal muscles are normally formed with anterior and posterior fascial sheaths intact, albeit laterally displaced with insertion at the midclavicular lines bilaterally, it is possible to do relaxing incisions both anteriorly and posteriorly in the rectus abdominis sheaths to allow rotation of the fascia to a medial location to close the abdominal wall defect. This fascial rotation can be used to close not only the midline abdominal wall defect but also to separate the peritoneal cavity from the mediastinum. This, however, still leaves the anterior thoracic defect and the pericardial defect present. The pericardial defect may be left until a later date, and the lower sternal defect, depending on the extent of the sternal deficiency, may be closed with a Gore-Tex patch to protect the heart. At a later date, the intracardiac defect may be addressed if this is necessary, as in the case with tetralogy of Fallot, or large VSD.

LONG-TERM OUTCOME

Due to the rarity of these cases and the few that have been successfully reconstructed, little information is available about the long-term outcome. We believe that long-term outcome should be most closely correlated with the severity of the intracardiac defect, as few sequelae are anticipated from the abdominal wall, diaphragmatic, and pericardial defects.

GENETICS AND RECURRENCE RISK

Pentalogy of Cantrell is primarily thought to be a sporadic defect. Karyotype abnormality is not a usual feature of pentalogy of Cantrell, but abnormalities of chromosomes 18 and 13 have been described (Fox et al., 1988). However, Martin et al. (1992) suggested that there was an association of sternal fusion defects with various cardiac, diaphragmatic, and anterior body wall defects, including pentalogy of Cantrell and ectopia cordis. This group reported a family in which three consecutively born brothers had extensive diaphragmatic defects; two of them had pentalogy of Cantrell.

It has been suggested that the inheritance pattern for ventral midline defects, including pentalogy of Cantrell, is X-linked. In studies of an extended family including 14 affected individuals, Carmi and Boughman (1992) obtained evidence of genetic linkage to markers in the region Xq22-q27. Additional results indicated that the thoracoabdominal syndrome (TAS) gene is located between the DXS425 and HPRT loci (Xq25-q26.1). Parvari et al. (1994) obtained significant evidence of linkage when the analysis used additional markers in Xq25-q26. Using microsatellite polymorphic markers, they narrowed the region of the TAS gene to an interval of approximately 2.5 Mb (Parvari et al., 1996).

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62 CHAPTER Omphalocele

Key Points

- Defect in ventral abdominal wall characterized by absent abdominal muscles, fascia, and skin. Defect is covered by membrane that consists of peritoneum and amnion.
- Incidence 1 in 4000 to 1 in 7000 livebirths.
- Principal sonographic diagnostic feature is umbilical cord insertion into the membrane covering the defect at a location distant from the abdominal wall.
- Differential diagnosis includes gastroschisis, body-stalk anomalies, pentalogy of Cantrell, and Beckwith–Wiedemann syndrome.
- There is a high incidence of both associated malformations and chromosome abnormalities. Prenatal karyotype is indicated. Fetal echocardiogram is recommended.
- Serial prenatal sonograms should be performed to assess fetal growth and amniotic fluid volume.
- Delivery at a tertiary care center provides optimal care for the newborn. Mode of delivery is debatable, except for cases of giant omphalocele or extracorporeal liver, in which cesarean section should be performed.
- Even with primary surgical repair, prospective parents should anticipate a long hospitalization for their neonate.

CONDITION

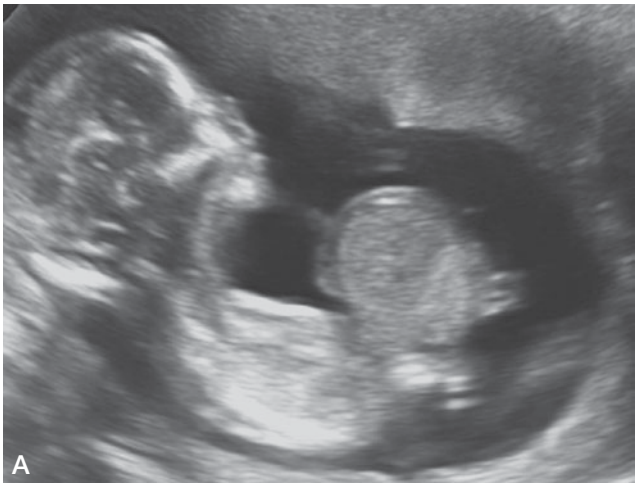
Omphalocele is a defect in the ventral abdominal wall that is characterized by an absence of abdominal muscles, fascia, and skin. The defect is covered by a membrane that consists of peritoneum and amnion. It can vary in size from a few centimeters to most of the ventral abdominal wall. Unlike gastroschisis, in omphalocele, the umbilical cord inserts into this membrane at a location distant from the abdominal wall (deVries, 1980). The defect is thought to be caused by an abnormality that occurs during the process of body infolding at 3 to 4 weeks of gestation (Dimmick and Kalousek, 1992). At that time, 3 folds occur simultaneously, and each is associated with a distinct type of omphalocele. Cephalic folding defects result in a high or epigastric omphalocele. An example of this is pentalogy of Cantrell (see Chapter 61), which consists of an epigastric omphalocele, anterior diaphragmatic defect, sternal cleft, pericardial defect, and associated intracardiac defects (Figure 62-1A) (Cantrell et al., 1958). A defect in lateral folding results in the classic omphalocele (Figure 62-1B) with a midabdominal defect. A defect in caudal folding results in a low or hypogastric omphalocele, as seen in bladder or cloacal exstrophy (see Chapters 64 and 65) (Duhamel, 1963; Meller et al., 1989; Vasudevan et al., 2006). The spectrum of severity of abdominal wall abnormalities can vary from a small umbilical hernia to a large defect with extrusion of the abdominal viscera.

INCIDENCE

The incidence of omphalocele ranges from approximately 1 in 4000 to 1 in 7000 livebirths (Baird and MacDonald, 1981; Lindham, 1981; Rankin et al., 1999; Stoll et al., 2001). The incidence of omphalocele is higher in combined livebirths and stillbirths (1 in 300 to 1 in 4000), reflecting the increased risk of intrauterine fetal death in cases of omphalocele. In fact, the overall incidence of abdominal wall defects is 20 times greater in stillborn than in liveborn infants (McKeown et al., 1953; Baird and MacDonald, 1981; Lindham, 1981; Carpenter et al., 1984). Unlike gastroschisis, there has not been a change in the incidence of this abnormality, which supports the notion that these are two separate entities with different causes (see Chapter 63). Unlike gastroschisis, omphalocele is associated with advanced, as opposed to younger, maternal age (Redford et al., 1985; Hwang and Kousseff, 2004).

SONOGRAPHIC FINDINGS

The diagnosis of omphalocele was made as early as 10 to 12 weeks of gestation by vaginal sonography, when an echogenic mass nearly equal to the size of the diameter of the fetal abdomen was found anterior to the fetal abdomen (Brown et al., 1989). The use of three-dimensional transvaginal ultrasound examination may facilitate this diagnosis early in gestation (Anandakumar et al., 2002; Tonni and Centini, 2006). The ultrasonographic appearance of omphalocele



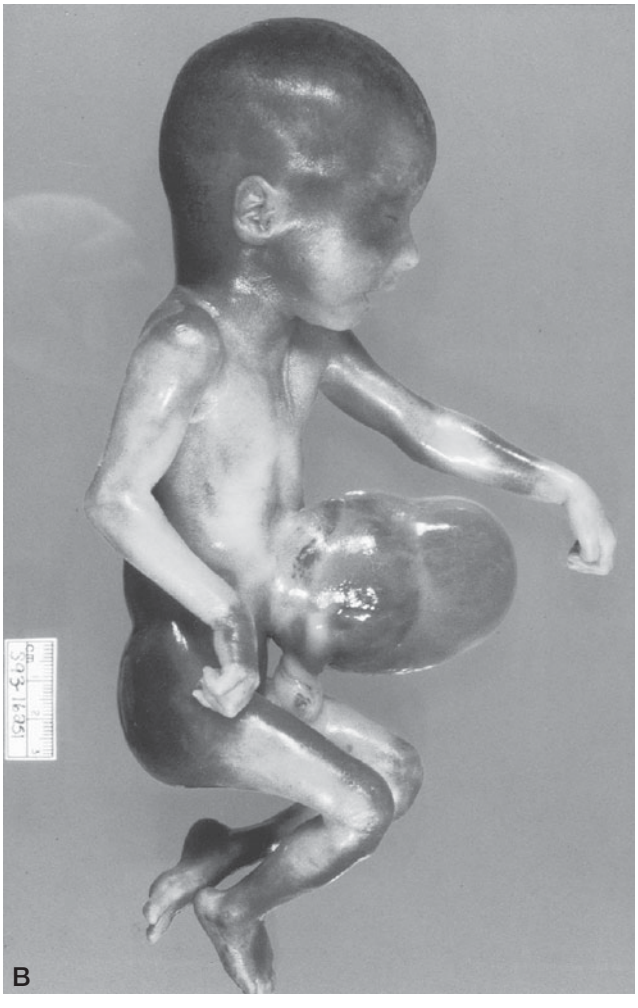


Figure 62-1 **A.** Sagittal image demonstrating the intact sac of a liver containing omphalocele in a fetus at 15 weeks; **B.** pathologic appearance of a fetus with omphalocele due to defect in lateral folding. *(Courtesy of Dr. Joseph Semple.)*

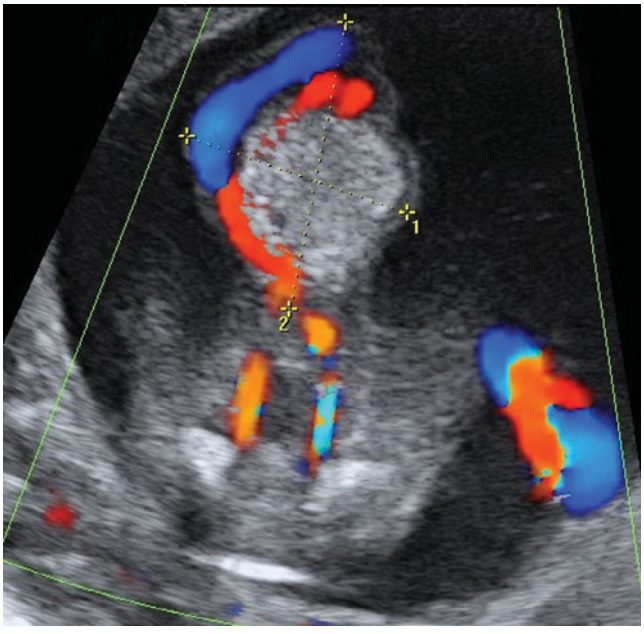


Figure 62-2 Color Doppler ultrasound of a fetus at 17 weeks' gestation with large omphalocele, demonstrating umbilical cord insertion into the membrane covering the abdominal wall defect.

varies depending on the size and location of the defect, the presence of ascites, and the organs contained within the defect. However, a principal diagnostic feature of omphalocele is the umbilical cord insertion into the membrane covering the abdominal wall defect (Figure 62-2). This contrasts with gastroschisis, in which the defect is immediately to the right of the normal umbilical cord insertion into the abdominal wall. The cord insertion site at the caudal apical portion of the omphalocele membrane can be visualized with color flow Doppler studies on sagittal or oblique images. An additional diagnostic feature is the presence of the intrahepatic portion of the umbilical vein coursing through the central portion of the defect. Omphaloceles are characterized in utero by the presence of a membrane; however, occasionally this membrane will rupture. In cases of ruptured omphalocele, the abdominal contents are floating free in the amniotic cavity, similar to gastroschisis. However, unlike gastroschisis, in ruptured omphaloceles, the defects are usually large and have at least exposed, if not extracorporeal, liver (Figure 62-3).

DIFFERENTIAL DIAGNOSIS

It is usually easy to distinguish sonographically between gastroschisis, with its cord insertion on the abdominal wall, and omphalocele, with the cord insertion at the apex of the membrane encompassing the abdominal wall defect. It sometimes is more difficult to distinguish between a small omphalocele and a hernia of the cord than between ruptured omphaloceles, gastroschisis, and body-stalk anomalies.

Two syndromes deserve mention in the context of omphalocele: pentalogy of Cantrell and Beckwith–Wiedemann syndrome (see Chapters 27, 61, and 123). Pentalogy of Cantrell is characterized by the presence of an epigastric omphalocele and defects of the sternum, anterior diaphragm, and diaphragmatic pericardium, with associated intracardiac lesions (Cantrell et al., 1958; Toyama, 1972; Spitz et al., 1975). Cantrell et al. (1958) hypothesized that the syndrome might have resulted from a developmental failure of a segment of lateral mesoderm around 14 to 18 days of embryonic life. Consequently, there is a lack of development of the transverse septum of the diaphragm and a lack of migration of the two paired mesodermal folds of the upper abdomen. A defect in the lower sternal region develops, allowing for protrusion of the heart and the upper abdominal organs. The syndrome is very rare. Fewer than 90 cases have been described (Craigo et al., 1992). Ghidini et al. (1988) reviewed the Yale experience and found 10 cases of pentalogy of Cantrell. Five pregnant patients elected termination and the remaining five delivered infants; there were no survivors beyond 3 months of age. A

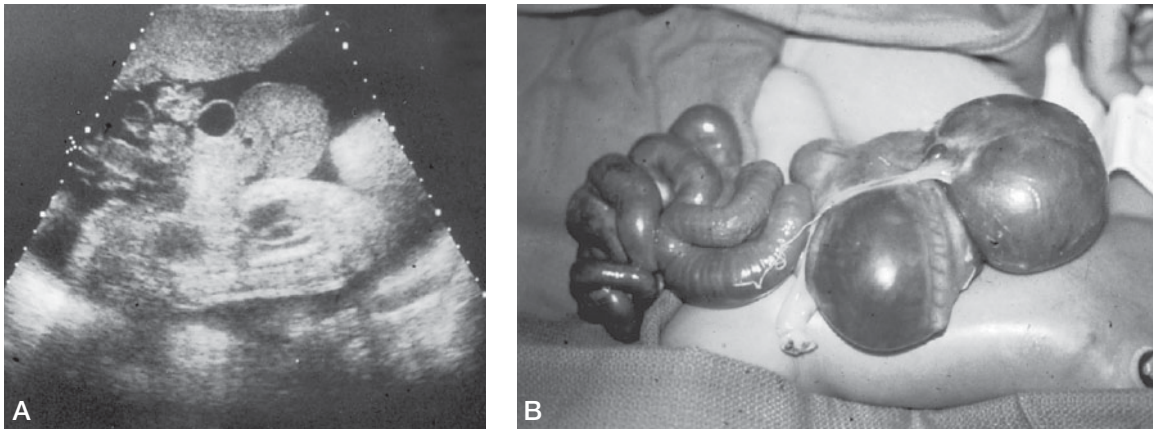


Figure 62-3 **A**. Ultrasound image of fetus with ruptured omphalocele seen in sagittal plane, demonstrating large ventral defect through which the entire liver, stomach, and intestines have herniated. No membrane is seen around the defect. **B**. The appearance of the infant immediately postnatally, with completely exteriorized liver, stomach, and small and large bowel.

number of other anomalies can be associated with pentalogy of Cantrell, including craniofacial abnormalities, chromosomal abnormalities, clubfeet, malrotation of the colon, hydrocephalus, and anencephaly (Craigo et al., 1992). The defects themselves can vary in severity, ranging from only rectus muscle diastasis to a large omphalocele. The most common cardiac abnormalities include atrial and ventricular septal defects, and tetralogy of Fallot (Bryker and Breg, 1990). The prognosis in pentalogy of Cantrell is directly related to the severity of the cardiac defect.

The Beckwith–Wiedemann syndrome, otherwise known as exomphalos-macroglossia-gigantism (EMG) syndrome, consists of the presence of omphalocele, visceromegaly, macroglossia, and severe neonatal hypoglycemia (see Chapters 27 and 123). Cardiac abnormalities are also frequently seen in this syndrome. Greenwood et al. (1977) found that 12 of 13 patients with this syndrome had cardiovascular malformations, and 7 of the 12 had structural abnormalities. Malignant tumors can develop in 10% of patients, including Wilms' tumor, hepatoblastoma, and adrenal tumors (Sotelo, 1977). This syndrome does not have any obligatory anomalies, and the diagnosis has been made without macroglossia or omphalocele (Cohen and Ulstrom, 1979). Evidence of macroglossia, or enlargement of adrenal glands, liver, kidneys, or pancreas, in the setting of omphalocele should alert one to the possible diagnosis of Beckwith–Wiedemann. These findings are rare and seldom seen prior to the third trimester.

ANTENATAL NATURAL HISTORY

Omphalocele can present as part of a syndrome or as an isolated defect. A list of the syndromes associated with omphalocele is given in Table 62-1 (Stoll et al., 2008). The most important prognostic variable is the presence of associated malformations or chromosomal abnormalities. Visceral malformations can accompany omphalocele in 50% to 70% of cases, and chromosomal abnormalities can be seen in 30% to 69% (Paidas et al., 1994; Brantberg et al., 2005; Lakasing et al., 2006). Interestingly, the absence of the liver in the omphalocele has been correlated with fetal karyotypic abnormalities and perinatal mortality.

Nyberg et al. (1989) were the first to report an association between omphalocele contents and fetal chromosomal abnormalities. Other investigators have validated the finding that small defects in omphalocele that contain only bowel are associated with an increased risk of chromosomal abnormalities (Benacerraf et al., 1990; Getachew et al., 1991). In one study, chromosomal abnormalities were present in all 8 fetuses with intracorporeal liver, as opposed to 2 of the 18 fetuses with an extracorporeal liver. They also found a significant association between advanced maternal age (33 years and older) and abnormal karyotype. Gilbert and Nicolaides (1987) found that in a series of 35 fetuses, there was a high rate of chromosomal abnormalities (54%) with a predominance of trisomy 18 (17 of 19 cases of chromosomal abnormalities). Brantberg et al. (2005) found a higher incidence of karyotypic abnormalities when the omphalocele was central (69%) as opposed to epigastric (12.5%) in location.

Table 62-1

Syndromes Associated with Omphalocele

Beckwith–Wiedemann syndrome
Cloacal exstrophy
Fibrochondrogenesis
Lethal omphalocele—cleft palate syndrome
Marshall–Smith syndrome
Meckel–Gruber syndrome
Triploidy
Trisomy 13
Trisomy 18

The constellation of other associated malformations varies greatly, ranging from single, minor, nonlethal abnormalities to multiple complex life-threatening abnormalities that influence long-term prognosis more than the omphalocele itself. The pediatric literature (as opposed to the obstetric literature) has reported a better prognosis for neonates with omphalocele, due to the fact that many of the fetuses with multiple associated anomalies die in utero or during the immediate perinatal period. The report from Rijhwani et al. (2005) from King's College Hospital is illustrative of this point, with survival of 34 of 35 neonates undergoing primary or staged closure. The same institution reported that fewer than 10% of the 445 prenatally diagnosed cases of omphalocele survived to repair (Lakasing et al., 2006).

Several investigators have described the impact of associated anomalies on survival in cases of omphalocele. Hughes et al. (1989) reviewed a series of 46 cases detected by prenatal ultrasound examination from three high-risk obstetric referral centers. In 43 of 46 cases, adequate follow-up information was available. Twenty-nine of the 43 cases (67%) had additional malformations, with 23 (79%) considered major and 6 (21%) considered minor. Three of the 29 pregnancies were terminated. There was a total of 58 individual anomalies in the 26 fetuses in which the pregnancy was continued. Cardiac anomalies were the most common (14 cases), including ectopia cordis (4). The other systems involved were skeletal (9), gastrointestinal (6), genitourinary (6), and central nervous (7). Fetal mortality was most strongly associated with the presence of concurrent malformations. Twelve of the 15 fetuses (80%) with concurrent malformations died, and the 3 that survived had isolated minor abnormalities. This

was in contrast to 7 fetuses without additional anomalies that survived. In the Hughes et al. (1989) series, the size of the omphalocele was not associated with fetal mortality. Six of the 10 survivors had a transverse omphalocele to abdomen ratio of >0.6 and two omphaloceles measured more than 10 cm. Abnormal amniotic fluid volume was present in 9 of the 12 fetuses that died spontaneously, and 3 of these had no abnormalities detected on sonographic examination.

Tucci and Bard (1990) reviewed a 5-year Canadian experience consisting of 28 cases of omphalocele. They initially divided their cases into two groups on the basis of the size of the defect, small (<5 cm) and giant (>5 cm). Of the 12 fetuses with small omphaloceles only 1 died, whereas 10 of the 16 infants with giant omphalocele died and all except 1 had severe associated anomalies. There were five cases of congenital heart disease, three diaphragmatic hernias, and two central nervous system malformations. Of note, none of the six surviving infants had associated severe malformations. In this series, four of the survivors had liver herniation, which suggests that giant omphaloceles can have a favorable prognosis if other severe anomalies are not present.

Nicolaides et al. (1992) compiled their 8-year experience with omphalocele and reviewed both the obstetric and pediatric literature regarding the presence of chromosomal abnormalities and associated malformations. Of the 116 cases of omphaloceles, 87 (75%) had associated malformations. They also found a higher incidence of chromosomal abnormalities when the omphalocele contained only bowel as compared with omphaloceles that contained liver and bowel (25 of 44 vs. 17 of 72). In their summary, of 349 cases detected antenatally, 229 (65.6%) had associated malformations. Summarizing 13 studies with postnatal follow-up, an overall incidence of associated anomalies is 50%. They also noted an association with neural tube defects in chromosomally normal fetuses (Ardinger et al., 1987).

More recently, Nicolaides' group reported their 11-year experience with 445 cases of omphalocele from the Harris Birthright Centre for Fetal Research at King's College Hospital (Lakasing et al., 2006). In 250 cases (56%) the karyotype was found to be abnormal, and in 130 cases (30%) the karyotype was normal, with the remainder declining karyotype analysis. In the group with karyotype abnormalities, 248 (99%) underwent termination of pregnancy or died in utero. Among the 130 cases with normal karyotype, 74 (56%) were found to have associated structural anomalies.

Lakasing et al. (2006) reported that during an 11-year period from 1991 to 2001, 445 cases of omphalocele experienced less than 10% survival from operative repair due to termination of pregnancy, intrauterine fetal demise, and neonatal death.

MANAGEMENT OF PREGNANCY

Elevated maternal serum α-fetoprotein (MSAFP) levels have traditionally been associated with open neural tube defects, but they are also associated with ventral abdominal wall defects (Brooke et al., 1979; Stiller et al., 1990; Killam et al., 1991). The sensitivity of MSAFP screening for the detection of abdominal wall defects will vary depending on whether it is omphalocele or gastroschisis and on the cutoff value of MSAFP used (Paidas et al., 1994). MSAFP screening has a much higher sensitivity for detecting gastroschisis than for detecting omphalocele. Palomaki et al. (1988) found that at each cutoff value of MSAFP, detection rates were higher for gastroschisis than for omphalocele. For example, at a cutoff value of >2.5 multiples of the median (MoM) and >3.0 MoM, the detection rates were more than 98% and 71%, and 96% and 65% for gastroschisis and omphalocele, respectively. The median MSAFP values for cases of omphalocele in this study were 4.1 MoM (Palomaki et al., 1988). The poorer detection rate for omphalocele is thought to be due to the presence of the intact amnioperitoneal membrane covering the abdominal cavities in unruptured omphalocele, as opposed to direct exposure of bowel to the amniotic fluid in gastroschisis (Paidas et al., 1994).

Once identified, a sonographic estimation of the size of the omphalocele, contents of the omphalocele sac, location of the umbilical cord insertion relative to the herniation, and the presence of an amnioperitoneal membrane should be documented. A careful sonographic search for other fetal anomalies should also be performed, including fetal echocardiography. Because of the high incidence of associated congenital cardiac disease (19%–32%), we recommend fetal echocardiography when an omphalocele is diagnosed (Greenwood et al., 1974; Carpenter et al., 1984; Crawford et al., 1985; Copel et al., 1986). The incidence of congenital heart disease is related to the embryology of the body fold defect. Ten percent of neonates with lateral fold defects have congenital heart disease, whereas the incidence approaches 100% if the cephalic fold is affected. Alternatively, if the caudal fold is involved, the incidence of associated congenital heart disease is low (Greenwood et al., 1974; Carpenter et al., 1984; Crawford et al., 1985; Copel et al., 1986).

Chromosomal analysis is strongly recommended due to the multiple studies that have documented a high rate of karyotype abnormalities. We have found that a team approach provides comprehensive counseling and advice for parents with a fetus diagnosed with this anomaly. In addition to maternal and fetal medicine specialists, the parents should meet with specialists in pediatric surgery, genetics, neonatology, and pediatric cardiology. This type of approach, coordinated by the maternal and fetal medicine specialists, affords the parents the opportunity to ask questions regarding postnatal surgery, postoperative care, and long-term outcome. If chromosomal abnormalities, associated anomalies, or a particular syndrome is suspected, these issues can be further discussed in detail. After a decision has been reached regarding continuation of the pregnancy, attention is then focused on antepartum surveillance for the development of preterm labor and intrauterine growth restriction. Both of these complications are frequently associated with omphalocele. Rates for preterm delivery range from 26% to 65% and for intrauterine

growth restriction from 6% to 35% (Carpenter et al., 1984; Sermer et al., 1987; Lafferty et al., 1989; Sipes et al., 1990 a,b). There is also a high rate of emergency cesarean delivery due to fetal distress (Moretti et al., 1990; Molenaar and Tibboel, 1993). Because of the high incidence of intrauterine growth restriction, we perform serial ultrasound examinations to assess fetal growth and amniotic fluid volume. In addition, during ultrasound assessment we observe for occasional rupture of the omphalocele membrane, which exposes the herniated intestines to amniotic fluid.

In up to 50% of cases, significant pulmonary hypoplasia and pulmonary hypertension may complicate the neonatal course, particularly in giant omphaloceles (Tsakayannis et al., 1996; Lee et al., 2006). We routinely recommend MRI for total lung volume assessment at 32 to 34 weeks' gestation to help identify fetuses at risk for these complications that, if present, become the overriding determinant of management in omphalocele.

The site and mode of delivery have been debated in the obstetric literature (Lewis et al., 1990; Lurie et al., 1999; Segel et al., 2001). The goal of the management of fetuses with omphalocele is to deliver the fetus as close to term as possible. Delivery at a tertiary care center provides optimal immediate care for the newborn (Hsieh et al., 1989; Lafferty et al., 1989; Lewis et al., 1990; Geijn et al., 1991). In addition, transporting the pregnant woman before delivery, rather than transporting the neonate after delivery, provides immediate neonatal surgical care and eliminates the risk of transporting a critically ill newborn.

Mode of delivery—vaginally or by cesarean—has been the subject of several retrospective reviews. No results from available prospective randomized trials have settled this issue. Older literature advocated the use of cesarean section (Cameron et al., 1978). However, the most recent retrospective reviews do not support the idea that cesarean delivery is associated with an improved survival rate (Sermer et al., 1987; Moretti et al., 1990; Sipes et al., 1990a; Kirk and Wah, 1983; Lurie et al., 1999; Segel et al., 2001). None of the six reported series show any benefit to cesarean delivery. The outcome of giant omphaloceles was not specifically addressed in these studies. Several other authors do not support routine cesarean delivery for fetuses with omphalocele (Carpenter et al., 1984; Hasan and Hermansen, 1986; Hsieh et al., 1989; Lafferty et al., 1989; Lewis et al., 1990; How et al., 2000). Labor itself does not seem to adversely affect outcome, based on the study by Lewis et al. (1990), who compared outcome data from infants delivered via elective cesarean section with those whose delivery was preceded by labor. In cases of small omphaloceles, we currently recommend vaginal delivery and reserve cesarean delivery for routine obstetric indications. However, in isolated cases of giant omphalocele with a defect in the fetal abdomen measuring 5 cm or greater by ultrasound examination, cesarean delivery may be necessary to avoid dystocia. Particularly in cases of extracorporeal liver, we recommend delivering by cesarean section. This approach underscores the need for re-evaluation of the defect as pregnancy progresses.

FETAL INTERVENTION

There are no fetal interventions for omphalocele.

TREATMENT OF THE NEWBORN

Delivery should occur in a tertiary care center, with neonatologists available for immediate resuscitation. Initial treatment consists of airway stabilization and sterile wrapping of the abdominal defect to preserve heat and minimize insensible fluid loss. A complete physical examination should be performed to rule out a syndromic diagnosis. Peripheral vascular access should be established and intravenous fluids given. Mechanical ventilation is frequently necessary, especially postoperatively, when abdominal contents replaced into a small abdominal cavity impede diaphragmatic occlusion and lung expansion. Antibiotics are generally given postoperatively. Initial treatment of the newborn is directed toward preoperative stabilization. Significant pulmonary hypoplasia and associated pulmonary hypertension may complicate the neonatal management of omphalocele from the delivery room on. This may be the most challenging management feature of up to 50% of neonates with giant omphaloceles (Tsakayannis et al., 1996; Lee et al., 2006).

SURGICAL TREATMENT

The surgical approach to the treatment of omphalocele has changed considerably over the past four decades. Until 1965, the only approach for the treatment of omphalocele was the skin flap technique described by Gross (1948). The principal disadvantage of this technique was the creation of a large disfiguring ventral hernia that ultimately required reoperation. This is usually not an insurmountable problem, and success has been reported for repair of these hernias. Considerable time (usually 6 months to 2 years, but sometimes longer) can lapse between initial surgery and final correction of the hernia (Swartz et al., 1985). If at all possible, primary fascial closure is the preferred method of repair because of a lower incidence of sepsis, biliary obstruction, and fistula and a reduced number of operations and rate of mortality in patients who undergo this repair (Figure 62-4) (Robin and Ein, 1976; Aaronson and Eckstein, 1977; Canty and Collins, 1983; Mabogunje and Mahour, 1984; Sauter et al., 1991).

For very large omphaloceles, a staged reduction using a prosthetic silo is preferred (Schuster, 1967; Allen and Wrenn, 1969; Othersen and Smith, 1986). This procedure consists of suturing a Silastic mesh to the rim of fascial defect, which then covers the herniated contents of the omphalocele (Figure 62-5). This technique consists of paralysis with neuromuscular blocking agents, enlargement of the fascial defect, and gradual stretching of the abdominal wall. Despite the success of the silon chimney (Allen and Wrenn, 1969), there remains a significant subset of patients in whom complete reduction

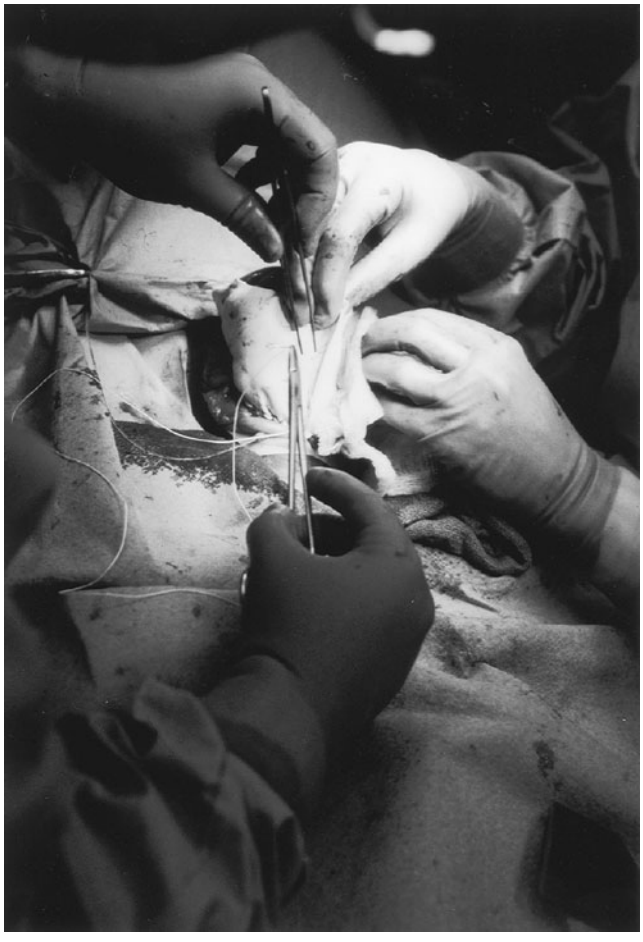


Figure 62-4 Silo repair of omphalocele.

is not achieved before complications of wound/fascial dehiscence, infection, enterocotomy, fistula, and systemic sepsis develop (Stringel and Filler, 1979; Towne et al., 1980; Hershenson et al., 1985; Hatch and Baxter, 1987; Adam et al., 1991; Lee et al., 2006). Nonoperative (conservative) approaches to the treatment of omphalocele have grown in popularity with greater success rates in cases of visceroabdominal disproportion and much lower mortality rates, but they have the disadvantages noted above, as well as prolonged hospitalization (Mabogunje and Mahour, 1984; Hatch and Baxter, 1987; Nuchtern et al., 1995; Tsakayannis et al., 1996). As long as the omphalocele membrane is intact, wrapping the newborn with elastic bandage wraps will gradually reduce the size of the omphalocele and enlarge the peritoneal cavity. A delayed primary repair can be performed after a period of days to weeks. We have found this approach particularly useful in premature infants with giant omphaloceles, and in cases in which there is significant pulmonary hypoplasia or diffuse tracheobronchial malacia with concomitantly difficult ventilatory management. In cases with pulmonary hypoplasia or tracheobronchial malacia, this approach is particularly appealing, as improvement in the respiratory status may take 1 to 2 years.

Although the presence of multiple associated anomalies accounts for the majority of deaths in cases of omphalocele, respiratory complications also account for a significant percentage of the morbidity and mortality due to this lesion (Paidas et al., 1994; Tsakayannis et al., 1996; Lee et al., 2006). Newborns with omphalocele, particularly giant omphalocele, have a high incidence of respiratory insufficiency and chest-wall deformity. Some evidence suggests that impaired lung growth and pulmonary hypoplasia may even be evident antenatally (Hershenson et al., 1985; Argyle, 1989; Thompson et al., 1993).

Neonates may require prolonged mechanical ventilation because of the need for positive pressure to expand a chest compressed by a large abdominal mass. Bronchopulmonary dysplasia and chronic lung disease are potential long-term complications. Tracheostomy may be necessary, either due to pulmonary hypoplasia complicated by the development of bronchopulmonary dysplasia, or for tracheobronchial malacia. It is not uncommon for severe tracheobronchial malacia

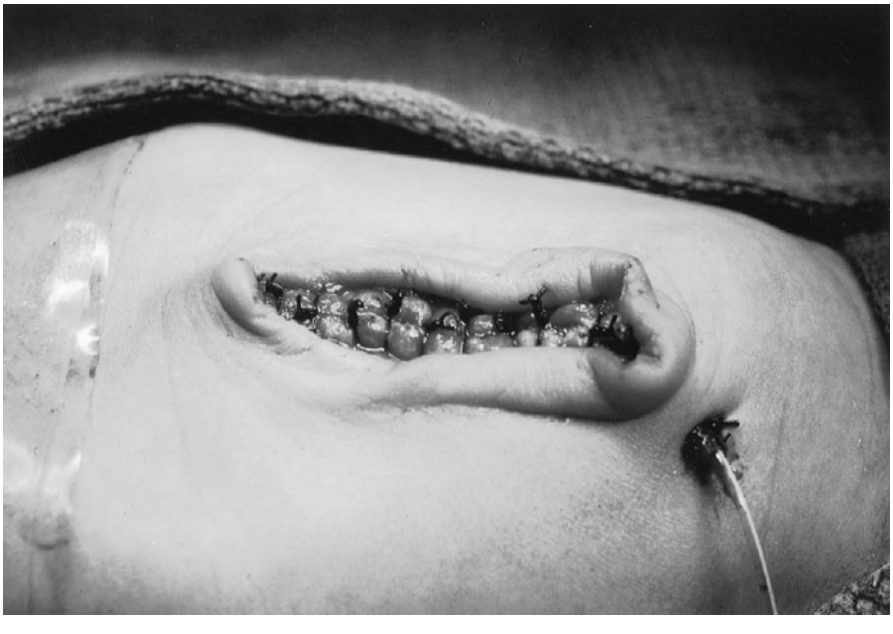


Figure 62-5 Intraoperative appearance following closure of newborn abdomen after primary omphalocele repair. The umbilical artery has been transposed to a right lower quadrant site for umbilical artery catheter placement for arterial blood pressure monitoring.

to be associated with giant omphaloceles and requires positive end-expiratory pressures (PEEP) of 10 or even 15 cm of H_2O to keep the airway open. There should be a low threshold for bronchoscopic assessment of the airway to exclude this complication in cases of giant omphaloceles.

LONG-TERM OUTCOME

Even with primary repair of omphalocele, a protracted stay in the newborn nursery should be anticipated. Under the best circumstances, except for hernias of the umbilical cord, some period of mechanical ventilation following omphalocele repair is required. In some cases of giant omphaloceles, there may be underlying pulmonary hypoplasia or tracheobronchial malacia that complicates ventilatory management. Following extubation most infants have feeding difficulties because of the prolonged period without oral stimulation and poor coordination of sucking and swallowing. In addition, many infants have high respiratory rates following omphalocele repair. Because of the compromised diaphragmatic excursion and chest wall motion, these infants maintain their minute ventilation by shallow, rapid breathing patterns. This rapid breathing often interferes with suckling, and gavage feeding may be necessary. Gastroesophageal reflux in these infants is common, which may require medical therapy, transpyloric feeding, or antireflux surgery.

As mentioned previously, the particular anomalies associated with omphalocele have a major impact on long-term outcome. This is especially true of chromosomal and cardiac defects. As survival rates of patients with omphalocele improve, more outcome data will become available, particularly with respect to other aspects that have an impact on the quality of life (Figure 62-6). Preliminary studies suggest that there are higher rates of behavioral problems and musculoskeletal abnormalities in children with abdominal wall defects (Ginn-Pease et al., 1991; Loder and Guiboux, 1993). Kaiser et al. (2000) suggest that a favorable long-term outcome can be anticipated, except in cases associated with severe congenital anomalies. There is one reported case of successful pregnancy in adulthood following the staged repair procedure for a large omphalocele (Ein and Bernstein, 1990).

GENETICS AND RECURRENCE RISK

The recurrence risk depends on the cause of the omphalocele. If the fetus has a chromosomal abnormality due to aneuploidy, such as trisomy 18, the recurrence risk is 1% or the age-related maternal risk, whichever is higher. If a syndrome is diagnosed, the recurrence risk is that of the syndrome (Stoll et al., 2008). Familial cases of Beckwith–Wiedemann syndrome may have as high as a 50% recurrence risk. Nonsyndromal (isolated) omphalocele is generally considered to be a sporadic event, with a negligible recurrence risk. However, at least 17 cases of familial omphalocele have been described (Osuna and Lindham, 1976; DiLiberti, 1982; Pryde et al., 1992). Most of these families appear to transmit the gene as an autosomal dominant gene. In one asymptomatic patient, five consecutive pregnancies by two different nonconsanguineous partners were complicated by fetuses with isolated omphalocele (Pryde et al., 1992).

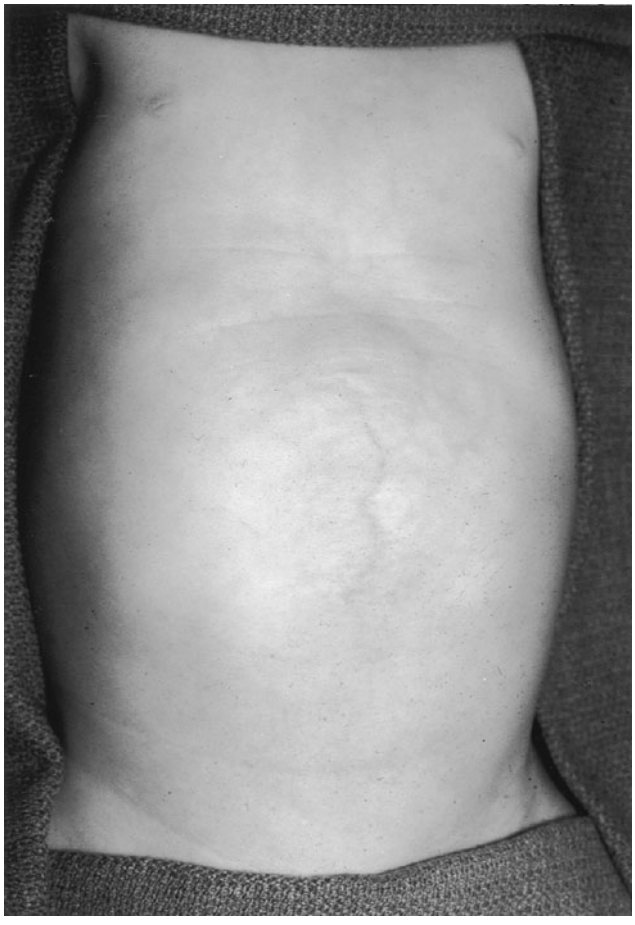


Figure 62-6 Abdominal appearance 1 year after primary repair of a large omphalocele. Note the absence of a normal umbilicus.

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63 Gastroschisis

CHAPTER

Key Points

- Isolated abdominal wall defect to right of normally inserted umbilical cord.
- Associated with young maternal age and maternal smoking.
- Associated with growth restriction and abnormalities of amniotic fluid.
- The efficacy of amnioexchange is under investigation.
- Increased incidence of intrauterine fetal demise in the third trimester.
- Intestinal atresia can complicate 10% to 15% of cases.

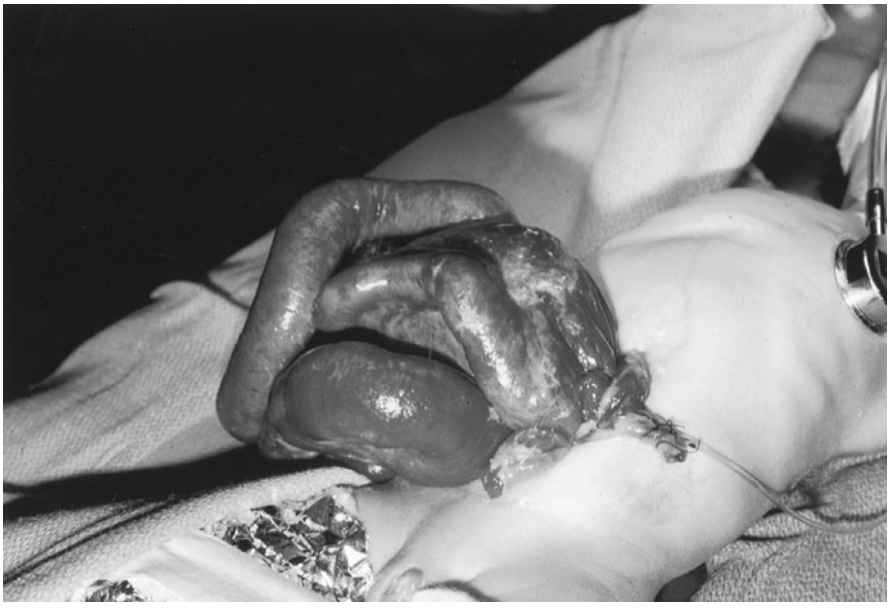

Figure 63-1 Newborn infant with gastroschisis demonstrating characteristic "peel."

CONDITION

Gastroschisis (Greek for belly cleft) is a full-thickness defect in the abdominal wall that occurs secondary to incomplete closure of the lateral folds during the 6th week of gestation (Moore and Stokes, 1953; Moore and Persaud, 1993). At birth, the eviscerated bowel characteristically has a thick edematous appearance described by Moore as a "peel" (Figure 63-1). The peel involves the serosa and is composed of fibrin and collagen. The peel in gastroschisis is thought to be caused by an inflammatory reaction as a result of exposure to amniotic fluid, combined with constriction at the abdominal wall defect (Amoury and Holder, 1977; Klein et al., 1983; Tibboel et al., 1986a,b; Amoury et al., 1988; Langer et al., 1990; Moore, 1992). Duhamel (1963) theorized that gastroschisis originates from a discrete teratogenic insult that results in an isolated defect in differentiation of the somatopleural mesenchyme. Others argue that gastroschisis is due to an in utero rupture of an umbilical cord hernia after completion of the infold in the anterior abdominal wall, but before complete closure of the umbilical ring (Shaw, 1975). In at least some cases, in utero rupture of a hernia of the cord that resulted in gastroschisis supports the argument for this being a cause (Glick et al., 1985). DeVries (1980) suggested that gastroschisis could be caused by a congenital weakness on the right side of the umbilical cord. From an umbilical cord hernia, premature atrophy or abnormal persistence of the right umbilical vein could predispose to disruption of the somatopleura at its junction with the body stalk. Because gastrointestinal defects such as atresia associated with gastroschisis are caused by vascular disruptions, Hoyme et al. (1983) suggested that gastroschisis may be caused by disruption of the right omphalomesenteric artery, which connects the yolk sac with the dorsal aorta. The fact that gastroschisis almost always occurs to the right of the umbilical ring is consistent with these latter theories (Torfs et al., 1990).

As second trimester maternal serum-α-fetoprotein (MSAFP) screening has become incorporated into routine prenatal care, more cases of gastroschisis are being detected prenatally. This is due to the association between elevated MSAFP levels and ventral abdominal wall defects (McKeown et al., 1953; Brock et al., 1979; Redford et al., 1985; Stiller et al., 1990; Killam et al., 1991). In one study, Larson et al. (1993) found a 58% incidence of major fetal congenital anomalies when extremely elevated MSAFP levels were detected between 15 and 20 weeks of gestation. Ten percent of these were due to abdominal wall defects. The sensitivity of MSAFP screening for the detection of abdominal wall defects varies depending on the type of abdominal wall defect, the geographical area, and the cutoff value of MSAFP used.

MSAFP screening has a higher sensitivity for detecting gastroschisis than omphalocele. In a population-based study of MSAFP screening, using patients from Maine and Rhode Island, Palomaki et al. (1988) found that the combined incidence of gastroschisis and omphalocele was 4.5 in 10,000 livebirths (excluding neural tube defects, twins, and autosomal chromosomal anomalies). At each cutoff of MSAFP, detection rates were higher for gastroschisis than for omphalocele. For example, at a cutoff of 2 multiples of the mean (MoM), the detection rate was more than 99% for gastroschisis and 78% for omphalocele. At cutoff values of 2.5 MoM and 3 MoM, the detection rates were more than 98% and 71%, and 96% and 65%, for gastroschisis and omphalocele, respectively. The median MSAFP value of the 20 cases of gastroschisis was 7 MoM and the median value for omphalocele was 4.1 MoM (Palomaki et al., 1988). Crandall et al. (1991) have shown that the higher the MSAFP level the greater the prevalence of adverse fetal outcome. A lower detection rate in omphalocele is likely due to the presence of an intact membrane covering the abdominal viscera in unruptured omphaloceles as opposed to the direct exposure of bowel to the amniotic fluid in gastroschisis.

Analysis of amniotic fluid α-fetoprotein and acetylcholinesterase pseudocholinesterase levels (ratio 0.13) is very sensitive in detecting gastroschisis (Goldfine et al., 1989). Human chorionic gonadotropin (hCG) levels have been measured in 16 pregnancies with abdominal wall defects (12 gastroschises, 4 omphaloceles) because this marker is already being increasingly used for fetal aneuploidy screening. It may have utility as an additional marker for the presence of abdominal wall defects. Using a cutoff value of 2.3 MoM, the detection rate using hCG was 31%, as compared with 81% for MSAFP. Using the two markers, the detection rate increased to 87.5%, by finding one additional case (Schmidt et al., 1993). More data are necessary to evaluate the usefulness of hCG levels to prospectively identify abdominal wall defects.

INCIDENCE

Before 1953, gastroschisis was not clearly distinguished from omphalocele (Moore and Persaud, 1993). Consequently, a reliable estimate of the frequency of gastroschisis before then is impossible. Several investigators have found that the prevalence of gastroschisis has increased over the past few decades in different geographic regions (Hwang and Kousseff, 2004). Roeper et al. (1987) documented in California that the rate of gastroschisis has increased from 0.006 in 1000 livebirths in 1968 to 0.089 in 1000 livebirths in 1977. Similarly, Florida, Sweden, Finland, and Spain have reported increased prevalence rates over the same period (Lindham, 1981; Hemmenki et al., 1982; Martinez-Frias et al., 1984; Hwang and Kousseff, 2004). The overall prevalence in Europe has been reported to be 0.07 in 1000 live- and stillbirths (Calzolari et al., 1993). Studies from British Columbia and Italy have not confirmed this trend (Baird and MacDonald, 1981; Calzolari et al., 1993).

Both older and more recent data from epidemiologic studies have consistently demonstrated that young maternal age is associated with an increased risk of gastroschisis (Colombani and Cunningham, 1977; Hemmenki et al., 1982; Martinez-Frias et al., 1984; Roeper et al., 1987). Goldbaum et al. (1990) compared 62 infants who had gastroschisis with 617 randomly selected, unaffected infants matched for the first year of birth in the state of Washington. They found that maternal age younger than 20 years was associated with a fourfold increased risk of having an infant with gastroschisis. A study by Werler et al. (1992) included patients from Boston, Philadelphia, and portions of Ontario and Iowa. They compared 76 cases of gastroschisis with 2582 malformed controls and found a strong inverse association with maternal age. Compared with women 30 years or older, the relative risks for maternal ages 25 to 29, 20 to 24, and younger than 20 were 1.7, 5.4, and 16, respectively (Werler et al., 1992).

In addition to young maternal age, maternal cigarette use has also been associated with an increased risk of gastroschisis. Goldbaum et al. (1990) were the first to suggest this relationship. In a prospective population-based study using 62,103 consecutive second trimester MSAFP samples, Haddow et al. (1993) found that women who smoked had a 2.1-fold greater risk of fetal gastroschisis than nonsmokers. Although their finding was not considered statistically significant, the trend was consistent with the report by Goldbaum et al. (1990). In contrast, Werler et al. (1992) found no association with cigarette use in early pregnancy when heavy (more than 15 cigarettes per day) and light (less than 15 cigarettes per day) were compared. However, when the results of these three studies are combined, the relative risk for having a baby with gastroschisis is 1.6 for women who smoke (Haddow et al., 1993).

Although reports are conflicting, the incidence of gastroschisis has also been associated with seasonal variation. These studies found an increased risk of gastroschisis in deliveries occurring during the first quarter of the year (Egenaes and Bjerkedal, 1982; Hemmenki et al., 1982; Goldbaum et al., 1990). However, three other studies found no seasonal variation (Paulozzi, 1986; Roeper et al., 1987; Haddow et al., 1993). Vascular disruption has been suggested by cases of gastroschisis observed in women who took medications with vasoactive properties during pregnancy (Van Allen, 1981). In a prospective screening study of maternal hair samples using gas chromatography with mass spectroscopy, Morrison et al. (2005) found a 25% incidence of periconceptual recreational drug use. The most commonly detected compounds were methamphetamine, including MDMA and MDEA, and cocaine. There is good evidence from animal data that methamphetamines cause fetal malformations including cardiac defects, facial clefts, eye abnormalities, skeletal malformations, kidney defects, and gastroschisis (Colado et al., 1997; Plessinger, 1998). Amphetamines and cocaine have similar maternal effects, as they are both central nervous system stimulants. They produce different fetal developmental effects (Little et al., 1988). Werler et al. (1992) reported on first trimester medication use in a case–control study of 76 cases of gastroschisis and 2142 matched controls. They found that the decongestant pseudoephedrine was associated with a greater than threefold risk of gastroschisis. Salicylates and acetaminophen were also associated with elevated risk, but these differences were not statistically significant. The authors also evaluated the use of these medications in pregnancies with other fetal anomalies that were presumed to have a vascular cause; no associations were found. Further studies are needed to clarify the role of vasoactive agents in the pathogenesis of gastroschisis.

SONOGRAPHIC FINDINGS

The diagnosis of abdominal wall defects during the first trimester is difficult because it is normal for the midgut to be herniated into the umbilical cord. Cyr et al. (1986) documented the events of bowel migration by abdominal sonographic examination of 10 normal first trimester fetuses, as well as by pathologic examination of several embryo specimens. The midgut that will normally form the small bowel,

cecum, and ascending and proximal transverse colon is connected to the yolk sac. This connection is reduced to a narrow yolk stalk as the amniotic cavity expands and the yolk sac is pulled away from the embryo. The mesentery suspending the midgut then rapidly elongates, creating a U-shaped loop of midgut that herniates into the umbilical cord. The loop of intestine then rotates 90 degrees in a counterclockwise direction about the axis of the superior mesenteric artery. As these loops of bowel return to the abdominal cavity by 11 weeks of gestation, the loops rotate counterclockwise another 180 degrees to complete the bowel rotation. Cyr et al. (1986) have suggested that ultrasound examination should be performed at 14 weeks of gestation because the bowel should be entirely intra-abdominal by 11 weeks, and this allows for errors in estimating gestational age. However, in 20% of fetuses, the bowel was still outside the abdomen at 12 weeks (Green and Hobbins, 1988). The size of the herniated gut may be helpful in distinguishing between physiologic and pathologic bowel herniation. The dimensions of bowel herniation have been reported to be 1 cm in the study by Cyr et al. (1986) and 7 mm in greatest dimension in the study by Bowerman (1993).

Vaginal sonography affords a closer look at the fetus in early gestation and may be helpful in distinguishing the contents of the herniation. In a series of 61 fetuses studied by vaginal sonography, by 12 weeks of gestation the midgut herniation no longer persisted (Timor-Tritsch et al., 1989). The earliest diagnosis of gastroschisis was 12 weeks 3 days (Guzman, 1990).

Gastroschisis is a full-thickness defect in the anterior abdominal wall almost invariably located to the right of the intact umbilical cord, measuring 2 to 3 cm in diameter (Figure 63-2) (Fonkalsrud, 1980). Color Doppler studies assist in demonstrating normal umbilical cord insertion with herniation of intestine to the right of the umbilical cord. Nyberg et al. (1993) have summarized the sonographic features of gastroschisis. In addition to the small abdominal wall defect located to the right of a normal umbilical cord insertion site, there is a variable amount of bowel protruding through the defect, floating in the amniotic fluid, which may be disproportionally large relative to the small size of the abdominal cavity (Figure 63-3).

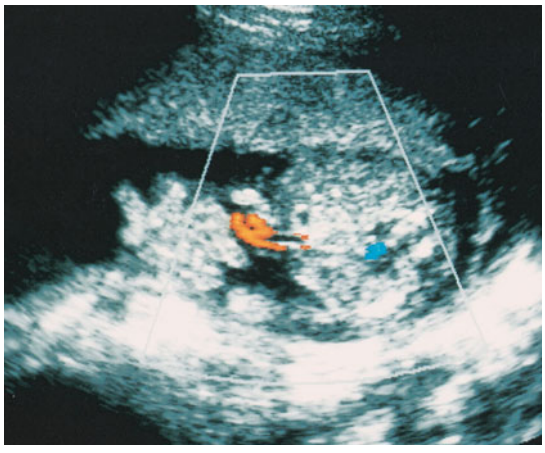

Figure 63-2 Color flow Doppler image in fetus with gastroschisis, demonstrating small defect with herniated midgut.

Despite the frequent use of antenatal ultrasound examination in obstetric care over the past two decades, there is still little information regarding the accuracy of routine ultrasound examination in the detection of abdominal wall defects (Hill et al., 1985; Rosendahl and Kivinen, 1989; Ewigman et al., 1993). Walkinshaw et al. (1992) reported on their experience in the United Kingdom for more than a 4-year period, extending from 1984 to 1988, during which 115 cases of anterior abdominal wall defects were found in 202,488 livebirths and intrauterine deaths beyond 22 weeks of gestation. They found that routine scanning identified 60% of the defects, with a false-positive rate of 5.3%. Gastroschisis

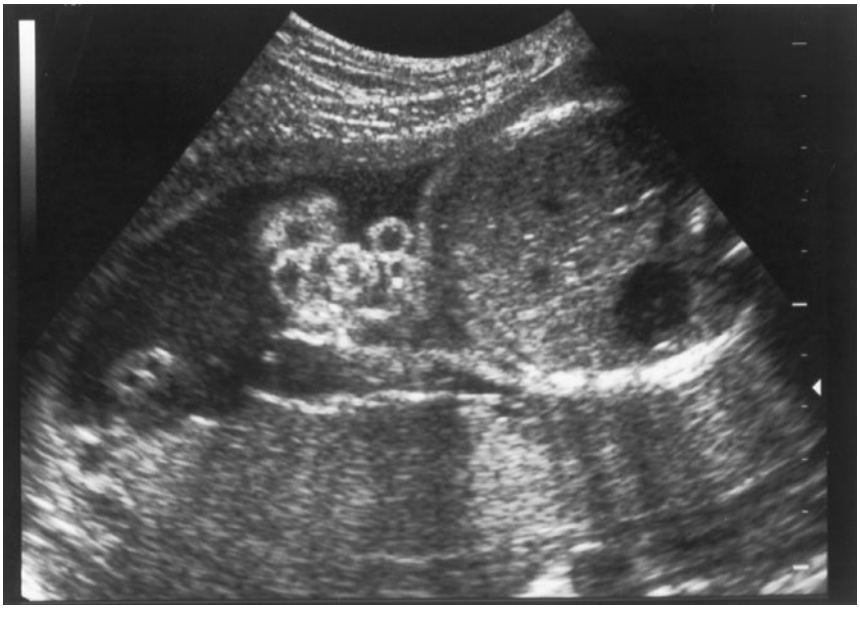

Figure 63-3 Prenatal ultrasound image demonstrating loops of intestine floating free in amniotic fluid.

and omphalocele were accurately distinguished in 79.3% of cases on initial diagnosis and 84.5% of cases after referral for further evaluation. Many factors contribute to the less than 100% detection of abdominal wall defects, including the quality of the ultrasound equipment, the experience of the sonographer, and the defect itself (Paidas et al., 1994). It is possible that one form of gastroschisis, due to rupture of a hernia of the cord as originally described by Moore (1962), would not be detected by routine ultrasound examination because it appears late in pregnancy. Knott and Colley (1987) have described two similar cases of gastroschisis not detected by antenatal ultrasound examination that were felt to occur as a result of late gestational rupture of a hernia of the cord.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of gastroschisis should include omphalocele, ruptured omphalocele, hernia of the cord, and limb–body wall complex. Gastroschisis is distinguished from omphalocele by having no membrane surrounding the herniated loops of intestine. In contrast, omphalocele has a peritoneo-amniotic membrane covering the defect and the size is significantly larger than the defect in gastroschisis. Ruptured omphalocele may be confused with gastroschisis, as the loops of intestine are observed to be floating free in the amniotic cavity. However, extracorporeal liver may be seen in ruptured omphalocele, but is never seen in gastroschisis. The limb–body wall complex may have an abdominal wall defect but is usually easily distinguished from gastroschisis by a short umbilical cord and numerous other associated structural anomalies.

ANTENATAL NATURAL HISTORY

The conventional wisdom regarding abdominal wall defects is that gastroschisis, unlike omphalocele, is not associated with chromosomal abnormalities. This discrepancy regarding the presence of associated chromosomal abnormalities has provided further impetus to distinguish these two entities by sonography. Reports in the literature have confirmed that chromosomal abnormalities are rare or absent in gastroschisis (Mayer et al., 1980; Mann and Ferguson-Smith, 1984; Sermer et al., 1987; Romero et al., 1988; Lewinsky et al., 1990; Sipes et al., 1990a). In the 17-year experience at the Children's Hospital in Columbus, Ohio, chromosomal analysis was available in 128 of 144 cases of gastroschisis and there was only 1 case of chromosomal abnormality (trisomy 18) (King et al., 1980; Caniano et al., 1990). Nicolaides et al. (1992) did not find any chromosomal abnormalities in 26 cases of gastroschisis detected during an 8-year period. Abdullah et al. (2007) found only four cases (0.1%) of aneuploidy among 4344 infants with gastroschisis in the United States. In the absence of sonographically detectable associated anomalies, the risks for fetal aneuploidy are probably comparable to the risks due to maternal age alone. If additional fetal abnormalities are detected sonographically, chromosomal evaluation should be recommended.

In contrast to omphalocele, gastroschisis is usually not associated with extragastrointestinal abnormalities. This is in part responsible for the better outcome observed in gastroschisis. In a survey of 13 years of the National Inpatient Sample Database and 3 years of the KIDs' Inpatient Database, Abdullah et al. found among 4344 cases of gastroschisis reported only 72 (1.7%) cases of pulmonary defects (including agenesis, hypoplasia, and bronchopulmonary dysplasia) and 379 cardiac defects, of which 190 were atrial septal defects (ASDs) and 214 patent ductus arteriosus cases that would not be detectable on prenatal ultrasound examination. There were also 138 cases of undescended testicles (6.8%) and 58 cases of hydronephrosis (1.3%) (Abdullah et al., 2007). However, in a report from Kunz et al. (2005) in a study of California hospital discharge data from 1972 to 1997, 25 of 621 infants with gastroschisis were found to have congenital heart disease (4% incidence). This group also found a significant increase of congenital heart disease if the gastroschisis was complicated by bowel atresia, or if the infant was African American. Gibbin et al. found an incidence of abnormal cardiac findings of 15%, but of the four, one was persistent pulmonary hypertension, two were supraventricular tachycardia, and the last was peripheral pulmonic stenosis (Gibbin et al., 2003). However, gastrointestinal anomalies can commonly be seen in gastroschisis, and occur in 20% to 40% of cases (King et al., 1980; Mayer et al., 1980; DeLorenzo et al., 1987; Nicolaides et al., 1992; Novotny et al., 1993). These gastrointestinal abnormalities may be secondary to the gastroschisis. These include malrotation, atresia, "Christmas-tree deformity," volvulus, and infarction.

Even in the rare cases in which they are present, nongastrointestinal abnormalities are not usually life-threatening. It is interesting that the data registry report from Abdullah et al. (2007) had a lower than expected 8.1% incidence.

Fetuses with gastroschisis are at risk for a number of complications that directly affect survival during the newborn period. Obstetric complications include intrauterine growth restriction (IUGR), which can affect up to 77% of fetuses (Carpenter et al., 1984; Molenaar and Tibboel, 1993). This may be due to nutritional deprivation rather than a constitutional limitation (Gutenberger et al., 1973). In an analysis of biometric data Royner and Richards (1977) found that IUGR was predicted in 43% of infants, but was present in only 23% at birth. This group thought that the prevalence of IUGR is increased in gastroschisis, but is overestimated with prenatal ultrasonography, primarily because of the smaller-than-average abdominal circumference. Carroll et al. (2001) suggested a novel explanation for the frequent observation of growth restriction among fetuses with gastroschisis; protein loss into the amniotic cavity. In a small series of 12 fetuses with prenatally diagnosed gastroschisis were compared with 29 control infants without gastroschisis. They found that fetuses with gastroschisis had significantly lower serum total

protein and significantly higher amniotic fluid total protein, and α-fetoprotein.

Despite the predisposition to IUGR, a more important factor in neonatal outcome is prematurity. Puligandla et al. (2004) found that in a retrospective series of 113 cases of gastroschisis, infants with IUGR had similar outcomes to non-IUGR infants. Factors that were more important with regard to neonatal outcome were prematurity and the presence of atresia (Puligandla et al., 2004).

Other obstetric complications include preterm labor, which occurs in more than one-third of cases due to associated polyhydramnios (Mayer et al., 1980; Kirk and Wah, 1983; Carpenter et al., 1984; Caplan and MacGregor, 1989; Molenaar and Tibboel, 1993). Abnormalities of amniotic fluid volume, both polyhydramnios and oligohydramnios, can accompany gastroschisis (Bair et al., 1986; Crawford et al., 1992). Mercer et al. (1988) reported that in their series of 22 cases of gastroschisis, marked amniotic fluid staining occurred in 73%. The association of amniotic fluid staining with fetal distress is controversial (Carpenter et al., 1984; Crawford et al., 1992).

Because the condition of the bowel at the time of birth is the single most important factor affecting long-term outcome for fetuses with gastroschisis, several investigators have monitored the ultrasonographic appearance of the bowel (Stringel and Filler, 1978; Luck et al., 1985). The extent of bowel damage is variable in gastroschisis and can range from only mild to severe, with bowel atresia and necrosis requiring resection with staged repair. These latter cases are often characterized on sonography by extreme intestinal hypoperistalsis and poor absorptive capacity (O'Neill and Grosfeld, 1974; Oh et al., 1978). Although the cause of bowel damage is not entirely understood, it seems that most of the damage is caused by constriction at the site of the abdominal wall defect and that this occurs primarily late in gestation (Langer et al., 1989, 1990). Based on experimental findings in fetal lambs, Langer et al. (1993) suggested that the mechanism of constriction-induced damage is related mainly to obstruction and not ischemia.

Bond et al. (1988) published a series of 11 cases of gastroschisis correlating the prenatal ultrasonographic appearance of the eviscerated bowel with clinical outcome. The presence of small-bowel dilation and mural thickening correlated with severe intestinal damage and poor clinical outcome. The absence of these findings was associated with a more benign clinical course. These authors suggested that these two ultrasonographic features—bowel dilatation and bowel thickening—could be useful in following fetuses with gastroschisis and in determining the time of delivery. Other reports have not found these findings to be at all predictive of outcome in gastroschisis (Lenke et al., 1990; Sipes et al., 1990b; Alsulyman et al., 1996). Early detection of signs of bowel damage would allow delivery at fetal lung maturity to prevent ongoing injury to the bowel and decrease the likelihood of hypoperistalsis syndrome. Three small series have not found that these two characteristics were useful in predicting outcome (Lenke et al., 1990; Sipes et al., 1990b; Alsulyman et al., 1996).

In a combined retrospective and prospective study, Langer et al. (1993) evaluated 24 fetuses with gastroschisis and found that bowel thickening was associated with an increased time to oral feeding, but this finding did not achieve statistical significance, possibly due to the small number of patients. As opposed to using a specific cutoff for bowel damage, these authors suggested using a value that had a specific threshold for gestational age. From their own data, fetuses above this threshold value had hypoperistalsis and below it only 30% had a hypoperistalsis. Interestingly, Aina-Mumuney et al. (2004) have noted that a dilated fetal stomach found in 13 of 34 prenatally diagnosed cases of gastroschisis was associated with a statistically significant greater incidence of nonreactive nonstress tests, volvulus, neonatal death, as well as delayed time to full oral feeding and longer hospitalization, compared to those that did not have a dilated stomach (Aina-Mumuney et al., 2004).

A disturbingly high incidence of intrauterine fetal demise and stillbirth during the third trimester has consistently been reported, with rates as high as 10.6% (Crawford et al., 1992; Burge and Ade-Ajayi, 1997). Broth et al. (2001) reported that among 78 cases of gastroschisis, the stillbirth rate after 28 weeks' gestation was 85 per 1000 births compared to a control group rate of 5.4 per 1000 births. The cause of stillbirth is thought to be either midgut volvulus or progressive cord compression by eviscerated bowel. Kalache et al. (2002) reported a case of gastroschisis complicated by sudden dilation of the bowel at 34 weeks' gestation with the development of notching of the umbilical artery waveform. This was thought to be due to compression, which has previously been reported with stomach herniation in gastroschisis (Robinson et al., 1997). Notching of the umbilical arterial Doppler waveform has also been observed in cord entanglement in monoamniotic twins (Kofinas et al., 1991). This sign should be looked for in third trimester fetuses with gastroschisis as an indicator for nonstress testing.

Although fetal imaging has not provided useful prognostic indicators of severity of gastroschisis, it is possible that amniotic fluid levels of β endorphins may. Mahieu-Caputo et al. (2002) have found that amniotic fluid β endorphin levels above 10 μg/L ($n = 4$) versus 5 μg/L ($n = 9$) correlated with longer duration of ventilation, parenteral nutrition, and duration of hospitalization. These investigators speculated that elevated β endorphin levels could result from fetal stress caused by bowel damage.

MANAGEMENT OF PREGNANCY

Crawford et al. (1992) have recommended biophysical profile testing for pregnancies with gastroschisis because they found a 12.5% rate of stillbirths. Because these deaths occurred late in the third trimester, they suggested that testing begin at 30 to 32 weeks of gestation.

We are currently monitoring our cases of gastroschisis with biophysical testing beginning at 30 weeks' gestation, and

by performing weekly sonography to assess bowel thickness, dilation, evidence of increased peristalsis, or dilated stomach. If sonographic evidence of bowel damage is detected, consideration can be given to delivery as soon as the lungs mature to prevent ongoing injury. However, detection of bowel dilation alone may be due to atresia, in which case delivery will have no benefit.

The recommended mode of delivery for fetuses with abdominal wall defects is controversial. Part of the difficulty in comparing the vaginal versus abdominal approach is the presence of multiple confounding factors, such as antenatal diagnosis of lesion, presence or absence of labor, maternal and neonatal transport, interval between delivery and surgery, and place of delivery. Kirk and Wah (1983) reported 74 cases of gastroschisis, 65 of which were delivered vaginally and 9 by cesarean section. There were five deaths in each group, resulting in a much higher mortality rate for fetuses delivered by cesarean section. Lenke and Hatch (1986) retrospectively reviewed their series of 24 cases of gastroschisis. Seven of 24 infants were delivered by cesarean section and all had a good outcome. There were 3 deaths among the remaining 17 delivered vaginally. Only 11 of the 17 cases of gastroschisis were able to have primary closure, as opposed to all of the infants delivered by cesarean section. These authors also commented that in all infants delivered by cesarean, there was no evidence of the inflammatory "peel," or inflamed serosa, on the eviscerated bowel seen in the worst cases of gastroschisis. Moretti et al. (1990) reported on 56 fetuses with gastroschisis, and did not find any differences in infant mortality, short- or long-term outcome, or frequency of associated major anomalies. However, in their experience, only 8% of the defects were detected antenatally. Other authors did not find any benefit to abdominal delivery (Kirk and Wah, 1983; Carpenter et al., 1984; Davidson et al., 1984; Calisti et al., 1987; Sermer et al., 1987; Sipes et al., 1990a; Puligandla et al., 2004). In an attempt to control for confounding variables, Lewis et al. (1990) reviewed their experience with 56 cases at level-three institutions and found no benefit to cesarean delivery. Coughlin et al. (1993) have reported the results of a trial of cesarean delivery with staff standing by in an adjacent operating room for immediate repair of the gastroschisis. In this small series of cases, cesarean delivery and immediate repair were associated with a greater rate of primary closure, a shorter period of mechanical ventilatory support, and a shorter interval to enteral alimentation, as compared with historical controls delivered vaginally who underwent more routine gastroschisis repair. As demonstrated in these reports, at present there is no compelling evidence for cesarean over vaginal delivery in gastroschisis except for routine obstetrical indications.

The neonatal outcomes in gastroschisis do not appear to be adversely affected by labor or rupture of membranes (Strauss et al., 2003). However, some have suggested that it is the timing, not the mode of delivery that results in improved outcome (Lenke and Hatch, 1986; Moore, 1988, 1992; Swift et al., 1992; Langer, 2003). These authors mention that most of the bowel injury occurs late in gestation, which may be avoided with early delivery. We recommend transferring the mother to a tertiary care center before delivery to better coordinate the obstetric, neonatal, and pediatric surgical teams (Carlan et al., 1990; Nicholls et al., 1993; Stoodley et al., 1993; Paidas et al., 1994).

In patients managed by vaginal delivery as opposed to elective cesarean section, continuous cardiotocography may be helpful in identifying fetal distress (Brantberg et al., 2004). In a series of all patients prenatally diagnosed with gastroschisis at the National Center for Fetal Medicine in Norway, Brantberg et al. found that cardiotocographic monitoring detected abnormalities in 22% of 64 fetuses. There was only a single case of intrauterine fetal demise (IUFD) in the series. They attributed the improved outcome to better detection of fetal distress.

FETAL INTERVENTION

There is currently no accepted fetal intervention for gastroschisis. However, there is interest in some centers for the use of amnioexchange to improve bowel function in gastroschisis. The rationale for this approach is that bowel damage occurs in utero from two mechanisms: constriction at the abdominal wall (Langer et al., 1989, 1990) and chemical irritants in the amniotic fluid, which stimulate an inflammatory response in bowel serosa (Langer et al., 1989; Albert et al., 1993; Luton et al., 2003). The first published case of amnioexchange to treat fetal gastroschisis was reported by Aktug (Aktuğ et al., 1995), with four amnioexchanges between 29 and 34 weeks of gestation. Enteral nutrition was achieved by 5 days and the infant was discharged to home at day 8.

Based on favorable results in a fetal sheep model demonstrating improved serosal fibrosis, decreased inflammatory cell infiltration and clearance of inflammatory and gastrointestinal waste product (Luton et al., 2000; Thebaud et al., 2002), Luton et al. (2003) conducted a pilot study in human gastroschisis. Amnioexchanges start at 30 weeks of gestation via transabdominal amniotic fluid drainage through a 20-gauge needle. Amniotic fluid is replaced serially 300 mL by 300 mL with warm sterile saline, for a total of 600 to 900 mL replaced at each procedure. Compared to a historical control group, the amnioexchange group had the same mean gestational age at delivery (36.9 ± 1.3 weeks), without chorioamniotic or premature rupture of membranes in the first 30 patients treated.

Analysis of the first 10 patients showed a nonsignificant trend for less severe perivisceritis, reduced time on mechanical ventilation, need for hospitalization, and hospital stay. The authors contend that if extrapolated to the full 30 patients, these trends would achieve statistical significance. This same group reported a favorable effect of amnioexchange on the extra-abdominal mesenteric artery Doppler index (Volumenie et al., 2001). There was, however, no correlation with postnatal outcome. Amnioexchange does not address the constrictive effects at the abdominal wall. As these investigations acknowledge, the data thus far do not prove

efficacy of amnioexchange. The problem with this approach is not the rationale for amnioexchange nor the potential for amnioexchange to reduce perivisceritis. Rather, the weakness lies in the lack of selection criteria. Most newborns with gastroschisis do not have severe perivisceritis or inflammatory peel and they do very well with conventional postnatal treatment. There is a subset of gastroschisis patients (representing 10%–15% of cases) in which there is a severe inflammatory peel, protracted need for parenteral nutrition, compromised gut mobility and prolonged hospitalization. Until accurate sonographic criteria are developed to identify this subset of fetuses with gastroschisis, it is unlikely that anmioexchange will improve outcome and has the potential to expose patients to the risk of this intervention with little hope of benefit.

TREATMENT OF THE NEWBORN

At delivery, the infant's lower body should be placed in a clear plastic bowel bag to minimize evaporative losses. The exposed bowel should be kept moist and handled in a sterile fashion. The intestines should be supported by bolsters of rolled gauze placed on either side of the abdominal wall defect to prevent kinking at the abdominal wall, which would result in venous congestion and subsequent acidosis. The infant should be placed in the right lateral decubitus position to minimize the chances of obstruction at the abdominal wall. The bowel should be covered with nonadherent sterile petroleum gauze and wrapped in sterile dry gauze and placed in a Lahey bag. A nasogastric tube should be inserted and placed for suction to prevent bowel distention from swallowing air. Venous access should be obtained in the upper extremities, antibiotics (ampicillin and gentamicin) should be administered, and crystalloid infusion begun as soon as possible to replace ongoing third-space losses. It is not uncommon for these newborns to become quite dehydrated because of the excessive evaporative losses of the exposed viscera. Adequate volume resuscitation is essential for proper treatment and prevention of necrotizing fasciitis.

SURGICAL TREATMENT

Success has been achieved with both primary closure and staged silo reduction, with the surgery tailored to each individual case (Ein and Rubin, 1980; King et al., 1980; Luck et al., 1985; DeLorenzo et al., 1987; Caniano et al., 1990; Novotny et al., 1993). No matter which operative strategy is employed, the infant is nutritionally supported by parenteral nutrition delivered via PICC line or broviac. The advantages of primary closure are shorter intervals to oral feeding, reduced hospital stay, and the lack of further extensive surgery. However, the success of primary closure depends on the degree of visceroabdominal disproportion. Excessive abdominal wall tension can cause vena caval compression, compromised respiratory function, postrenal oliguria from ureteral obstruction, and even bowel ischemia. Intragastric pressure and central venous pressure recordings have been advocated to detect excessively high intra-abdominal pressures during attempted closure (Yaster et al., 1989). In a review of 30 cases of gastroschisis, Bryant et al. (1985) found that the interval to return to oral alimentation was not related to the type of closure.

The risk of ongoing evaporative water loss, heat loss, and metabolic derangements that occur as a result makes rapid coverage of the bowel a priority (Ledbetter, 2006). In the delivery room or upon arrival in the NICU, the bowel can be placed in a prefabricated, spring-loaded, silastic silo. These preformed silos can be placed at the bedside without anesthesia. If the fascial ring is too small, the defect can be enlarged with local anesthesia and sedation (Minkes et al., 2000). The placement of a prefabricated silo converts the operative closure to an elective procedure once the gravity has reduced the bowel edema, allowing bowel loops to return to the abdominal cavity. This process usually takes 5 to 7 days and can be facilitated by gently reducing the bowel and placing an umbilical tape tie to keep the bowel reduced. The process can usually be accomplished without the need for the infant to be intubated, ventilated, or the use of muscle relaxants. Once the bowel has been completely reduced, the infant is taken to the operating room for a delayed primary closure of the fascia.

Introduction of the silo by Schuster (1967) was a major advance in management of gastroschisis with severe visceroabdominal disproportion. Creation of a silo sutured to the fascia can be performed as a primary procedure or if reduction with a preformed silo is unsuccessful. The viscera are gradually reduced into the abdomen by sequential tightening of the silastic silo (Figure 63-4). The goal of this therapy is the gradual reduction of viscera over 3 to 5 days. After 7 days, the risks of infection with this technique increase significantly. The infant may be intubated and neuromuscular paralysis

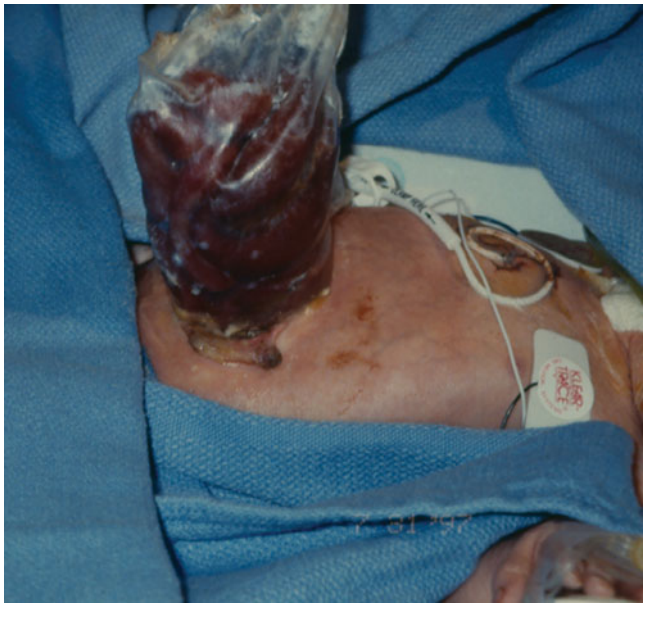

Figure 63-4 Intraoperative view during creation of silo for staged closure of gastroschisis.

induced to allow maximal relaxation of the abdominal wall. Once all of the viscera are reduced, the infant is returned to the operating room, where the silastic silo is removed and a fascial closure is performed. Other methods of closure useful in selected cases include extensive skin flaps, umbilical cord patch, Ringer clamp, or Gore-Tex patch closure (Muraji et al., 1989; Zivkovle, 1991; Sawin et al., 1992; Stringel, 1993).

Potential postoperative complications are numerous and include intestinal ischemia, bowel infarction, enterocutaneous fistula, necrotizing enterocolitis, and prolonged intestinal dysfunction (Ein et al., 1988; Oldham et al., 1988; Caniano et al., 1990). Intestinal atresia can complicate gastroschisis, and is reported to occur in 5.5% to 23% of patients (Amoury and Holder, 1977; Pokorny et al., 1981; DeLorenzo et al., 1987; Gornall, 1989; Shah and Woolley, 1991). These may be single or multiple, and may involve the small or large bowel.

The primary goal in gastroschisis complicated by atresia is abdominal wall closure either by primary closure, use of prefabricated silo, or operative silo creation. Even if the atresia is recognized, no attempt should be made at resection of the atresia as the bowel is usually edematous and inflamed. Resection and primary anastomosis are at high risk for breakdown. By 2 weeks following primary repair of the abdominal wall defect, there is complete resolution of edema, inflammation, and peel, making resection and anastomosis readily accomplished (Snyder et al., 2001). Even in the rare instance in which there is perforation at the time of delivery, the proximal and distal bowel should be ligated. There should be at least a 2-week interval from abdominal wall repair to resection of atresia and primary repair.

LONG-TERM OUTCOME

The duration of hospitalization is directly related to the degree of gastrointestinal compromise or presence of gastrointestinal atresia. Some patients with gastroschisis will have hypoperistalsis syndrome. These infants remain dependent on parenteral nutrition for an indefinite period, sometimes permanently. The average hospital stay following closure of gastroschisis is usually on the order of 3 to 4 weeks. Often feeding difficulties after repair of gastroschisis will delay discharge because of the need for gavage feedings. Although primary closure may be achieved and infants are weaned from mechanical ventilatory support, they often remain quite tachypneic, which impairs their ability to suck. Once further abdominal wall relaxation and accommodation has had time to occur, there is less tension and pressure on the diaphragm and the respiratory rate decreases. Once a respiratory rate of less than 70 breaths per minute is achieved, infants can suck effectively and be weaned from supplemental gavage feeding.

Hospitalization for infants with gastroschisis requiring a repair of an atresia can be longer, related to the need for a second procedure to address the atresia. The hospitalization in these infants may be prolonged by several weeks.

There are usually no long-term sequelae from gastroschisis if there is no associated hypoperistalsis syndrome (Lunzer et al., 2001). Inguinal hernias will develop not uncommonly in infants with gastroschisis because of increased intra-abdominal pressure. Occasionally, incisional hernias seen as bulging from attenuated fascia at the closure site will require remedial surgery months or years later.

GENETICS AND RECURRENCE RISK

Gastroschisis has been generally considered to be a sporadic event, with a multifactorial cause, but there have been reports of familial recurrence (Salinar et al., 1979; Lowry and Baird, 1982; Hershey et al., 1989; Schmidt et al., 2005). Torfs et al. (1990) described a 4.3% sibling recurrence rate in a population-based study. An approximately 4% recurrence risk implies a mixture of genetic predisposition with environmental factors (Torfs and Curry, 1993). A single-gene defect is unlikely for this condition. Families should receive genetic counseling regarding recurrence risk. They should be offered MSAFP testing and prenatal sonography in future pregnancies.

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64 CHAPTER Cloacal Exstrophy

Key Points

- Arises from maldevelopment of the cloacal membrane, which prevents migration of mesenchymal tissue and impedes normal development of the lower abdominal wall.
- Consists of exstrophy of the urinary bladder, exstrophy of the small or large intestine, anal atresia, hypoplasia of the colon, omphalocele, and malformed genitalia.
- Incidence 1 in 200,000 to 400,000 livebirths.
- Associated sonographic signs may include: large infraumbilical anterior midline defect with a protruding omphalocele, absent bladder, narrowed thorax, distorted spine, sacral myelomeningocele, and bilateral clubfeet. However, a correct prenatal diagnosis is rarely made.
- Differential diagnosis includes bladder exstrophy, omphalocele, gastroschisis, amniotic band syndrome, myelomeningocele, and the limb–body wall deformity.
- Management of pregnancy should include MRI, karyotype, and multidisciplinary consultation with surgery, urology, endocrinology, and genetics.
- Delivery should occur in a tertiary center.
- If the fetus is genetically male, the parents should be counseled about the potential need to reassign gender.

CONDITION

Cloacal exstrophy represents a spectrum of rare congenital anomalies that are thought to arise from maldevelopment of the cloacal membrane, which prevents migration of mesenchymal tissue and impedes normal development of the lower abdominal wall. The cloacal membrane separates the coelomic cavity from the amniotic space during the early embryogenic period. The position and the timing of the disruption of the cloacal membrane will determine the variant of the exstrophy that results. For example, inferior perforation results in epispadias; midperforation results in classic exstrophy; and the superior perforation results in superior-vesicle fissure (Jeffs, 1987). When cloacal exstrophy is present in its classic form, the constellation of severe abnormalities is among the most difficult for the pediatric surgeon to reconstruct. It consists of exstrophy of the urinary bladder, exstrophy of the small or large intestine, anal atresia, hypoplasia of the colon, omphalocele, and malformed genitalia, and associated neural tube defects in 50% of cases (Figure 64-1) (Fujiyoshi et al., 1987).

The anatomy in cloacal exstrophy is complex, with a ventral abdominal wall defect consisting of an omphalocele at the superior margin of the defect and exposed bowel and bladder at the inferior extent (Figure 64-2). The hemibladders are separated in the midline by a zone of intestinal mucosa. Each hemibladder may have a ureteral orifice and the intestinal zone separating the hemibladders may have the orifices of the proximal gut superiorly and the distal gut inferiorly, with one or two appendiceal orifices in between (Warner and Zeigler, 1993). The proximal bowel orifice often prolapses in the characteristic "elephant-trunk" deformity. The distal gut

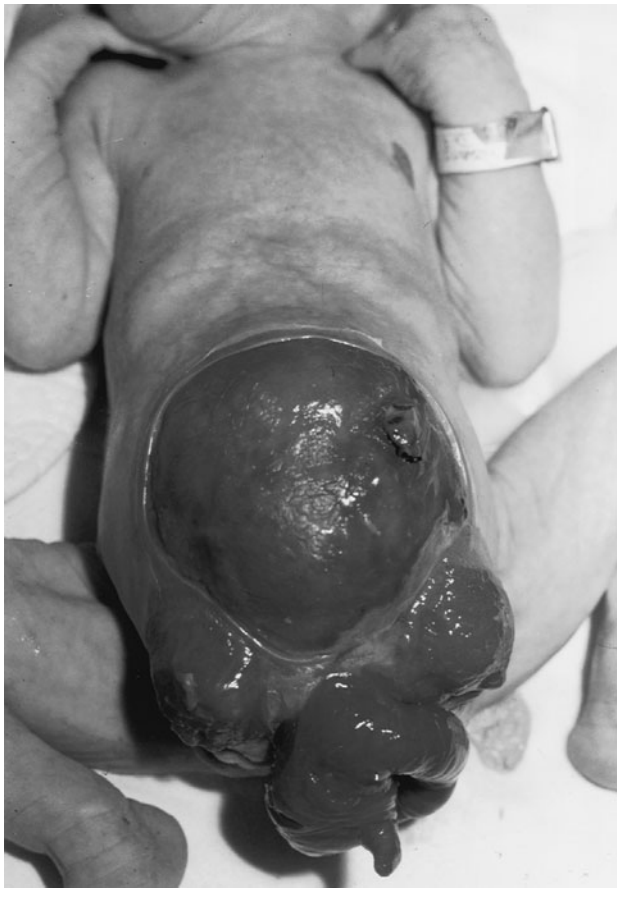

Figure 64-1 Appearance of a newborn genetic male infant with classic cloacal exstrophy. The infraumbilical omphalocele can be seen at the superior aspect of the defect. There is a prominent elephant-trunk deformity prolapsed throughout the midline intestinal zone. The widely splayed bifid penis can be seen at the lateral aspect of the defect.

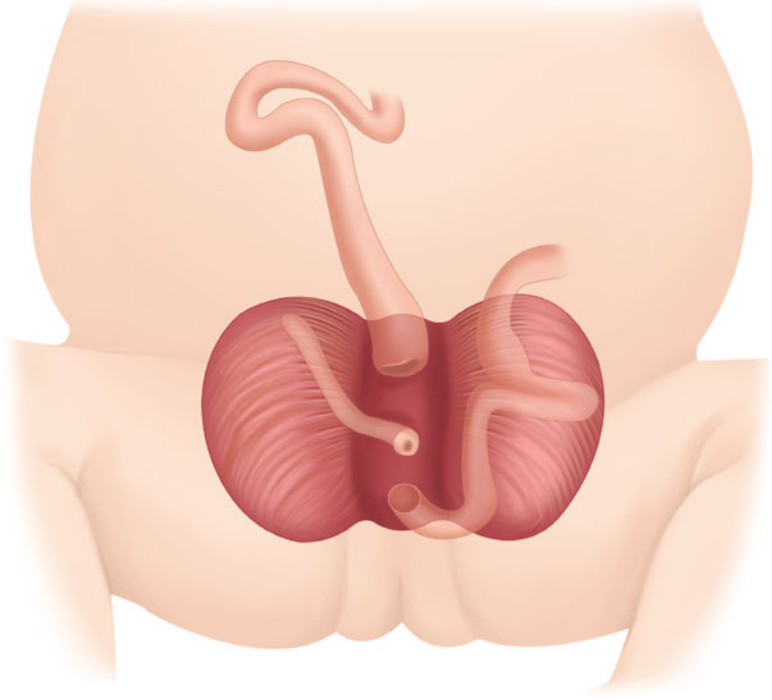

Figure 64-2 Schematic representation depicts the location of the various components of cloacal exstrophy. The omphalocele is at the superior aspect of the defect and is not seen in this diagram. The hemibladders are separated by a midline intestinal zone that has the orifice of the ileum from which prolapse of ileum forms the elephant-trunk deformity. There may also be one or two appendiceal orifices as well as the orifice to the more distal blind-ending rectal pouch. Lateral to the midline intestinal zone are the hemibladders, which each have a ureteral orifice.

is a blind pouch, as these infants all have imperforate anus. All genetically male cases have associated genital anomalies, including undescended testicles and a bifid penis, with each half attached to widely separated pubic rami (Johnston and Penn, 1966).

Although cloacal exstrophy was recognized as early as 1909, it was not until 1960 that the first successful reconstruction was reported (Rickham, 1960; Warner and Zeigler, 1993). It is only in recent decades that repair of this complex anomaly has been routinely undertaken. For years most infants were allowed to die because of the multiple and complex congenital anomalies (Molenaar, 1996). However, in the past two decades, survival after reconstruction for cloacal exstrophy has increased to 90% to 100%, albeit with substantial and lifelong physical and emotional burdens for these patients and their families (Manzoni et al., 1987).

During early development, the cloacal membrane separates the coelomic cavity from the amniotic cavity. The cloaca is first evident in the midline as an area in which ectoderm and endoderm are in opposition, with no mesoderm in between. By the 4th week of development, the cloacal membrane forms the anterior wall of the urogenital sinus at the base of the allantois. Cephalad and lateral to the cloacal membrane are the primordia of the genital tubercle. These primordia enlarge and fuse in the midline superior to the cloacal membrane to form the genital tubercle. At the same time there is ingrowth of mesoderm toward the midline, increasing the distance between the body stalk and the cloacal membrane, setting up the development of normal infraumbilical body wall. The cloaca becomes divided into the urogenital sinus and the rectum by the urorectal septum, which extends in a medial and caudal direction to the cloacal membrane (Pohlman, 1911; Patten and Barry, 1952).

Patten and Barry (1952) suggested the caudal displacement theory for the genesis of cloacal exstrophy. According to this theory, abnormal caudal displacement of the paired primordia of the genital tubercle is responsible for cloacal exstrophy. Epispadias alone would occur if fusion of the primordia in the midline occurred at the level where the urorectal septum joins the cloacal membrane. Exstrophy of both bowel and bladder would be present if even further caudal displacement of the primordia occurred at a level caudal to the anal portion of the cloaca.

In contrast, Marshall and Muecke (1962) suggested that the "wedge effect" of an abnormally large cloacal membrane was responsible for cloacal exstrophy. This abnormally large cloacal membrane acts as a wedge to the developing structure of the abdominal wall. Rupture of this membrane prior to descent of the urorectal septum and fusion of the genital tubercles results in the midline infraumbilical defect, exposure of bladder and bowel mucosa, with bifid genitalia that have epispadias. In a chick embryo model, Muecke (1964) was able to demonstrate that a plastic graft placed in the region of the cloacal membrane produced a wedge defect with persistent cloacal membrane and varying degrees of infraumbilical defects. These theories do not account for involvement of bowel, prolapse of ileum, and foreshortened gut in cloacal exstrophy. Magnus (1969) suggested that a loop of midgut or hindgut prolapses between bladder halves and becomes strangulated. Alternatively, Johnston (1913) suggested that the growth of the hindgut is restricted by its involvement in the exstrophy.

More recently Bruch et al. observed sonographic progression in a fetus with a dilated cloacal abnormality at 18 weeks of gestation associated with oligohydramnios and hydronephrosis. Repeat ultrasound examination performed at 24 weeks of gestation demonstrated rupture of the cloacal abnormality with resolution of both the hydronephrosis and oligohydramnios. This newborn had the classic features of cloacal exstrophy, challenging previous theories of its embryogenesis (Bruch et al., 1996).

Cloacal exstrophy is associated with anomalies of organ systems other than the central defect in up to 85% of cases (Hurwitz et al., 1987) (Table 64-1). Anomalies of the urinary tract are common and in several series occurred in 42% to 60% of cases (Spencer, 1965; Johnston and Penn, 1966; Tank and Lindenauer, 1970; Zeigler et al., 1986; Hurwitz et al., 1987). Vertebral anomalies occur in 48% to 78% of patients (Spencer, 1965; Tank and Lindenauer, 1970; Hurwitz et al., 1987) and myelodysplasia in 29% to 46% of patients (Zeigler et al., 1986; Hurwitz et al., 1987).

INCIDENCE

Fortunately, cloacal exstrophy is rare, with a frequently quoted incidence of 1 in 200,000 to 1 in 400,000 livebirths (Zeigler et al., 1986). However, this may be an underestimate because many fetuses with cloacal exstrophy die in utero or are stillborn (Paidas et al., 1994). Its incidence has been reported to fluctuate in some areas, suggesting possible epidemics (Evans et al., 1985). In one study, preconceptional maternal exposure to smoking was significantly more common in parents whose fetus has cloacal exstrophy than in other related anomalies (Gambhir et al., 2008).

SONOGRAPHIC FINDINGS

The anatomic features of cloacal exstrophy are seen on ultrasound examination, thus enabling prenatal diagnosis of these complex congenital abnormalities (Meizner and Bar-Ziv, 1985; Mirk et al., 1986; Romero, 1988; Nyberg et al., 1990; Langer et al., 1992). Cloacal exstrophy should be suspected when there is a lower abdominal wall defect with absence of a normal bladder. Splaying of the pubic rami may also be present. The association of neural tube defects along with these findings also supports the diagnosis.

At least 14 reported cases of cloacal exstrophy have been prenatally diagnosed by sonography (Gosden and Brock, 1981; Meizner and Bar-Ziv, 1985; Mirk et al., 1986; Chitrit et al., 1993; Meizner et al., 1995; Bruch et al., 1996; Kaya et al., 2000). However, three of these cases were probably body-stalk

Table 64-1

Anomalies Associated with Cloacal Exstrophy

Omphalocele
Split symphysis anomaly
Bladder exstrophy
Two exstrophied hemibladders
Interposed midline colonic segment
Ileocecal exstrophy
Superior orifice prolapsed ileum
Single- or double-inferior orifice short blind-ending hindgut
Usually duplicate appendiceal stumps in intermediate position
Imperforate anus
Bifid external genitalia
Diminutive penis
Bifid clitoris and labia
Cryptorchidism
Duplex mullerian strictures
May have exstrophied vaginas at base of bladder mucosa
May have atretic vaginas
Myelomeningocele
Other defects
Talipes equinovarus
Vertebral anomalies (scoliosis)
Renal anomalies
Agenesis or multicystic
Megaloureter
Hydronephrosis
Fusion anomalies, ectopia

Adapted from Ziegler MM, Duckett JW, Howell C. Cloacal exstrophy. In: Welch KJ, Randolph JG, Ravitch MM, et al., eds. Pediatric Surgery. *Chicago: Medical Year Book; 1986:764-771.*

anomalies (Gosden and Brock, 1981). In an effort to establish criteria for early prenatal diagnosis of cloacal exstrophy, Meizner et al. (1995) reviewed the sonographic findings in six cases of cloacal exstrophy and compared them with the sonographic features of other anterior abdominal wall defects. In all six cases, specific sonographic signs were observed: (1) large infraumbilical anterior midline defect with a protruding omphalocele; (2) an absent bladder; (3) a narrowed thorax; (4) a distorted spine; (5) a large sacral myelomeningocele; and (6) bilateral clubfeet. In all cases the bowel was noted to be floating in a large amount of ascitic fluid. Polyhydramnios was present in four of the six cases. Although not done prospectively, this report has helped to define sonographic features of cloacal exstrophy that may allow early prenatal diagnosis (Figures 64-3 to 64-5). These sonographic features may assist the sonographer in distinguishing cloacal exstrophy from other midline anterior abdominal wall defects. The fetus with suspect cloacal exstrophy may benefit from ultrafast fetal MRI, which may be a useful adjunct to sonography in defining the anomalous pelvic anatomy as well as the potential associated myelomeningocele.

A correct prenatal diagnosis of cloacal exstrophy is rarely made, even if pelvic or genitourinary abnormalities are suspected on prenatal ultrasound examination. In a recent retrospective review by Livingston et al. of prenatal sonographic studies of patients evaluated and treated postnatally at the Children's Colorectal Center at Cincinnati Children's, the most common abnormality noted prenatally was hydronephrosis. The correct diagnosis was rarely suspected (Livingston et al., 2007).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of cloacal exstrophy includes bladder exstrophy (see Chapter 65), omphalocele (see Chapter 62), gastroschisis (see Chapter 63), amniotic band syndrome (see Chapter 100), myelomeningocele (see Chapter 19), and the limb–body wall complex (see Chapter 60). The sonographic features of each of these allow it to be distinguished from cloacal exstrophy. In bladder exstrophy, there is a small soft tissue mass on the surface of the abdominal wall and no normal-appearing bladder, omphalocele, spinal abnormalities or clubfeet. Omphaloceles are usually more cephalad on the abdomen and lack other features of cloacal exstrophy. The loops of intestine floating free in the amniotic fluid in gastroschisis usually can be easily distinguished from the omphalocele of cloacal exstrophy, even with the "elephant-trunk" deformity with a loop of intestine floating in amniotic fluid.

The amniotic band syndrome and limb–body-wall complex usually lack the lower abdominal omphalocele and myelomeningocele, and a normal bladder can usually be seen in the pelvis. Cases of limb–body wall complex usually have large gastropleuroschises with a distorted spine.

ANTENATAL NATURAL HISTORY

Because of the rarity of cloacal exstrophy, and the even rarer prenatal diagnoses of these cases, little is known about its antenatal natural history. In the cases studied by Meizner et al. (1995), four of the six developed polyhydramnios, which may predispose to preterm labor and delivery. The cause of polyhydramnios in cloacal exstrophy is not known. There appears to be an increased incidence of intrauterine fetal death and stillbirth in cloacal exstrophy.

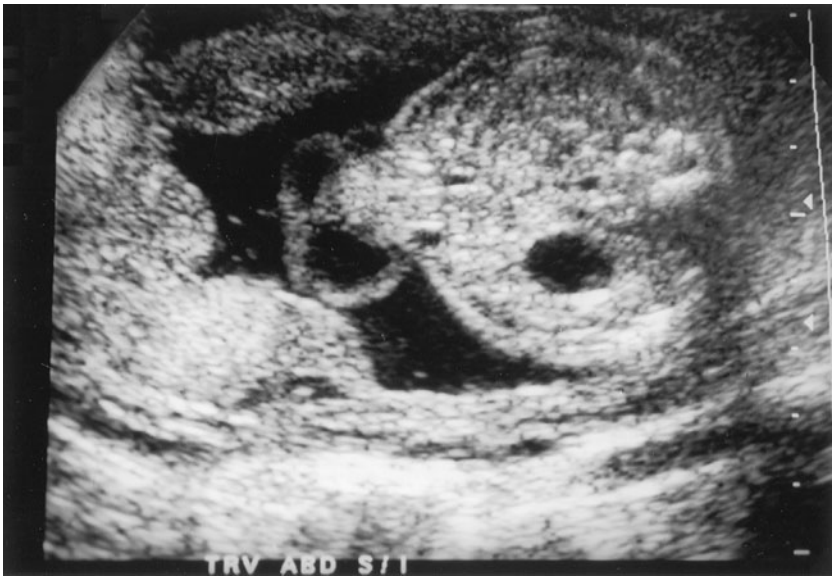

Figure 64-3 Prenatal sonogram of a fetus with cloacal exstrophy demonstrating several sonographic features of cloacal exstrophy. In this image, seen in transverse at the level of the umbilical cord insertion, the lower abdominal-wall defect and omphalocele membrane are evident.

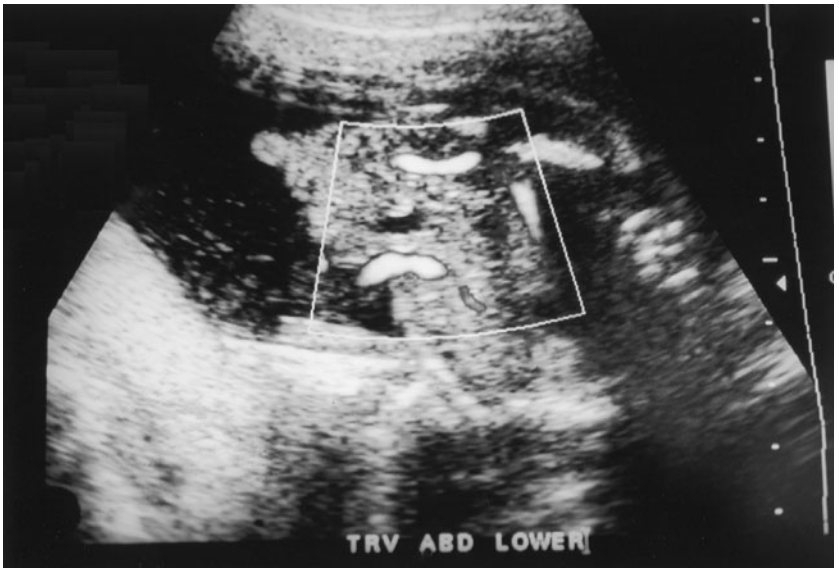

Figure 64-4 A lower abdominal transverse image in the same fetus seen in Figure 64-3, in which no bladder is seen between the umbilical arteries, which appear bright white in this black-and-white version of a color Doppler image, and the elephant-trunk deformity caused by prolapse of the ileum is also seen.

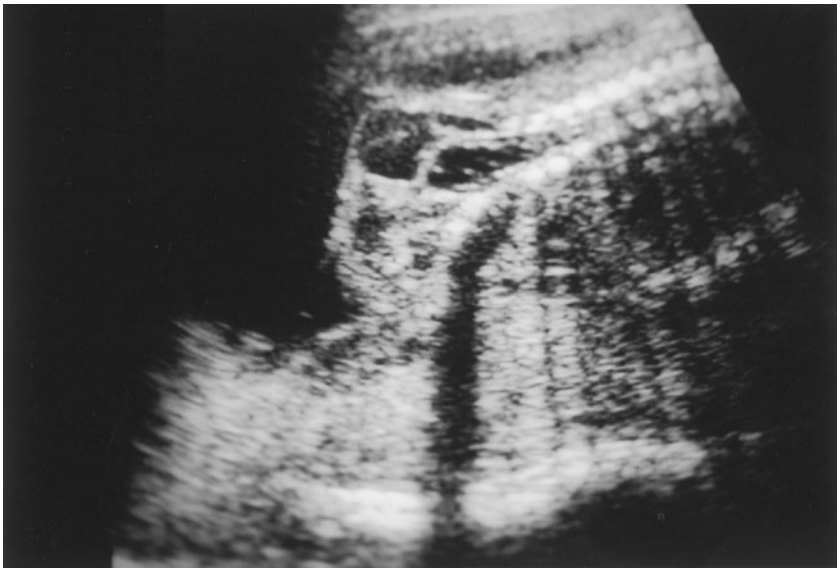

Figure 64-5 The same fetus as in Figures 64-3 and 64-4 is seen in sagittal section of the spine, demonstrating the large sacral myelomeningocele.

MANAGEMENT OF PREGNANCY

The pregnant woman carrying a fetus in which cloacal exstrophy is suspected should be referred to a tertiary care center for level II prenatal sonographic evaluation. If the features of cloacal exstrophy cannot be completely defined sonographically, fetal magnetic resonance imaging (MRI) may be indicated. If the diagnosis is made prior to 24 weeks of gestation, the parents should be offered pregnancy termination. If the parents decide to proceed with the pregnancy, amniocentesis should be performed to determine the genetic sex of the fetus. However, even if the karyotype is 46,XY, female gender reassignment may be a consideration due to the inadequacy of phallic development, which may make reconstruction as a male impossible. The parents should be counseled about the nature of this complex anomaly by a team consisting of a pediatric surgeon, pediatric urologist, pediatric neurosurgeon, neonatologist, geneticist, and pediatric endocrinologist. The delivery should be planned in a center capable of reconstructing this complex lesion, or immediate postnatal transport to a tertiary pediatric center should be planned. The pregnancy may be complicated by polyhydramnios during the third trimester, which may predispose to preterm labor and delivery. The parents should be made aware of the possible increased incidence of intrauterine fetal death and stillbirth in cloacal exstrophy.

FETAL INTERVENTION

There are no fetal interventions for cloacal exstrophy.

TREATMENT OF THE NEWBORN

Ideally, a fetus with cloacal exstrophy should be delivered with neonatologists in attendance. The presence of the omphalocele sometimes predisposes to pulmonary hypoplasia and respiratory insufficiency at birth. The infant should have nonadhesive dressings applied to cover the exposed bladder and bowel mucosa. The increased insensible water loss from the exstrophied bladder and bowel should be factored into the infant's fluid management. Immediate consultation should be obtained from a pediatric surgeon, a pediatric urologist, and a pediatric neurosurgeon. However, emergency surgical correction is not indicated for an infant with cloacal exstrophy. An extensive preoperative evaluation of all defects is essential before operative intervention occurs. Ultrasound examination of the upper urinary tract provides important information regarding position, size, and presence or absence of kidneys. Ultrasound examination will also detect hydronephrosis and hydroureter, which may require preoperative decompression. The infant's spinal cord should be evaluated by sonography and MRI to detect tethered cord, myelodysplasia, and other abnormalities. Radiographic films should be obtained to exclude vertebral or sacral anomalies. Cranial ultrasound examination should be performed to exclude hydrocephalus. Radiographs of the pelvis are also necessary to detect such anomalies as split symphysis and congenital hip dislocation. Karyotype analysis should be obtained if not done prenatally, as gender assignment should be established as soon as possible.

SURGICAL TREATMENT

Before 1960, cloacal exstrophy was uniformly fatal, with intestinal obstruction and urosepsis the leading causes of death. There has been significant progress in the management of cloacal exstrophy, with recent reports of survival ranging from 83% to 100%. This is due to improvements in intravenous alimentation, intensive care, and surgical reconstructive techniques.

Despite improvements in survival, cloacal exstrophy remains a formidable surgical challenge, usually approached in staged procedures. In some cases, gender reassignment as female will be necessary due to insufficient phallic tissue for penile reconstruction in genetic males. If a prenatal diagnosis of cloacal exstrophy is made and karyotype analysis shows 46,XY, the parents should be counseled antenatally about the possibility of gender reassignment. This is a complex area and it may be the most difficult aspect of cloacal exstrophy for the parents to cope with. Gonadectomy is usually performed during the first procedure. Despite early gonadectomy, reconstruction as a phenotypic female and rearing as a female, many individuals will self-identify as male as they mature (Reiner and Gearhart, 2004). This is due to the effects of exposure of the fetal brain to testosterone.

The gastrointestinal tract is often shortened in cloacal exstrophy. Specifically, the colon is usually short and small. Despite this, colonic pull-through to reconstruct the anus is possible in approximately 50% of patients. The remainder of cases are precluded from pull-through procedures by neurologic deficits related to myelomeningocele, sacral malformation, or a sphincter muscle complex that is inadequate for fecal continence.

Reconstruction of the urinary tract in cloacal exstrophy presents a particular challenge for achieving the goals of adequate bladder capacity and outlet resistance. This usually requires bladder augmentation. Due to the shortened gut associated with cloacal exstrophy, the use of the stomach in a gastrocystoplasty has emerged as the preferred technique of bladder augmentation. The advantages of gastrocystoplasty in bladder augmentation include less mucous secretion than small bowel, lower incidence of bladder calculi, and avoidance of hyperchloremic metabolic acidosis seen with the use of intestine. The disadvantages of gastrocystoplasty include problems with excessively acidic urine, with perineal excoriation if incontinence occurs. Various methods of ensuring bladder outlet resistance and continence have been reported, including bladder-neck narrowing with local tissue, using

tapered bowel or ureter to make a urethra, or appendicovesicostomy (Mitchell et al., 1988). In addition, upper urinary tract anomalies that may also require surgical correction may be present occur in up to 45% of patients.

In genital reconstruction, the genetic female can have the rudimentary vagina joined to the perineum. Genetic males undergoing gender reassignment will usually have reconstruction deferred until the teenage years because a vagina is unnecessary for egress of menses and will only be used for coitus.

The condition of the neonate is critical for the decision to proceed with a one-stage versus a two-stage reconstruction (Docimo et al., 1997). In either a one- or two-stage closure, the omphalocele is closed and the bowel is separated from the two bladder halves. The lateral vesicointestinal fissure is closed in continuity and a short colostomy is created from the end of the distal colon segment. The hemibladders are then reapproximated in the midline to create a single exstrophic bladder. In a one-stage procedure, the bladder is closed completely after a bilateral anterior innominate osteotomy has been performed. Table 64-2 shows the one- and two-stage surgical approaches to reconstruction in cloacal exstrophy.

LONG-TERM OUTCOME

With current care, long-term survival is in the range of 90% to 100%. Rare deaths are due to complications of prematurity or associated complex anomalies (Zeigler et al., 1986; Hurwitz et al., 1987; Docimo et al., 1997). Because of the low incidence of this anomaly and the relatively recent success of surgical reconstructive procedures, data on other aspects of long-term outcome are lacking.

Genetic males (46,XY) who undergo gender reassignment are infertile. In successfully reconstructed genetic females (46,XX) there have been documented cases of successful conception and childbirth (Docimo et al., 1997). Bladder continence in patients undergoing reconstructive procedures for cloacal exstrophy can be expected in up to 75% of patients (Hendren and Hendren, 1990). Bowel continence depends on the adequacy of pelvic musculature and innervation. Even after a pull-through procedure, most patients have difficulty with continence and require a bowel regimen, usually daily enemas, to prevent soiling. Alternatively, some patients opt for a permanent colostomy or ileostomy. Recently, the use of a continent catheterizable cecostomy has been used to perform daily antegrade enemas in patients with cloacal exstrophy who have had pull-through procedures, but in whom bowel control is lacking (Malone et al., 1990). As children who have undergone reconstruction grow older, we will learn more about other aspects of long-term outcome, including psychologic adjustment and sexual function.

It has become apparent that genotypic male infants with phallic inadequacy reconstructed as females have a high incidence of male gender identity despite gonadectomy (Reiner and Gearhart, 2004). In a follow-up study of 16 genetic male

Table 64-2

Staged Functional Reconstruction in Cloacal Exstrophy

- Neonatal assessment
  - Evaluate associated anomalies
  - Decide whether to proceed with reconstruction
- Functional reconstruction
  - One-stage repair (few associated anomalies)
    - Excise omphalocele
    - Separate cecal plate from hemibladders
    - Join and close bladder halves
    - Bilateral anterior innominate osteotomies
    - Gonadectomy in males with duplicated or absent penis
    - Terminal ileostomy or colostomy
    - Genital revision if needed
  - Two-stage repair
    - Stage I—newborn period
      - Excision of omphalocele
      - Separate cecal plate from hemibladders
      - Joining bladder halves
      - Gonadectomy in males with duplicated or absent penis
      - Terminal ileostomy or colostomy
    - Stage II—4 to 6 months of age
      - Closure of joined bladder halves
      - Bilateral anterior innominate osteotomy
      - Genital revision if needed
- Anti-incontinence or reflux procedure—4 to 5 years of age
  - Bladder capacity >60 mL minimum
    - Young–Dees–Leadbetter bladder-neck reconstruction
    - Bilateral Cohen ureteral reimplantations
    - Marshall-Marchetti bladder-neck suspension
  - Bladder capacity <60 mL
    - Young–Dees–Leadbetter bladder-neck reconstruction
    - Bilateral Cohen ureteral reimplantations
    - Bowel segment used to augment bladder
    - Continent diversion with abdominal or perineal stoma
- Vaginal reconstruction
  - Vagina reconstructed or augmented using colon, ileum or full-thickness skin graft

Adapted from Gearhart JP. Anomalies of the bladder. In: Kalalis PP, King L, Belman AB, eds. Clinical Pediatric Urology. *3rd ed. Philadelphia: WB Saunders; 1992:1971-1977.*

patients with cloacal exstrophy and phallic inadequacy, 14 underwent neonatal gender reassignment and 2 were raised as male Reiner and Gearhart, 2004). Despite gonadectomy, 8 of the 14 declared themselves male. Both of the infants raised as male had male gender identity. The results of this study raise serious questions about the wisdom of gender reassignment in genetic male infants with cloacal exstrophy.

GENETICS AND RECURRENCE RISK

Cloacal exstrophy occurs as a sporadic event without a recognized associated chromosomal abnormality. There is a higher incidence of cloacal exstrophy in families in which one member is affected as compared with the general population, although the genetic aspects of this malformation are not well understood (Jeffs, 1987).

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65 CHAPTER Bladder Exstrophy

Key Points

- Bladder exstrophy is a severe abnormality of the anterior abdominal wall in which the bladder protrudes under the umbilical cord, the pubic bones are separate causing rectus divergence, and frequently is associated with inguinal hernia.
- In females the mons, clitoris, and labia are separated, with hemiclitoris on either side of the bladder, and there is frequently duplication of the vagina and uterus.
- In males the penis is short and broad, with a dorsal urethral plate, dorsal chordee, and splayed glans.
- Bladder exstrophy is very rare, being seen in 1 in 3000 to 1 in 50,000 births, and there is a significant male preponderance.
- Prenatal sonographic diagnosis is possible by noting an absent bladder, but with normal amniotic fluid volume, together with a lower midline abdominal wall mass and abnormal appearing external genitalia.
- Pregnancy management is generally unchanged by the prenatal diagnosis of bladder exstrophy, and the only role for genetic amniocentesis is to assist in assignment of gender if external genitalia are unclear.
- The goal of surgical management is to achieve bladder closure, epispadias repair, and achievement of urinary continence; this can be achieved either in a three-stage process over 4 years or as a single primary repair.
- Bladder exstrophy is generally considered a sporadic abnormality, although there may be a 3%–4% recurrence risk in siblings.

CONDITION

Exstrophy of the bladder has been recognized for centuries, but it was not until the 19th century that surgical correction was first attempted (Hall et al., 1953). The first attempts at diversion of urine into the colon were made in 1850, and the first successful closure of bladder exstrophy was performed in 1862 (Canning et al., 1996). In contrast to patients with cloacal exstrophy that have other unrelated abnormalities, infants with bladder exstrophy have defects confined to the bladder, abdominal wall, perineum, genitalia, and bony pelvis.

At birth the diagnosis of bladder exstrophy is easily made by the presence of characteristic findings. The bladder plate protrudes immediately beneath the umbilical cord (Figure 65-1). The rectus muscles are divergent due to separated pubic bones. There is an outward rotation of the innominate bones and eversion of the pubic rami (Sponsellor et al., 1991). The phallus is short, with a dorsal urethral plate, splayed glans, and dorsal chordee. In females, the mons pubis, clitoris, and labia are separated and the vaginal orifice may be displaced anteriorly. Bilateral inguinal hernias are commonly seen at birth because of the large internal and external inguinal ring caused by the splaying of the rectus musculature and lack of obliquity of the inguinal canal. Hussman et al., (1990) reported that 56% of males and 15% of females have inguinal hernias. In a report by Peppas et al., (1995) in patients presenting with hernia within one year of primary closure, 10%–53% of the hernias were incarcerated.

In bladder exstrophy the umbilical cord inserts low on the abdomen and the anus and scrotum tend to be more anteriorly placed than normal (see Figure 65-1). Although the rectus abdominis muscles insert normally at the pubic tubercles, the diastasis of the pubic symphysis and lateral displacement of the iliac bones causes splaying of the rectus muscles. This lateral displacement of the rectus muscles widens the inguinal canal, predisposing to indirect inguinal hernias in these patients (Connor et al., 1989; Hussman et al., 1990; Stringer et al., 1994). Because the bladder is external, the peritoneal reflection is deeper in the pelvis than normal and the ureters course deeply through the pelvis and enter the

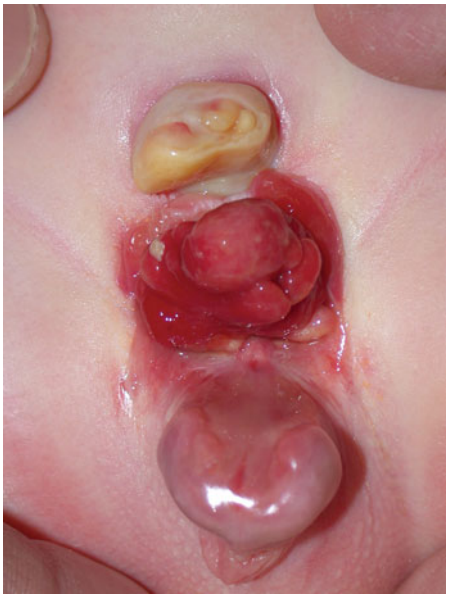

Figure 65-1 Newborn female infant with bladder exstrophy demonstrating the presence of a low umbilical cord with a protruding bladder plate and a hemiclitoris on each side of the bladder.

bladder with almost no submucosal tunnel, which predisposes them to vesicoureteral reflux (Nisonson and Lattimer, 1968).

The penis in males with bladder exstrophy is short and broad because of pubic bone separation, which prevents the midline joining of the corpora cavernosa. Figure 65-1 illustrates the appearance of the female infant with bladder exstrophy. The overall length of the corpora cavernosa is shortened but reasonable length may be obtained with epispadias repair from the deep corporal bodies (Woodhouse and Kallett, 1984). There is usually a marked dorsal chordee and the penile curvature is compounded by shorter dorsal tunica albuginea. Females with bladder exstrophy (Figure 65-1) have a hemiclitoris on each side of the bladder and the vaginal orifice may be duplicated and displaced anteriorly (Damario et al., 1994). The uterus may be duplicated, but the fallopian tubes and ovaries are usually normal.

All patients with bladder exstrophy have some degree of pubic diastasis, with the hips rotated outward. Many patients have a waddling gait in early childhood, but long-term hip or gait problems are rare.

In normal development the cloacal membrane occupies the infraumbilical position of the abdominal wall, and this bilaminar membrane is infiltrated by mesenchyme to form the lower abdominal musculature. The genital folds fuse superiorly to form the genital tubercle. The most widely accepted theory for the cause of exstrophy is based on the work of Muecke, (1964), in chick embryos. In this model, overgrowth or persistence of a thickened cloacal membrane results in truncated mesenchymal migration. Later rupture of the membrane without the mesenchymal reinforcement results in exstrophy. Bladder exstrophy results if the rupture occurs after the descent of urorectal septum. If rupture occurs in the absence of the urorectal septum, then cloacal exstrophy occurs. The prenatal sonographic observation by Langer et al. of an intact cloacal membrane that subsequently ruptured during the second trimester suggests that the presence or absence of the urorectal septum and not timing of membrane rupture distinguishes bladder exstrophy from cloacal exstrophy (Langer et al., 1992).

INCIDENCE

A broad range of incidences have been reported for bladder exstrophy, from 1 in 3000 to 1 in 50,000 livebirths (Lattimer and Smith, 1996; Sanders, 1996). Rickham estimated the incidence of bladder exstrophy at 1 in 10,000 livebirths (Rickham, 1960). The International Clearinghouse for Birth Defects Monitoring Systems estimated the incidence of bladder exstrophy at 3.3 in 100,000 livebirths (Lancaster, 1987). All reports have consistently shown a male predominance, which, derived from multiple series, averages 2.3:1 (Bennett, 1973; Harvard and Thompson, 1951; Higgins, 1962; Jeffs et al., 1982). Individual reports exist that describe a male predominance as high as 5:1 or 6:1 (Ives et al., 1980; Lancaster, 1987). There are no estimates available for the prenatal incidence of bladder exstrophy.

While no definite teratogenic effect has been demonstrated, there is a slightly increased risk of bladder exstrophy with maternal progestin use (Blickstein and Katz, 1991). Also, a single case of bladder exstrophy has been reported in the child of a user of lysergic acid diethylamide. A slightly increased risk of bladder exstrophy has been observed in mothers less than 20 years of age (Lancaster, 1987).

SONOGRAPHIC FINDINGS

The prenatal sonographic diagnosis of bladder exstrophy is based on the association of several findings, including inability to visualize the bladder, normal amniotic fluid volume, presence of a mass on the anterior abdominal wall in the suprapubic region, small penis with an anteriorly displaced scrotum, low umbilical cord insertion, splayed iliac crests, umbilical arteries situated alongside the bulging mass protruding from the lower abdominal wall, malformation of the external genetalia (Barth et al., 1990; Bronshtein et al., 1993; Gearhart et al., 1995a; Jaffe et al., 1990; Lee et al., 2003: Meizner and Bar-Ziv, 1986; Mirk et al., 1986; Pinette et al., 1996; Richards et al., 1992). The fetal bladder is most easily identified between the umbilical arteries, using color Doppler sonography. If completely empty, the bladder may not be seen, but since it normally fills and empties every 5–15 minutes, persistent observation should identify the normal bladder (Gearhart et al., 1995a). However, the normal bladder may not be imaged if there is a lack of urine production, either due to bilateral renal agenesis or bilateral multicystic

dysplastic kidneys. The use of 3-D ultrasound may be particularly useful in identifying the lower abdominal mass in bladder exstrophy (Evangelidis et al., 2004). Similarly, ultrafast fetal MRI may be useful as an adjunct to ultrasound if the diagnosis is not clear as a result of technical limitations of ultrasound such as fetal position or maternal body habitus.

All of the features of bladder exstrophy may not be seen in every patient. In the report by Gearhart et al., (1995a), in 17 fetuses with prenatal sonographic examinations in whom a retrospective diagnosis of bladder exstrophy could be made, not every feature was present. In 71% of cases there was persistent nonvisualization of the fetal bladder. In only 47% of cases were a persistent lower abdominal wall mass or bulge seen. A very small penis with an anteriorly displaced scrotum was seen in 57% of fetuses. Even less commonly appreciated was the low umbilical cord insertion (29%) and abnormal widening of the iliac crests (18%).

In a female, the clitoris is bifocal and there are widely separated labia, but this may be difficult to discern sonographically.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of bladder exstrophy includes cloacal exstrophy, persistent urachus, omphalocele, and gastroschisis. However, the lower abdominal wall bulge with low cord insertion immediately cephalad to the exstrophied bladder usually allows its identification. The kidneys are usually normal in bladder exstrophy. In contrast, in cloacal exstrophy, unilateral renal agenesis is common, as is hydronephrosis. In addition, there is often prolapse of the ileum through the cloaca to form the "elephant trunk" deformity (see Chapter 64). Myelomeningocele and omphalocele are also commonly associated with cloacal exstrophy. Rarely, a small omphalocele may be seen in bladder exstrophy (Gearhart et al., 1989b). The lower abdominal wall bulge or soft tissue mass in cloacal exstrophy is usually larger and more heterogeneous than in bladder exstrophy (Pinette et al., 1996). A persistent urachus may resemble the normal bladder and complicate the diagnosis. However, prolonged observation demonstrates the structure to be constant in size and shape lacking any voiding episodes excluding the possibility of a normal bladder (Goldstein et al., 2001, see Table 65-1).

ANTENATAL NATURAL HISTORY

Although few prospectively diagnosed cases of bladder exstrophy have been reported, review of retrospective cases suggests that this diagnosis has no implications for the pregnancy. These are usually isolated sporadic anomalies, without increased risk for intrauterine death, or neonatal compromise at birth.

MANAGEMENT OF PREGNANCY

Once there is a diagnosis of bladder exstrophy, an attempt to completely define the anomaly should be made. The position of the abdominal wall bulge and umbilical cord insertion, sex of the fetus, and the size and position of the penis should be determined. If the sex of the fetus is in doubt, genetic amniocentesis may be indicated to help counsel the parents and plan the postnatal reconstruction. Prenatal consultation with a pediatric urologist is extremely helpful in advising parents about the reconstructive procedures that will be necessary and about the long-term prognosis. There is no need to alter the delivery plan, and cesarean section should be reserved for obstetrical indications. Because bladder closure is best accomplished during the first 3 days of life, delivery in a tertiary care center with pediatric urologists and anesthesiologists is preferred, but transportation of the newborn to a pediatric center is also possible.

FETAL INTERVENTION

There are no fetal interventions for bladder exstrophy.

TREATMENT OF THE NEWBORN

In the management of bladder exstrophy, staged functional reconstruction and urinary diversion are the two most commonly employed strategies. Urinary diversion is usually undertaken only when reconstruction is unavailable or repeated attempts at functional reconstruction have failed. Gender reassignment is almost never necessary, given modern reconstructive techniques, and is reserved for rare cases in which no other option is available. The staged functional reconstruction is undertaken with specific goals for each stage. During the newborn period, the goal is bladder closure with protection of the upper urinary tract, and preservation for later continent reconstruction. In the second stage, at about 1 year of age in the male, the goal is to optimize genital structure and function and to increase bladder outlet resistance to foster growth of the bladder. In the final stage of functional reconstruction, undertaken at about 4 years of age, the goal is to achieve urinary continence.

SURGICAL TREATMENT

The most commonly used technique for bladder closure involves the conversion of an exstrophied bladder to an incontinent epispadias (Gearhart and Jeffs, 1989b, 1990 a and 1990b; Jeffs et al., 1982). An incision circumscribes the exstrophied bladder extending distal to the verumontanum on both sides

Table 65-1

Absent Bladder

	Kidneys	Amniotic Fluid	Doppler Umbilical Artery	Renal Arteries	Uterine Arteries	Other Findings
Failure of urine production						
BRA	Absent	–	N	–	–	
Severe BRD	Small and large cysts	–	N	N/A		
Severe IUGR	Small and large cysts normal		A	N	A	
Failure to store urine	N/HN	N	N	N	N	–
Bilateral ectopic ureters	N	N	N	N	N	Lower abdominal mass, abnormal external genitalia low umbilical, insertion, splayed iliac bones
Cloacal exstrophy	N, absent or HN	N	N	N	N/A	Omphalocele, cystic anterior mass, meningomyelocele, kyphoscoliosis, lower limb defects, single umbilical artery

N, normal; A, abnormal; HN, hydronephrosis; BRA, bilateral renal agenesis; BRD, bilateral renal dysplasia; IUGR, intrauterine growth retardation.

of the prostatic urethra, resulting in a wide plate of bladder neck and prostatic urethra. The bladder is completely mobilized and the corpora cavernosa directed off the inferior pubic cavernosa with care to preserve the neurovascular bundles. The corpora cavernosa are approximated in the midline. The neourethra, with or without paraexstrophy flaps, is tubularized. Ureteral stents suprapubic to the vesicostomy site are exteriorized prior to closing the bladder. The pelvic ring is closed by a nonabsorbable monofilament suture. The midline abdominal defect is then closed by approximation of the rectus fascia and skin. Pubic approximation is possible during the first days of the life, without osteotomy. After staged reconstruction, all patients should be maintained on prophylactic antibiotics because of the high incidence of vesicoureteral reflux. Although most children will have vesicoureteral reflux, it is unusual for them to require an antireflux procedure before subsequent bladder neck reconstruction.

The second stage of functional reconstruction, undertaken between 6 and 12 months of age, focuses on phallic reconstruction. Epispadias repair and urethroplasty not only reconstruct the phallus, but also result in increased outflow resistance and enhanced bladder capacity (Gearhart and Jeffs, 1989a). The goals of epispadias repair are to provide length for the phallus and to release the dorsal chordee (Gearhart and Jeffs, 1990a; Hendren, 1979; Hinman, 1958). In addition, the urethra is reconstructed to place the meatus at the tip of the glans penis (Kajbafzadeh et al., 1995; Mitchell and Bagli, 1996; Ransley et al., 1989).

The last stage of functional reconstruction in bladder exstrophy is undertaken at about four years of age (Perlmutter et al., 1991). It is important that the child's bladder capacity be at least 60 ml in order to have functional capacity following bladder neck reconstruction (Jeffs et al., 1982). The Young–Dees–Leadbetter technique remains the most commonly used technique to reconstruct the bladder neck (Gearhart and Jeffs, 1990b; Leadbetter, 1964; Marshall et al., 1949; Woodhouse and Kallett, 1984). The ureters are reimplanted in a cephalad position in either a cross-trigonal or cephalotrigonal procedure to prevent vesicoureteral reflux (Brock and O'Neill, 1998; Canning et al., 1990). Next, the posterior bladder mucosa is tubularized over a Foley catheter to create a neourethra, and the muscular layer of bladder is closed over the neourethra to create a new bladder neck. If capacity is inadequate, bladder augmentation is then performed (McLaughlin et al., 1995). The bladder neck and urethra are then sutured to the undersurface of the pubis.

Recently, complete primary exstrophy repair has gained popularity. The procedure combines the goals of the staged reconstruction into a single procedure: bladder closure, epispadius repair, and achievement of urinary continence, all without formal bladder neck reconstruction. Complete primary exstrophy repair offers preservation of renal function and better continence in many patients. However, this is a surgical option best employed only at centers with highly experienced surgeons because of the risk of significant complications including penile ischemia and hypospadias (Husman et al., 2006).

Urinary diversion is reserved for patients who have inadequate anatomy for reconstruction at birth or when attempts at reconstruction have failed. Among the most commonly employed technique is the ureterosigmoidostomy, which allows continence, and with nonrefluxing ureterocolonic anastomoses, protection of the upper urinary tracts. However, long-term hyperchloremic metabolic acidosis, ureteral obstruction, and colonic malignancy are possible complications. Ileal conduits are not considered suitable for urinary diversion in children due to long-term complications. A colon conduit may be an alternative, with fewer long-term complications than ileal conduits. Once a child achieves anal continence, anastomosis of the colon conduit to the rectosigmoid can be performed.

LONG-TERM OUTCOME

One report reviewed the experience at the Johns Hopkins Hospital with 87 patients treated for exstrophy of the bladder (Baker et al., 1999). The age at follow-up ranged from 8 months to 22 years. Bladder neck reconstruction was performed in 58 of 87 patients, with 47 (81%) continent of urine. Among the remaining 11 patients, 4 were less than 6 months from bladder neck repair, 2 were lost to follow-up, 1 was diverted, 1 awaits bladder augmentation, 2 have had bladder augmentation, and 1 is totally incontinent of urine. The average time to continence during the day ranged from 3 months to 5 years (mean, 2 years), and to nighttime continence, a mean of 4 years. Other centers have reported continence rates in the 69%–71% range with bladder neck reconstruction (Jones et al., 1993; Lottman et al., 1996; Mollard et al., 1994).

Patients who do not achieve continence within 1–2 years of bladder neck reconstruction seldom have sufficient continence over time (Gearhart, 1998). These patients may require remedial approaches, including repeat bladder neck reconstruction, often with concomitant bladder augmentation. The majority of patients in whom initial bladder neck reconstruction fails need bladder augmentation (Gearhart et al., 1990a, 1995b).

There may be significant psychologic consequences to this anomaly and the results of reconstructive procedures. Ben-Chaim et al., (1996) reported the results of a diagnostic psychiatric questionnaire and interview with 20 patients with bladder exstrophy and their parents. Behavioral, social, and school competency problems were experienced by 70% of the adolescents and 33% of the school-aged children. In nearly 70% of the participants, concern was present about the sexual function or disfigurement. The mechanics of sexual intercourse and anxiety about the appearance and adequacy of their genitalia were perceived as barriers to relationships by both adults and adolescents.

Children with bladder exstrophy have recently been recognized to be at increased risk for clinically significant anxiety disorders (Reiner et al., 2006). These anxiety disorders are thought to be due, at least in part, to hypothalamic-pituitary-adrenal axis and other neurobiologic developmental disruptions. It is speculated that early anesthetic, surgical, and/or other medical interventions may affect highly active neurobiologic developmental processes. Some of the anxiety problems in these children tend to abate with age, after successful surgical resolution of functional abnormalities (Reiner et al., 2006).

The issue of sexual function, fertility, and self-esteem become more important long-term issues for children born with bladder exstrophy who undergo reconstruction. Ben-Chaim et al., (1996) reported the results of an anonymous questionnaire and chart review in 20 adult patients (16 men and 4 women). Of the 20 patients, 6 are married (4 men, 2 women), 2 men have fathered children, and 1 woman has had two children. Ten of the 16 men ejaculate a volume of 2 ml, with history of retrograde ejaculation in 6. Semen analysis was performed in 4 men, with an average ejaculate volume of 0.4 ml with azoospermia in 3 and oligospermia in 1. All patients experienced normal erections, but were unsatisfactory in 7 because of a small penis, and 12 of 16 experienced satisfactory orgasms. Stein et al., (1994) have suggested that in males, bladder neck reconstruction may be performed at the expense of fertility. Fertility in males is of secondary concern in reconstructive surgery of the urethra and bladder neck. Erectile and sexual functions are well preserved but patients are bothered by small penile length and dorsal chordee. In contrast, females appear to have normal fertility, sexuality, and sexual function (Gearhart, 1998). However, uterine prolapse after pregnancy and delivery is common and is thought to be due to intrinsic weakness of the pelvic floor (Krisiloff et al., 1978). Uterine prolapse is less common after early pelvic closure with osteotomy (Jeffs et al., 1982). Rectal prolapse occurs frequently in untreated patients, possibly due to bladder mucosal irritation–induced straining. This disappears with bladder closure (Jeffs et al., 1982).

There is a higher incidence of latex allergies in children with bladder exstrophy (Ricci et al., 1999). The latex sensitivity is thought to be a consequence of multiple surgical procedures with latex exposure and may cause life-threatening reactions. Infants with bladder exstrophy are best cared for an in a latex-free environment.

Adenosarcoma of the bladder occurs in patients with bladder exstrophy approximately 400 times more commonly than in the normal population (Kanzari et al., 1974; Krishnansetty et al., 1988). It is the most common bladder

tumor occurring in patents with untreated bladder exstrophy (Davillas et al., 1991) and has been reported in adults who had bladder closure after infancy (Facchini et al., 1987). While bladder malignancy has yet to be reported in patients who had bladder closure at birth, long-term monitoring with cytologic evaluation is recommended (Canning et al., 1996).

GENETICS AND RECURRENCE RISK

Bladder exstrophy, in general, is a rare sporadic anomaly. However, there are families at increased risk for recurrence. Of 2500 index cases, Shapiro et al., (1984) found 9 affected siblings with a risk of a second affected family member of 3.6%. A total of 29 familial cases of this otherwise sporadic condition have been reported (Kajbafzadeh et al., 2006; Messelink et al., 1994; Shapiro et al., 1984). It has been suggested, based on anecdotal case reports, that some familial cases may be inherited as an autosomal dominant (Froster et al., 2004). The risk to offspring of a patient with bladder exstrophy is estimated at 1.4%, and the risk of 2 affected siblings is about 1% (Carter, 1984).

The exstrophy epispadius complex appears to occur more frequently in children conceived by in vitro fertilization (Wood et al., 2003). Bladder exstrophy in one study was found to have a 7.3-fold higher risk than normal after in vitro fertilization.

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Cystic Lesions of the Abdomen

66
CHAPTER

Key Points

- Cystic abdominal lesions are relatively common.
- Diagnosis of the underlying etiology of a cystic abdominal mass may be difficult but intimate association with adjacent structures may provide clues to diagnosis.
- Fetal MRI may be helpful in determining the cyst's origin.
- Sonographic evidence of associated anomalies should be sought.
- Obstruction of bowel and compression of adjacent organs is common and may result in polyhydramnios.
- Cyst aspiration in utero is rarely indicated.

CONDITION

The prenatal diagnosis of abdominal cystic lesions is relatively common (McEwing et al., 2003). Cystic abdominal masses may either represent a normal structural variant or pathologic entity that may require surgical intervention postnatally (Sherwood et al., 2008). Abdominal cystic lesions may be exceedingly difficult to accurately diagnose prenatally (Khong et al., 2003). In other chapters, we have already addressed many of the lesions in the differential diagnosis including choledochal cysts (Chapter 67), ovarian cysts (Chapter 68), meconium pseudocysts (Chapter 70), and extralobar bronchopulmonary sequestration (Chapter 34). This chapter will focus on some less common, but important, causes of cystic abdominal lesions including hepatic cysts, splenic cysts, pancreatic cysts, duplication cysts, and mesenteric cysts.

Hepatic cysts are most often isolated, simple cysts. Hepatic cysts are thought to arise from aberrant bile ducts (Cowles and Mulholland, 2000; Otani et al., 2005) or intrahepatic, peribiliary glands (Kida et al., 1992). These simple cysts are more common in girls (Otani et al., 2005) and do not communicate with the biliary system (Rogers et al., 2007). At least one case of prenatal hepatic cyst has been found to be a mesothelial cyst (Komori et al., 2008).

The majority of simple unilocular hepatic cysts detected prenatally tend to shrink or resolve postnatally (Rogers et al., 2007). There are cases of hepatic cysts reaching very large sizes with progressive enlargement resulting in symptoms (Byrne and Fonkalsrud, 1982).

Splenic cysts are usually simple serous epithelial-lined cysts in the upper pole of the spleen (Saada et al., 2006). These cysts are often diagnosed prenatally in the third trimester and may be difficult to distinguish from adrenal or pancreatic cysts.

Pancreatic cysts arise from a developmental anomaly of the pancreatic ductal system usually in the body or tail of the pancreas (Choi et al., 2007). These cysts are epithelial lined and are not pseudocysts. Pancreatic cysts can occur as part of Beckwith–Wiedemann syndrome, polycystic disease of the pancreas and kidney, or Hippel–Lindau disease but are usually multiple in these cases (Vane et al., 1993).

Duplication cysts can occur at any point along the gastrointestinal tract (Bhargava et al., 1976). Enteric duplications

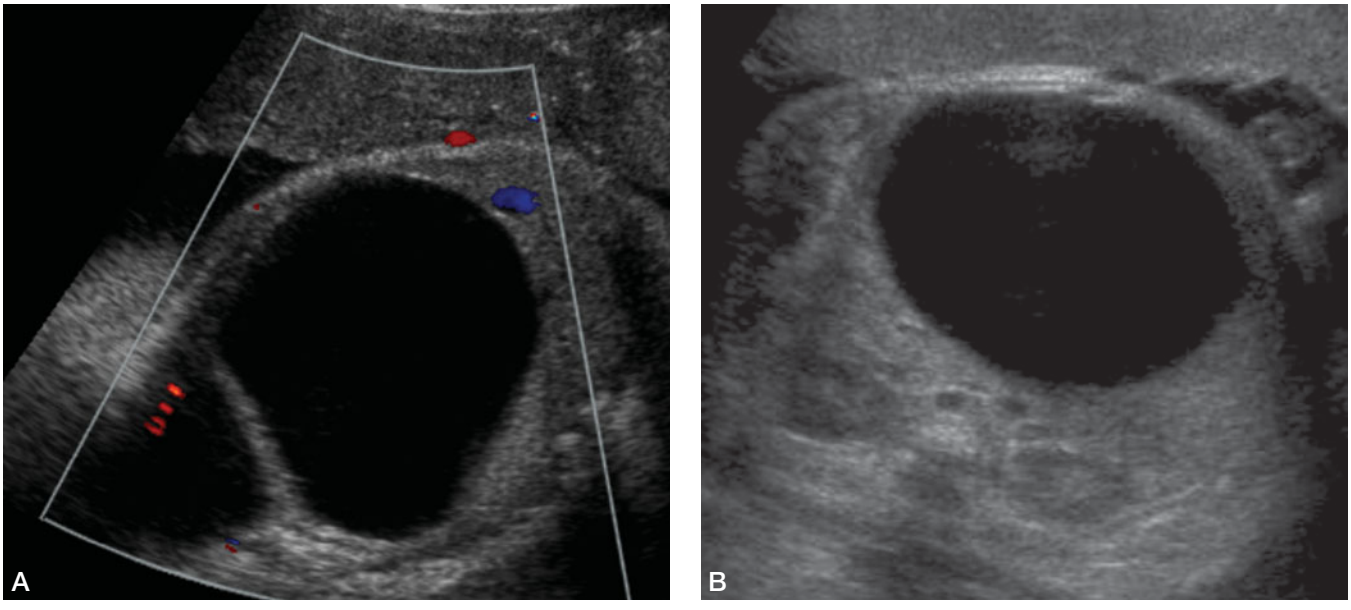

Figure 66-1 **A**. Saggittal ultrasound image demonstrating an anechoic unilocular cyst in the lower fetal abdomen that proved to be a mesenteric cyst on postnatal imaging. Note the absence of internal echogenic lining, absence of septations, and proximity to bowel and mesentery. **B**. Transverse ultrasound image of the same fetus as in (A).

most commonly occur in the jejunum (53%) with 18% occurring in the colon, 6% in the duodenum, and 4% gastric (Khanna et al., 2004). There are several theories that have been proposed to account for enteric duplications ranging from errors in recanalization, partial twinning, embryonic diverticula, and split notochord theory (Goyert et al., 1991; Heis, 1997; Jimenez et al., 1999; Behrman et al., 2000). Colonic duplications frequently present with obstruction of the adjacent bowel (Jimenez et al., 1999). Colonic duplications may be associated with duplications of the genitourinary system (Heis, 1997; Jimenez et al., 1999). Duplication of the intestine may also occur in association with vertebral and spinal cord anomalies such as hemivertebrae, anterior myelomeningocele, duplication of an otherwise normal cord, or a bond between the cyst and the cervical or thoracic spine (Heis, 1997; Behrman et al., 2000).

INCIDENCE

These cystic lesions of the abdomen are sufficiently unusual that no accurate estimates of their incidence are available.

SONOGRAPHIC FINDINGS

Hepatic cysts tend to be simple unilocular cysts but may vary considerably in size. Simple hepatic cysts are thought to develop from aberrant bile ducts or intrahepatic peribiliary glands (Kida et al., 1992; Cowles and Mulholland, 2000; Otani et al., 2005; Rogers et al., 2007). These cysts may enlarge to significant proportions causing bowel obstruction. It may be difficult at times to recognize it as a cyst as it can entirely fill the peritoneal cavity (Figure 66-1A and 66-1B). This can be distinguished from ascites by its compression of the bowel into the retroperitoneum behind the cyst. While there are case reports of cyst aspiration, they do not often require treatment (Rogers et al., 2007; Ito et al., 1997; Arzt et al., 1998).

Determining the origin of a cyst as hepatic, splenic, mesenteric, or pancreatic may be exceedingly difficult unless the cyst is clearly surrounded by parenchyma of a specific organ. Pancreatic cysts usually develop from the ductal system in the body and tail of the pancreas and are usually epithelial lined. Usually these are solitary unilocular nonenzymatic cysts (Choi et al., 2007). Fetal MRI may be a useful adjunct to ultrasound in defining the etiology of a cystic lesion of the abdomen (Veyrac et al., 2004; Wong et al., 2006).

ANTENATAL NATURAL HISTORY

The prenatal diagnosis of intrabdominal cysts is not uncommon but large series of cysts of a given type to help define the prenatal natural history are unavailable. Charlesworth et al. reported a series of fifteen cases of prenatally diagnosed hepatic cysts of which nine had serial ultrasound scans (Charlesworth et al., 2007). In five cases there was cyst enlargement, no change in three cases, and decrease in size in one case during sonographic surveillance. In only one case was cyst aspiration undertaken due to massive enlargement filling the entire abdomen causing polyhydramnios. This was performed at 35 weeks' gestation with 300 mL of fluid removed.

Enteric duplication cyst may present with findings suggestive of bowel obstruction with dilated proximal loops of bowel. Gastric, pyloric, duodenal, or jejunal enteric duplications are more likely to cause polyhydramnios than more distal enteric duplications (Gul et al., 2004; Khanna et al., 2004; Nakazawa et al., 2005; Shah et al., 2005).

Mesenteric cystic lymphangiomas can occur as unilocular or multilocular cystic masses (Deshpande et al., 2001; Chateil et al., 2002; Ho et al., 2002; Groves et al., 2003; Rasidaki et al., 2003). The growth of these cysts is hard to predict but compression of the bowel and obstruction by a cystic mesenteric lymphangioma is possible, although uncommon. The importance of the diagnosis of a cystic mesenteric lymphangioma is the potential for associated problems including genetic syndromes such as Turner, Noonan, or Fryns as well as aneuploidy such as trisomy 18 and 21 (Teixeira et al., 2007).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of a cystic abdominal mass can be lengthy if there are no clues to the underlying cause and include: choledochal cyst, Caroli's disease, gastric or pyloric duplication, hepatic cyst, splenic cyst, pancreatic cyst, mesenteric cyst, ovarian cyst, meconium pseudocyst, jejunal or ileal duplication cyst, adrenal hemorrhagic cyst, renal cyst, colonic or rectal duplication cysts. This long list can be narrowed by relying upon anatomic relations and associated findings such as the inner echogenic strip seen in duplication cysts, calcifications seen in meconium pseudocysts, intimate relationship with the hepatic artery in choledochal cyst, or the surrounding parenchyma in hepatic splenic, pancreatic, or adrenal cysts (Malone et al., 1997).

MANAGEMENT OF PREGNANCY

The fetus noted to have a cystic abdominal mass should undergo a detailed sonographic evaluation not only to define the origin of the cyst, but also to exclude possible associated anomalies. In some instances other abnormalities such as single umbilical artery, or other soft markers for aneuploidy may be detected that would indicate the need for a genetic amniocentesis. A fetal MRI may be very helpful in defining the origin of the cyst and its anatomic relations with other structures (Veyrac et al., 2004; Wong et al., 2006). In most cases, even if the exact etiology is not established prenatally, the potential for partial or complete bowel obstruction is present. All cases should be followed sonographically for the development of polyhydramnios and the increased risk of associated preterm labor. In the event that the cyst becomes symptomatic prenatally, consideration should be given to delivering in a setting where immediate evaluation by a pediatric surgeon is available. In most cases, antenatal consultation with a neonatologist and pediatric surgeon is advisable. A consultation with a geneticist may also be indicated if there are indications that the cyst may be one manifestation of a syndrome or there is the potential for aneuploidy.

FETAL INTERVENTION

Fetal abdominal cysts rarely require intervention and with the exception of ovarian cysts (see Chapter 68) there have only been anecdotal reports of cyst aspirations in utero (Ohama et al., 1986; Chen et al., 1997, 2006; Chen, 2001; Charlesworth et al., 2007). These cyst aspirations are often performed to facilitate the diagnosis, as in the case of meconium peritonitis (Chen et al., 2004), choledochal cyst (Chen, 2001), and enteric duplication of the tongue (Ohama et al., 1986; Chen et al., 1997). Current imaging capabilities by ultrasound and MRI, however, obviate the need for cyst decompression to make a diagnosis. In some cases, cyst aspiration may alleviate compression of adjacent organs, including the bowel, and thereby relieving polyhydramnios. In most instances, however, reaccumulation of cyst fluid would be anticipated. To date, there have been no reports of shunting procedures to decompress large abdominal cysts as the risks of such a procedure would likely be greater than the consequences of cyst left undrained.

TREATMENT OF THE NEWBORN

The most important aspect of management of a newborn diagnosed prenatally with an abdominal cyst is an accurate diagnosis and exclusion of associated conditions. A detailed physical exam should identify any dysmorphic features, and a genetic consultation is indicated if findings of concern are identified. Plain abdominal and cross-table radiographs should be obtained to evaluate for possible signs of bowel obstruction. If there was a maternal history of polyhydramnios, such bowel obstruction is likely to be the case. If dilated loops of bowel are present, a nasogastric tube should be placed to decompress the proximal gastrointestinal tract. Bedside ultrasound may indicate the origin of the cyst if this was not identified prenatally. There is no great urgency to take the infant to surgery, and it is helpful to obtain complete preoperative imaging as needed to define the underlying etiology. For right upper quadrant cystic lesions, an MR cholangiogram may help define or exclude choledochal cyst from the differential. MRI scanning of the abdomen may help to refine the differential diagnosis. In the setting of partial or complete bowel obstruction, surgical exploration will be necessary to relieve the obstruction. However, smaller cysts that are not symptomatic do not necessarily require resection. This is true for adrenal cysts, splenic cysts, and small mesenteric or hepatic cysts, provided that the diagnosis is certain. In other cases such as enteric duplication, the risk of bleeding from the duplication should prompt resection even in the absence of

obstruction. In addition, if there is doubt about the etiology of the cyst it may be more prudent to surgically remove them.

Cysts that are not removed should be followed sonographically to exclude further size increase or risk for future complications.

SURGICAL TREATMENT

The surgical approach to an abdominal cyst depends on the underlying etiology, hence the importance of accurate preoperative diagnostic imaging. Choledochal cysts require excision with Roux-en-Y reconstruction to prevent infectious complications and cholangiocarcinoma. Enteric duplications can sometimes be resected with preservation of the adjacent bowel loop. Alternatively, resection of the affected loop and primary anastomosis are required. Splenic and hepatic cysts can often be resected intact. In other cases, the cyst can be resected down to the parenchyma and the lining stripped off. It is rarely indicated to resect underlying normal parenchyma.

Cystic lymphangiomas are a special case in which complete resection may not be advisable leaving open the possibility of recurrence. The goals of this surgery should be to remove as much as is safely possible without risk to adjacent structures.

LONG-TERM OUTCOME

In the majority of cases, cystic abdominal lesions can be dealt with in the newborn period and have few long-term sequelae. One exception to this are choledochal cysts that require long-term follow-up as patients remain at risk for cholangitis. Most other etiologies have no long-term sequelae beyond the risk of laparotomy for adhesive small-bowel obstruction.

GENETICS AND RECURRENCE RISK

There are no reports of familial recurrence of cystic abdominal lesions with the exception of choledochal cyst, which is extremely rare (Clifton et al., 2006). Other exceptions would be cases of mesenteric lymphangiomas that can be associated with a range of genetic syndromes. The potential for recurrence would then be specific to the particular syndrome.

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67 Choledochal Cyst

CHAPTER

Key Points

- Choledochal cyst refers to dilation of the common bile duct, with type I being the most common and the only prenatally diagnosed form.
- Prenatal diagnosis is based on the visualization of a single simple cystic structure near the gallbladder.
- Differential diagnosis includes hepatic, adrenal or renal cysts, duodenal duplication, and gallbladder duplication.
- There is no need to alter the management of pregnancy, nor the timing or mode of delivery, following the prenatal diagnosis of choledochal cyst.
- During the newborn period, detailed imaging of the biliary system is required to exclude biliary atresia, including radionuclide imaging.
- Definitive treatment requires surgical excision of the cyst, and long-term outcome is excellent.

CONDITION

Choledochal cysts are rare congenital cystic dilations of the biliary tree and are classified by the portion of the biliary tree affected. The most common form consists of fusiform dilation of the common bile duct (Figure 67-1). Type I choledochal cyst accounts for 85% to 90% of all cases. All cases of choledochal cyst that have been diagnosed prenatally, to date, have been of the type I variety (Bancroft et al., 1994). The less common forms of choledochal cyst include diverticulum of the common bile duct (type II), which are intraduodenal or intrapancreatic; choledochocele (type III); multiple extrahepatic cysts with or without intrahepatic cysts (type IV); and Caroli's disease, which consists of single or multiple intrahepatic cysts associated with hepatic fibrosis and a normal extrahepatic biliary tree (type V) (Caroli et al., 1958).

The wall of a choledochal cyst is usually thickened with dense connective tissue interlaced with strands of smooth-muscle fibers associated with some inflammatory reaction (O'Neill et al., 1987). Normal biliary mucosal lining is absent, although sparse islands of columnar epithelium and microscopic bile ducts within the wall may be seen. In older patients, stones may be seen within the choledochal cyst or within intrahepatic ducts (Landing, 1974; Bhagat and Chaudhrey, 1989). Most newborns with choledochal cysts have complete biliary obstruction at the level of the duodenum, which has been likened to a form of biliary atresia (Landing, 1974; Vergnes et al., 1990). Approximately 60% of choledochal cysts

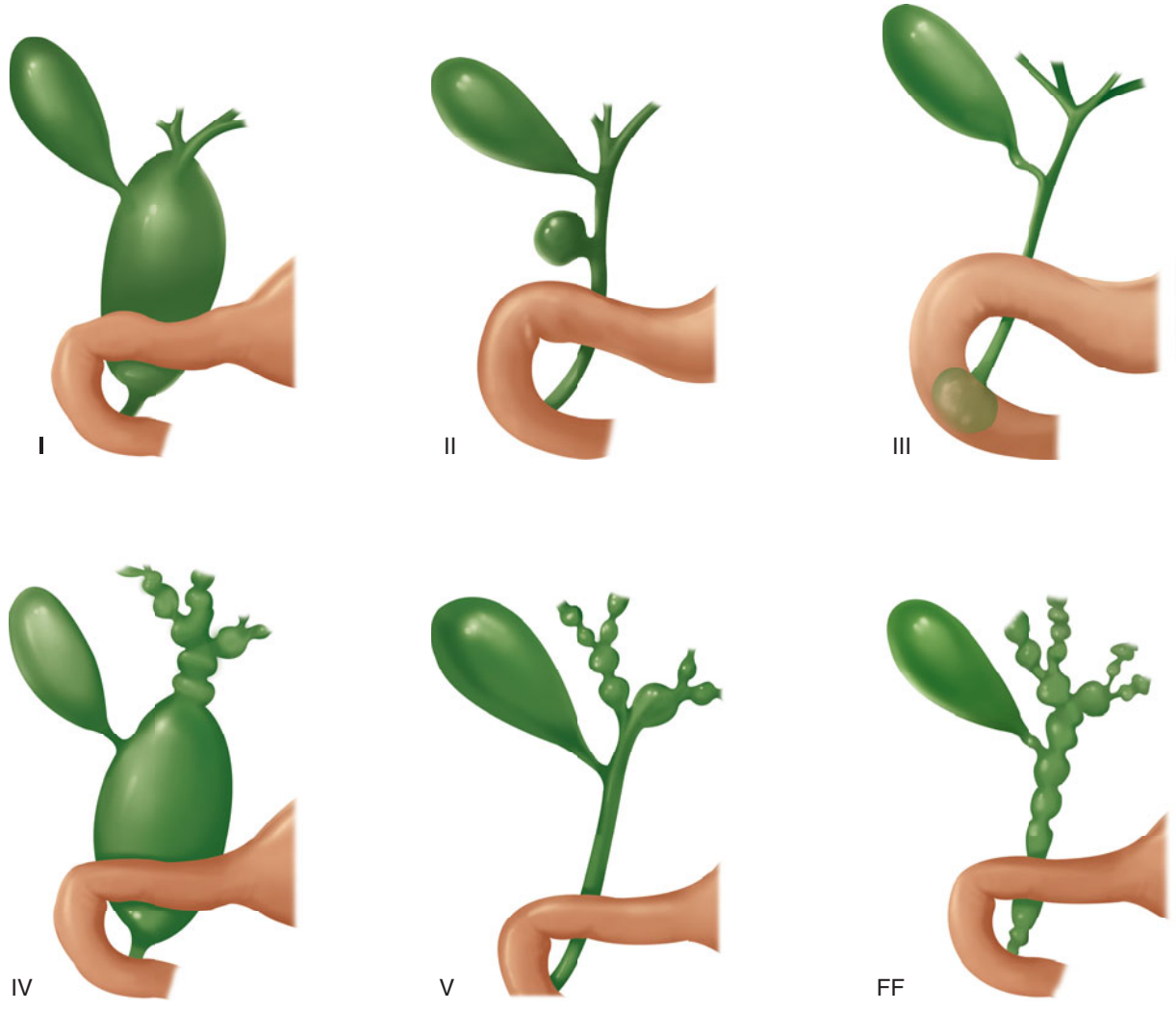

Figure 67-1 Classification scheme of choledochal cysts. Type I is the most common form, with cystic dilation of the extrahepatic bile ducts but normal intrahepatic ducts. Type II is a cystic diverticulum of the common bile duct. Type III is a diverticulum of the distal common bile duct or choledochocele. Both types II and III are rare. Type IV is the second most common form, with cystic dilation of both the extrahepatic and intrahepatic ducts. Type V, or Caroli's disease, has cystic dilation of the intrahepatic ducts but relatively normal extrahepatic ducts. In forme fruste (FF), the extrahepatic ducts are diseased but have only mild or negligible cystic dilation and the intrahepatic ducts have cystic dilation.

detected prenatally were found postnatally to have complete obstruction of the distal bile duct (Bancroft et al., 1994). Liver histology in infants with choledochal cysts is usually normal, but may show mild bile duct proliferation consistent with chronic biliary obstruction (Hanai et al., 1967). Rare cases have been reported with coexistence of choledochal cysts and congenital hepatic fibrosis (Murray-Lyon et al., 1973; Mall et al., 1974; Yamaguchi, 1980; Orenstein and Whittington, 1982; Ramirez et al., 1989). Although malignancies, usually adenosquamous or small cell carcinomas, have been reported in association with choledochal cysts, these lesions occur only after decades of chronic inflammation and recurrent cholangitis, and have not been reported in an infant or a child (Joseph, 1980).

Theories regarding the cause of choledochal cyst disease have evolved from abnormalities in the early stages of embryonic development, to congenital weakness of the wall combined with distal obstruction, to the "common channel" hypothesis (O'Neill et al., 1987). Some authors have suggested that choledochal cysts result from embryologic abnormalities in the growth of hepatic diverticulum and support their assertion by the frequently observed associated anomalies of duplications, gallbladder agenesis, and duodenal atresia (Barlow et al., 1976; Martin and Rowe, 1979). Miyano et al. (1980) have emphasized that weakness of the choledochal wall results primarily from obstruction of the distal duct during fetal development. Spitz (1977) was able to produce cystic dilatation of the common bile duct in neonatal lambs by ligation of the distal common bile duct. In contrast, only dilatation of the gallbladder occurred in their adult controls. The cause of distal common bile duct obstruction in choledochal cyst has been variously suggested to be due to congenital stenosis,

persistence of epithelial membrane, abnormal valves, or neuromuscular incoordination of the sphincter (Ito et al., 1984). Kusanoki et al., (1988) suggested that the obstruction may be due to aganglionosis of the distal bile duct, similar to Hirshsprung's disease of the colon.

Todani et al. (1977) noted that the majority of patients with choledochal cyst have an anomalous arrangement of the pancreatic or biliary duct system in which the pancreatic duct enters at an abnormal angle proximal to the circular muscle fibers of the ampulla of Vater (Todani et al., 1977; Giordani et al., 1984). They suggested that this arrangement would permit reflux of pancreatic enzymes containing trypsin upward into the common bile duct, resulting in damage to the duct wall in utero (Oguchi et al., 1988).

Rustad and Lilly (1987) noted that the "long common channel" that results from an anomalous pancreaticobiliary junction is quite common and seen in up to 50% of patients with biliary disorders other than choledochal cyst. In addition, choledochal cyst has been diagnosed as early as 15 weeks of gestation, well before the development of pancreatic exocrine function (Schroeder et al., 1989). This raises doubts about the common channel theory as the cause for choledochal cyst disease.

INCIDENCE

Choledochal cyst is a rare congenital anomaly with an estimated occurrence ranging from 1 case in 100,000 to 150,000 livebirths (Lippett and Pitt, 2003) to 1 case in every 2 million livebirths (Dewbury et al., 1980). It is more common in females in all ethnic groups, with a ratio of 2.5:1, which some have suggested may indicate that it is a sex-linked defect (Alonzo-Lej et al., 1959; Kim, 1981). Asian populations, particularly Chinese and Japanese, have a much higher incidence of choledochal cyst than any other race.

SONOGRAPHIC FINDINGS

The characteristic sonographic finding in fetal choledochal cyst is a simple anechoic cyst in the upper abdomen in close proximity to the porta hepatis (Figure 67-2). Rarely, the cyst can be imaged in continuity with the bifurcation of the right and left hepatic ducts or joined by the cystic duct from the gallbladder. Elrad et al. (1985) were the first to describe finding dilated ducts leading into a cystic mass that was later confirmed to be a choledochal cyst (Frank et al., 1981). It may be difficult to distinguish a choledochal cyst from gallbladder duplication, duodenal atresia, mesenteric cyst, or even an ovarian cyst that has migrated up into the upper abdomen (Crombleholme et al., 1997). Color flow Doppler studies may be helpful in demonstrating the cyst in relation to the portal vein, hepatic artery, and umbilical vein (Gallivan et al., 1996). Recently, fetal MRI has been used to diagnose choledochal cyst (MacKenzie et al., 2001; Chen et al., 2004; Want et al., 2005).

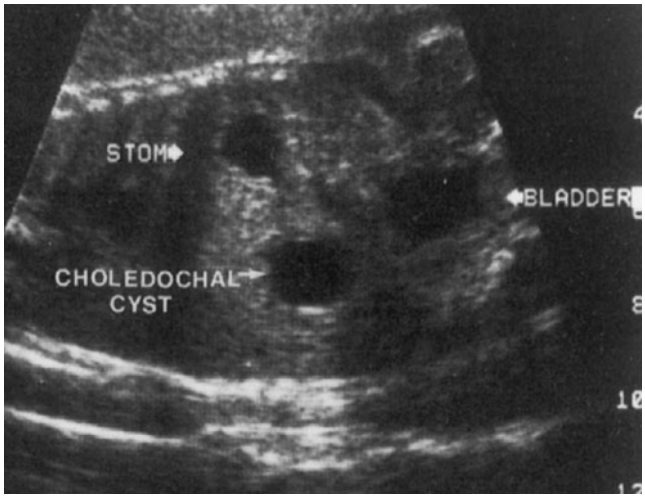

Figure 67-2 A 17-week-old fetus with an anechoic mass in porta hepatis, which postnatal evaluation confirmed to be a type I choledochal cyst. *(Reprinted, with permission, from Gallivan EK, Crombleholme TM, D'Alton ME, et al. Early prenatal diagnosis of choledochal cyst. Prenat Diagn. 1996;16:934-937. Copyright John Wiley & Sons Limited. Reproduced with permission.)*

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of a cystic mass in the right upper quadrant includes hepatic or omental cysts, adrenal cysts, renal cysts or hydronephrotic renal pelvis of the right kidney, dilated loop of bowel, mesenteric cysts, duodenal duplications, gallbladder duplications, simple hepatic cysts, duodenal atresia, and situs inversus. Because of the small fetal pelvis, ovarian cysts can move up into the right upper quadrant (Crombleholme et al., 1997). A diagnosis of choledochal cyst is more likely if the location is subhepatic and intraperitoneal and there is no change in appearance with observed peristalsis of the fetal bowel. Color Doppler studies that demonstrate an intimate association of the cyst with the hepatic artery and portal vein also suggest a biliary origin (Gallivan et al., 1996). The diagnosis is most convincing if tubular structures can be identified entering and leaving the cyst.

Dilation of intrahepatic bile ducts occurs in the fetal liver, most often in association with infantile polycystic kidney disease. Substantial ectasia with grossly identifiable cyst formation is rare, but may be seen in Meckel–Gruber syndrome, infantile polycystic kidney disease, and a variant of Ivemark syndrome (Strayer and Kissone, 1979; Blankenberry et al., 1987).

ANTENATAL NATURAL HISTORY

The earliest reported prenatal diagnosis of a choledochal cyst has been at 15 weeks' gestation (Schroeder et al., 1989) (Table 67-1). This early prenatal diagnosis challenges one commonly held theory that choledochal cysts arise from the reflux of

Table 67-1

Clinical Summary of Patients Diagnosed Prenatally with Choledochal Cyst

Report	GA at Diagnostic (wk)	Neonatal Symptoms	Values of Total Bilirubin/ Direct Bilirubin	Surgery	Cholangiogram	Liver Biopsy	Outcome
Schroeder et al., 1989	15	Asymmetry	3.9/NR	5 wk	Type I DO	NR	Well at 4 mo
Gallivan et al., 1997	17	Jaundice	5/NR	1 wk	Type I DO	Mild fibrosis	Well at 3 yr
Bancroft et al., 1994	17	Jaundice	16.4/5.1	1 wk	Type I DO	Moderate fibrosis, DP	Well at 2 yr
Bancroft et al., 1994	17	Jaundice	10.2/4.0	1 wk	Type I DO	Slight fibrosis, DP	Cholangitis postoperatively; well at 3 yr
Frank et al., 1981	25	Asymmetric mass	NR/NR	NR	Type I, patent distal duct	NR	NR
Frank, 1981	25	Asymmetry	Normal/ Normal	6 mo	Type I	NR	NA
Wiedman et al., 1985	27	Asymmetry	NR/NR	2 wk	Type I, patent distal duct	NR	Well
Bancroft et al., 1994	29	Jaundice	12.8/9.5	11 wk	Type I, DO	NR	SBO, well at 2 yr
Elrad et al., 1985	29	Asymmetry	NR/NR	1 wk	NR	NR	Well at 1 wk
O'Neill et al., 1987	31	Jaundice	5.6/0.6	1 wk	Type I, patent distal duct	NR	Well at 7 yr
Howell et al., 1983	31	Jaundice, mass	5.6/0.4	2 wk	Type I, patent distal duct	Slight fibrosis	Well at 4 mo
Bancroft et al., 1994	32	Jaundice	12.8/9.5	6 wk	Type I, DO	Fibrosis, DP	Postoperative ascites; poor growth; well at 4 yr
Bancroft et al., 1994	35	Jaundice	5.0/NR	12 wk	Type I, DO	Fibrosis, DP	Well at 4 yr
Dewbury et al., 1980	36	Jaundice, mass	NR/NR	1 wk	Type I, DO	Cirrhosis	Well at 4 mo
Lugo-Vincente, 1995	37	Asymmetric mass	0.3/NR	4 mo	Type I, patent distal duct	Normal	Well at 2 yr

GA, gestational age; DO, distal obstruction; DP, distal proliferation; NR, not reported; SBO, small-bowel obstruction.

pancreatic enzymes into the common bile duct via the "long common channel." At this gestational age, pancreatic acini are only just appearing and zymogen granules are immature, with no evidence of secretion on electron microscopy (Laitio et al., 1974).

The diagnosis of choledochal cyst in utero is important in identifying a fetus that will require postnatal evaluation as a newborn. It is essential to rule out other cystic masses in the differential diagnosis, which may have a different prenatal history. Our understanding of fetal choledochal cyst is limited to the information gleaned from the relatively few antenatal cases that have been reported to date. This diagnosis has no implications for the pregnancy and has not been associated with adverse fetal or maternal consequences.

Only 1 of 12 cases of fetal choledochal cyst reported had significant cirrhosis, presumed to be due to chronic biliary obstruction in utero (Table 67-1). This infant was observed for a time and it is unknown if early delivery and immediate decompression may have averted some damage to the liver. The other cases did not show evidence of cirrhosis; however, ductal proliferation consistent with bile duct obstruction was common. One case had fibrosis on biopsy but no cirrhosis. Several cases of neonatal choledochal cyst have been reported in association with congenital hepatic fibrosis. This is a slowly progressive condition in which hepatic synthetic function is preserved but significant portal hypertension develops as a result of the progressive hepatic fibrosis (Orenstein and Whittington, 1982).

MANAGEMENT OF PREGNANCY

The prenatal diagnosis of a choledochal cyst has no implications for the method or timing of delivery. In addition, there is no need to refer the pregnant patient for delivery in a tertiary care setting. Sonographic surveillance during the remainder of the pregnancy is unnecessary if the diagnosis is firmly established. This can be difficult, however, and repeated scans may be helpful in arriving at a definitive diagnosis. The infant can be delivered as planned and referred during the immediate postnatal period for complete evaluation of the biliary tract.

It is our practice to have the prospective parents meet with a pediatric surgeon to fully detail the postnatal investigation required to evaluate a newborn with suspected choledochal cyst and to explain the nature of the surgery required for treatment. Although nothing can be done until the baby arrives, this prenatal consultation serves to allay parental fears and minimize anxiety for the remaining weeks of gestation.

FETAL INTERVENTION

There are no fetal interventions for choledochal cyst.

TREATMENT OF THE NEWBORN

The newborn with suspected choledochal cyst should be observed closely for the passage of normal-colored meconium and development of persistent direct hyperbilirubinemia. Although these infants are usually healthy at birth, complete choledochal obstruction is common, and postnatal evaluation in a center familiar with the diagnosis and treatment of both choledochal cyst disease and biliary atresia should be obtained during the immediate postnatal period. It is important to impress on parents that without proper postnatal evaluation choledochal cyst cannot be distinguished from biliary atresia. In biliary atresia, it is important to establish bile drainage within the first 2 months of life, as the success rate for the Kasai procedure (hepaticojejunostomy) drops significantly after that age. In addition, even in cases of choledochal cyst, prompt decompression may be essential to prevent liver damage. Harris and Kahler (1978) reported about an infant who died at 5 months of age from liver failure resulting from an untreated choledochal cyst.

After a detailed physical examination, which often will reveal a nontender cystic mass in the right upper quadrant, baseline liver function studies should be obtained, including total and direct bilirubin, alkaline phosphatase, aspartate and alanine aminotransferases, lactate dehydrogenase, and a blood count with differential. The laboratory values, most often abnormal in choledochal cysts, are conjugated bilirubin and serum alkaline phosphatase. A minimally abnormal coagulation profile may also be seen with prolongation of prothrombin time. There is no confirmatory laboratory study for choledochal cyst and a definitive diagnosis requires imaging studies. A right upper quadrant ultrasound examination should be obtained to confirm prenatal findings, and more importantly, to exclude other causes of cystic masses. If any doubt exists regarding the nature of the cyst, a CT scan with intravenous and oral contrast is indicated (Weissmann et al., 1979; Hoglund et al., 1990). If the postnatal sonogram is consistent with prenatal findings, the next logical study is a ^{99m}Tc-diisopropyliminodiacetic acid (DisHIDA) scan. This nuclear isotopic scan is used in the diagnosis of choledochal cyst, as the radionuclide is taken up by the liver and excreted in the biliary canaliculi, where it becomes concentrated. While the nuclide is usually excreted into the duodenum, in choledochal cysts there is characteristic delay of excretion of the radionuclide in the cyst. In cases of biliary atresia, no excretion of radionuclide will be observed even after priming with the choleretic agent phenobarbital. In order to accurately assess the extent of choledochal cyst disease and distinguish it from biliary atresia, the entire biliary tree must be visualized. While this can readily be done preoperatively by endoscopic retrograde cholangiopancreatography (ERCP) in the older child, in the newborn intraoperative cholangiography is necessary (Hermansen et al., 1979; O'Neill, 1992).

The clinical presentation of infants with choledochal cysts is indistinguishable from infants with biliary atresia and complete biliary obstruction (O'Neill et al., 1987).

Alonzo-Lej et al. (1959) described a classic triad of clinical findings of pain, mass, and jaundice, but the infantile form usually presents with jaundice alone (O'Neill et al., 1987). Howell et al. (1983) suggested that in most prenatally diagnosed cases of choledochal cysts, jaundice develops 1 to 3 weeks after birth. However, in the report by Bancroft et al. (1994), half of the infants diagnosed prenatally with choledochal cyst had jaundice at birth.

SURGICAL TREATMENT

All patients with choledochal cysts (types I to IV), even in absence of obstruction, should undergo cyst excision because of the certainty of complications resulting from remaining cysts, varying from recurrent cholangitis, cirrhosis, portal hypertension, pancreatitis, and malignant transformation (O'Neill, 1992). The first step in the operative management of these cases is the demonstration of the intrahepatic and extrahepatic biliary anatomy to exclude biliary atresia, define cyst type, and plan the resection and reconstruction. This is performed by placing a small cholangiocatheter through a purse-string suture in the dome of the gallbladder for contrast injection (Figure 67-3).

Although internal and external drainage of choledochal cysts was once an accepted form of therapy, it is clear that these procedures are fraught with complications and the results with cyst excision are far superior (O'Neill, 1992). In type I choledochal cysts, excision of the cyst to the confluence of the normal hepatic ducts and reconstruction by Roux-en-Y hepaticojejunostomy is the preferred procedure. Some have advocated intussuscepted nipple valves, jejunal interposition, hepaticoduodenostomy, or nonrefluxing biliary appendicoduodenostomy for reconstruction, but none of these procedures have been proven to be superior to Roux-en-Y hepaticojejunostomy (Raffensperger, 1980; Todani et al., 1981; Reynolds et al., 1985; Crombleholme et al., 1989; Gonzalez et al., 1989; Okada et al., 1989; O'Neill, 1992).

LONG-TERM OUTCOME

The common complications of recurrent cholangitis, cirrhosis, portal hypertension, and malignant transformation comprise the natural history of untreated choledochal cysts. These complications have been eliminated by resection and hepaticojejunostomy (O'Neill, 1992). If recurrent cholangitis occurs in patients who have had total resection, an evaluation to exclude anastomotic stricture at the hepaticojejunostomy must be undertaken (Ohi et al., 1990).

Although the risk of recurrent cholangitis is quite low following hepaticojejunostomy for choledochal cyst, prophylactic antibiotics should be considered when intrahepatic cysts remain, as in Caroli's disease. The overall long-term outcome for patients with choledochal cysts is excellent. Although cure is likely in these patients, lifelong follow-up is necessary, including liver function tests and occasional ultrasound examinations to detect late obstruction of the hepaticojejunostomy (O'Neill, 1992).

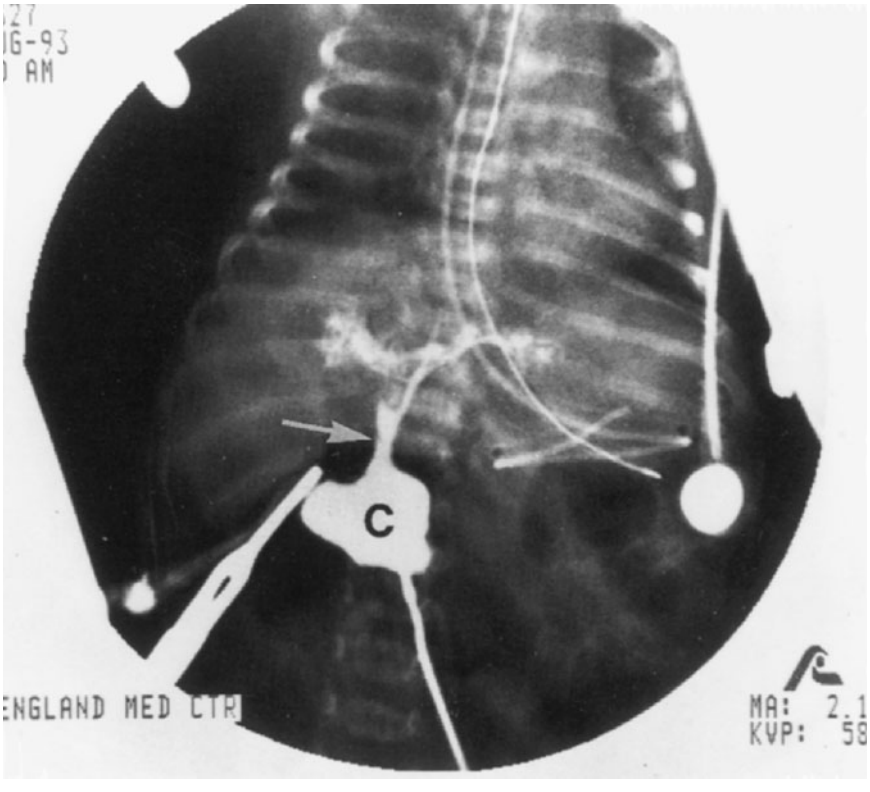

Figure 67-3 Postnatally, intraoperative cholangiography was performed in the same fetus shown in Figures 67-2, demonstrating a type I choledochal cyst. *(Reprinted, with permission, from Gallivan EK, Crombleholme TM, D'Alton ME, et al. Early prenatal diagnosis of choledochal cyst. Prenat Diagn. 1996;16:934-937. Copyright John Wiley & Sons Limited. Reproduced with permission.)*

GENETICS AND RECURRENCE RISK

There have only been 10 (Iwata et al., 1998; Clifton et al., 2006) familial cases of choledochal cyst disease reported. These case reports described four cases of mother–daughter transmission, one case of father–daughter transmission, two affected sisters, and two affected pairs of brother and sister (Hamada et al., 1998). Only one pair of eight reported monozygous twins has been concordant for choledochal cyst (Alonzo-Lej et al., 1959; Clifton et al., 2006; Narita et al., 1990a, 1990b; Iwata et al., 1998). In addition, there has been one reported case of twins with Coroli's disease (Ribeiro et al., 1996). The lack of concordance among twins and rare Mendelian pedigrees argues that a complex pattern of inheritance is likely for the majority of families (Clifton et al., 2006).

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68 CHAPTER Ovarian Cysts

Key Points

- The cause of fetal ovarian cysts is unclear but is most likely due to stimulation of the fetal ovaries by fetal gonadotropins, maternal estrogens, and placental chorionic gonadotropin.
- Fetal ovarian cysts are most often unilateral but there have been reported cases that are bilateral.
- Two types of cysts have been described: simple cysts and complicated cysts.
- The antenatal natural history is variable with some cysts resolving, some becoming complex, most likely due to torsion, and some remaining stable.
- Fetal intervention (cyst aspiration) is controversial but should be considered when the cyst is simple in nature and greater than 4 cm in diameter.
- Delivery should occur in a center with appropriate pediatric surgical expertise available.
- After delivery, the neonate should have an ultrasound to confirm the diagnosis.
- Many simple cysts will resolve in the neonatal period. Surgery should be considered for complex cysts.

CONDITION

Ovarian cysts arise from ovarian follicles. The primary stimulus for follicular development is follicle-stimulating hormone (FSH) secreted by the fetal pituitary, but maternal estrogens and placental human chorionic gonadotropin (hCG) also contribute to follicle growth in utero (Pryse-Davies and Dewhurst, 1971). Primary follicles can be seen as early as the 20th week of gestation, and graafian follicles first appear after 28 weeks of gestation (Pryse-Davies and Dewhurst, 1971; Peters et al., 1978). At birth, maternal estrogen and hCG levels decrease sharply, and FSH production is decreased by the inhibitory mechanism of the hypothalamus–pituitary–ovarian axis (Grumbach and Kaplan, 1975). This decrease in circulating estrogen and hCG levels at birth usually precludes the formation of simple ovarian cysts during childhood.

Ovarian cysts develop from mature follicles in hormonally active ovaries and are therefore most often seen after puberty. The cause of fetal ovarian cysts is unclear but is most likely stimulation of the fetal ovaries by fetal gonadotropins, maternal estrogens, and placental chorionic gonadotropin. The increased incidence of ovarian cysts seen in infants of mothers with diabetes mellitus, rhesus sensitization, and preeclampsia—(conditions that are associated with excessive levels of serum chorionic gonadotropins (DeSa, 1975; Nussbaum et al., 1988)—supports this pathogenesis. The association with fetal hypothyroidism has also been reported (Jafri et al., 1984). However, in most cases the cysts are detected in otherwise normal pregnancies (Sakala et al., 1991). It is most common for fetal ovarian cysts to be unilateral; however, bilateral fetal ovarian cysts have been reported. In the review by Sakala et al. (1991) of 65 cases of fetal ovarian cysts, 62 (95%) were unilateral, whereas 3 were bilateral.

INCIDENCE

Ovarian and genital abnormalities account for 20% of all newborn abdominal masses, second only to those of urinary-tract origin (Griscom, 1965; Wilson, 1982). The first report of prenatal diagnosis of a fetal ovarian cyst was by Valenti et al. (1975); subsequently, over 300 cases of prenatally diagnosed ovarian cysts have been reported (Holzgreve et al., 1989). Kirkinen and Jouppila (1985) reported 8 ovarian cysts detected antenatally in 21,000 pregnancies, for an incidence of 1 in 2625. DeSa (1975) found small follicular cysts in 113 (34%) of 332 stillborn fetuses and neonatal deaths. The cysts were defined as cystic structures lined by recognizable granulosa epithelium, with the greatest diameter in excess of 1 mm on microscopical section.

SONOGRAPHIC FINDINGS

The following criteria are used to identify fetal ovarian cysts during fetal ultrasound examination:

1. The presence of a cystic structure, usually located on one side of the fetal abdomen.
2. Identification of normal genitourinary tract (kidneys, ureter, and bladder).
3. Identification of a normal gastrointestinal tract (stomach, small and large bowel).
4. Female fetus.

Two types of cysts have been described: a simple cyst that is completely anechoic (Figure 68-1) and complicated cysts containing internal echoes and fluid levels, internal septations, or anechoic areas intermixed with echogenic foci (Figure 68-2). The antenatal diagnosis of an echogenic cyst is an accurate sonographic indicator of ovarian torsion. In several series of echogenic cysts detected prenatally, postnatal surgery has confirmed the diagnosis (Nussbaum et al., 1988; Brandt et al., 1991; Meizner et al., 1991; Giorlandino et al., 1994).

The distinction between a pathologic cyst and a physiologic, mature follicle is based on size alone, with fetal ovarian cysts >2 cm considered pathologic (Grapin et al., 1987). Cysts may vary in size from 2 × 2 cm to 8 × 11 cm in diameter (Grapin et al., 1987).

DIFFERENTIAL DIAGNOSIS

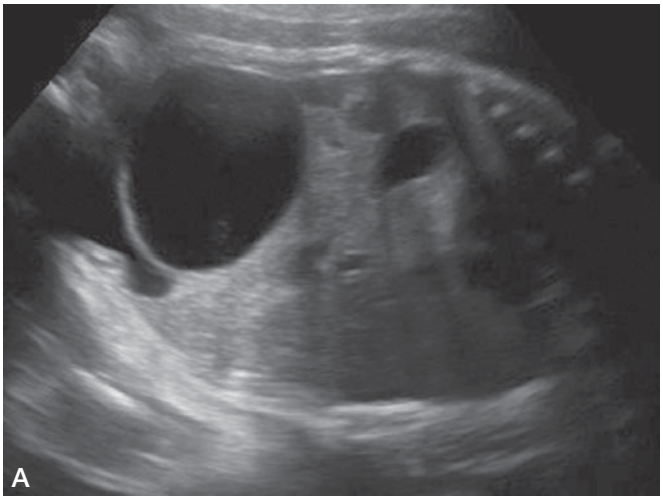
The diagnosis of a fetal ovarian cyst is usually presumptive because mesenteric cysts, urachal cysts, or enteric duplications cannot be ruled out with absolute certainty prenatally. Factors more indicative of a fetal ovarian cyst include bilaterality, echogenicity, and cyst septations. Most cysts are benign; while ovarian neoplasms have been reported, they are extremely rare (Croitoru et al., 1991). Confirmation of normal kidneys and bladder will reduce the potential to confuse renal cysts or posterior urethral valves with persistent distention of the bladder as an ovarian cyst.

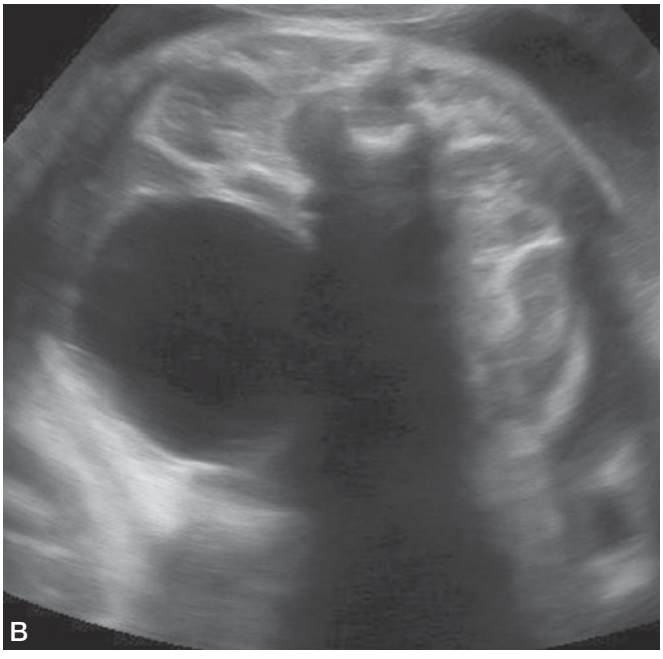
ANTENATAL NATURAL HISTORY

Most cases of fetal ovarian cysts have been reported after 28 weeks of gestation (Brandt et al., 1991). Cases have been reported during the second trimester, beginning as early as 19 weeks (Meizner et al., 1991; Foley et al., 2005). With the exception of a report of congenital hypothyroidism (Jafri et al., 1984), all other series report no associated congenital anomalies.

The size of most cysts remains unchanged in utero. A few cases have been reported to resolve in utero completely (McKeever and Andrews, 1988; Rizzo et al., 1989). Polyhydramnios is present in approximately 18% of cases and is more commonly seen with cysts >6 cm (Sakala et al., 1991). The mechanism of the polyhydramnios has been suggested to be due to partial bowel obstruction secondary to compression by a large cyst (Carlson and Griscom, 1972).

Anechoic cysts have the potential to become complex cysts, with the presence of echogenicity, fluid levels, and internal echoes (Figure 68-3). The presence of these sonographic findings is usually an indicator that the cyst has undergone torsion. The incidence of antenatal torsion documented in a large series of cases is 40%. Torsion is the most common complication of prenatally diagnosed ovarian cysts. It is more common in large cysts (Nussbaum et al., 1988) but has occurred in cysts as small as 2 cm (Grapin et al., 1987). Of the cysts that remain anechoic in utero, a significant proportion, approximately 50%, will undergo spontaneous resolution after birth. There is an ongoing risk of torsion during the neonatal period that underscores the need for neonatal follow-up. It is interesting to note that the longer the cyst is followed in utero, the greater the likelihood that it will become complex (Foley et al., 2005).





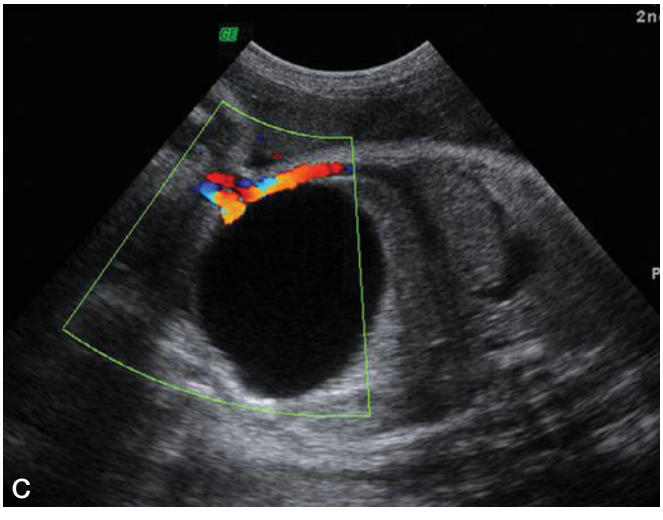


Figure 68-1 **A.** Sagittal image demonstrating large anechoic cystic mass superior to the fetal bladder and inferior to the fetal stomach. This represents a simple ovarian cyst. **B.** Transverse image showing the same cyst anterior to the left kidney. **C.** Large anechoic cyst in lower fetal abdomen at 24 weeks' gestation.

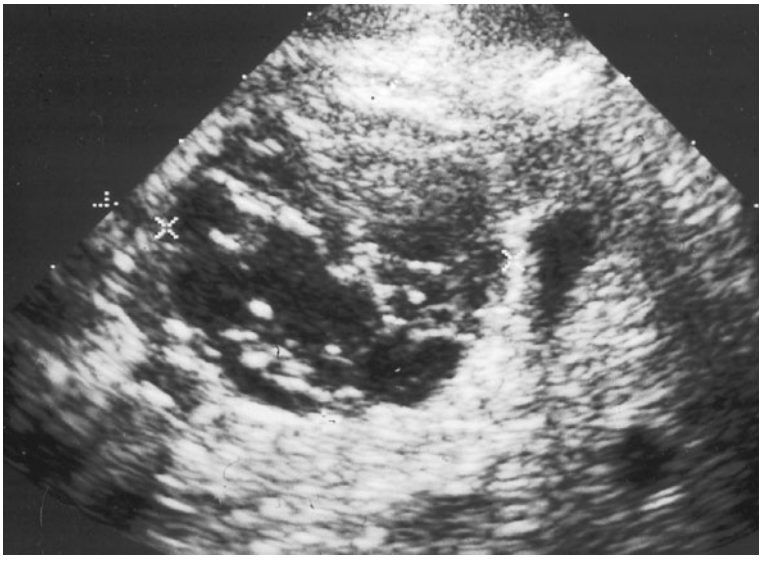


Figure 68-2 Ultrasound image of a complicated ovarian cyst, demonstrating internal echoes and anechoic areas interspersed with echogenic foci.

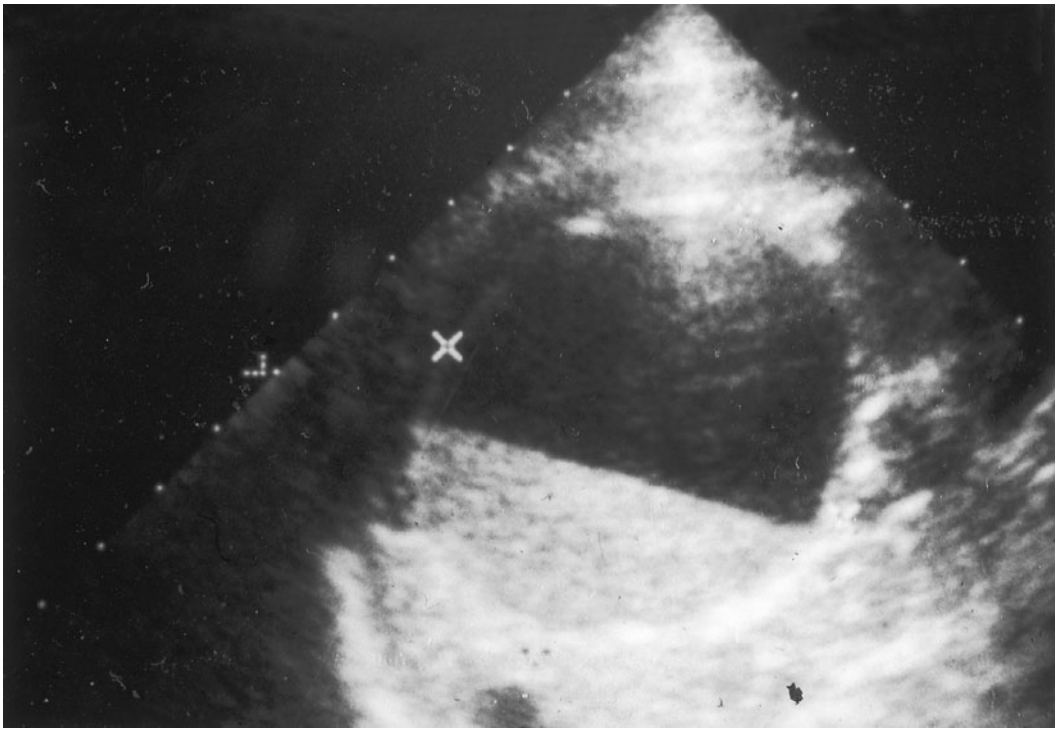


Figure 68-3 Ultrasound image of a cyst demonstrating fluid levels. This is another example of a complicated ovarian cyst.

MANAGEMENT OF PREGNANCY

Amniocentesis for karyotype is not indicated because there is no associated risk of aneuploidy, in excess of the background risk for the patient. No specialized antenatal fetal surveillance testing is necessary unless it is for other obstetric reasons. If a cyst is diagnosed to be echogenic, referral to pediatric surgery or pediatric gynecology is appropriate because all such cysts will require removal during the postnatal period owing to torsion. Delivery should occur in a center with appropriate pediatric surgical expertise available. Premature delivery is not indicated. Previous recommendations for cesarean delivery were based on anecdotal cases of poor outcomes for neonates with ovarian cysts that ruptured or caused soft tissue dystocia. In the most recent series, vaginal delivery has been performed, and cesarean was reserved for obstetric indications.

FETAL INTERVENTION

The indications for fetal intervention in ovarian cysts remain undefined, and in utero aspiration to prevent complications and subsequent oophorectomy remains controversial (Holzgreve and Evans, 1983; Heling et al., 2002; Bryant and Laufer, 2004; Comparetto et al., 2005).

In utero aspiration of cysts >4 cm should be considered. Valenti et al. (1975) reported in utero aspiration for a 7 × 9-cm ovarian cyst with the intent of preventing intrapartum rupture. Landrum et al. (1986) reported aspiration of an 8 × 11-cm cyst in a 31-week-old fetus, ostensibly to prevent pulmonary hypoplasia. Pulmonary hypoplasia from a pelvic mass is unlikely, especially at 31 weeks. Aspiration to prevent in utero torsion and preserve ovarian tissue is a more appropriate goal (Figure 68-4) (Crombleholme et al., 1997). In a review of seven cases of fetal ovarian cyst, indications for prenatal decompression included size >4 cm, the presence of a "wandering" mass, or rapid enlargement of a cystic mass. Analysis of the aspirated fluid revealed high levels of progesterone and testosterone, which was helpful in confirming the diagnosis (Crombleholme et al., 1997).

Giorlandino et al. (1990) have reported a case of an ovarian cyst treated by cyst aspiration and sclerosis with tetracycline. Although this treatment was successful, the use of tetracycline as a sclerosing agent in the fetus is not advised. Subsequently, Giorlandino et al. (1994) reported four cases of successful in utero cyst aspiration for cysts ranging from 5–8 cm in diameter with an 18-gauge needle. Cytologic evaluation of the aspirated fluid showed the presence of cyst-lining epithelial cells. No neonatal surgery was required.

D'Addario et al. (1990) reported in utero aspiration in two cases. One cyst ruptured during aspiration, and both cases required neonatal surgery. No other details were reported. Of the 20 cases reported describing this type of management, there have been no perinatal complications attributed to the intervention.

The disadvantages cited to prenatal aspiration of cysts are the limited published experience, the accuracy of differential diagnosis and the possibility that another type of cysts could be mistakenly aspirated, and that aspiration may

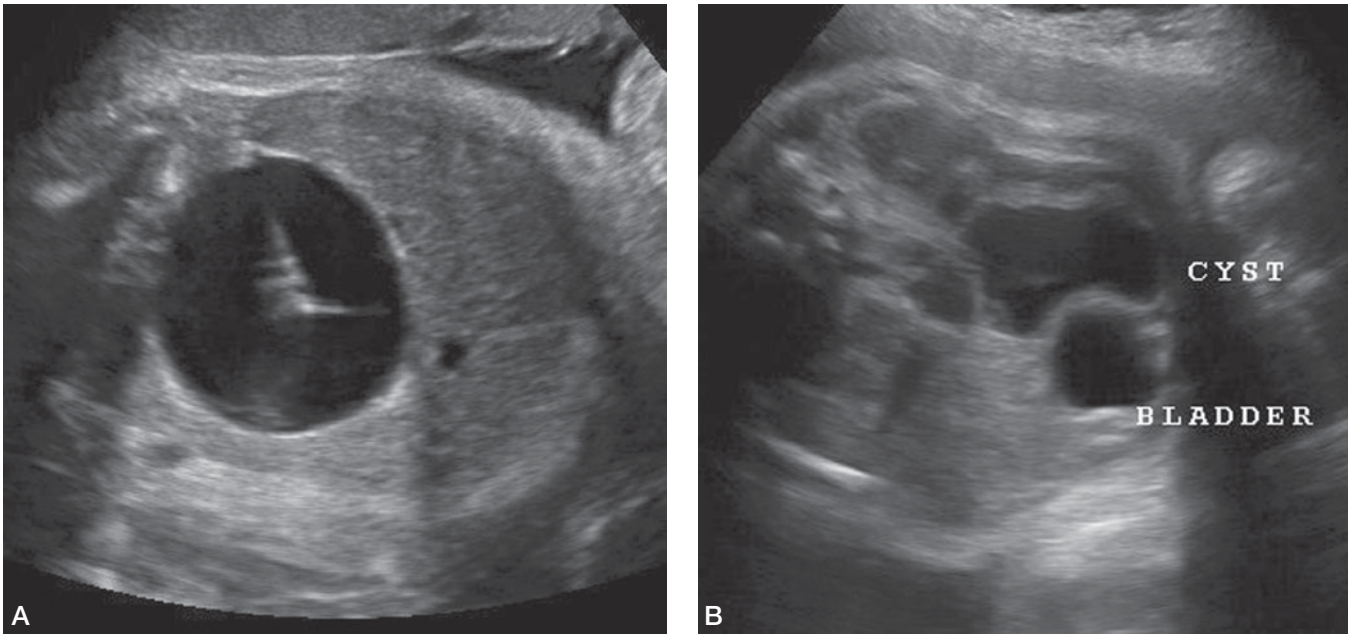


Figure 68-4 **A.** Prenatal image documenting ultrasound-guided drainage of a fetal ovarian cyst; **B.** axial image showing the same fetal ovarian cyst after aspiration.

be less likely to be effective in utero because of continued hormonal stimulation (Brandt et al., 1991). Cyst aspiration is not recommended for echogenic cysts. This sonographic finding indicates that the cyst has already undergone ovarian torsion; thus cyst aspiration would be of no benefit. If cyst aspiration is considered, magnetic resonance imaging (MRI) may be useful as a diagnostic adjunct (Foley et al., 2005).

TREATMENT OF THE NEWBORN

After delivery the neonate should have an ultrasound examination to confirm the antenatal diagnosis. If the postnatal scan demonstrates the presence of an echogenic cyst, surgery should be performed. Surgery usually consists of oophorectomy, because in most cases no viable ovarian tissue can be seen (Figure 68-5) (Brandt et al., 1991). The pathologic reports of most reported series have revealed follicular cysts; however, many cases have been necrotic, with no specific epithelial findings (Figure 68-6). (Nussbaum et al., 1988; D'Addario et al., 1990; Brandt et al., 1991).

Serious complications may arise if complex cysts are observed without being treated during the neonatal period. Although the unsalvageable necrotic ovarian tissue can theoretically resorb, complex cysts may represent tumors and other pathologic conditions (Hollenbeck et al., 1978; Croitoru et al., 1991). Necrotic ovarian cysts can also adhere to the bowel. These adhesions carry the risk of internal hernias, volvulus, and intestinal hemorrhage. Other reported complications of ovarian torsion include intestinal perforation (Grapin et al., 1987; McKeever and Andrews, 1988) and urinary tract obstruction (Nussbaum et al., 1988).

Many simple ovarian cysts resolve spontaneously after birth. However, there is concern that torsion will develop during observation of an ovarian cyst during the neonatal period. The incidence of torsion in neonatal cysts has been reported to be as high as 50%–78% (Nussbaum et al., 1988; Debeugny et al., 1989). This has led many authors to recommend early surgical intervention (Holzgreve et al., 1985; Grapin et al., 1987). We now know that many of these torsions occur antenatally and that even the earliest surgical intervention would have failed to preserve the ovary in these cases.

In Brandt et al. (1991) review of the literature, ultrasonographic evidence of torsion at or before birth was found in 92% of patients with torsion. This suggests that most torsions occur prenatally and that the risk of torsion may be low in ovarian cysts that are managed conservatively during the neonatal period. In Giorlandino et al. (1994) series, 3 of 12 cases of anechoic cysts developed torsion and 9 demonstrated spontaneous resolution.

SURGICAL TREATMENT

Surgery is performed in infants with ovarian cysts in order to prevent torsion and to save the ovary (see Figure 68-6). Sometimes technical difficulties in separating the cyst from the normal ovary lead to removal of the ovary, an unfortunate outcome as the surgery designed to protect the ovary results in removal of the ovary. Surgery should be considered for these simple anechoic cysts if there is an increase in size or if the cysts persist during postnatal sonographic follow-up. Surgery should also be performed in cases in which clinical symptoms such as abdominal distention, vomiting, or persistent irritability develops.

If surgical exploration is performed, every attempt should be made to salvage the ovary. Even if no ovary is macroscopically identifiable, ovarian tissue may nevertheless

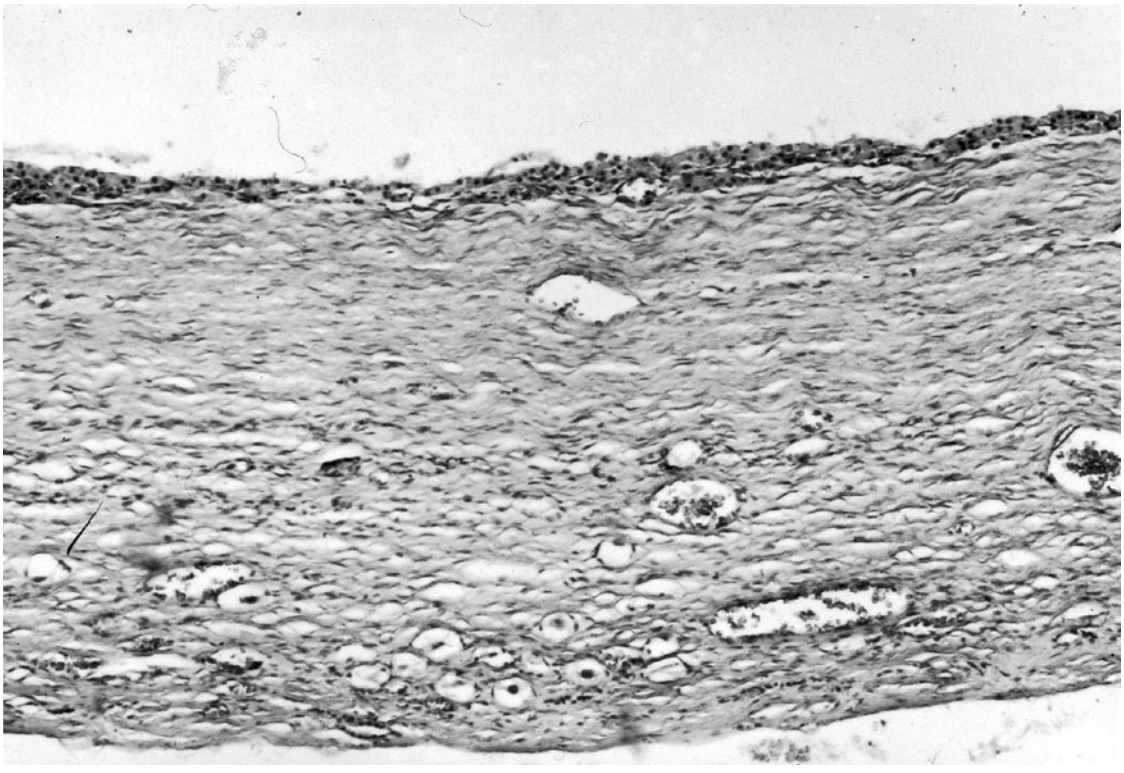


Figure 68-5 Histologic specimen from ovarian cyst demonstrating follicles in the cyst wall.

be present, and surgery should be limited to removal or unroofing of the cyst. Aspiration of large, simple neonatal ovarian cysts has been documented. There have been no reported complications, and recurrence has been noted only in one case (Henrion and Helardot, 1987; Liapi and Evain-Brion, 1987; Eggermont et al., 1988; Debeugny et al., 1989).

LONG-TERM OUTCOME

There are no long-term consequences for a female child with an uncomplicated ovarian cyst diagnosed prenatally. If the cyst has already undergone torsion there may be adverse fertility effects, although there are no long-term data to support or refute this issue.

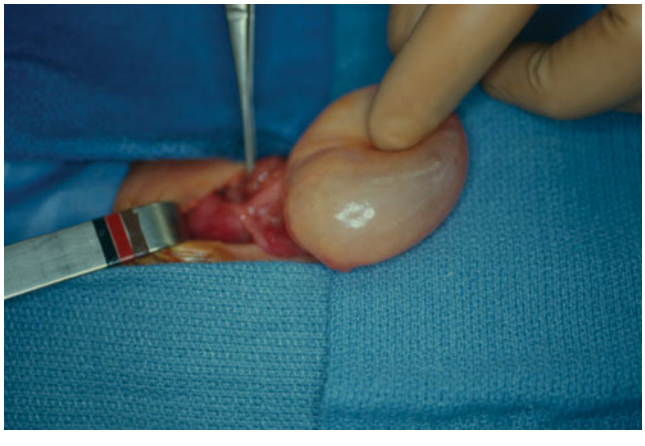


Figure 68-6 Appearance of an ovarian cyst at surgery. Differentiation of normal ovary from the ovarian cyst is usually extremely difficult.

GENETICS AND RECURRENCE RISK

Ovarian cysts are not considered to have a genetic etiology or to be inherited in a specific pattern. The recurrence risk is likely negligible.

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69 CHAPTER Intra-abdominal Calcifications—Hepatic

Key Points

- Fetal liver calcifications are found in 1 in 1700 (0.05%) pregnancies.
- One-third is isolated, while two-thirds are associated with other fetal abnormalities.
- Following the diagnosis of calcifications on the surface of the fetal liver, it is important to rule out meconium peritonitis.
- Differential diagnosis includes infection, liver tumors, vascular calcification, and fetal aneuploidy.
- Management should include detailed fetal anatomical scan to look for associated anomalies, maternal TORCH titers, amniocentesis for karyotype and CMV culture, and fetal MRI if an intrinsic hepatic mass is suspected.
- Prognosis depends on presence or absence of associated abnormalities.
- If a detailed work-up is unremarkable, the fetal prognosis is excellent.

CONDITION

Fetal hepatic calcifications can be divided into three main categories: peritoneal, parenchymal, and vascular. Peritoneal hepatic calcifications present as calcified masses on the surface of the fetal liver. Most commonly, this is due to meconium peritonitis resulting from in utero bowel rupture. Meconium peritonitis is the most common cause of fetal abdominal calcifications (Lince et al., 1985) (see Chapter 70). Parenchymal calcifications are due to the presence of intrauterine infection or tumor. Fetal tumors may be primary in the liver or metastatic, presenting as a complex mass with areas of increased echogenicity and possible shadowing. Fetal tumors encompass both benign and malignant varieties, including hemangioendotheliomas, hamartomas, and hepatoblastomas. Parenchymal calcifications appear as scattered nodules, with or without additional evidence of other affected organs. The most common in utero infections that can cause fetal liver calcifications include varicella and the TORCH agents (Figure 69-1). Hepatic calcifications due to vascular abnormalities result from calcified portal or hepatic venous clots, which are due to hypoperfusion or thromboembolism (Nguyen and Leonard, 1986; Bronshtein and Blazer, 1995).

INCIDENCE

With the increased utilization of prenatal sonographic screening, fetal hepatic calcifications are detected prenatally more frequently than they are observed in newborn infants. In one study, evidence of hepatic calcifications was noted in 14 of 24,600 fetuses, an incidence of approximately 1 in 1700 (0.05%) of screened fetuses (Bronshtein and Blazer, 1995). In a population of 1500 spontaneously aborted fetuses, 33 were demonstrated to have hepatic calcification, an incidence of 2.2% in this abnormal patient population (Hawass et al., 1990). In the 33 affected fetuses, 17 hepatic calcifications were found in the first trimester and 16 in the second trimester.

SONOGRAPHIC FINDINGS

Fetal liver calcifications can be detected reliably by the beginning of the second trimester of pregnancy (Figure 69-2). Bronshtein and Blazer (1995) reported their 8-year experience in extensive targeted second trimester sonographic screening for fetal abnormalities, which included hepatic calcifications in 24,600 consecutive pregnancies. Hepatic calcification was identified in 14 fetuses; of these, 12 had one or two areas of focal calcifications. One fetus had evidence of four different foci of calcifications. In one fetus, there were diffuse hepatic, peritoneal, and intestinal calcifications. No correlation was seen between the number or location of calcifications and the occurrence of malformations or eventual outcome for the child. Of the 14 affected fetuses, 13 had persistent hepatic calcifications noted on serial sonographic scans. In one case initially diagnosed at 15 weeks of gestation, calcifications resolved by 24 weeks. Four fetuses had associated anomalies, which included two cases of trisomy 18, one case of dwarfism and hydronephrosis, and one case of polyhydramnios and bowel calcifications. This last fetus died in utero at 32 weeks of gestation and no autopsy was performed. Of the remaining

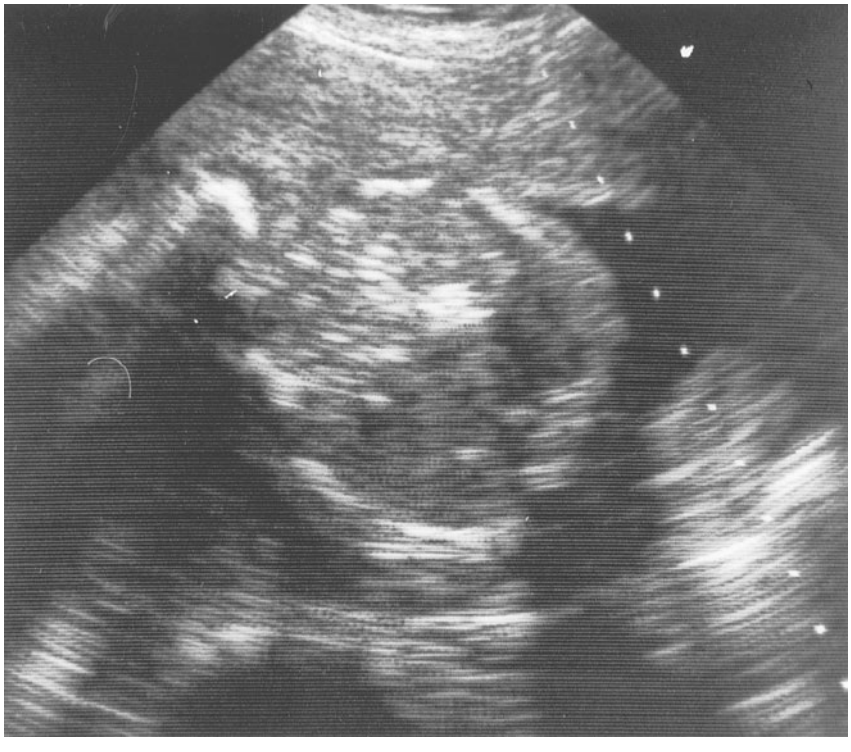

Figure 69-1 Transverse scan through the abdomen of a fetus with varicella infection demonstrating multiple areas of intraparenchymal calcification. *(Reprinted, with permission, from Drose JA, Dennis MA, Thickman D. Infection in utero: US findings in 19 cases. Radiology. 1991;178:369-374.)*

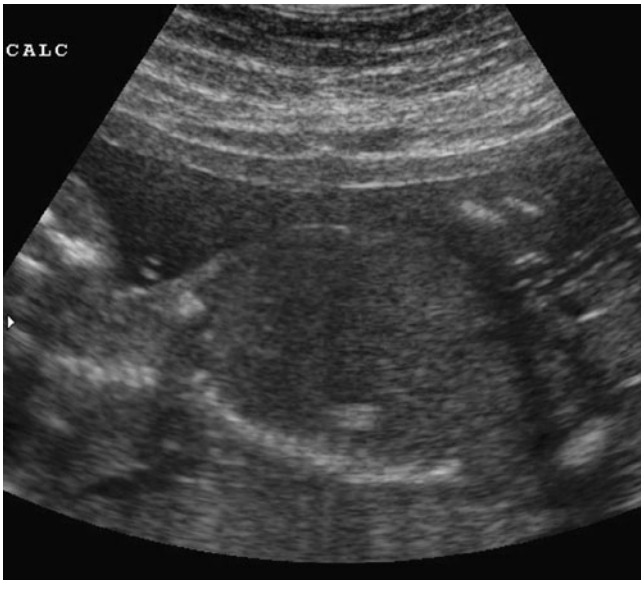

Figure 69-2 Sagittal abdominal scan showing fewer, more punctate, areas of intraparenchymal calcifications. This is the more commonly seen fetal presentation.

10 fetuses, all were normal at birth with no sequelae from the calcifications. Koopman and Wladimiroff (1998) reported their experience with seven fetuses with intrahepatic hyperechogenic foci. One case of trisomy 18 was identified. Another case had associated encephalocele and unilateral renal agenesis. Outcome was normal in five fetuses with isolated intrahepatic findings. More recently, Simchen et al. (2002) performed a 10-year prospective study of the cause and outcome of 61 cases of fetal liver calcifications; 21 of 61 (35%) cases were isolated and 40 (65%) had additional abnormalities. Of the isolated cases, 1 had trisomy 21, 1 had parvovirus B19 infection, 4 were lost to follow-up, and the remaining 15 infants did well. Of the 40 cases with associated abnormalities, 9 had minor findings, such as echogenic bowel or growth restriction. In this group, two were lost to follow-up and seven infants did well. Of the group with major associated sonographic abnormalities ($n = 31$), 10 had abnormal karyotypes and 1 had cytomegalovirus (CMV) infection. There was 1 fetal demise and 18 pregnancies were terminated. The most frequently associated anomalies included central nervous system ($n = 13$), cardiac ($n = 12$), cystic hygroma ($n = 12$), skeletal ($n = 11$), and hydrops fetalis ($n = 9$). Importantly, these investigators found no differences regarding cause and outcome when stratifying their cases by parenchymal or surface calcification; startifying cases by isolated or with additional abnormalities was more informative (Simchen et al., 2002).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of peritoneal surface hepatic calcifications includes meconium peritonitis (see Chapter 69) and ruptured hydrometrocolpos. The differential diagnosis of parenchymal calcifications includes infectious causes, specifically herpes simplex virus type II, varicella–zoster virus (Taylor et al., 1993), rubella virus, CMV (Stein et al., 1995), echovirus 11, syphilis (Kogutt, 1991), parvovirus (Simchen et al., 2002), and toxoplasmosis (Shackelford and Kirks, 1977). The primary tumors likely to cause parenchymal fetal liver calcification include hepatic hemangioma (Pott Bärsch et al., 2003), hemangioendothelioma, hamartoma, teratoma, and hepatoblastoma (Shih et al., 2000). Metastatic neuroblastoma also can cause fetal hepatic calcifications (Friedman et al., 1981). Intrahepatic vascular calcification can be due to portal venous thromboemboli (Blanc et al., 1967; Friedman et al., 1981), hepatic venous thrombi, ischemic necrosis secondary to vascular insufficiency, and subcapsular hematomas, which can be due to hydrops or fetal chromosomal abnormalities (Buxton et al., 1991). Fetal hepatic calcifications have been described in a set of monozygotic twins, most likely due to a thrombotic event (Richards et al., 1988). Fetal hepatic calcifications have been postulated to be a secondary effect of cordocentesis in a fetus with trisomy 9 (Satge et al., 1994). It is hypothesized that such calcifications may have been due to placentofetal embolization from chorionic vein thrombi or intravascular clotting caused by maternal release of thromboplastin. Both of these events are more common in aneuploid fetuses. Many aneuploidies are associated with fetal liver calcifications, including trisomies 13, 18, 21, and 45,X.

ANTENATAL NATURAL HISTORY

In a study biased by ascertaining only miscarried fetuses, Hawass et al. (1990) detected hepatic calcifications in 33 of 1500 cases. Of the 33 affected cases, calcified hepatic venous thrombi were demonstrated in 18. In 12 cases, calcified portal venous thrombi were documented. In only two of the cases were parenchymal calcifications documented, and one case showed mixed findings. In this patient population, 85% of fetuses had associated anomalies. The most common finding was intraluminal meconium calcifications (seen in 27% of fetuses), cystic hygroma (seen in 18% of fetuses), and bony metaphyseal defects (seen in 18% of fetuses) (Hawass et al., 1990). It is unclear whether severe fetal illness or hypoperfusion predisposed the fetus to calcification of the hepatic or portal veins. Since this population spontaneously miscarried, these findings cannot be generalized to a population of pregnant women with continuing pregnancies.

In both the Bronshtein and Blazer (1995) and the Simchen et al. (2002) studies, fetal liver calcifications remained largely unchanged on follow-up scans. With the exception of one case, they did not resolve and no additional findings developed over time. Thus, serial sonographic studies are not necessary.

MANAGEMENT OF PREGNANCY

Recommendations for follow-up of fetal hepatic calcifications include a detailed fetal sonographic examination to look for

associated anomalies. Amniocentesis should be performed for fetal karyotyping as well as obtaining amniotic fluid for CMV culture. Maternal serologic samples should be obtained to diagnose infection with toxoplasmosis, rubella, CMV, or herpes. It is important to document CMV because if it is present, the risk of preterm delivery is increased and the fetus is at risk for hearing damage and developmental abnormalities (Watt-Morse et al., 1995). Simchen et al. (2002) offered cystic fibrosis mutation testing to all women. None screened positive. Thus, CF testing is probably not necessary for fetal liver calcifications.

If the fetal karyotype is normal, TORCH serology is negative, and the CMV culture is negative, the overall prognosis for the fetus is excellent (Bronshtein and Blazer, 1995; Simchen et al., 2002).

However, if fetal hepatic calcifications are associated with an intrahepatic mass, an effort should be made to determine the underlying cause, because the presence of a hepatic tumor has potentially adverse implications for pregnancy outcome. Fetal magnetic resonance imaging (MRI) should be considered. If multiple areas of intraparenchymal calcification are demonstrated, the adrenal glands and sympathetic chain should be examined sonographically to rule out primary neuroblastoma (see Chapter 113).

The recommended hospital site and route of delivery depends on the underlying cause of the calcifications. If the antenatal workup has been completely within normal limits, delivery can take place in the community hospital setting. If, however, other abnormalities have been detected and prolonged postnatal workup requiring pediatric specialists is anticipated, the delivery should occur in a tertiary care center to keep the mother and baby together.

FETAL INTERVENTION

There are no fetal interventions for hepatic calcifications.

TREATMENT OF THE NEWBORN

In the newborn, an infectious cause for hepatic calcifications should be excluded if relevant prenatal infectious disease studies have not been completed. For example, if amniotic fluid was not cultured for CMV, a urine CMV culture should be obtained during the newborn period. Similarly, cultures for newborn TORCH infection should be sent. A detailed physical examination to rule out features suggestive of genetic or chromosomal abnormalities is indicated. Auditory screening is recommended. If antenatally the calcifications were suspected to be due to meconium peritonitis, consideration should be given to obtaining a plain abdominal X-ray film to follow postnatal passage of air throughout the bowel and to rule out intestinal perforation. Consideration should be given to performing abdominal sonography on the newborn infant to determine if the calcifications are still present after birth. If the calcifications are parenchymal, suggesting the presence of tumor, postnatal imaging studies may include abdominal computed tomographic (CT) scanning or MRI. If the pattern of calcifications appears to suggest a vascular accident in utero, consideration should be given to obtaining liver function tests in the infant.

LONG-TERM OUTCOME

Determining long-term prognosis requires knowledge of the location and configuration of calcifications plus the presence or absence of other abnormalities (Nguyen and Leonard, 1986). The long-term outcome will be related to the underlying cause, if determined, of the hepatic calcifications. Bronshtein and Blazer's (1995) study provided reassuring information that all the 10 fetuses with negative cultures, normal karyotype, and absence of additional sonographic abnormalities were confirmed as normal at birth. The gestational age at delivery for these infants was between 37 and 41 weeks, and all were appropriately developed for gestational age. At 4 months to 4.5 years of postnatal life, all of these children were healthy and thriving. Because of this information, parents who have undergone full prenatal testing with completely normal results can, in general, be reassured that the outcome for their fetuses will be good.

GENETICS AND RECURRENCE RISK

When associated sonographic abnormalities are detected there is an association between hepatic calcifications and chromosome abnormalities (Simchen et al., 2002). Autosomal aneuploidies found in cases of liver calcification include trisomies 9, 13, 18, 21, and 45,X. In such cases, recurrence risk will be determined by the underlying chromosomal abnormality. Other unbalanced karyotypes described include 4p−, 22q+, and 8p+. There is a rare autosomal recessive disorder known as idiopathic infantile arterial calcinosis, which is characterized by calcium deposition in the internal elastic lamina of medium and large arteries, and may present with fetal liver calcifications (Wax et al., 2001).

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70 CHAPTER Intra-abdominal Calcifications

Key Points

- Causes of intra-abdominal calcification include meconium peritonitis, enterolithiasis, cholelithiasis, and fetus in fetu.
- Meconium peritonitis is the most common cause of intra-abdominal calcifications.
- Cystic fibrosis is seen in only 8% to 13.5% of cases of fetal meconium peritonitis in contrast to 15% to 40% postnatally.
- Enterolithiasis is often associated with rectourinary fistula as in imperforate anus or cloaca.
- Enterolithiasis can be seen in bowel obstruction such as jejunoileal atresia or total colonic Hirschsprung's disease.
- Fetus in fetu is distinguished by the presence of well-formed long bones or vertebral bodies.

CONDITION

The most common causes of intra-abdominal calcifications include hepatic calcifications, meconium peritonitis, enterolithiasis, cholelithiasis, and fetus in fetu. The topic of hepatic calcification is fully covered in Chapter 69 and will not be covered further except to indicate how these can be distinguished from other causes of intra-abdominal calcifications.

Perforation of the bowel that occurs antenatally leads to a sterile chemical peritonitis referred to as meconium peritonitis, which is the most common cause of intra-abdominal calcifications. The peritonitis can be localized or diffuse and can lead to a fibrotic reaction with intraperitoneal calcifications. The clinical manifestations of meconium peritonitis depend on its underlying cause, timing, and whether or not the perforation heals spontaneously. The spectrum of disease ranges from asymptomatic intra-abdominal calcifications to

giant cystic meconium peritonitis (Robertson et al., 1994; Dirkes et al., 1995; Kamata et al., 2000; Tseng et al., 2003; Zangheri et al., 2007). Meconium peritonitis has been associated with intestinal atresia or stenosis, meconium ileus, internal hernia, bowel ileus, intussusception, gastroschisis, Meckel diverticulum, and cytomegalovirus infection (Pletcher et al., 1991; Petrikovsky et al., 1993).

The presence of associated anomalies is unusual and depends on the underlying cause of meconium peritonitis. Up to 15% to 40% of neonates with meconium peritonitis have cystic fibrosis (Park and Grand, 1981; Payne and Nielsen, 1983). However, in prenatally diagnosed meconium peritonitis, cystic fibrosis is reported to be the cause in only 8% to 13.5% of cases (Foster et al., 1987; Dirkes et al., 1995; Casaccia et al., 2003). This apparent discrepancy may be due to the increased sensitivity of prenatal sonographic imaging in detecting abdominal calcification, as compared with postnatal plain films (Williams et al., 1984). It has also been suggested that sonographically detected calcifications could be due to fetal viral infection due to parvovirus B19, cytomegalovirus, herpes viruses, or even taxoplasmosis (Casaccia et al., 2003). It is also possible that cystic fibrosis is less likely to cause calcification due to the deficiency of pancreatic enzymes (Foster et al., 1987). The incidence of cystic fibrosis increases if there are other additional sonographic findings such as dilated bowel and hyperechoic bowel. The presence of calcifications alone suggests the risk of cystic fibrosis of 13% and if associated with evidence of obstruction at 24% (Casaccia et al., 2003). The risk of cystic fibrosis in meconium peritonitis is 330 times the risk in the general population, and the risk of cystic fibrosis in neonatal bowel obstruction is 600 times as high as the general population (1 in 2500) (Casaccia et al., 2003). Enterolithiasis, which is intraluminal calcification of meconium, is a more unusual course of intra-abdominal calcification (Lubusky et al., 2006). Enterolithiasis has been described in association with a number of conditions including imperforate anus, gastrointestinal atresias or stenosis, functional ileal obstruction, and total colonic Hirschsprung's disease (Rickham, 1957; Berdon et al., 1975; Felman et al., 1975; Martin et al., 1976; Cook, 1978; Fletcher and Yullish, 1978; Daneman and Martin, 1979; Berger and Bar-Maor, 1980; Bear and Gilsanz, 1981; Yousefzadeh et al., 1984; Pouillaude et al., 1987; Anderson et al., 1988). Perhaps the most commonly diagnosed setting is in patients with anorectal malformation and rectourinary fistula (Anderson et al., 1988). However, only 10 cases of prenatally diagnosed enterolithiasis associated with anorectal malformations have been reported (Mandell et al., 1992; Pohl-Schickinger et al., 2006; Pohl-Rolle et al., 2008).

The mechanism of calcification of intraluminal meconium has not been fully elucidated. It is assumed that meconium, urine, stasis, and low intraluminal pH may be prerequisites (Shimotake et al., 2006). Most cases of anorectal malformation and rectourethral fistula, however, do not have enterolithiasis. Rolle et al. speculated that relative urinary outflow obstruction would cause reflux of more urine into the colon predisposing to calcification of meconium (Rolle et al., 2008). Shimotake et al., (2006) performed infrared spectrophotometry of intraluminal meconium calculi occurring in a case of anorectal malformation with associated rectourethral fistula. These stones were found to consist of ammonium hydrogen urate having the combined constituents of urine and meconium.

Enterolithiasis can occur in the absence of a rectourethral fistula presumably as a result of stasis and low intraluminal pH. Enterolithiasis has been observed in such cases because of intestinal atresia and total colonic Hirschsprung's disease (Cook, 1978; Fletcher and Yullish, 1978; Yousefzadeh et al., 1984; Miller et al., 1988; Dirkes et al., 1995). It has been suggested that in these cases, the bowel proximal to the intestinal obstruction will have stasis of meconium and swallowed urine (amniotic fluid), in which case urate would become concentrated by fluid resorption by the bowel predisposing to stone formation.

Little is known about the natural history of fetal cholelithiasis. Analysis of a fetal gallstone has never been performed, and it is currently unknown if these stones are primarily made up of cholesterol or pigment or are of mixed type. Cholesterol stones occur as a result of numerous factors, present to varying degrees, acting in concert to promote hepatic secretion of bile saturated with cholesterol, gallbladder stasis, and altered gallbladder secretory function (Carey, 1989). Bile supersaturated with cholesterol is a prerequisite for cholesterol stone formation (Gilger, 1993). Pigment gallstone formation requires bile stasis and the enzymatic hydrolysis of bilirubin glucuronide into free bilirubin and glucuronic acid. Free unconjugated bilirubin, which is insoluble in water, then combines with calcium in the bile to produce the calcium bilirubinate matrix of pigment stones. Brown et al. (1992) observed a number of fetuses with echogenic material in the fetal gallbladder, which they presumed to be sludge. Allen et al. (1981) have demonstrated in adults that this echogenic sludge is composed of calcium bilirubinate crystals.

While numerous predisposing factors for gallstones have been identified in infants and children, with the exception of one case, no predisposing risk factors have been present in reported cases of fetal cholelithiasis (Beretsky and Lonkin, 1983; Heigne and Ednay, 1985; Klingensmith et al., 1988; Brown et al., 1992; Devonald et al., 1992; Suchet et al., 1993; Clarke and Roman, 1994; Munjuluri et al., 2005; Sheiner et al., 2006). One infant diagnosed prenatally with gallstones was found to have hereditary spherocytosis (Beretsky and Lonkin, 1983). Similarly, maternal predisposing factors, other than pregnancy, have been rare. Predisposing factors were present in only four mothers with hemolytic anemia, gallstones in one, and the presence or history of gallstones in three others. While six other mothers had sickle cell trait and one had hemoglobin A_{1C} trait, neither condition is associated with hemolysis.

Fetus in fetu is a rare anomaly in which a fetus incorporates well-differentiated tissue of its monozygotic twin (Khadaroo et al., 2000). Fetus in fetu occurs most commonly in the retroperitoneum of the upper abdomen, although it has been reported to occur in the scrotum, skull,

mediastinum, mouth, and adrenal gland (Aoki et al., 2004; Brand et al., 2004). Fetus in fetu may be confused with meconium pseudocyst or a teratoma. The feature that distinguishes fetus in fetu is the presence on histologic examination of well-differentiated tissues or organs (Gross and Clatworthy, 1951; Griscom, 1965)

INCIDENCE

Meconium peritonitis occurs in approximately 1 in every 35,000 livebirths (Olson et al., 1982; Pan et al., 1983). No estimates are available for enterolithiasis. The incidence of fetal cholelithiasis is not known. Unlike cholelithiasis in children or adults, there is no apparent sex predominance for fetal cholelithiasis. Fetus in fetu is estimated to occur in fewer than 1 in 500,000 livebirths (Iyer et al., 2003).

SONOGRAPHIC FINDINGS

A spectrum of findings may be observed with meconium on prenatal sonographic examination. The most consistent finding is extraluminal abdominal calcifications, which are present in 85% of cases (Figure 70-1A). Meconium peritonitis is the most common cause of fetal intra-abdominal calcifications. The sonographic criteria used for the diagnosis of meconium peritonitis include intra-abdominal calcifications often plaquelike or linear echogenicities that cause acoustic shadowing not caused by solid organ, intraluminal, intravascular, biliary, or tumor calcifications. Other associated findings include polyhydramnios, in 50% fetal ascites, and bowel dilatation in 27% of cases (Foster et al., 1987). The presence of dilated bowel, cysts, or ascites usually predicts complicated meconium peritonitis that will require postnatal surgical intervention. Dirkes et al. (1995) divided sonographically diagnosed cases of fetal intra-abdominal calcifications into simple and complex categories. Simple meconium peritonitis has isolated calcifications seen without any bowel dilatation, meconium pseudocysts, ascites, or polyhydramnios (see Figure 70-1A). Intra-abdominal calcifications in association with any of these features are classified as complex meconium peritonitis (see Figure 70-1B).

While not sufficient for a diagnosis, meconium peritonitis often starts as an echogenic bowel that goes on to perforate with subsequent formation of intraperitoneal calcifications. Serial sonography is indicated to follow this progression. Similarly, simple meconium peritonitis may evolve into complex meconium peritonitis with the development of bowel dilatation, meconium pseudocyst, ascites, or polyhydramnios (Dirkes et al., 1995). Conversely, complex meconium peritonitis with calcifications associated with ascites may see the perforation with resolution of ascites converting from complex to simple meconium peritonitis. The bowel in these cases may heal without atresia or stenosis. This is the presumed sequence of events in which the only evidence of meconium peritonitis is meconium periorchitis (Várkonyi et al., 2000).

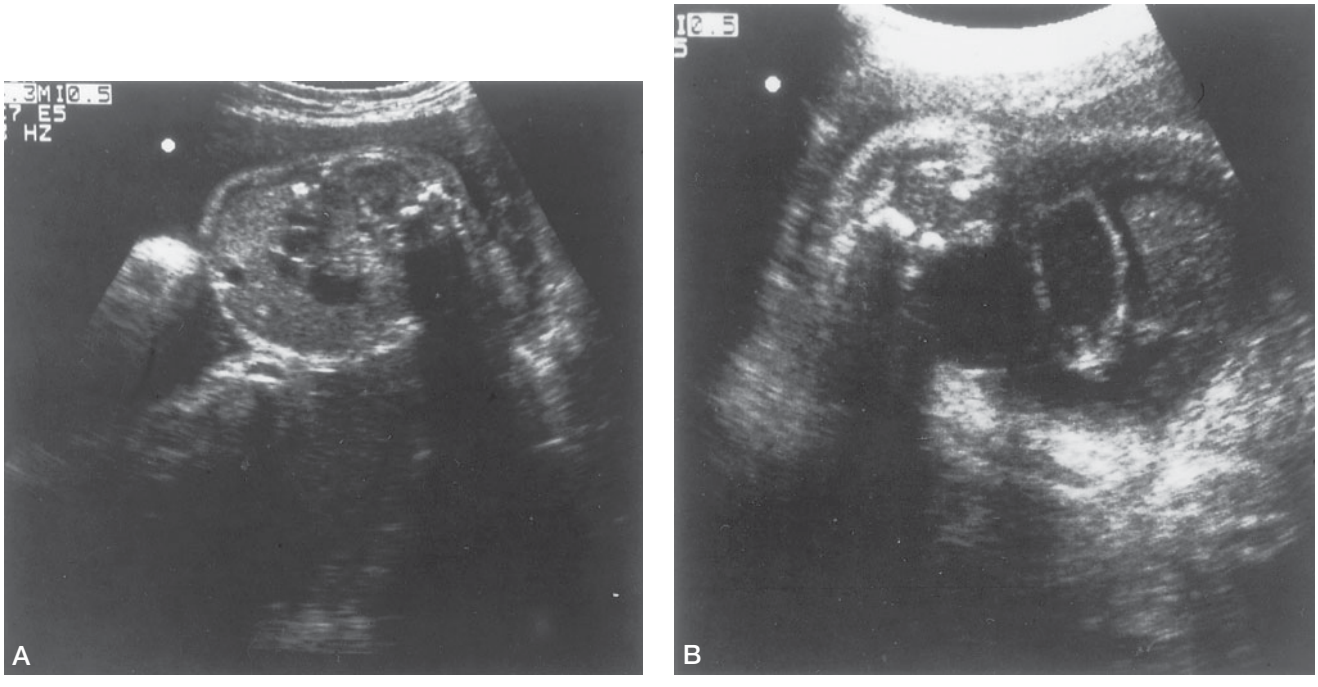

Figure 70-1 **A.** Prenatal sonographic image demonstrating isolated intraperitoneal calcifications with acoustic shadowing. This represents a case of simple meconium peritonitis. **B.** In contrast, this fetus has intraperitoneal calcifications with an associated meconium pseudocyst and ascites. This is an example of complex meconium peritonitis.

Some have proposed classification schemes dividing meconium peritonitis into type I (large meconium ascites), type II (large pseudocyst), or type III (intra-abdominal calcifications and/or resolving ascites or shrinking pseudocyst) (Tseng et al., 2003).

Zangheri et al. (2007) suggest grade 0 for isolated intra-abdominal calcifications; grade 1 for intra-abdominal calcifications and ascites, pseudocyst, or bowel dilation; grade 2 for two associated findings; and grade 3 for all sonographic features present.

In contrast to meconium peritonitis, enterolithiases are calcifications within the bowel lumen. These are often multiple, small, stippled calcifications in contrast to linear, plaquelike calcifications seen in meconium peritonitis. Enterolithiasis often is seen in association with dilated bowel loops and evidence of urinary tract dilation. Calcifications with the bladder may also be observed in the setting of communication between bowel and bladder as in rectourinary fistula or cloaca.

Fetal gallstones are seen as echogenic foci within the lumen of the gallbladder, with associated distal shadowing (Figure 70-2). Brown et al. (1992) have also included echogenic foci within the gallbladder's lumen with either no associated distal shadowing or "comet-tail" or V-shaped artifact. However, echogenic foci without associated distal shadowing more likely represent biliary sludge due to calcium bilirubinate. It is important to distinguish intraluminal calcifications because of fetal gallstones from intrahepatic calcifications, calcified hemangiomas or hamartomas in the liver, or intra-abdominal calcifications due to meconium peritonitis. The best sonographic confirmation is seeing the echogenic foci with associated distal shadowing clearly within the echolucent gallbladder lumen (see Figure 70-2). Sepulveda et al. (1995) reported 8 cases of cholecystomegaly, in which three were found to have aneuploidy (two trisomy 18 and one trisomy 13). While they suggested that cholecystomegaly may be a sonographic marker of aneuploidy, Petrikovsky and Klein (1995) challenged this view. They suggested that the cholecystomegaly may have been due to gallstones or sludge and did not represent a new marker for aneuploidy.

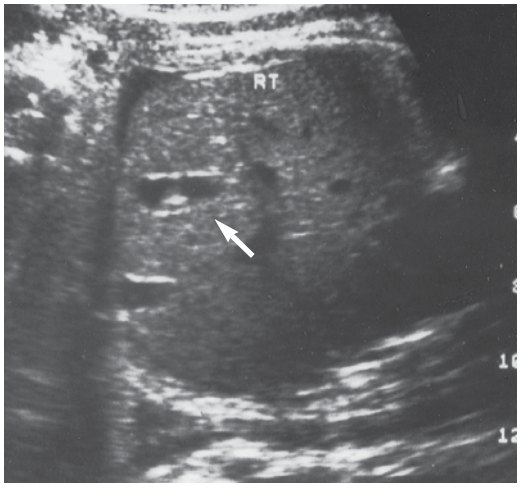

Figure 70-2 Ultrasound of a fetus at 24 weeks of gestation demonstrating dilated gallbladder and an echogenic gallstone with acoustic shadowing (*arrow*).

Fetus in fetu may be mistaken for meconium pseudocyst or teratoma. However, when well-formed vertebral bodies or long bones are seen, this allows a definitive diagnosis to be made.

MRI may be useful in distinguishing not only the cause of intra-abdominal calcifications but also associated findings such as bowel dilation due to atresia, stenosis, volvulus, or intussusception. The presence and definition of complex anorectal malformations with rectourethral fistula or cloaca may be diagnosed. Similarly, characteristic features of fetus in fetu may be more apparent when MRI is obtained as an adjunct to ultrasound.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of intra-abdominal calcification includes meconium peritonitis, fetal gallstones, hepatic calcifications, calcifications within hemangiomas, hematomas, and tumors such as dermoid, hepatoblastoma, neuroblastoma, or teratoma, and in fetus in fetu. Calcifications may also be observed in congenital infections such as cytomegalovirus and toxoplasmosis. Intra-abdominal calcifications also may be due to intraluminal calcification from reflux of urine into the colon in imperforate anus with retrourethral fistula or from stasis due to intestinal atresia or total colonic Hirschsprung's disease.

Several lesions associated with calcifications may be mistaken for gallstones. Calcifications may be seen in the fetal liver within hematomas, hemangiomas, or hamartomas. Calcifications may also be seen in the right upper quadrant as the result of meconium peritonitis, calcified adrenal cyst, hematoma, or neuroblastoma (see Chapters 69 and 113). Calcifications may occur within the lumen of the colon in cases of imperforate anus with rectourethral fistula as a result of urine reflux into rectal lumen (Selke and Cowley, 1978; Miller et al., 1988). These calcifications may be seen proximal to the transverse colon. Hematomas and polyps within the wall of the gallbladder are echogenic but do not cause acoustic shadowing (Durrell et al., 1984).

ANTENATAL NATURAL HISTORY

The natural history of intra-abdominal calcifications depends on the underlying etiology. In meconium peritonitis diagnosed in utero, the natural history is markedly different from meconium peritonitis diagnosed in the newborn nursery. The overall mortality rate in antenatal reports is 11% to 15% (Foster et al., 1987; Chabulinski et al., 1992; Dirkes et al., 1995;

Zangheri et al., 2007). This differs markedly from the mortality rates of 40% to 50% in postnatal series (Park and Grand, 1981; Payne and Nielsen, 1983; Tibboel et al., 1986). A major factor in the survival of patients with meconium peritonitis is the underlying cause. Tibboel et al. (1986) found that primary intestinal obstruction was present in 53% of 1084 neonatal cases of meconium peritonitis reviewed and reported a 54% mortality rate among their own 22 cases (Tibboel et al., 1986). Brugman et al. (1979) reported a 62% mortality rate in cases of meconium peritonitis that were associated with obstruction caused by atresia.

Prenatally diagnosed meconium peritonitis differs from postnatally diagnosed meconium peritonitis in reduced morbidity, lower incidence of cystic fibrosis, and an overall better prognosis (Dunne et al., 1983; Chabulinski et al., 1992; Dirkes et al., 1995; Tseng et al., 2003; Zangheri et al., 2007). It is clear that a prenatal ultrasound examination is more sensitive in detecting intra-abdominal calcifications than postnatal plain radiographs, and this may account for more cases with less severe meconium peritonitis being detected in utero (Dunne et al., 1983; Williams et al., 1984; Foster et al., 1987; Zangheri et al., 2007). Asymptomatic calcifications in hernia sacs, scrotal masses, and the abdomen are common incidental findings detected postnatally (Berdon et al., 1967; Thompson et al., 1973; Gunn et al., 1978; Marchildon, 1978; Várkonyi et al., 2000). These asymptomatic patients may have had bowel perforations in utero that sealed spontaneously and represent the postnatal equivalent of simple meconium peritonitis. Estroff et al. (1992) reported a case of fetal ascites that resolved, leaving abdominal calcifications that were asymptomatic at birth. Because many cases are clinically silent, neonatal series of meconium peritonitis are skewed by sicker infants with more severe meconium peritonitis and a higher attendant morbidity and mortality rate (Dirkes et al., 1995). The natural history of meconium peritonitis diagnosed in utero more clearly reflects the entire spectrum of the disease (Dirkes et al., 1995).

The natural history of enterolithiasis will vary depending on the underlying cause ranging from isolated atresia to complex anorectal malformations with rectourinary fistula. Cases of small-bowel atresia without associated cystic fibrosis have an excellent prognosis. These cases may develop polyhydramnios in the third trimester if the level of obstruction is sufficiently proximal. A small-bowel atresia or obstruction due to intussusception may go on to perforation resulting in meconium peritonitis (see above). Enterolithiasis that occurs as a result of urine refluxing into the colon in cases of complex anorectal malformations has a variable prognosis. Polyhydramnios is unusual in these cases because of the low level of obstruction. At the most severe end of the spectrum would be anorectal septum malformation sequence consisting of the absence of the perineal and anal opening in association with ambiguous genitalia and urogenital, colonic, and lumbosacral anomalies. This is usually lethal in the newborn period because of pulmonary hypoplasia from oligohydramnios (Lubusky et al., 2006). But less severe forms such as cloaca or imperforate anus with rectourinary fistula can have a much more favorable outcome albeit with the need for complex reconstructive surgery.

Although fewer than 35 cases of fetal gallstones have been reported, some aspects of the antenatal natural history have been established. The diagnosis of fetal gallstones has no adverse consequences for the pregnancy. It requires no alteration in the delivery plan and is not associated with fetal loss. Despite recognized associations with gallstones postnatally, few prenatally diagnosed cases have had risk factors for gallstones, with the exception of a single case of hereditary spherocytosis (Beretsky and Lonkin, 1983; Brown et al., 1992). Similarly, predisposing factors, other than pregnancy, were identified rarely in mothers, the most common maternal risk factor being a history of gallstones (Brown et al., 1992). In one case there had been placental abruption with placental hematoma and it was suggested that a possible pigment load might predispose to fetal gallstones (Brown et al., 1992).

Stasis of bile within the gallbladder has been shown to be a critical factor in the pathogenesis of gallstones of any type. Bile stasis is thought to be an important causative factor in gallstone formation during pregnancy (Braverman et al., 1980). It is possible that the hormonal influences predisposing to maternal bile stasis and gallstone formation may affect their fetuses similarly.

Estrogen is a recognized risk factor for gallstones and its levels are known to increase in pregnancy from 14 to 40 weeks (Beischer and Brown, 1972). Estrogen is known to increase cholesterol secretion in bile and depress bile acid synthesis (Cotran et al., 1989). This progressive rise in estrogen levels during the later trimesters may account for fetal cholelithiasis being observed only in the third trimester.

Infants diagnosed prenatally with gallstones appear to have no clinical sequelae. If echogenic foci are associated with distal shadowing, 20% resolve postnatally, but 62% resolve if associated with comet-tail shadowing, and 75% resolve if associated with no distal shadowing (Brown et al., 1992). The remainder of infants with cholelithiasis appear to be asymptomatic. However, awareness of fetal cholelithiasis is important because symptoms referable to the biliary tract may be difficult to diagnose in infants and children. Only awareness of gallstones as a potential cause of symptoms will allow prompt recognition and treatment and minimal morbidity (Jacir et al., 1986).

The natural history of fetus in fetu is remarkably good, usually having no impact on the prenatal course of the pregnancy. It is important to distinguish fetus in fetu from teratoma as the latter has the risk of malignancy developing in up to 10% of patients (Coolen et al., 2007). There has been only a single case of malignant recurrence in fetus in fetu (Hopkins et al., 1997).

MANAGEMENT OF PREGNANCY

Fetal intra-abdominal calcifications detected by prenatal ultrasound examination should prompt an effort to determine

whether these represent biliary, vascular, intraluminal, solid organ, or tumor calcifications; enterolithiasis; intraperitoneal calcification of meconium peritonitis; or fetus in fetu. Intrahepatic calcifications are discussed in Chapter 69. The presence of associated findings, such as dilated loops of bowel, meconium pseudocysts, ascites, and polyhydramnios should be excluded. Because these findings may develop later in gestation, serial sonography is advisable. In the absence of the findings that characterize complex meconium peritonitis, bowel obstruction, or severe complex anorectal anomalies such as urorectal septum malformation sequence, an excellent prognosis can be anticipated and delivery in a community setting can be safely recommended (Dirkes et al., 1995). In cases of enterolithiasis, atresia, or anorectal malformation, delivery in a setting in which these anomalies can be fully evaluated and treated postnatally should be considered. Even in simple meconium peritonitis, however, a postnatal abdominal radiographic examination should be obtained, and if normal, feedings can be initiated. The presence of other associated findings such as pseudocyst, ascites, bowel obstruction, enterolithiasis, anorectal malformation, or fetus in fetu will require additional diagnosis-specific evaluation using a combination of ultrasound, MRI, and voiding cystourethrogram (VCUG).

In cases of meconium peritonitis in which associated abnormalities such as bowel dilatation, meconium cysts, ascites, or polyhydramnios are prenatally diagnosed, there is up to a 52% chance that surgical intervention will be required during the newborn period (Dirkes et al., 1995; Tseng et al., 2003; Zangheri et al., 2007). Consideration should be given to delivery of the infant with complex meconium peritonitis in a tertiary care center.

Although the reported incidence of cystic fibrosis in neonatal meconium peritonitis ranges from 15% to 40%, three of the patients reported by Dirkes et al. (1995) had normal sweat tests and the remaining patients had no clinical manifestations of cystic fibrosis. Other prenatal series of meconium peritonitis have reported only an 8% incidence of cystic fibrosis (Boureau and Pat, 1974; Park and Grand, 1981; Finkel and Slovis, 1982; Foster et al., 1987; Chabulinski et al., 1992). Why the incidence of cystic fibrosis is lower in prenatally diagnosed meconium peritonitis is unknown. Finkel and Slovis (1982) postulated that pancreatic enzymes, which are deficient in 80% of patients with cystic fibrosis, may be necessary for calcification to occur (Boureau and Pat, 1974). Conversely, Foster et al. (1987) speculated that the thick tenacious nature of meconium in cystic fibrosis precludes free spillage into the peritoneum.

Sonographic detection of meconium peritonitis can alert the obstetrician to a fetus potentially at risk for complications from obstruction, perforation, pseudocyst formation, ascites, and polyhydramnios that may precipitate preterm labor and premature delivery. Pediatric surgical consultation may be helpful in providing counseling about the overall favorable prognosis in cases of prenatally diagnosed meconium peritonitis. In cases of complex meconium peritonitis, the parents can be advised of a more guarded prognosis, with a 50% chance of surgical intervention during the neonatal period. Parental DNA testing to define the fetal risk for cystic fibrosis may be appropriate in cases of meconium peritonitis (Robertson et al., 1994). This can be performed by a referral laboratory on blood samples or mouth swabs from the parents. If both parents are carriers and the pregnancy is at less than 24 weeks of gestation, fetal testing for cystic fibrosis mutations may be indicated if termination of the pregnancy is an option for the parents. If an amniocentesis is being performed for other reasons, consideration should be given to testing amniocytes for mutations seen in cystic fibrosis.

A fetus with enterolithiasis should be followed closely for complications related to bowel obstruction, including polyhydramnios and preterm labor. Fetal MRI is indicated to help delineate the underlying etiology, the presence of rectourinary fistula, cloaca, imperforate anus, or intestinal atresia. Delivery should be planned in a setting with appropriate pediatric surgical expertise to manage any of the causes of enterolithiasis.

The diagnosis of fetal gallstones has no implications for the management of the pregnancy. A detailed history should be obtained for risk factors for maternal cholelithiasis. In addition, the mother should have an ultrasound examination to screen for the presence of gallstones.

The fetus diagnosed with fetus in fetu is not likely to develop complications but bowel compression and polyhydramnios can occur. Delivery should take place in a facility with pediatric surgical and radiologic expertise to manage this problem in the newborn.

FETAL INTERVENTION

There are no fetal interventions for any of the causes of intra-abdominal calcifications.

TREATMENT OF THE NEWBORN

The infant should undergo abdominal examination immediately after delivery and an abdominal radiograph and ultrasound study of the abdomen should be obtained to confirm the prenatal findings (Figure 70-3). In the case of meconium peritonitis, an upper gastrointestinal study with small-bowel follow-through using water-soluble contrast may be necessary to confirm or exclude perforation, stenosis, atresia, or meconium pseudocysts (Figure 70-4). Postnatal treatment is directed by the underlying cause of meconium peritonitis. Abdominal radiography will confirm intra-abdominal calcification and demonstrate the presence or absence of cystic lesions or intestinal obstruction. Asymptomatic neonates with calcifications and otherwise normal plain abdominal radiographs and abdominal sonographic examinations may be cautiously observed and fed. If dilated bowel, meconium cysts, or ascites

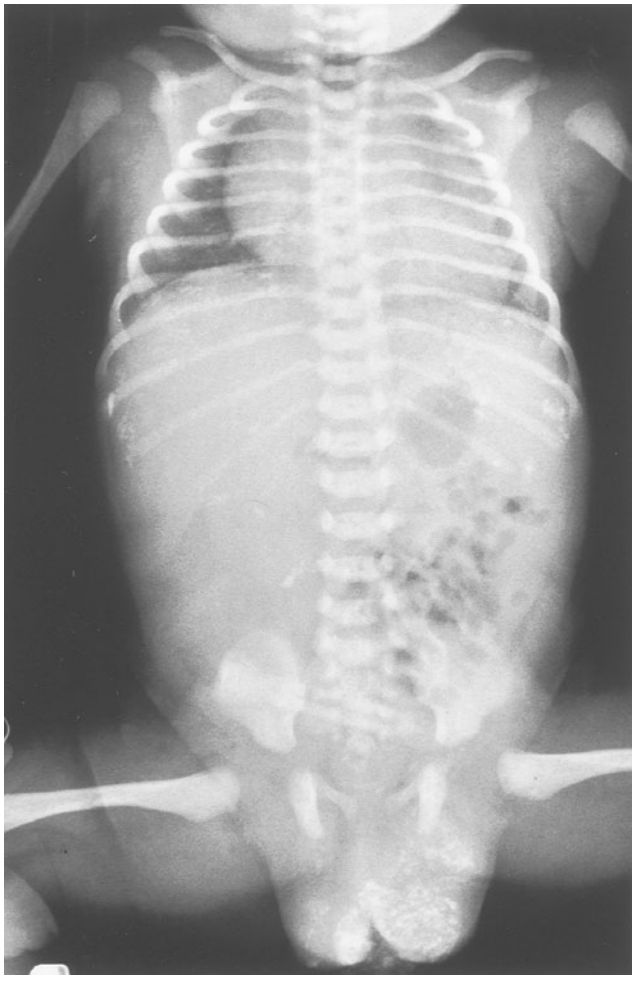

Figure 70-3 Plain abdominal radiograph in a newborn demonstrating intra-abdominal calcifications, particularly over the dome of the liver and in the scrotum.

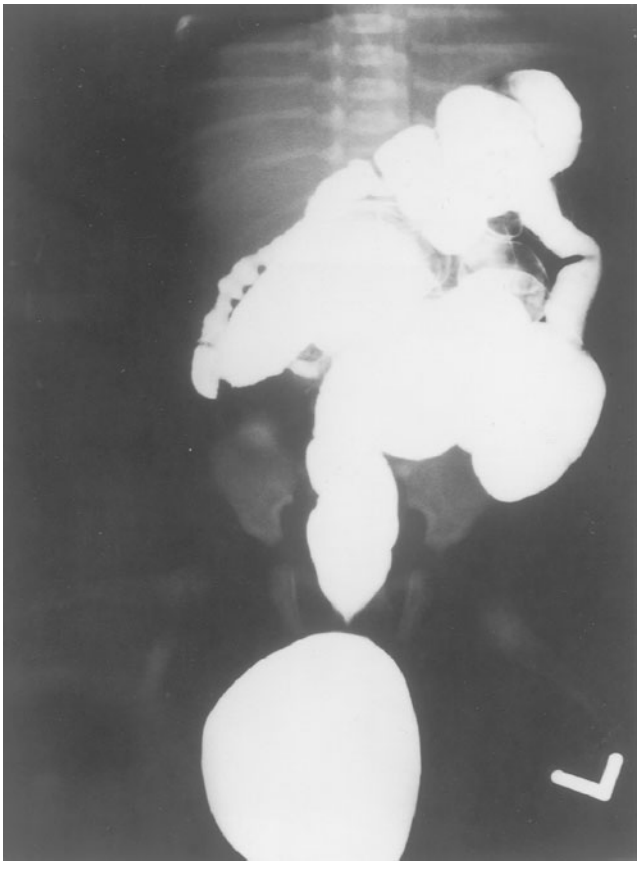

Figure 70-4 Upper gastrointestinal contrast study with small-bowel follow-through demonstrating extra-abdominal contrast in a meconium pseudocyst in the right lower quadrant.

are present, nasogastric decompression and intravenous fluids should be administered. Associated anomalies should be evaluated and surgical correction performed when the infant is stable. A sweat chloride test or testing for DNA mutations should be performed during the postoperative period to exclude or definitively diagnose cystic fibrosis in all cases of meconium peritonitis. DNA analysis is preferable in newborns presenting with gastrointestinal symptoms. If DNA analysis reveals the presence of a mutation in the cystic fibrosis transmembrane regulator gene, sweat testing is unnecessary, as some mutations have been found in patients with normal sweat tests (Highsmith et al., 1994).

Physical examination in cases of prenatally diagnosed enterolithiasis is important to exclude imperforate anus or cloaca as an underlying cause. Plain radiographs and ultrasound may be helpful in making a diagnosis, but contrast studies and MRI scans may be necessary to define the anatomy.

The newborn with a prenatal diagnosis of fetal cholelithiasis should have a postnatal ultrasound examination performed during the newborn period. In healthy term infants, sonographic observation alone is indicated unless symptoms develop. The diagnosis of acute or chronic cholelithiasis may be difficult in an infant, but should be suspected with vomiting, irritability, or ileus. Gallstones associated with predisposing risk factors that are detected during the newborn period resolve spontaneously in 75% of cases with elimination of these risk factors—for example, by treatment with diuretics or total parenteral nutrition. It is unclear if gallstones with distal shadowing on an ultrasound examination performed in utero will spontaneously resolve during infancy. The only data on this came from Brown et al. (1992), who observed spontaneous resolution in 40% of cases of fetal gallstones when associated with acoustic shadowing. The higher rate of spontaneous resolution they observed, when echogenic foci were present without acoustic shadowing, may have been because they were "sludge" rather than true gallstones.

In cases of suspected fetus in fetu, ultrasound and plain radiographs may be adequate to confirm the diagnosis if a well-formed long bone or vertebral column is observed. CT or MRI may provide anatomic relations helpful in planning surgical resection.

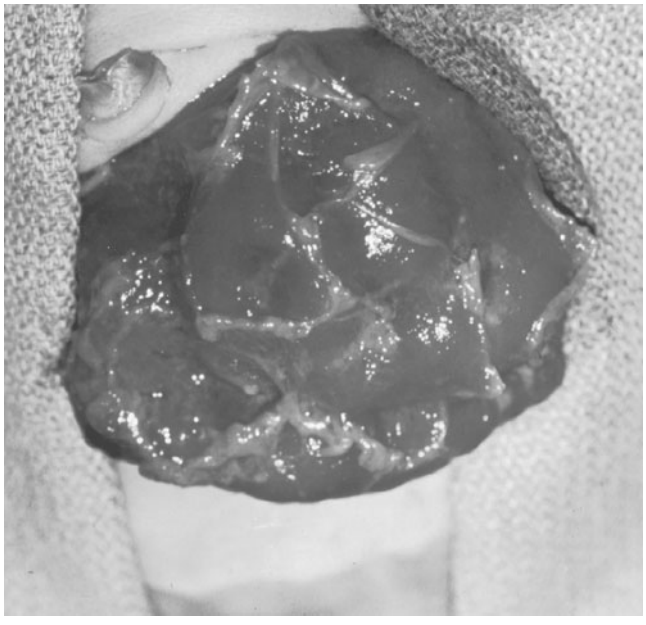

Figure 70-5 Intraoperative appearance of meconium peritonitis in a newborn with a perforated colon. Note the adhesions, which are the results of an inflammatory reaction that occurred in utero.

SURGICAL TREATMENT

The infant with complex meconium peritonitis will require surgical intervention in 50% of cases (Dirkes et al., 1995). The indications for surgery include intestinal perforation with ascites, meconium pseudocyst, intestinal atresia or stenosis, or volvulus. Surgical exploration for complications of meconium peritonitis may be extremely difficult because of the intense inflammatory reaction that occurs within the peritoneal cavity (Figure 70-5). Because of this and bacterial contamination of the peritoneal cavity, cases of meconium peritonitis complicated by perforation or meconium pseudocyst are best managed by resection and enterostomy. In cases of volvulus, the nonviable intestine is resected and proximal and distal stomas are created. In cases involving the proximal intestine, long-term venous access can be obtained to provide parenteral nutritional support until gastrointestinal continuity can be established.

Atresias most often will be amenable to resection and primary anastomoses but may require significant parenteral nutritional support if short gut or dysmotility are associated with the atresia. Anorectal malformations, particularly when associated with rectourinary fistula usually require initial diversion (see Chapter 76) as does a persistent cloaca (see Chapter 85).

The surgical management of fetus in fetu is usually straight forward with resection of the retroperitoneal mass causing few difficulties. Adjacent structures are usually displaced and there is a clear plane of dissection.

In asymptomatic infants diagnosed with fetal gallstones, we currently recommend observation only. If gallstones are radiopaque, periodic plain radiographs may be obtained to observe for spontaneous resolution. If stones are radiolucent, sonographic surveillance is recommended. We have a low threshold for performing cholecystectomy, as symptoms of acute or chronic cholecystitis in infants are often vague and nonspecific, and once it is symptomatic, acute cholecystitis is associated with a high rate of complications (Brill et al., 1982).

In infants undergoing abdominal surgery for other indications, such as pyloric stenosis or intestinal atresia, we recommend a cholecystectomy, as it can be performed with little additional morbidity.

LONG-TERM OUTCOME

The long-term outcome of infants with intra-abdominal calcification depends on the underlying cause. In fetuses with simple meconium peritonitis, the prognosis is excellent. In complex meconium peritonitis, the prognosis relates to the underlying cause of the perforation. In isolated meconium peritonitis, without cystic fibrosis, Hirschsprung's disease, or intestinal pseudo-obstruction, the prognosis is excellent. In infants with cystic fibrosis or chronic pseudo-obstruction, however, the prognosis is more guarded. Enterolithiasis associated with urorectal septal malformations has a grim prognosis, but patients with anorectal malformation or cloaca have an excellent prognosis following reconstruction. The awareness of cholelithiasis in an infant leads to early intervention once symptoms referable to the gallbladder develop. Asymptomatic gallstones require no intervention. There are no long-term sequelae associated with a diagnosis of fetal cholelithiasis. Similarly, cases of fetus in fetu have an excellent outcome following resection.

GENETICS AND RECURRENCE RISK

There is no known risk of recurrence for intra-abdominal calcifications. However, the approximately 8% of antenatally diagnosed meconium peritonitis associated with cystic fibrosis are at a 25% risk for recurrence in subsequent pregnancies. Enterolithiasis has not been reported to recur in subsequent pregnancies.

There are no data on risk of recurrence of cholelithiasis in subsequent pregnancies. If maternal risk factors for cholelithiasis are present, such as a history of hemolytic anemia or of gallstones, a prenatal ultrasound examination during the third trimester is indicated to screen for an affected fetus. Hereditary spherocytosis is inherited as an autosomal dominant disorder. If the family history reveals that either parent is affected, the fetus has a 50% risk of inheriting this gene. Sickle cell anemia is inherited as an autosomal recessive

disorder, with a 25% risk of recurrence. Other inherited enzyme abnormalities of the erythrocyte, such as pyruvate kinase deficiency, are associated with development of gallstones.

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Pyloric Atresia and Stenosis

71 CHAPTER

Key Points

- Condition presents only rarely antenatally.
- Incidence of pyloric atresia is 1 in 1 million livebirths. Hypertrophic pyloric stenosis occurs in 1.5–4 per 1000 livebirths.
- Usually associated with polyhydramnios and a "single bubble."
- Differential diagnosis of a dilated fetal stomach includes duodenal atresia or stenosis, malrotation with midgut volvulus, duodenal duplication, and antral duplication.
- Pyloric atresia can be associated with epidermolysis bullosa, a serious and often fatal skin condition that has autosomal recessive inheritance.
- Delivery should occur in a tertiary center with pediatric surgical, dermatologic, and genetic expertise present.

CONDITION

Gastric outlet obstruction due to atresia or membranous antral web is rare, constituting one of the most unusual causes of gastrointestinal obstruction. On the other hand, gastric outlet obstruction due to hypertrophic pyloric stenosis is among the most common causes of gastrointestinal obstruction in the neonate. This condition only rarely presents antenatally (Zimmerman, 1978; Nebekura et al., 1983; Mitchell and Risch, 1993).

A classification system for pyloric stenosis has been proposed: type A, a pyloric membrane or web; type B, the pyloric channel is a solid cord; type C, there is a gap between the stomach and the duodenum. Prenatal diagnosis should preempt consideration of other intestinal atresias (Usta, 2000; Ilce et al., 2003).

INCIDENCE

The incidence of pyloric atresia has been reported at 1 in 1 million livebirths, representing less than 1% of all gastrointestinal atresias (Geber and Aberdeen, 1965; Thompson et al., 1968). Hypertrophic pyloric stenosis occurs in 1.5 in 1000 to 4 in 1000 livebirths among whites, but it is less prevalent in blacks and Asians (Mitchell and Risch, 1993; Grant and McAleer, 1996). The incidence of prenatally diagnosed cases of these conditions is unknown.

SONOGRAPHIC FINDINGS

Prenatal diagnosis of pyloric atresia is associated with polyhydramnios in 61% of reported cases (Colin, 1989). The prenatal sonographic image usually shows polyhydramnios and associated gastric distention (Figure 71-1). If the fetus has recently vomited or if the obstruction is incomplete, the stomach may appear normal in size and polyhydramnios may be absent (Rizzo et al., 1995). This is especially true early in gestation, as polyhydramnios tends to develop during the third trimester. Sonographically, pyloric atresia and stenosis are associated with a "single bubble" as opposed to the "double bubble" observed in duodenal atresia. This appearance is due to either high-grade stenosis or complete atresia of the gastric outlet, resulting in marked dilation of the stomach. However, one should be cautious in the fetus with a "double bubble" sign, as this can be seen due to massive gastric distention and folding of the stomach on itself. The ultrasound beam can pass through the dilated fundus and then through the antrum, giving the impression of a double bubble. The sonographic features of hypertrophic pyloric stenosis are similar to pyloric atresia (Zimmerman, 1978; Nebekura et al., 1983). Isolated gastric distention is seen, but unlike in pyloric atresia, the hypertrophied pylorus is also seen. Because hypertrophic pyloric stenosis creates only a partial obstruction, more distal fluid-filled loops of bowel are seen in contrast to pyloric atresia, in which they are not observed. The hypertrophied pylorus seen in cross section has a characteristic "target" or "bull's-eye" appearance. No prenatal parameters for mural thickness, diameter, or pyloric length exist. However, postnatal values for hypertrophic pyloric stenosis can be used. In the neonate, a pylorus that demonstrates a mural thickness >4 mm, a diameter >11 mm, or a pyloric length of >16 mm is consistent with a diagnosis of hypertrophic pyloric stenosis. It should be pointed out, however, that measurements that do not meet these criteria do not rule out this diagnosis. Hypertrophic pyloric stenosis tends to be progressive, and increases in these parameters are to be expected. Because of the partial gastric outlet obstruction, polyhydramnios may be seen in pyloric stenosis, but not to the same extent as in pyloric atresia.

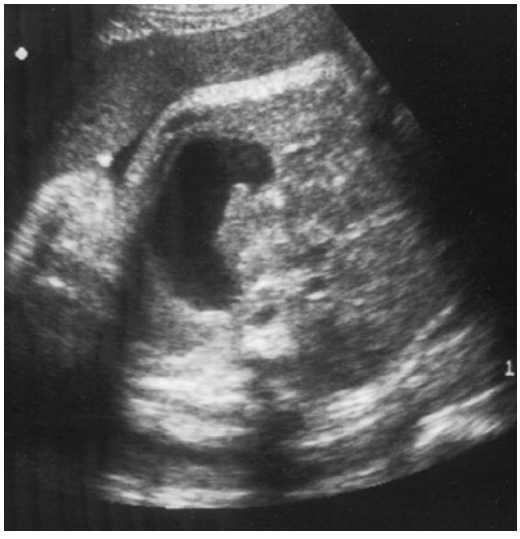

Figure 71-1 Sonographic image demonstrating an enlarged fetal stomach. This can be due to gastric outlet obstruction as a result of pyloric atresia.

DIFFERENTIAL DIAGNOSIS

In addition to pyloric atresia, the differential diagnosis of a dilated fetal stomach includes duodenal atresia or stenosis (see Chapter 72), malrotation with midgut volvulus, duodenal duplication, and antral duplication. The presence of the double bubble sonographic sign is more consistent with the diagnosis of duodenal atresia, but in pyloric atresia, the stomach may become so grossly distended that in a single ultrasonographic image both the fundus and the antrum may give the appearance of a double bubble (Malone et al., 1997). Polyhydramnios is present in each of these conditions and is less useful in making a distinction between them. In pyloric or duodenal atresia, no distal bowel will be visualized sonographically, but in pyloric stenosis or duodenal stenosis more distal intestine will be seen.

Pyloric atresia associated with epidermolysis bullosa was first reported by Swinburne and Kohler (Swinburne

and Kohler, 1968). Pyloric atresia, in addition to its association with epidermolysis bullosa, has also rarely been reported with esophageal atresia and tracheoesophageal fistula (Korber and Glasson, 1977; Peterson and Hertel, 1977; El Shafie et al., 1979) as well as with cardiovascular and genitourinary anomalies (Lepinard et al., 2000).

It is now recognized that there is a distinct autosomal recessive condition, epidermolysis bullosa with pyloric atresia, also known as Carmi syndrome. This condition presents with congenital pyloric atresia, blistering of the skin with little or no predisposing trauma, and associated renal anomalies, such as multicystic kidney, hydronephrosis, and ureterocele. When associated with pyloric atresia, epidermolysis bullosa is often a fatal disease in infancy. Some authors have recommended that surgical correction of pyloric atresia be withheld for those with a histologic diagnosis of epidermolysis bullosa (Rosenbloom and Ratner, 1987).

ANTENATAL NATURAL HISTORY

The cause of pyloric atresia is thought to be an in utero vascular compromise. This cause is similar to that of other intestinal atresias. The obstruction is due to a solid membranous structure in 67% of cases. Actual absence of the pylorus with a gap between the distal stomach and the duodenum is found in only a fifth of the cases. A fenestrated or nonfenestrated antral membrane is present in 5% of cases (Kume et al., 1980). Gastric outlet obstruction from pyloric atresia results in significant polyhydramnios. The polyhydramnios predisposes these infants to preterm labor and premature delivery. A search for other possible associated anomalies should be undertaken, including malformed ears and genitourinary anomalies (Lepinard et al., 2000). It is worth noting that in cases of pyloric atresia associated with epidermolysis bullosa (EB), both alphafetoprotein and acetylcholinesterase can be elevated (Lepinard et al., 2000).

MANAGEMENT OF PREGNANCY

The fetus diagnosed with gastric outlet obstruction consistent with a diagnosis of pyloric atresia or stenosis should be evaluated to determine the underlying diagnosis and evaluate the possibility of associated epidermolysis bullosa. The pregnant woman should be evaluated by a maternal and fetal medicine specialist, a medical geneticist, and a pediatric surgeon. Level II sonography should specifically look for the presence of renal or ureteral anomalies, which may be a sign of epidermolysis bullosa. A careful family history should be obtained to rule out epidermolysis bullosa and/or consanguinity. If the diagnosis of pyloric atresia is made prior to 24 weeks of gestation, consideration may be given to fetal skin biopsy for electron microscopy to diagnose epidermolysis bullosa (Rodeck et al., 1980). Shimizu et al. (1996) have described the use of immunohistochemistry to demonstrate absence of detectable α_6 integrin in a fetal skin biopsy in pyloric atresia–junctional epidermolysis bullosa syndrome in a family at risk for recurrence. This diagnostic test is appropriate only if the parents would not continue the pregnancy if the fetus was affected. If the familial mutation has been identified because of a prior affected fetus, DNA analysis can be performed on amniocytes or chorionic villi for a genetic diagnosis of EB as early as 10 weeks' gestation (Pfendner et al., 2003).

The pregnancy should be followed closely because of the common occurrence of polyhydramnios and the predisposition to preterm delivery. Cesarean section delivery should be considered to reduce skin trauma if the infant has epidermolysis bullosa with pyloric atresia. The infant should be delivered in a tertiary care center, with pediatric surgical and medical genetic expertise available.

FETAL INTERVENTION

There are no fetal interventions for pyloric atresia and stenosis.

TREATMENT OF THE NEWBORN

The infant born with pyloric atresia should have immediate nasogastric decompression to prevent aspiration and perforation from gastric distention. Intravascular volume and electrolyte deficit should be corrected with intravenous fluid administration. Radiographs demonstrating a distended stomach with no gas in distal viscera confirm the diagnosis of gastric outlet obstruction. An immediate upper gastrointestinal contrast study should be obtained to exclude the possibility of malrotation with midgut volvulus. The surgical repair used depends on the nature of the atresia but usually includes pyloroplasty with or without excision of a pyloric web. The presence of epidermolysis bullosa requires meticulous skin care, using atraumatic technique, minimal handling, and avoidance of adhesive tape. A diagnostic skin biopsy should be performed in consultation with a pediatric dermatologist. If the infant has epidermolysis bullosa, DNA analysis should be performed in consultation with a medical geneticist. Blistering of the skin can lead to fluid and electrolyte loss and severe infection.

SURGICAL TREATMENT

The newborn with pyloric atresia will require a Heineke–Mikulicz pyloroplasty if the duodenum or stomach are in continuity with each other. If complete atresia with separation of stomach and duodenum is present, then a primary gastroduodenostomy should be performed. A period of nasogastric decompression lasting several days may be required until return of gastric function. A transanastomic nasojejunal feeding tube may be placed for enteral nutrition until gastric ileus resolves.

In the case of pyloric stenosis, a pyloromyotomy alone is indicated. This is usually well tolerated, with resumption of feeding within 6 hours of the procedure.

LONG-TERM OUTCOME

Infants who have isolated pyloric atresia treated by pyloroplasty, need to be evaluated for the possibility of dumping syndrome due to excessively rapid gastric emptying. This may be manifested either in irritability, sweating, pallor, or tachycardia immediately following feedings, or by diarrhea and failure to thrive.

Infants diagnosed with pyloric atresia in association with epidermolysis bullosa will require continued meticulous skin care to avoid breaks in the skin. The potential for long-term survival has been demonstrated in patients with pyloric atresia and epidermolysis bullosa even with gradual improvement in symptoms of epidermolysis bullosa over time. However, significant mortality is associated with this combination by 1 year of age (Azarian et al., 2006).

GENETICS AND RECURRENCE RISK

Pyloric atresia occurs as both an isolated anomaly and in association with epidermolysis bullosa. An inherited form of isolated pyloric atresia has been described in several families (Tan and Murugasu, 1973; Olson and Gratte, 1976; Konvolinka and Stewart, 1978; Usta, 2000).

The recessive form of pyloric atresia with epidermolysis bullosa (Carmi syndrome) is associated with mutations in three genes: integrin beta 4 (*ITGB4*) (80% of cases), integrin alpha 6 (*ITGA6*) (5% of cases), and plectin 1 (*PLEC1*) (15% of cases) (Pfendner et al., 2003; Pfendner and Uitto, 2005; Pfendner and Lucky, 2008). Diagnostic DNA testing is clinically available; it has a very high likelihood of finding the causative mutation. Parental DNA should be studied, as the recurrence risk in a future pregnancy is 25%. If the parental mutations are diagnosed, preimplantation diagnosis is available. Alternatively, CVS or amniocentesis can be performed; this is recommended over sonography to diagnose recurrence.

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Duodenal Atresia and Stenosis

72 CHAPTER

Key Points

- Often presents due to uterine size greater than the size of dates as a result of polyhydramnios.
- Characteristically diagnosed by ultrasound examination, which shows a "double bubble" sign.
- Differential diagnosis includes annular pancreas, malrotation, gastric or duodenal duplication, and preduodenal portal vein.
- Associated with trisomy 21 in 30% of cases. Amniocentesis should be performed.
- Associated with congenital heart disease in 17% to 33% of cases. Echocardiography should be performed.
- Polyhydramnios rarely develops before 24 weeks' gestation but can contribute to preterm labor.
- Delivery should occur in a tertiary center with pediatric surgical and neonatal expertise available.

CONDITION

Duodenal atresia, or stenosis, is a leading cause of intestinal obstruction in newborns and one of the most common gastrointestinal anomalies that can be diagnosed prenatally. A commonly held developmental theory is that at 1 month of gestation, the lumen of the duodenum is thought to be obliterated by proliferating epithelium. This solid core of epithelium undergoes vacuolization and recanalization, restoring the lumen. Failure of recanalization of the solid stage is thought to result in duodenal atresia or stenosis. Atresia is more common than stenosis and occurs in approximately 70% of cases (Boyden et al., 1967; Skandalakis et al., 1994). Skandalakis et al. (1994) have described 3 types of duodenal atresia. The most common duodenal anomaly (69% of cases) is membranous mucosal atresia (type I) with an intact muscular wall. The proximal duodenum is ballooned out while the duodenum distal to the atresia is narrowed. This mucosal membrane may take on the shape of a "wind sock" because of peristalsis and increased proximal intraluminal pressure (Rowe et al., 1968). The origin of the wind-sock membrane is usually intimately associated with the ampulla of Vater. A type II duodenal atresia is rare (2% of cases) and has a short fibrous cord connecting the two ends of the atretic duodenum. Type III duodenal atresia has a complete separation between the two ends of the duodenum and can be associated with biliary tract anomalies in 6% of cases (Reid, 1973a and b; Jona and Berlin et al., 1976; Paine and Noblett, 1977; Knechtle and Filston, 1990). Duodenal stenosis accounts for the remaining 23% of cases. These anatomic relations are rarely evident sonographically. An annular pancreas occurs in 20% to 30% of patients with duodenal atresia or stenosis (Fonkalsrud et al., 1969; Reid, 1973a and b; Wesley and Mahour, 1977). The developmental relationship between annular pancreas and duodenal atresia and stenosis is unclear.

An annular pancreas can produce extrinsic compression and result in stenosis, but it is more commonly associated with an intrinsic obstruction due to complete atresia (Merrill and Raffensperger, 1976).

INCIDENCE

Duodenal stenosis or atresia occurs in approximately 1 in 10,000 livebirths (Fonkalsrud et al., 1969; Forrester and Merz, 2004).

SONOGRAPHIC FINDINGS

Prenatal sonographic diagnosis of duodenal obstruction has been made as early as 20 weeks of gestation (Hancock and Wiseman, 1989). The majority of cases, however, are not diagnosed until the third trimester. The most common indication for sonography is uterine size greater than dates because

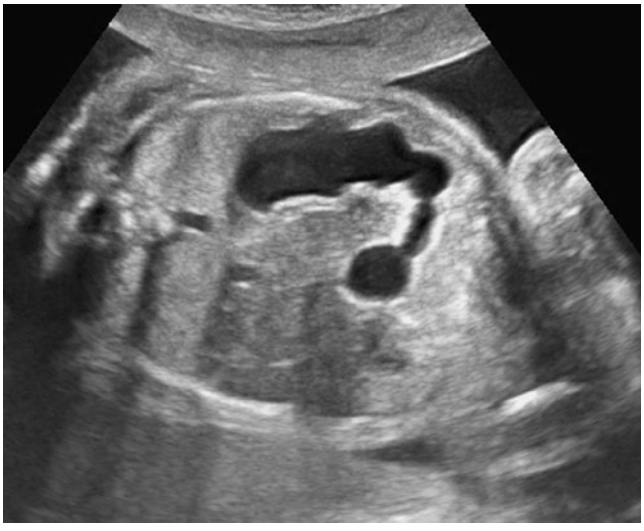

Figure 72-1 Fetus with trisomy 21 at 24 weeks of gestation demonstrating the ''double bubble" sign consistent with duodenal atresia. The distal portion of the stomach is seen communicating with the dilated proximal portion of the duodenum.

of polyhydramnios, which is present in up to 53% of cases (Girvan and Stephens, 1974; Farrant et al., 1981). Prenatal sonography may show the characteristic "double bubble" sign (Figure 72-1) that represents the dilated fluid-filled stomach and proximal duodenum (Balcar et al., 1984; Langer et al., 1989). Although occasionally seen earlier, duodenal atresia is not usually diagnosed prior to 24 weeks of gestation. If the fetus has recently vomited (Figure 72-2), or in cases of stenosis in which sufficient amounts of amniotic fluid pass the obstruction, these features may be subtle or absent (Bowie and Clair, 1982). If the diagnosis of duodenal atresia or stenosis is suspected, serial ultrasound examination may be required to prove the diagnosis. Because 30% of patients with duodenal atresia will have trisomy 21, other sonographic features

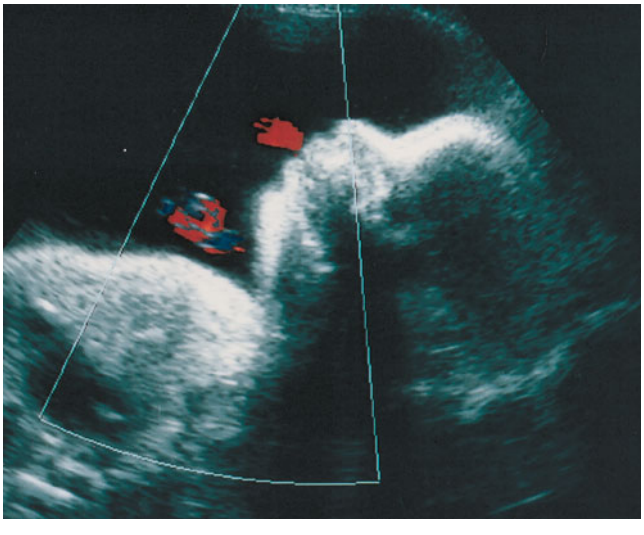

Figure 72-2 Color flow Doppler study demonstrating fetal vomiting in a case of duodenal atresia.

of Down syndrome should be sought, including nuchal fold thickening, hypomineralization of fifth finger middle phalanx (clinodactyly), and elevated biparietal diameter and fetal length ratio (Lockwood, 1993), (see Chapters 2 and 3).

MRI has been used as an adjunct to ultrasound examination in the diagnosis of duodenal atresia. On T2-weighted sequences, the fluid within the stomach and duodenum will appear hyperintense and the post atretic bowel will have normal size bowel loops. The bowel produces sufficient secretions to yield a normal appearance by MRI (Veyrac et al., 2004).

DIFFERENTIAL DIAGNOSIS

A persistently dilated fluid-filled fetal duodenum is always abnormal and should raise the suspicion of possible duodenal atresia or stenosis. This can be a difficult diagnosis to make prior to 24 weeks of gestation (Nelson et al., 1982; Bovicelli et al., 1983). The differential diagnosis, in addition to duodenal atresia or stenosis, should include annular pancreas, malrotation with either obstructing Ladd's bands or midgut volvulus, gastric or duodenal duplications, and preduodenal portal vein. Isolated duodenal stenosis may be indistinguishable from annular pancreas with associated duodenal stenosis until surgical exploration. Malrotation may give a similar "double bubble" appearance but, unlike atresia, there will be some amniotic fluid in loops beyond the duodenum. Ladd's bands may partially obstruct the duodenum, mimicking duodenal stenosis. One sonographic clue to midgut volvulus is the reversed relation of the superior mesenteric vein and artery by Doppler ultrasound study, in which the superior mesenteric vein appears anterior to the superior mesenteric artery. Large gastric or duodenal duplications can be indistinguishable from duodenal atresia (Figure 72-3) (Malone et al., 1997). Anomalous development of the paired embryonic vitelline veins contributes to the myriad complex anatomic defects of this region. Persistence of a primitive vitelline vein results in an anterior or preduodenal portal vein that passes over the pancreas and third portion of the duodenum, which can partially obstruct the duodenum.

ANTENATAL NATURAL HISTORY

More than half of the fetuses with duodenal atresia have associated anomalies. Trisomy 21 is the most frequently associated condition, occurring in 27% to 34% of cases (Fonkalsrud et al., 1969; Nixon and Tawes, 1971; Reid, 1973a and b; Girvan and Stephens, 1974; Davey, 1980; Hancock and Wiseman, 1989) (Table 72-1). In several large series, congenital heart disease was also commonly associated, occurring in 17% to 33% of cases (Fonkalsrud et al., 1969; Nixon and Tawes, 1971; Reid, 1973a and b; Girvan and Stephens, 1974; Davey, 1980; Hancock and Wiseman, 1989). The most common cardiac lesions encountered are atrial or ventricular septal defect. Other

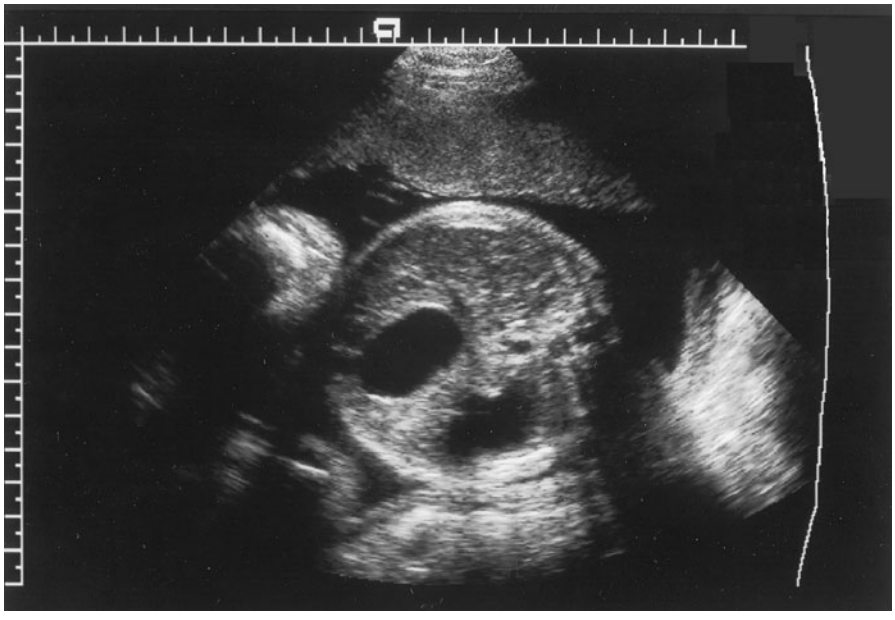

Figure 72-3 Cross-section of fetal abdomen demonstrating the double bubble characteristic of duodenal atresia. This infant proved to have a large duodenal duplication (see Fig. 72-5).

anomalies associated with duodenal atresia include malrotation, annular pancreas, esophageal atresia, tracheoesophageal fistula, and genitourinary and anorectal malformations. Numerous pancreatic and biliary anomalies have been reported in association with duodenal atresia and stenosis. These include biliary atresia, choledochal cyst, pancreatic lipomatosis, pancreas divisum, and persistent dual biliary duct drainage to duodenum proximal and distal to the atresia. Unusual biliary duct anomalies that occur in association with duodenal atresia are seen in infants with type III defects. The association of congenital anomalies with maternal and gestational and preexisting diabetes (Schaefer-Graf et al., 2000) is also thought to increase the frequency of duodenal atresia (Ozturk et al., 2007). Adeyemi (1988) has identified an association between duodenal atresia, partial situs inversus, and right-sided diaphragmatic hernia through the foramen of Bochdalek. This is an extremely rare condition known as multiple organ malrotation syndrome (MOMS) (Adeyemi, 1988).

As to whether or not prenatal diagnosis of duodenal atresia improves postnatal outcome, Bittencourt et al. found that prenatal diagnosis reduced morbidity and shortened hospitalization (Bittencourt et al., 2004). Their series was from São Paulo, Brazil, with a system of regional referral for surgical services. These findings are consistent with those reported by others (Romero et al., 1988; Murshed et al., 1999).

Table 72-1

Fetal Conditions Associated with Duodenal Atresia

Associated Anomaly	% of Cases
Trisomy 21	31
Congenital heart disease	30
Bowel rotation	20
Annular pancreas	20
Esophageal atresia	10
Anorectal atresia	6
Genitourinary	5

MANAGEMENT OF PREGNANCY

If duodenal atresia is suspected, the fetus should undergo genetic amniocentesis because of the high incidence of associated chromosomal anomalies. Fetal echocardiography should also be performed to evaluate possible associated congenital heart anomalies, even in the presence of a normal karyotype. Early detection of associated anomalies may influence decisions regarding continuation of the pregnancy. Although of uncertain clinical value, amniotic fluid bile acid concentration has been found to be markedly elevated in intestinal obstruction (Deleze et al., 1977). Abnormal bile acid concentration has been described in two pregnant women with polyhydramnios, one whose fetus had duodenal atresia and the other ileal atresia. While the amniotic fluid bilirubin and amylase concentrations were normal, the bile acid concentrations were 30.3 and 83.1 μmol/L (normal, 1.2–2.4 μmol/L), respectively (Deleze et al., 1977). Studies of experimentally created intestinal obstruction showed no differences in amniotic fluid values of bilirubin, amylase, or lipase from controls (Touloukian, 1977).

Duodenal atresia is complicated by polyhydramnios in 17% to 53% of cases (Girvan and Stephens, 1974; Farrant et al., 1981; Hancock and Wiseman, 1989; Robertson et al., 1994). Polyhydramnios can contribute to the development of preterm labor. Forty-three percent of affected infants are premature and may be small for gestational age (Jolleys, 1981). We recommend a prenatal pediatric surgical consultation with parents to help alleviate anxiety and to provide answers to questions concerning postnatal intervention. Delivery should be planned in a center with appropriate neonatal and pediatric surgical support.

FETAL INTERVENTION

There are no fetal interventions for duodenal atresia.

TREATMENT OF THE NEWBORN

In the delivery room, the newborn with duodenal atresia should have immediate nasogastric decompression to prevent aspiration of gastric contents and gastric perforation from overdistension. The gastric aspirate will usually be bile stained, since 85% of cases of duodenal obstruction are distal to the entry of the bile ducts. Failure to decompress the stomach will result in bilious vomiting shortly after birth. Intravascular fluid deficit should be corrected with intravenous fluid administration. Nasogastric fluids should be replaced volume for volume, and attention should be paid to electrolyte and acid–base abnormalities induced by large proximal gastrointestinal fluid losses. Abdominal radiography will verify tube placement and confirm the diagnosis in cases of duodenal atresia. The classic "double bubble" sign is seen with absence of gas in the rest of the bowel (Figure 72-4). In cases of duodenal stenosis, the high-grade partial obstruction may allow gas to pass into the small bowel, and the clinical presentation may be indistinguishable from that of bowel rotation with midgut volvulus or high jejunal obstruction. In such cases, or whenever there is doubt about the diagnosis, an emergency radiographic contrast study should be performed to exclude malrotation with midgut volvulus (Figure 72-5).

SURGICAL TREATMENT

The surgical reconstruction is usually performed on the day of delivery after the infant is assessed for the presence or absence of associated anomalies and appropriate volume resuscitation and correction of electrolyte disturbances has occurred. However, as long as the diagnosis of duodenal atresia is certain, nasogastric decompression alone may suffice while other anomalies are addressed, e.g., congenital heart defect, or clinical condition is stabilized, e.g., respiratory distress syndrome. The most common site of obstruction in both duodenal atresia and stenosis is in the second portion of the duodenum adjacent to the ampulla of Vater. In duodenal atresia, there is usually an intrinsic web causing the obstruction. Although some have advocated excision of this web, risk of injury to the ampulla of Vater has prompted most surgeons to bypass this obstruction. This is most commonly done by either a duodenoduodenostomy or a duodenojejunostomy. In cases of suspected stenosis, one must be certain to exclude the presence of a wind-sock deformity. Once the proximal duodenum is opened, a Foley catheter can be passed distally and the inflated balloon can then be withdrawn. In a wind-sock deformity, the membrane can be delivered and safely excised. In 1% to 3% of cases, a second more distal obstruction by an intrinsic web may be detected by this technique. In cases of gross dilatation of the proximal duodenum, it should be tapered or imbricated to prevent stasis, bacterial overgrowth, and complications of blind loop syndrome (Grosfeld and Rescorla, 1993). Because of the risk of late blind loop syndrome, we avoid duodenojejunostomy. In most instances, we employ a transverse proximal duodenum to longitudinal distal duodenal or diamond-shaped anastomosis (Kimura, 1977; Kimura et al., 1990) (Figure 72-6). We perform a proximal imbricating duodenal enteroplasty to prevent late complications of megaduodenum (Table 72-2). Because of chronic in utero obstruction, transient proximal dysmotility may prevent initiation of normal feeding for 10 to 14 days postoperatively.

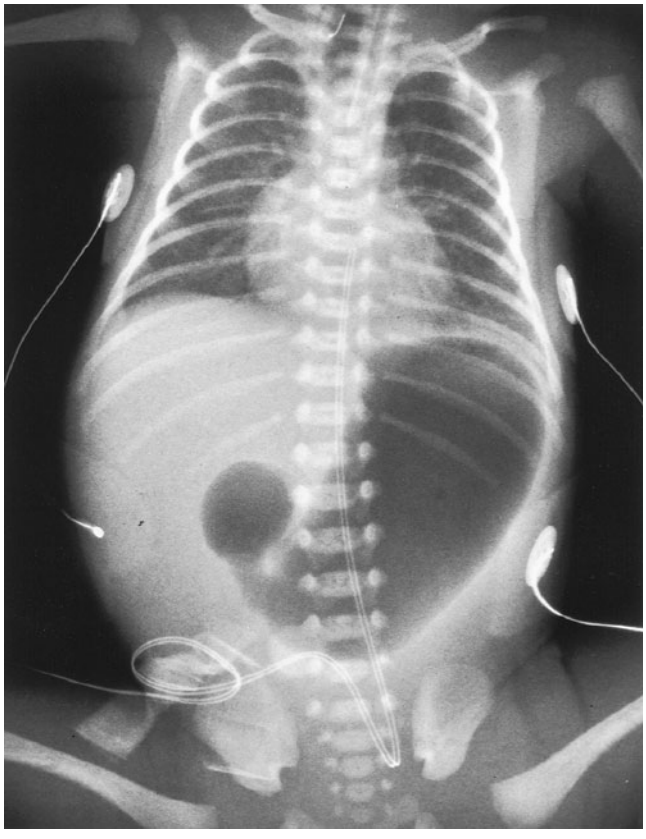

Figure 72-4 Plain radiograph of a newborn, showing dilated stomach and proximal duodenum with lack of air distal to the obstruction.

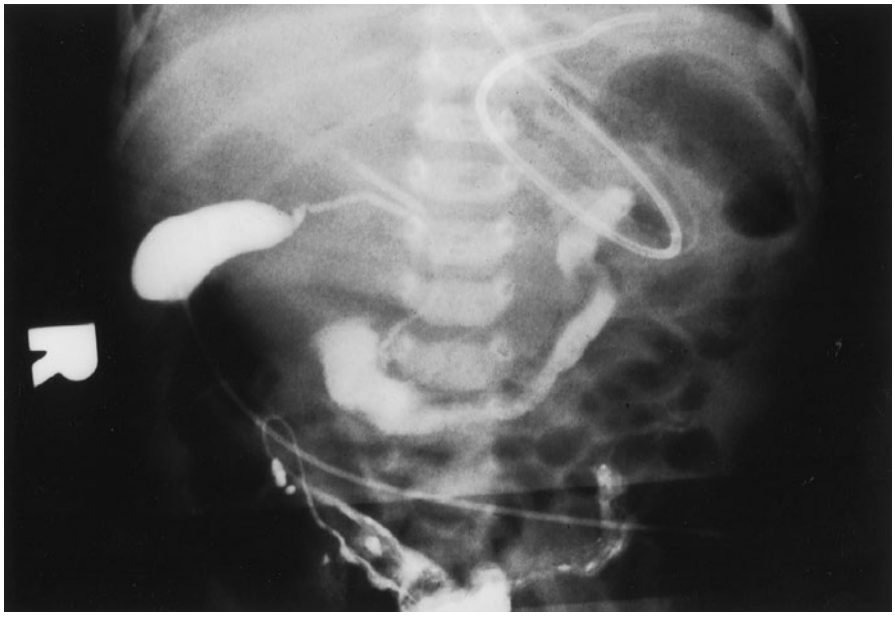

Figure 72-5 Upper gastrointestinal contrast study demonstrating displaced but patent duodenal sweep as a result of a large duodenal duplication.

A transanastomotic nasojejunal feeding tube is passed that allows enteral alimentation until proximal gastroduodenal motility returns. Breast milk can be used often, supplemented by formula as needed. In cases associated with trisomy 21, some surgeons favor the placement of a gastrostomy tube at the time of duodenal atresia repair because of the difficulties these infants have transitioning to oral feedings.

During the past 25 years, there has been steady improvement in the survival of babies with duodenal atresia, from 68% in 1968 to 95% in 1991 (Fonkalsrud et al., 1969; Hancock and Wiseman, 1989; Stauffer and Schwoebel, 1998). The majority of deaths today occur in infants with associated complex congenital heart defects (Hancock and Wiseman, 1989). The improvement in survival, although certainly due in part to advances in neonatal, anesthetic, and surgical care, may also reflect prenatal selection. While often diagnosed after 24 weeks of gestation, duodenal atresia is increasingly being diagnosed earlier. In the setting of a fetal diagnosis of Down syndrome, or severe associated anomalies, the option of pregnancy termination can be discussed with the prospective parents.

LONG-TERM OUTCOME

Late complications of duodenal atresia have been reported to be related to dysmotility of the proximal duodenum, including blind loop syndrome, megaduodenum, duodenal gastric reflux, gastritis, gastroesophageal reflux, pancreatitis, cholelithiasis, and cholecystitis (Grosfeld and Rescorla, 1993; Escobar et al., 2004). Most cases of blind loop syndrome

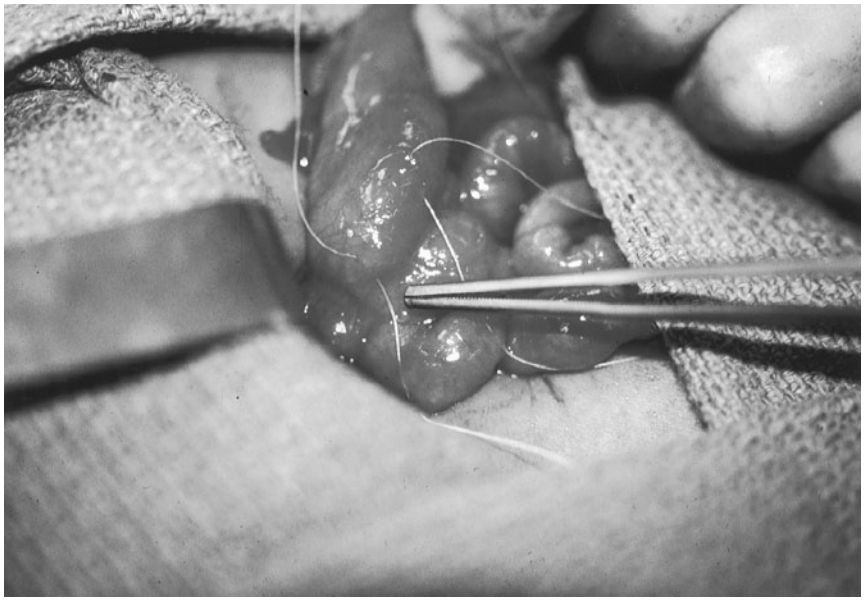

Figure 72-6 Intraoperative view of duodenal atresia at the time of duodenoduodenostomy.

Table 72-2

Late Complications of Duodenal Atresia and Stenosis

Megaduodenum
Dysmotility
Duodenogastric reflux
Gastritis
Peptic ulcer
Gastroesophageal reflux
Choledochal cyst
Cholelithiasis
Cholecystitis

are seen in patients initially treated by duodenojejunostomy, which can be corrected by conversion to duodenoduodenostomy. Similarly, megaduodenum may be treated by tapering duodenoplasty or duodenal plication. Other complications, such as duodenal gastric reflux or gastritis, may be treated medically to enhance motility by the use of parasympathomimetic agents such as bethanechol, metaclopromide. Similarly, H_2 blocker or proton pump inhibitor therapy may be effective in treating peptic ulcer and gastroesophageal reflux (see Table 72-2). Awareness of these late complications associated with duodenal atresia requires close observation for prompt recognition and institution of appropriate medical or surgical therapy.

GENETICS AND RECURRENCE RISK

More than one-half of the fetuses with duodenal atresia have associated anomalies. Trisomy 21 is the most frequently associated condition, occurring in 27% to 34% of cases (Fonkalsrud et al., 1969; Nixon and Tawes, 1971; Reid, 1973a and b; Girvan and Stephens, 1974; Davey, 1980; Hancock and Wiseman, 1989). In most cases, isolated duodenal atresia or stenosis is a sporadic condition, although Fonkalsrud (1979) has suggested an autosomal dominant pattern of inheritance in some families. Duodenal atresia has also been reported as part of Feingold syndrome, which has an autosomal dominant inheritance as well (Holder-Espinasse et al., 2004). Feingold syndrome consists of duodenal and esophageal atresia, tracheoesophageal fistula, microcephaly, hand and foot anomalies, facial dysmorphism, and developmental delay.

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Jejunoileal Atresia and Stenosis

73 CHAPTER

Key Points

- Most common cause of intestinal obstruction.
- Proximal jejunum and distal ileum are the most common locations.
- Vascular disruption is the etiology but this may be precipitated by intussusception or volvulus.
- Cystic fibrosis may be an underlying factor in up to 10% of cases.
- MRI may be helpful in excluding other diagnoses or defining associated intra-abdominal cysts in an evaluation of echogenic bowel.

CONDITION

Jejunoileal atresia and stenosis are among the most common causes of neonatal intestinal obstruction. Atresia is a complete obstruction of the lumen of the bowel. It is far more common than stenosis or partial luminal obstruction. These lesions can occur anywhere in the small bowel but are most common in the proximal jejunum or distal ileum, where they account for 31% and 36% of cases, respectively (Robertson et al., 1994). In addition, multiple atresias of the small bowel are found in 6% of cases (deLorimier et al., 1969). These conditions are thought to result from intrauterine vascular accidents such as volvulus, intussusception, internal hernia, or vascular constriction (Louw and Barnard, 1955). In utero vascular compromise as a cause of intestinal atresias was first suspected because of associated volvulus, intussusceptions, constriction at the abdominal wall defect in gastroschisis, and kinking of bowel that were often found in association with intestinal atresias. This was supported by experimental work by Louw and Barnard (1955), who were able to replicate the pathophysiology of small intestinal atresias in animals by in utero ligation of mesenteric vessels.

The bowel lumen distal to an atresia contains bile (bile is first seen at 11 weeks of gestation), planocellular epithelium (first seen at 12 weeks), and lanugo (first seen at 6–7 months), which suggests that a vascular accident occurred well after organogenesis was complete (Romero et al., 1988). In keeping with the theory of a mesenteric vascular accident, the incidence of associated chromosomal and extraintestinal anomalies associated with jejunoileal atresia is quite low. In addition to sporadic occurrence of jejunoileal atresias, they have also been reported as a complication of amniocentesis (Richwood, 1977; Swift et al., 1979; Therkelson and Rohder, 1981). Intussusception had been considered to be a rare cause of vascular disruption resulting in atresia (Nixon and Tawes, 1971; Dalla Vecchia et al., 1998). Komuro and colleagues suggest that antenatal intussusception with or without associated volvulus may be a more important etiology of small bowel atresia than has been previously recognized (Komuro et al., 2004). In a single institution's review of 48 newborns with small bowel atresia, this group found evidence of intussusception in 12 and volvulus in 13 cases at the time of surgery. They noted that neither intussusception nor volvulus was observed in cases of high jejunal atresia, apple peel deformity, or multiple atresias.

The most useful and commonly accepted classification of intestinal atresias is that proposed by Louw and Barnard in 1955, with numerous subsequent modifications (Figure 73-1). Type I atresias have an intraluminal diaphragm in continuity with the muscular coats of the proximal and distal segments; they account for 32% of cases. Type II atresias have a fibrotic cord connecting the two blind-ending bowel segments with an intact mesentery; they account for 25% of cases. Type III atresias are divided into those with complete separation of the blind-ending loops of bowel with a U-shaped mesenteric defect (type IIIa); they comprise 15% of cases. The other, type IIIb atresia, is associated with an extensive mesenteric defect and an associated "apple peel" deformity. The terminal ileum is perfused in a retrograde fashion from a single ileocolic artery around which the distal ileum coils, giving the appearance of an apple peel. Although these are unusual atresias, accounting for only 11% of cases, they are frequently seen in extremely premature infants and result in significant shortening of bowel length and the short-bowel syndrome (Dickson, 1970). They may also recur in families. Type IV lesions are multiple atresias of the small intestine and account for 6% to 17% of cases.

When associated anomalies occur in jejunoileal atresia, they generally involve the gastrointestinal tract. While the incidence of extragastrointestinal anomalies is very low, other gastrointestinal anomalies may be seen in up to 45% of patients. These abnormalities include malrotation (23%), intestinal duplications (3%), microcolon (3%), and esophageal atresia (3%) (de Lorimier et al., 1969; Nixon and Tawes, 1971). Meconium ileus and meconium peritonitis occur in 12% and 8% of cases, respectively. Associated cardiac and chromosomal anomalies are rare (Rescorla and Grosfeld, 1985) (Table 73-1).

Meconium ileus may be the underlying cause of jejunoileal atresia in infants with cystic fibrosis, who have signs of prenatal volvulus or meconium peritonitis as a result of small-bowel perforation. The incidence of meconium ileus is 20% in most series of jejunoileal atresia (Santulli et al., 1970). For this reason, cystic fibrosis mutation testing or sweat chloride analysis is advisable for all cases of jejunoileal

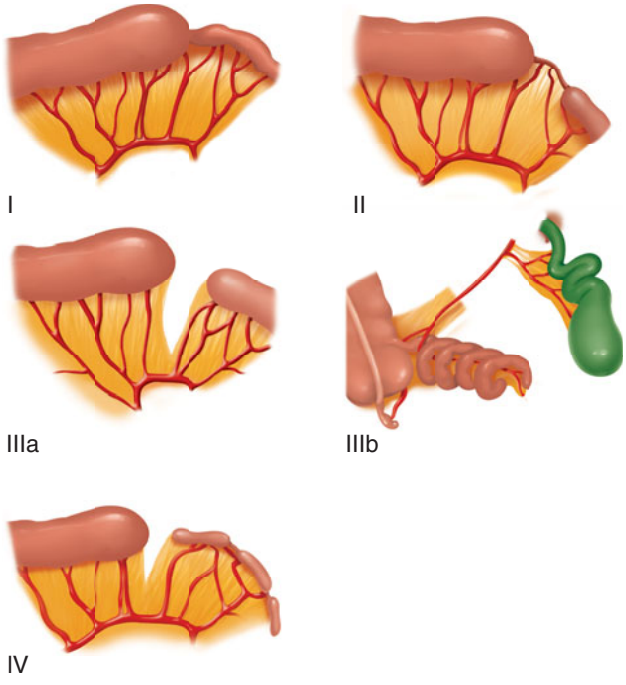

Figure 73-1 Classification of intestinal atresias.

Table 73-1

Associated Anomalies Seen in Jejunoileal Atresia

Anomaly	Percentage of Cases
Malrotation	13
Meconium ileus	12
Meconium peritonitis	8
Volvulus	5
Abdominal wall defect	4
Heart disease	3
Trisomy 21	1

Source: Rescorla FJ, Grosfeld JL. Intestinal atresia and stenosis: analysis of survival in 120 cases. Surgery. *1985;98:668-675.*

atresia. Gastroschisis is also associated with jejunoileal atresia and is thought to be due to ischemic injury to the bowel from constriction at the abdominal wall defect (see Chapter 63).

It has been also observed that there is an association between small-bowel atresia, particularly multiple atresia and placental vascular abnormalities (Komuro et al., 2004b). In a small series of 48 cases, 4 infants had significant abnormalities associated with either apple peel abnormality or multiple intestinal atresia. The placental abnormalities included marginal cord insertion, placental infarction, calcification, and cyst formation. In contrast to most cases of jejunoileal atresia, these cases were associated with extragastrointestinal abnormalities including brain, ophthalmic, and skeletal anomalies (Komuro et al., 2004b).

INCIDENCE

Jejunoileal atresias occur relatively commonly, with approximately 1 case in every 3000 livebirths. However, the incidence of intestinal atresia has been reported to range from 1 in 400 to 1 in 5000 livebirths, with boys and girls affected equally (Touloukian, 1993). This anomaly is about twice as common as esophageal atresia and three times more common than Hirschsprung's disease (Rowe et al., 1995).

SONOGRAPHIC FINDINGS

The only abdominal structures that normally contain fluid are the stomach and gallbladder, and these are readily visible on prenatal ultrasound examination (Goldstein et al., 1987). Swallowing of amniotic fluid begins at approximately 16 weeks of gestation, and meconium accumulates in the small bowel and colon throughout the second and third trimesters. The diagnosis of obstruction before 18 weeks of gestation is uncommon, and it remains difficult to detect up to 24 weeks. The bowel becomes progressively more visible and peristalsis can be seen with increasing gestational age. The meconium-filled lumen becomes increasingly echogenic as compared with the hypoechogenic muscular wall. Dilated loops of bowel with an internal diameter greater than 7 mm should be considered abnormal and may suggest obstruction (Nyberg et al., 1987). Proximal gastrointestinal obstruction often leads to polyhydramnios, which occurs in 0.4% to 1.5% of pregnancies (Wallenburg and Wladimoroff, 1977). Up to 63% of fetuses with jejunoileal atresia associated with polyhydramnios have additional anomalies, one-third of which involve the gastrointestinal tract (Damato et al., 1993).

Some authors have suggested that the association of polyhydramnios and dilated loops of bowel are markers of more severe bowel obstruction with a larger need for parenteral nutrition and longer predicted length of stay (Iacobelli et al., 2006). In this group's experience, the presence of dilated loops and polyhydramnios were more likely to result in disproportional size of proximal and distal loops of bowel, making delayed anastomosis more likely. This information should be incorporated into prenatal counseling (Basu and Burge, 2004; Iacobelli et al., 2006).

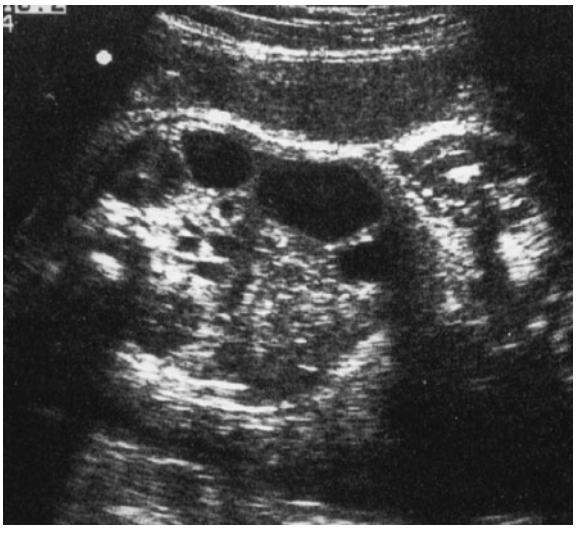

Figure 73-2 Prenatal sonographic image of a fetus with jejunal atresia demonstrating multiple loops of dilated, thick-walled bowel, which was associated with increased peristalsis and polyhydramnios. *(Reprinted, with permission, from Robertson FM, Crombleholme TM, Paidas M, et al. Prenatal diagnosis and management of gastrointestinal anomalies. Semin Perinatol. 1994;18:182-195.)*

Jejunal obstruction may be visualized on prenatal ultrasound examination by the presence of fluid-filled loops and bowel demonstrating increased peristalsis (Figure 73-2). Floating particulate matter may also be observed (Kirkinen and Jouppila, 1984). The abdomen may appear distended, and in the case of meconium ileus, increased bowel echogenicity can be present (Muller et al., 1984). Polyhydramnios occurs in approximately 25% of cases and is seen more commonly in cases of proximal obstruction. Polyhydramnios may be absent in proximal stenosis or very distal obstruction, where adequate absorption of swallowed amniotic fluid occurs. The extent of bowel dilation and mural thickening may correlate with the presence of obstruction. The incidence of obstruction increases significantly when the bowel diameter is greater than 17 mm. Similarly, the incidence of obstruction is approximately 40% with a mural thickness of greater than 3 mm (Langer et al., 1993). Visualization of increased peristalsis associated with bowel dilatation increases the likelihood of obstruction.

In recent years, magnetic resonance imaging has been used more commonly to characterize gastrointestinal anomalies (Quinn et al., 1998; Shinmoto et al., 2000; Ertl-Wagner et al., 2002; Saguintaah et al., 2002). The utility of MRI is in not only characterizing gastrointestinal tract abnormalities but also in demonstrating normal bowel close to an intra-abdominal cyst (Veyrac et al., 2004) MRI is best used as an adjunct to ultrasound examination or in combination with amniotic fluid enzyme analysis (Garel et al., 2006). MRI may

be informative in evaluating sonographically detected bowel dilatation or echogenic bowel (Carcopino et al., 2007).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of dilated, thick-walled loops of intestine, possibly with associated increased peristalsis, includes jejunoileal atresia, meconium ileus, meconium peritonitis, total colonic Hirschsprung's disease, malrotation with or without volvulus, bowel duplication, intestinal hernia, and functional obstruction due to drug ingestion by the mother. Other diagnoses that may produce intra-abdominal anechoic images include ovarian cyst, duodenal atresia, and hydronephrosis.

ANTENATAL NATURAL HISTORY

The fetus with jejunoileal atresia usually comes to medical attention as a result of polyhydramnios. The more proximal the atresia, the greater the likelihood is of developing polyhydramnios. Conversely, the more distal the atresia, the less likely it is that polyhydramnios will develop. If polyhydramnios occurs, it will be late in gestation. Even in proximal jejunal atresia, polyhydramnios rarely develops before the third trimester.

MANAGEMENT OF PREGNANCY

After detection of bowel atresia, subsequent prenatal management includes a complete fetal anatomic survey. In the absence of other structural anomalies or echogenic bowel (see below), no further workup is required. Serial sonographic surveillance should be planned to observe for the development of polyhydramnios, ascites, or meconium cyst formation. If echogenic bowel is present, amniocentesis for fetal karyotype and cystic fibrosis DNA mutation analysis should be performed. If amniocentesis is planned for karyotype analysis in the setting of bowel dilation and echogenic bowel, consideration should be given to amniotic fluid digestion enzyme assays including gamma-glutamyl transpeptidase (GGTP), aminopeptidase (AMP), total alkaline phosphatase (ALP) and its isoenzymes including the intestinal form (iALP) and total protein (Muller et al., 1994; Garel et al., 2006). Muller et al. (1994) have attempted to correlate elevations of amniotic fluid $\gamma\gamma$-glutamyltranspeptidase (GGTP) and intestinal alkaline phosphatase (iALP) in patients who underwent amniocentesis for karyotype analysis because of bowel dilation seen on prenatal ultrasound. Gastrointestinal malfunction was confirmed in 46 of 55 cases. In the 34 cases of gastroduodenal dilation, amniotic fluid GGTP above the 99th percentile was 71% sensitive but 100% specific for an anatomic defect, usually duodenal atresia. However, among fetuses with dilated loops of more distal bowel, high levels of GGTP and/or iALP were only 69% sensitive and 83% specific for fetal gastrointestinal tract anomaly. Normal values of these enzymes in amniotic fluid, however, did not exclude the diagnosis of either duodenal or more distal obstruction.

Delivery should be planned in a center with appropriate high-risk obstetric, neonatal, and pediatric surgical support.

FETAL INTERVENTION

There are no fetal interventions for jejunoileal atresia and stenosis.

TREATMENT OF THE NEWBORN

Postnatal management of jejunoileal atresia or stenosis includes immediate nasogastric decompression and intravenous fluid administration sufficient to correct fluid and electrolyte deficits. Plain abdominal radiography will verify tube placement and may suggest the level of obstruction. Air throughout the intestine with proximal dilated loops of bowel is suggestive of jejunal stenosis. An emergency upper gastrointestinal contrast study may be required to rule out malrotation with midgut volvulus. Associated anomalies should be excluded and surgical correction performed as soon as the infant is adequately resuscitated and prepared for surgery, usually within hours of delivery. During the postoperative period, if not performed antenatally, a sweat chloride test or cystic fibrosis DNA mutation analysis should be performed in cases of atresia associated with meconium peritonitis to evaluate the possibility of cystic fibrosis (Santulli et al., 1970). In the premature infant, DNA analysis is the preferred diagnostic test because of the difficulty of obtaining an adequate sweat sample.

SURGICAL TREATMENT

The infant with intestinal atresia will sequester "third-space" fluid within the bowel lumen, and dehydration is common if fluid resuscitation is inadequate. Although bacterial colonization of the gastrointestinal tract takes 24 to 36 hours to complete, prophylactic intravenous antibiotics (ampicillin/gentamicin) are routinely administered. Nasogastric decompression with a sump-style tube (Replogle or Anderson) is essential to decompress the bowel and prevent perforation as well as minimize risks of aspiration at the time of anesthesia induction.

A transverse supraumbilical abdominal incision provides excellent exposure to the entire gastrointestinal tract.

The site of proximal obstruction is usually obvious, even in cases of type I atresia (membranous intraluminal diaphragm), because of the marked dilatation of the proximal bowel. It is important to exclude other distal atresias that may not be evident from the external appearance of the bowel (Grosfeld et al., 1979). This can be assessed after the bowel is opened, or the atretic segment resected, by instilling normal saline into the lumen of the distal bowel. The fluid will distend the bowel all the way to the anus unless another type I atresia is encountered. If another atresia is found, it is important to again instill fluid distal to it to exclude the "string of sausages" effect of multiple atresias or associated colonic atresia. In cases of multiple atresias, extensive bowel resection is avoided and multiple anastomoses are performed in an effort to preserve bowel length and prevent complications of the short-bowel syndrome.

The dilated proximal bowel, although viable, should be resected to prevent functional obstruction at the anastomoses because of poor motility in this segment (Touloukian, 1993; Ozguner et al., 2005). In addition to poor motility, this dilated loop may be prone to development of blind loop syndrome. Even with resection of the dilated 15 to 20 cm of proximal intestine, a significant size discrepancy exists between proximal and distal bowel (Figure 73-3). This size discrepancy can be minimized by plicating the proximal intestine, which reduces the circumference and may also enhance motility (deLorimier and Harrison, 1983; Yamataka et al., 2005). In addition, the distal loop of intestine can be cut obliquely to spatulate this smaller-caliber bowel and minimize size discrepancy. In cases associated with significant shortening of intestinal length, plicating the proximal intestine preserves intestinal length and mucosal absorptive surface area and minimizes dysmotility. In cases in which considerable bowel length has been already lost, some surgeons have used the serial transverse enteroplasty techniques as a means of preserving bowel length and avoiding complications of the short-gut syndrome (Wales and Dutta, 2005; Modi et al., 2007).

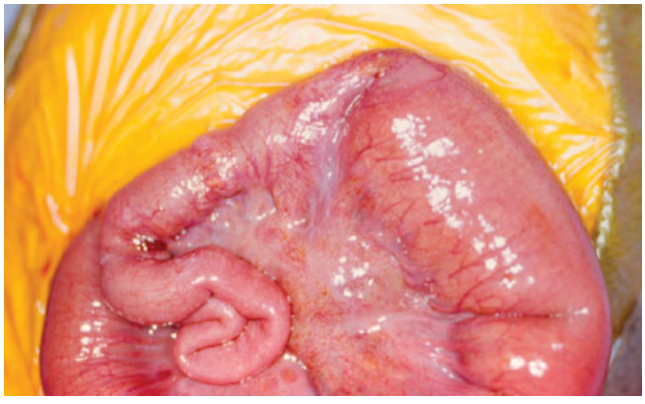

Figure 73-3 Intraoperative photograph of a newborn with jejunoileal atresia. Note the grossly distended proximal jejunum as compared with the bowel distal to the most proximal atresia.

The apple peel deformity in jejunal atresia may be particularly challenging because of loss of intestinal length, marked discrepancies between distal and proximal segments, and the short-bowel syndrome that results from it (Figure 73-4) (Dickson, 1970; Zerella and Martin, 1976; Ahlgren, 1987; Seashore et al., 1987).

In cases in which the jejunal atresia is quite proximal, a transanastomotic nasojejunal feeding tube may be placed to allow enteral feedings to be initiated during the immediate postoperative period. In cases of more distal atresia, we usually place a central venous catheter for parenteral nutrition until normal gut activity has returned. In cases in which foreshortened intestine is found or where short-bowel syndrome is anticipated, a more permanent Broviac intravenous catheter should be placed at the time of surgery.

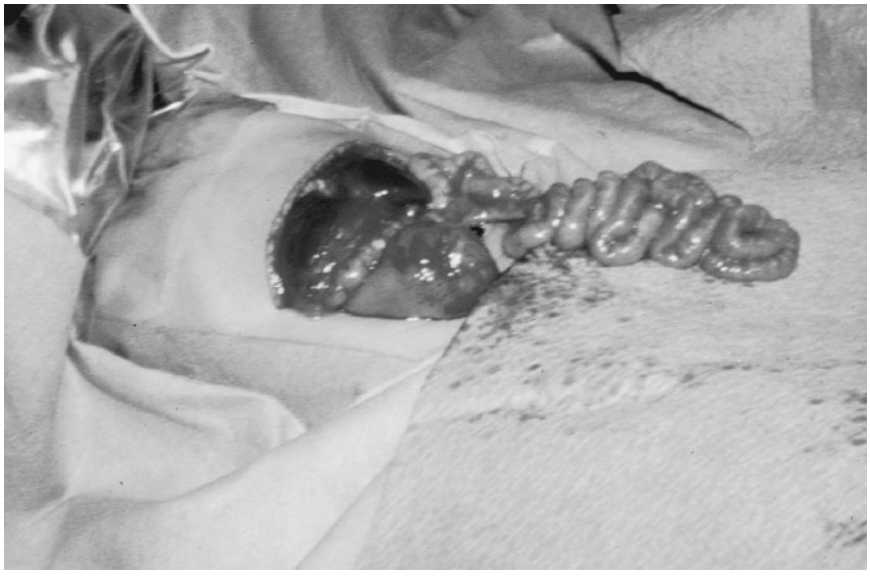

Figure 73-4 Intraoperative appearance of the apple peel deformity seen in type IIIb jejunal atresia.

LONG-TERM OUTCOME

In general, the outcome in infants with jejunoileal atresia is excellent. During the past two decades, there has been progressive improvement in survival from approximately 70% in the late 1960s to 95% in the 1990s. The rare deaths are usually complications of the short-bowel syndrome, such as line sepsis or liver failure, or more rarely, due to cystic fibrosis. Postoperative deaths in jejunoileal atresias are usually due to severe cardiac defects or ventilator-dependent chronic lung disease (Touloukian, 1993).

Some infants will have a problem with pseudo-obstruction or blind loop syndrome in the dilated proximal bowel loops, but usually these respond to medical management.

The prognosis for isolated jejunoileal atresia is excellent. However, in cases in which significant loss of intestinal length has occurred, complications of the short-bowel syndrome will prolong hospitalization and complicate recovery. Loss of the distal ileum will predispose to megaloblastic anemia from vitamin B_{12} deficiency and gallstones. In cases of isolated atresia, a 7- to 14-day hospitalization can be anticipated. If proximal bowel has become dilated, a prolonged postoperative ileus can be anticipated. These infants require close observation for complications of bacterial overgrowth and secondary growth failure. It is important to emphasize that the majority of infants with jejunoileal atresia have an excellent prognosis. Long-term follow-up by a pediatric surgeon and pediatric gastroenterologist, however, is advisable.

GENETICS AND RECURRENCE RISK

Type IIIb atresia, with apple peel deformity, short bowel, and retrograde perfusion of distal ileum, has an estimated recurrence risk of 18% (Al-Awadi et al., 1981; Arnal-Monreal et al., 1983). This condition has an autosomal recessive pattern of inheritance. Siblings, however, may have atresias of other types or other anomalies.

There is familial recurrence with other types of atresia, including type IV (Dimmick and Hardwick, 1992; Shorter et al., 2006). Hereditary multiple atresia syndrome was first described in the French Canadian population but is increasingly being recognized (Shorter et al., 2006). Consanguinity occurring in the affected families suggests an autosomal recessive mode of transmission. Guttman et al. (1973) reported familial occurrence of both duodenal and jejunoileal atresias (Martin and Zerella, 1976; Arnal-Monreal et al., 1983). Sonographically, this syndrome is of special interest, as in all 5 cases reported by Guttman et al., intraluminal calcified radiopaque densities were diagnosed in utero (Guttman et al., 1975).

Parents of patients who have been identified as having cystic fibrosis in association with the jejunoileal atresia should be advised regarding the 25% risk of recurrence. Preimplantation genetic diagnosis and DNA-based prenatal diagnosis are available for subsequent pregnancies. Shorter et al. have proposed a classification system for familial cases of intestinal atresia based on likely etiologic factors (Shorter et al., 2006). These investigators suggest that familial cases occur as a result of embryologic failure of vessels to develop. They suggest classifying familial cases of gastrointestinal atresia into the following classes, most of which have an autosomal recessive pattern of inheritance: class 1—pyloric atresia; class 2—duodenal atresia limited to the second or third portion of the duodenum; class 3—hereditary multiple atresia syndrome, which includes intraluminal calcification, normal rotation, and cystic dilation of the atresia (possible X-linked inheritance).

In general, parents of patients with jejunoileal atresia and stenosis should receive genetic counseling.

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Colonic Atresia

74
CHAPTER

Key Points

- Accounts for up to 15% of intestinal atresias. Incidence is about 1 in 20,000 livebirths.
- On prenatal sonogram appears as multiple dilated loops.
- Fetal MRI may demonstrate dilated proximal colon and absence of meconium in distal colon.
- Colonic atresia can be associated with gastrointestinal anomalies or Hirschsprung's disease.
- Diagnosis has no implications for timing or route of delivery.
- Overall prognosis is excellent.

CONDITION

Colonic atresia is a rare cause of intestinal obstruction and accounts for less than 10% to 15% of all cases of intestinal atresia (Sturim and Ternberg, 1966; Coran and Eraklis, 1969; Bowles et al., 1976; Powell and Raffensperger, 1982; Touloukian, 1993a). Colonic atresia was first recognized in 1673 by Bininger (Powell and Raffensperger, 1982). The first survivor with this condition, treated by colostomy, was not reported until 1922 (Gaub, 1922). Potts (1947) was the first to report a survivor after primary anastomosis. Few series of appreciable size have been reported subsequently because of the rarity of isolated colonic atresia or stenosis (Philippart, 1986). The pathogenesis is thought to be similar to the mechanism responsible for jejunoileal atresia and stenosis (see Chapter 73). The majority of colonic atresias, which occur proximal to the splenic flexure, include a significant segment of absent colon with distal microcolon (Rescorla and Grosfeld, 1985). Anomalies associated with colonic atresia are unusual, but can include gastroschisis and jejunal atresia, Hirschsprung's disease, as well as ocular and skeletal anomalies (Bowles et al., 1976; Powell and Raffensperger, 1982; Rescorla and Grosfeld, 1985; Jackman and Brereton, 1988; Etensel et al., 2005; Draus et al., 2007). The skeletal anomalies most often seen with isolated colonic atresia include syndactyly, polydactyly, absent radius, and clubfoot (Philippart, 1986). Major cardiac anomalies and genetic defects are rare, although they have been reported (Robertson et al., 1994). Colonic atresias may be seen as a complicating factor in abdominal wall defects such as gastroschisis, omphalocele, or vesicointestinal fistulas (Bowles et al., 1976; Powell and Raffensperger, 1982). Hirschsprung's disease has also been reported to occur in association with colonic atresia (Johnson and Dean, 1981). However, it is important to remember that in two-thirds of the cases, colonic atresia occurs as an isolated defect without associated abnormalities. Multiple colonic atresias have been reported but are extremely rare (Touloukian, 1993b).

The classic demonstration by Louw and Barnard (1955) that jejunal atresia results from an in utero mesenteric vascular accident is widely accepted and is thought to also apply to colonic atresia. Vascular compromise may occur as a result of a primary vascular accident in utero, or it may be secondary to a mechanical event, such as intestinal volvulus. Because colonic atresia, proximal and distal to the splenic flexure, differs, the cause may also differ in these regions. Other cases of colonic atresia have been reported due to internal hernia, compression of the tranverse mesocolon by a choledochal cyst, or in association with gastroschisis (Etensel et al., 2005; Al Wafi et al., 1998; Basaran et al., 2002). Rare causes of colonic atresia include those attributed to multiple intestinal atresias due to disturbed intestinal morphogenesis (Fourcade et al., 2001), fetal varicella infection (Hitchcock et al., 1995), and familial cases (Benawra et al., 1981).

INCIDENCE

The occurrence rate of colonic atresia has been reported to vary from 1 in 1498 to 1 in 66,000 livebirths (Sturim and Ternberg, 1966; Davenport et al., 1990). The former appears to overestimate the incidence of colonic atresia and the latter is thought to be an underestimate. One in 20,000 appears to be more nearly correct, based on experience at major pediatric surgical centers (Philippart, 1986). In such centers the occurrence rate approximates 1 case per year of isolated colonic atresia or stenosis. The incidence of colonic atresia is equal in males and females. When there are other associated developmental anomalies, the incidence of colonic atresia increases significantly. Within the gastrointestinal tract, however, only gastric atresia is rarer (Philippart, 1986).

SONOGRAPHIC FINDINGS

The prenatal sonographic appearance of colonic atresia may be indistinguishable from other forms of distal intestinal obstruction. Prenatal diagnosis of colonic atresia may be extremely difficult to make with certainty. The sonographic image in colonic atresia is that of multiple dilated loops of bowel (Figure 74-1). It may be difficult to distinguish dilated loops of small bowel from dilated loops of colon. Polyhydramnios is an unusual finding in isolated colonic atresia and its presence should raise suspicions about a more proximal intestinal obstruction. Perforation may occur proximal to the atresia, with resulting ascites and meconium peritonitis (Agrawala et al., 2005) (Figure 74-2).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of these sonographic findings includes anorectal atresia, cloaca, and Hirschsprung's disease (see Chapters 75 and 76).

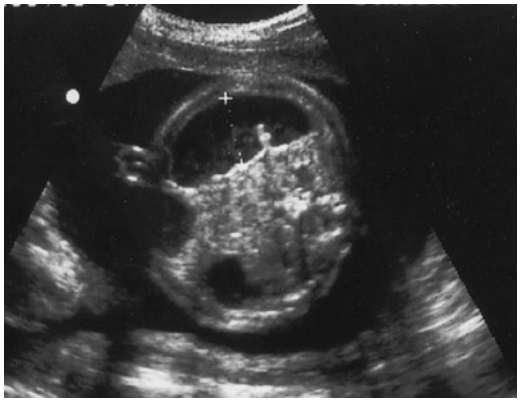

Figure 74-1 Fetal sonographic image demonstrating multiple dilated loops of intestine due to an isolated descending colonic atresia.

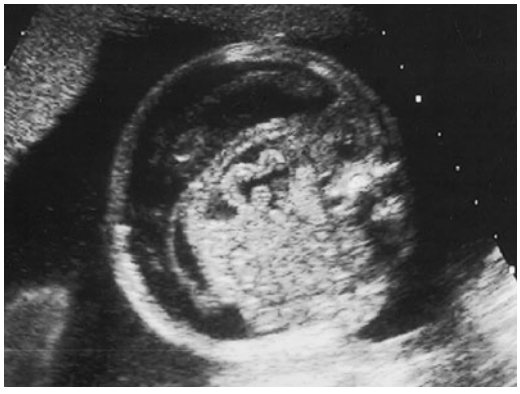

Figure 74-2 Sonographic examination of the same fetus in Figure 74-1 performed 2 weeks later, demonstrating decompression of the loops of intestine but with the new finding of fetal ascites. This was proven to be due to proximal perforation above the descending colonic atresia with secondary meconium peritonitis.

ANTENATAL NATURAL HISTORY

Half of colonic atresias occur proximal to the splenic flexure and half occur distal to it (Coran and Eraklis, 1969; Etensel et al., 2005). Atresia of the colon proximal to the splenic flexure is more likely to be associated with loss of proximal colon. Atresia distal to the splenic flexure is less likely to result in loss of bowel length. This difference appears to be related to the watershed nature of the blood supply to the colon at the splenic flexure. The atresias occurring in the colon vary from luminal webs to full mesenteric defects. The rarity of colonic atresia and the lack of prospective prenatally diagnosed cases of colonic atresia limit our understanding of its antenatal natural history. We do not believe that this diagnosis has any adverse implications for the pregnancy, and because associated anomalies are less frequent, the overall prognosis is excellent.

MANAGEMENT OF PREGNANCY

Because of the potential for associated anomalies, when colonic atresia is suspected, the fetus should undergo a detailed sonographic examination with special attention to the skeletal system and the four-chamber view of the heart. If the cardiac anatomy is poorly seen, fetal echocardiography should be performed. There is no indication for karyotype analysis in fetuses in which colonic atresia is suspected, except as indicated by maternal age, or if seen in association with anomalies known to be associated with chromosomal abnormalities, such as omphalocele. Colonic atresia is not associated with prematurity, and this diagnosis has no implications for timing or mode of delivery. However, because of the need for radiographic evaluation and surgery during the immediate postnatal period, we recommend delivery in a tertiary care center, with pediatric surgeons, pediatric radiologists, and neonatologists available.

FETAL INTERVENTION

There are no fetal interventions for colonic atresia.

TREATMENT OF THE NEWBORN

In the nursery, the infant with colonic atresia will show abdominal distention, and either fail to pass meconium or pass only a small amount. Plain abdominal radiographs will demonstrate multiple loops of dilated bowel with air-fluid levels consistent with obstruction. A sump-style nasogastric tube should be passed for intestinal decompression and venous access obtained for volume resuscitation. Due to the distal location of the obstruction, fluid can be sequestered within more proximal loops of bowel. Antibiotics should be started and a pediatric surgical consultation obtained.

A plain radiograph of colonic atresia may be indistinguishable from a more proximal intestinal atresia or meconium ileus. Because of this differential diagnosis, a contrast enema should be performed. In cases of meconium ileus, surgery may be avoided if Gastrografin enema is successful in relieving the obstruction. In colonic atresia, a microcolon is noted distal to the site of obstruction. Perforation of the microcolon has been reported during barium enema for colonic atresia (Sturim and Ternberg, 1966).

SURGICAL TREATMENT

In the past, survival was rare for cases of colonic atresia not diagnosed during the first 3 days of life. Most morbidity and mortality associated with colonic atresia occurs in unrecognized cases. In the presence of a competent ileocecal valve, unrecognized colonic atresia may result in a closed-loop obstruction, which may then go on to perforation. Once a diagnosis has been made and the infant has been resuscitated with volume, surgery should be performed. The procedure is determined by the nature and location of the atresia and the physiologic status of the infant. Previously, a primary anastomosis was performed for right-sided atresias because newborns often did not tolerate ileostomy well. Conversely, because colostomy was well tolerated in newborns, this was the preferred procedure in left-sided atresias. Currently, we favor resection, or tapering enteroplasty of the dilated proximal colon with primary anastomosis in colonic atresias of either the left or right colon. It is essential, however, to obtain frozen sections of the more distal colon to rule out Hirschsprung's disease if a primary anastomosis is planned. Failure to diagnose Hirschsprung's disease inevitably leads to breakdown of the anastomosis. In cases in which Hirschsprung's disease is present in association with colonic atresia, either a resection

and leveling colostomy or resection and an endorectal pull-through can be performed. Which of these approaches is preferred depends on the location of the atresia and the degree of dilatation of the proximal colon. In infants who may be compromised by other factors, such as sepsis or severe respiratory distress, we perform a proximal colostomy or ileostomy with closure at a later date when the infant is more stable. Current means of nutritional support have diminished concerns about ileostomy in a newborn.

LONG-TERM OUTCOME

Because of the rarity of isolated colonic atresia, most reported series are small and encompass several decades of observations. Experience with this unusual lesion, as well as marked improvements in supportive care, have improved survival, which currently is greater than 90% (Bowles et al., 1976; Powell and Raffensperger, 1982; Etensel et al., 2005; Draus et al., 2007). Deaths usually occur only as a result of associated congenital anomalies, a marked delay in the recognition of the colonic atresia, or failure to recognize associated Hirschsprung's disease (Philippart, 1986; Etensel et al., 2005; Draus et al., 2007). In most historical reviews, deaths usually occurred prior to the 1970s because of preoperative colonic perforation. Delayed function of the distal colonic segment has been observed in several patients and occasionally required intravenous nutritional support. In such cases, a biopsy to detect the presence of ganglion cells is appropriate to exclude distal aganglionosis consistent with Hirschsprung's disease (Wolloch and Dintsman, 1976; Currie et al., 1983). Occasionally, contrast enemas obtained in patients who have undergone surgery for correction of colonic atresia will demonstrate persistent tapering of the distal segment. In the absence of symptoms, this radiographic feature is of no concern.

GENETICS AND RECURRENCE RISK

Cases of colonic atresia due to genetic or familial occurrence have been reported (Guttman et al., 1973; Benawra et al., 1981; Puri and Fujimoto, 1988). We are aware of one case report of a family in which congenital colonic atresia was present in two maternal half brothers and their maternal uncle (Benawra et al., 1981). The pattern of inheritance was consistent with autosomal dominance with reduced penetrance, or X-linked. A familial syndrome of pyloric atresia associated with small-bowel and colonic atresia has also been described (Guttman et al., 1973). In general, however, recurrence of colonic atresia is rare.

There is recent work in transgenic mice that shows that decreased expression of the fibroblast growth factor receptor 2b in the gastrointestinal tract results in decreased proliferation and increased apoptosis, resulting in atresia (Fairbanks et al., 2004). It is not clear, however, that this proposed genetic mechanism plays any role in colonic atresia.

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Hirschsprung's Disease

75 CHAPTER

Key Points

- One of the most common causes of intestinal obstruction in the newborn. Characterized by severe constipation due to functional colonic obstruction with megacolon.
- Hirschsprung's disease rarely presents prenatally, but when it does it is usually due to total colonic aganglionosis.
- Sonographic features may include dilated loops of small intestine occasionally with enterolithiasis.
- About a quarter of affected patients have associated anomalies. There is a strong association with Down syndrome.
- Hirschsprung's disease diagnosed prenatally is at increased risk for syndromic associations by being long segment aganglionosis.
- Level II sonogram and antenatal karyotype are recommended.
- Diagnosis requires postnatal rectal biopsy to confirm aganglionosis.
- Treatment is a pull-through procedure to bring normal ganglionated bowel to the dentate line.

CONDITION

Hirschsprung's disease is one of the most common causes of intestinal obstruction in newborns (Richardson and Brown, 1989; Kleinhaus and Boley, 1993). It usually presents as a low intestinal obstruction without sepsis. In the least severe cases, delayed passage of meconium may be the only abnormality (Potter, 1989; de Lorijn et al., 2007). In more severe cases, the neonate presents with abdominal distention and bilious or feculent vomiting, in addition to failure to pass meconium. In its most serious form, infants present with overwhelming sepsis due to enterocolitis; a smaller number will present with peritonitis from perforation of a normal intestine proximal to the aganglionic segment. The age at diagnosis varies considerably, but half of the cases are diagnosed during the newborn period, 75% within 3 months, and 80% within the first year of life (Ikeda and Goto, 1984; Rowe et al., 1995).

Hirschsprung's disease is characterized by severe constipation due to functional colonic obstruction with megacolon. The condition bears the name of Harald Hirschsprung, a Danish pediatrician, who in 1888 described the autopsy findings of two unrelated infants who died with congenital megacolon. While at least 12 cases had been reported prior to 1888, Hirschsprung's complete description of the clinical and postmortem findings resulted in his name becoming attached to the condition. Hirschsprung focused his attention on the dilated hypertrophied megacolon, but the underlying abnormality was not determined until 1920, when Dalla Valle reported the absence of ganglion cells in the Auerbach plexus in the nondilated transition zone. The absence of ganglion cells in the distal nondilated segment involves the Auerbach plexus (myenteric), the Henle (deep submucosal), and the Meissner plexuses (submucosal) (Skandalakis and Gray, 1994). The dilated proximal segment of colon ends in a funnel-shaped transition zone, which tapers into the narrowed, patent, but functionally obstructed distal segment. This distal segment is usually normal in caliber and appears narrow only compared to the proximal megacolon (Figure 75-1). The peristalsis of the proximal normal colon tends to dilate the proximal aganglionic segment, and so the transition zone is part of the aganglionic segment.

The abnormal innervation in Hirschsprung's disease always extends proximally from the anus, including the internal sphincter (Puri, 1996). Histologically, in the absence of ganglion cells there are hypertrophied parasympathetic nerve bundles in the submucosa and between the muscular layers of the bowel. The parasympathetic (cholinergic) and sympathetic (adrenergic) nervous systems innervate the normal colon. The parasympathetic system is excitatory to the colon and inhibits the internal sphincter. Conversely, the

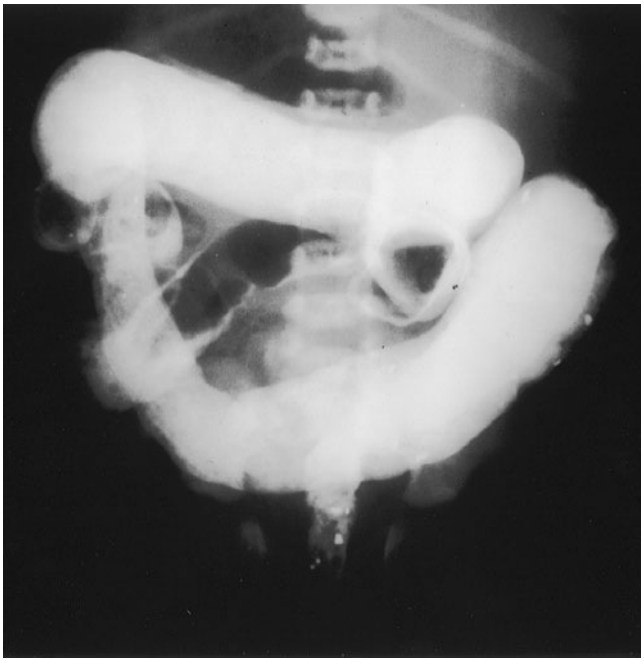

Figure 75-1 Barium enema radiograph from an infant with Hirschprung's disease. The dilated proximal bowel is the segment of bowel with normal ganglion cells. Note the narrow rectum and wide sigmoid. *(Courtesy of Dr. R. S. McCauley.)*

sympathetic nervous system inhibits the colon and excites the internal sphincter. In addition, the colon normally receives intrinsic innervation via purinergic, serotonergic, and peptidergic systems (Nirasawa et al., 1986). Ganglion cells receive impulses from both cholinergic fibers and intrinsic nonadrenergic inhibitory fibers. In Hirschsprung's disease the extrinsic innervation is present with increased cholinergic and adrenergic fibers, but the intrinsic innervation is absent (no purinergic, serotonergic, or peptidergic fibers). In Hirschsprung's disease the wave of relaxation that normally precedes each propulsive peristaltic wave does not occur. In addition, the normal reflex relaxation of the internal sphincter following rectal distention does not occur.

The ganglion cells coordinate intrinsic and extrinsic impulses, and in their absence a functional obstruction results. Absence of the intrinsic nervous system is the underlying neurophysiologic abnormality in Hirschsprung's disease.

During embryonic life, neurenteric ganglion cells migrate from the neural crest to the upper end of the alimentary tract and then follow vagal fibers caudad (Dereymaeker, 1943; Van Campenhout, 1946; Yntema and Hammond, 1947). Ganglion cells can be seen in the proximal small bowel by 7 weeks of gestation, and the rectum by 12 weeks of gestation (Okamoto and Ueda, 1967). Why ganglionic migration stops is unknown. It is not due to failure of vagal fibers to innervate the bowel. Postganglionic fibers from normal ganglia proximal to affected segments and preganglionic parasympathetic vagal fibers that fail to connect with ganglion cells continue to elongate (Bodian et al., 1951; Kamijo et al., 1953; Nixon, 1964).

Megacolon is not always due to Hirschsprung's disease. It is now recognized that several anomalies of the myenteric plexus may produce a similar clinical presentation to Hirschsprung's disease, including neuronal loss, abnormal nerves, and intestinal neuronal dysplasia (Puri and Wester, 1998; Scharli and Sossai, 1998). Several reports have appeared describing a clinical presentation that is indistinguishable from Hirschsprung's disease in which ganglia were present but there was either hypoganglionosis, immature ganglia, or other neuronal abnormalities (Burghaighis and Emery, 1971; Tanner et al., 1976; Munakata et al., 1978).

The internal sphincter is involved in all cases, but the proximal extent of aganglionosis varies. The rectosigmoid is involved in about half of the patients, and an additional 15% have involvement of the splenic flexure or hepatic flexure or have total colonic Hirschsprung's disease. In 8% of the cases, aganglionosis may extend to the small bowel (Bickler, 1992). Rare cases of discontinuous aganglionic segments with normal functioning intervening bowel have been reported (Sprinz et al., 1961; Anderson and Chandra, 1986; Seldenrijk et al., 1986; Skandalakis and Gray, 1994).

INCIDENCE

The incidence figures quoted for Hirschsprung's disease have increased from the earliest report by Hautau in 1960 of 1 in 41,200, as a result of greater appreciation of the spectrum of disease. The incidence of Hirschsprung's disease is now thought to be 1 in 5000 livebirths, second only to pyloric stenosis as a cause of intestinal obstruction in newborns (Passarge, 1967; Parisi and Kapur, 2000). Hirschsprung's disease may be slightly more common in Japan, with an incidence of 1 in 4697 to 5343 (Suita et al., 2005). The highest incidence reported is in the Federated States of Micronesia with a rate of 1 in 1370 livebirths or 3 to 5 times the rate observed in the West (Meza-Valencia et al., 2005). There is no racial predilection. Males are more commonly affected than females, with a ratio of approximately 4:1 (Kleinhaus et al., 1979; Sherman et al., 1989). The number of females with Hirschsprung's disease has varied from 5% to 22% of cases (Bodian et al., 1949; Keefer and Mokrohisky, 1954; Richardson and Brown, 1962). These incidence figures are based on livebirths. It is unknown if Hirschsprung's disease is associated with lethal malformations, as aganglionosis often cannot be recognized grossly at autopsy in a fetus or newborn because dilation and hypertrophy have not yet developed.

Numerous anomalies are associated with Hirschsprung's disease. Two percent of patients with aganglionosis have Down syndrome (Passarge, 1967). Coran et al. (1978) noted that 26% of their patients had associated anomalies, including congenital heart disease, Smith–Lemli–Opitz syndrome, and multiple renal anomalies. Other large series have confirmed this finding, with 16% to 32% of patients having one or more associated anomalies. Except for Down syndrome and anomalies of the genitourinary tract, there is no consistent pattern of associated malformations (Passarge, 1967; Lister, 1977; Seldenrijk et al., 1986) (Table 75-1).

Table 75-1

Anomalies Associated with Hirschsprung's Disease

	Syndromes	MIM	Key Features
Syndromic NCC disorders	WS4 (Shah–Waardenburg)	277580	Pigmentary anomalies (white forelock, iris hypoplasia, patchy hypopigmentation
	Yemenite deaf-blind-hypopigmentation	601706	Hearing loss, eye anomalies (microcornea, coloboma, nystagmus), pigmentary anomalies
	BADS	227010	Hearing loss, hypopigmentation of the skin and retina
	Piebaldism	172800	Patchy hypopigmentation of the skin
	Haddad	209880	Congenital central hypoventilation
	MENZA		Medullary thyroid carcinoma, pheochromocytoma, hyperplasia of the parathyroid
	Riley-Day	223900	Autonomic nervous system anomalies
HSCR mandatory	Goldberg–Shprintzen	235730	Mental retardation, polymicrogyria, microcephaly, CF, coloboma, facial dysmorphic features
	HD with limb anomalies	235740	Polydactyly, unilateral renal agenesis, hypertelorism, deafness
		235750	Postaxial polydactyly, ventricular septal defect
		235760	Hypoplasia of distal phalanges and nails, dysmorphic features
		604211	Preaxial polydactyly, heart defect, laryngeal anomalies
		306980	Brachydactyly type D
	BRESHEK		Brain abnormalities, retardation, ectodermal dysplasia, skeletal malformation, Hirschsprung disease, ear/eye anomalies, kidney dysplasia
HCSR occasionally associated	Mowat–Wilson	235730	Mental retardation, microcephaly, epilepsy, facial gestalt, hypospadias, renal anomalies, ACC, CCD
	Bardet–Biedl syndrome and/or	209900	Pigmentary retinopathy, obesity, hypogenitalism, mild mental retardation, postaxial polydactyly
	Kauffman–McKusick	236700	Hydrometrocolpos, postaxial polydactyly, congenital heart defect
	Smith–Lemli–Opitz	270400	Growth retardation, microcephaly, mental retardation, hypospadias, 2–3 toes syndactyly, dysmorphic features
	Cartilage-hair hypoplasia	250250	Shortlimb dwarfism, metaphyseal dysplasia immunodeficiency
	HSAS/MASA	307000	Hydrocephalus, aqueductal stenosis, spasticity adducted thumbs, ACC, mental retardation
HSCR rarely associated	Fukuyama congenital muscular dystrophy	253800	Muscular dystrophy, polymicrogyria, hydrocephalus, MR, seizures
	Clayton–Smith	258840	Dysmorphic features, hypoplastic toes and nails, ichthyosis
	Kaplan	304100	Agenesis of corpus callosum, adducted thumbs, ptosis, muscle weakness
	Okamoto	308840	Hydrocephalus, cleft palate corpus callosum agenesis
	Werner mesomelic dysplasia	188770	
	Pitt–Hopkins	610954	Epileptic encephalopathy, facial dysmorphic features, bouts of hyperventilation, dysautonomia
	Jeune asphyxing thoracic dystrophia	208500	

(*continued*)

Table 75-1

Anomalies Associated with Hirschsprung's Disease (*Continued*)

	Syndromes	MIM	Key Features
Miscellaneous associations	Pallister-Hall (CAVE)	140510	N/A
	Fryns	229850	N/A
	Aarskog	100050	N/A
	Fronto-nasal dysplasia	136760	N/A
	Osteopetrosis		N/A
	Goldenhar	164210	N/A
	Lesch-Nyhan	308000	N/A
	Rubinstein-Taybi	180849	N/A
	Toriello-Carey	217980	N/A
	SEMDJL	271640	N/A

SONOGRAPHIC FINDINGS

The sonographic findings of Hirschsprung's disease are nonspecific and rare. Hirschsprung's disease has been suspected or diagnosed prenatally in only three cases (Wrobleski and Wesselhoeft, 1979; Vernesh et al., 1986; Eliyahu et al., 1994). The combination of polyhydramnios, diffuse and progressive fetal-bowel distention, and increased abdominal circumference raises the possibility of fetal Hirschsprung's disease (Figure 75-2). Some have argued that because most cases occur in term infants, and cases are rarely symptomatic within the first 24 hours, Hirschsprung's disease does not occur prenatally. The three reported cases challenge this view, as Hirschsprung's disease can present in at least the third trimester. However, these cases resulted from total colonic aganglionosis, and presented with small-bowel dilation and polyhydramnios. Total colonic Hirschsprung's disease accounts for only 3% to 12% of cases (Wildhaber et al., 2005). The majority of cases, however, involve the rectosigmoid region and are unlikely to result in polyhydramnios. Given the absorption of amniotic fluid that occurs in the ileum and colon proximal to this region, functional obstruction at this level would also not be expected to cause bowel dilation.

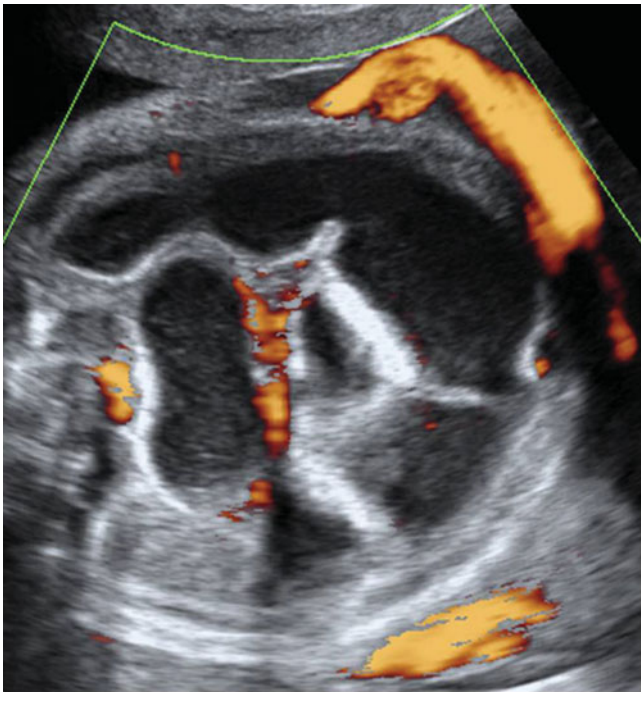

Figure 75-2 Axial section through fetal abdomen demonstrating dilated bowel loops.

Another sonographic finding that has been suggested as a possible sign of fetal Hirschsprung's disease is echogenic bowel (Wrobleski and Wesselhoeft, 1979). However, no case of Hirschsprung's disease has been diagnosed based solely on the sonographic finding of echogenic bowel. Total colonic Hirschsprung's disease can mimic meconium ileus and result in enterolithiasis present in the terminal ileum (Cowles et al., 2006).

DIFFERENTIAL DIAGNOSIS

The sonographic findings of bowel dilation associated with polyhydramnios suggests a differential diagnosis that includes jejunal, ileal, or colonic atresia or stenosis, persistent cloaca, meconium ileus, and imperforate anus (Table 75-2). The prenatal sonographic features of bowel atresias, especially ileal or colonic, can be indistinguishable from Hirschsprung's disease. Atresias are a more common cause of fetal small-bowel obstruction, however. The sonographic features of persistent cloaca should distinguish it from Hirschsprung's disease. In neonates, perforation of the colon proximal to the aganglionic segment can occur. This has not been reported prenatally, but would be expected to present with sonographic features of meconium peritonitis such as intraabdominal

Table 75-2

Differential Diagnosis of Hirschsprung's Disease

Meconium ileus
Meconium plug syndrome
Neonatal small left colon syndrome
Malrotation with volvulus
Incarcerated hernia
Jejunoileal atresia
Colonic atresia
Intestinal duplication
Intussusception
Necrotizing enterocolitis
Sepsis
Intracranial hemorrhage
Hypothyroidism
Maternal drug ingestion/administration
Adrenal hemorrhage
Hypermagnesemia
Hypokalemia

calcifications, ascites, or pseudocyst formation. Total colonic Hirschsprung's disease can result in enterolithiasis due to complete functional obstruction and precipitation of urate within the lumen. In the absence of reflux of urine into the colon in imperforate anus, resulting in intra-abdominal calcification, there are no specific sonographic features for imperforate anus. It is unusual to see bowel dilation in utero with imperforate anus. This must be considered in the differential diagnosis of a fetus with dilated loops of intestine.

ANTENATAL NATURAL HISTORY

The paucity of case material has precluded our defining the natural history of Hirschsprung's disease. However, dilated loops of bowel associated with polyhydramnios are more likely to be the result of a condition other than Hirschsprung's disease. In prenatal cases in which Hirschsprung's disease is suspected, it is likely to be the result of total colonic aganglionosis or aganglionosis extending even further proximally to the small bowel, which results in polyhydramnios.

MANAGEMENT OF PREGNANCY

A suspected case of fetal Hirschsprung's disease is unlikely to affect the management of the pregnancy except for the associated polyhydramnios. There is no need to change the timing or site of delivery. Polyhydramnios may result in uterine irritability between labor and delivery. We reserve amnioreduction, however, for cases in which the increased uterine size results in maternal respiratory compromise. Because of the strong association with other anomalies (Table 75-1), a detailed level II sonographic examination should be performed and amniocentesis for karyotype analysis should be offered.

In cases of fetal dilated bowel and polyhydramnios, the parents should be referred to a center with pediatric surgeons and a pediatric radiologist available for immediate postnatal evaluation. This is not primarily because of the Hirschsprung's disease, which generally does not present as a neonatal surgical emergency, but because of the more common conditions such as jejunal or ileal atresia that do. There is no indication for cesarean section in suspected cases of Hirschsprung's disease except for standard obstetrical indications.

FETAL INTERVENTION

There are no fetal interventions for Hirschsprung's disease.

TREATMENT OF THE NEWBORN

The infant in whom Hirschsprung's disease is suspected should have a careful abdominal and rectal examination to rule out imperforate anus. A plain abdominal radiograph may be helpful after 8 to 12 hours of age to detect dilated loops of intestine after swallowing air. The infant should be observed for the passage of meconium without stimulation. If the infant fails to have spontaneous passage of meconium within 48 hours, a barium enema should be performed. In newborns, the absence of a transition zone detected on contrast enema does not exclude the diagnosis of Hirschsprung's disease, as sometimes days to weeks are required before proximal bowel dilation is evident.

The infant in whom Hirschsprung's disease is suspected prenatally must be evaluated immediately postnatally with the entire differential diagnosis of lower intestinal or functional obstruction in mind (Table 75-2). The differential diagnosis of Hirschsprung's disease is quite lengthy and an

orderly approach to the evaluation is required. The infant with meconium ileus will present with a picture of distal ileal obstruction due to cystic fibrosis. Barium enema in meconium ileus, in contrast to Hirschsprung's disease, reveals a microcolon and characteristic pellets of inspissated meconium in the ileum. However, the presence of right lower calcifications due to enterolithiasis should raise the possibility of long segment intestinal aganglionosis (Cowles et al., 2006).

In the meconium plug syndrome, a characteristic meconium plug is seen with a smaller-than-normal left colon. The infant begins producing stools normally after contrast enema and passage of the plug. The plug is not obstructive and is thought to form as a result of left colonic dysmotility, which improves postnatally. A small percentage of infants with the meconium plug syndrome will subsequently be diagnosed with Hirschsprung's disease and for that reason all cases of meconium plug syndrome should undergo suction rectal biopsy. The neonatal small left colon syndrome is similar to the meconium plug syndrome except that no plug is observed and it is most often seen in infants of diabetic mothers. There appears to be a transition zone at the hepatic flexure in a small left colon syndrome. However, the rectum is normal and the functional obstruction in small left colon syndromes is self-limited.

Other diagnoses listed in Table 75-2 can mimic Hirschsprung's disease but are usually distinguished by their associated clinical or radiographic findings: volvulus by bilious vomiting and proximal bowel obstruction; necrotizing enterocolitis in a premature infant with pneumatosis intestinalis observed on plain radiography; functional obstruction from administration of drugs such as magnesium sulfate to the mother; intracranial hemorrhage, hypothyroidism, adrenal hemorrhage, or hypermagnesemia and hypokalemia.

Once suspicion of Hirschsprung's disease has been raised, plain abdominal radiographs with anteroposterior and cross-table lateral decubitus views should be obtained to evaluate for evidence of intestinal obstruction and to rule out free intraperitoneal air. This can then be followed by barium enema, anorectal manometry, or a suction or full-thickness rectal biopsy.

The characteristic radiographic features of a narrowed rectosigmoid with proximal colonic dilatation forming a transition zone are sometimes missed during the newborn period (Figure 75-1). Some have questioned the usefulness of barium enema during the newborn period. However, if a transition zone is seen, it is diagnostic of Hirschsprung's disease. Failure to evacuate the barium within 24 hours after the study is also highly suggestive of Hirschsprung's disease.

The internal sphincter is invariably involved in all cases of Hirschsprung's disease. Some have used anorectal manometry as a noninvasive bedside diagnostic test for Hirschsprung's disease. The limitation of this approach is the difficulty of positioning the balloon and the lack of sensitivity of the equipment in infants less than 39 weeks of postconceptual age or less than 2.7 kg (Tobon et al., 1968; Holschneider et al., 1976; Tarmate, 1984). This is a technique more commonly employed in Japan (Ikeda and Goto, 1984).

Swenson (1950) established rectal biopsy as the definitive test for the diagnosis of Hirschsprung's disease, which is based on the absence of ganglion cells in the plexuses of Auerbach, Henle, and Meissner. This is often associated with hypertrophic nerve bundles in the aganglionic segments. Because of the need for general anesthesia and occasional postprocedure rectal bleeding, Aldridge and Campbell (1968) suggested the use of suction rectal biopsy. This procedure can be performed without anesthesia, at the bedside, and because it is not a full-thickness biopsy, it does not make a subsequent pull-through procedure more difficult.

SURGICAL TREATMENT

The traditional approach to the treatment of Hirschsprung's disease has been with a prompt diverting colostomy (Figure 75-3). In the past, the major cause of mortality was the development of enterocolitis prior to the diagnosis of Hirschsprung's disease. Colostomy may be lifesaving in an infant with enterocolitis. This is referred to as a "leveling colostomy" because the level of the colostomy is determined by full-thickness biopsies obtained to avoid making the colostomy in the transition zone, which will result in a functionally obstructed colostomy.

There are three commonly performed surgical procedures; each has some modifications. The first procedure, described by Swenson et al. in 1949, involves resection of the aganglionic segment and anastomosis of ganglionated

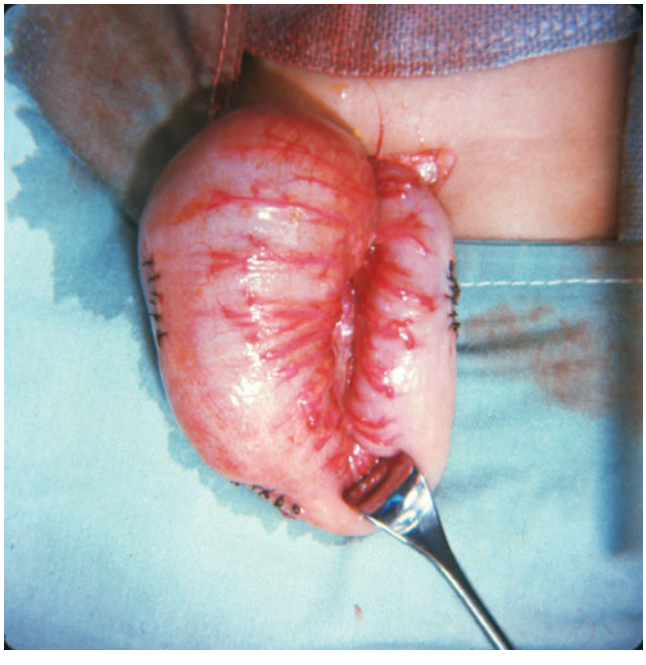

Figure 75-3 Intraoperative view of a typical case of Hirschsprung's disease at the level of the transitional zone. The distal bowel with the relatively normal caliber is the aganglionic segment while the dilated proximal bowel has normal ganglion cells. Sutures are at site of biopsies to check for ganglion cells.

proximal colon to the distal rectum. One concern with this procedure is the need to maintain the dissection immediately adjacent to the rectal wall to avoid injury to the pelvic nerves responsible for rectal, bladder, and sexual function. In 1964 Duhamel, in order to avoid the risk to pelvic innervation, introduced this procedure, which limits dissection to the retrorectal space and anastomoses ganglionated colon to the pectinate line in an end-to-side fashion. The disadvantage of this technique was the long-retained rectal septum and stump of a ganglionated bowel. Martin and Candill (1967) proposed opening the wall between aganglionic rectum and the ganglionated pulled-through colon to alleviate these problems. This procedure has the advantage of technical ease and can be performed in the case of a failed Swenson procedure.

Soave introduced the endorectal pull through in 1964, with subsequent modification by Boley (1984). The major difference between Soave's procedure and Swenson's is that the dissection of the rectum is performed in a submucosal plane protecting the pelvic innervation. The ganglionated bowel is pulled through the aganglionic muscular rectal cuff and anastomosed at the dentate line. The aganglionic muscular rectal cuff is split in the posterior midline to prevent interference with normal function of the pullthrough.

More recently, many pediatric surgeons have begun performing a definitive pull-through procedure at the time of diagnosis without preliminary colostomy, with good results (So et al., 1988; Teitelbaum and Coran, 1998). This is, of course, limited to infants with no evidence of enterocolitis. Georgeson et al., (1995) have also reported success with a laparoscopic Swenson procedure without a need for preliminary colostomy. This approach not only avoids colostomy, but is associated with more rapid postoperative recovery and discharge from the hospital (Craigie et al., 2007). In newborns with a transition zone at the distal descending colon a primary transanal Soave procedure can be performed which avoids even laparoscopy. This approach allows the infant to be discharged within 2 to 3 days of the procedure (Albanese et al., 1999; Langer et al., 1999).

LONG-TERM OUTCOME

The longest follow-up information available for patients with Hirschsprung's disease who have undergone pull-through procedures was reported by Swenson et al. in 1985. The long-term functional results were excellent, with no cases of impotence or urinary incontinence, and a 1.4% incidence of chronic fecal soiling. Normal bowel habits were experienced by 89.7% of these patients. However, these results have not been reproduced by other surgeons performing Swenson's operation. This has led to the more common use of the Soave or Duhamel procedures.

There is growing appreciation of the potential complications observed during long-term follow-up of patients with Hirschsprung's disease. Up to 23% of patients experience enterocolitis despite this pull-through procedure (Surana et al., 1994; Teitelbaum and Coran, 1998; Menezes et al., 2006). Patients with Down syndrome appear to be at increased risk for this complication (Teitelbaum, 1997; Teitelbaum and Coran, 1998; Menezes et al., 2006). The incidence of fecal incontinence ranges from 3% to 10% (Menezes et al., 2006; Swenson et al., 1985). The incidence of constipation following pull-through procedures for Hirschsprung's disease ranges from 6% to 34% (Puri and Nixon, 1977; Quinn et al., 1992; Rescorla et al., 1992; Marty et al., 1995; Yanchar and Soucy, 1999; Saleh et al., 2004). A consistent observation is that bowel function continues to improve with time, regardless of the type of pull-through procedure performed (Menezes et al., 2006).

GENETICS AND RECURRENCE RISK

There is good evidence for a genetic predisposition to Hirschsprung's disease. Siblings of female index patients have 360 times the risk of developing Hirschsprung's disease than that of the general population (recurrence risk, 7.2%). Siblings of male index patients have a risk of the disease 130 times that of the general population (recurrence risk, 2.6%). The proportion of affected siblings also increases when the index patient has a "long" aganglionic segment extending beyond the sigmoid colon (Swenson, 1950; Duhamel, 1964; Passarge, 1967; Carter et al., 1981; Raffensperger, 1990).

It is estimated that mutations in the *RET* proto-oncogene may account for as many as 20% of cases of Hirschsprung's disease (Martucciello and Holschneider, 1998). The association with Down syndrome and other chromosomal abnormalities also suggests a genetic component to the cause of some cases of Hirschsprung's disease. Trisomy 21 is the most common chromosomal abnormality associated with Hirschsprung's disease, occurring in 4.5% to 16% of cases (Polley and Coran, 1986; Puri, 1993; Menezes et al., 2006). Other chromosomal abnormalities associated with Hirschsprung's disease include partial trisomies of 22q11 and 11q23 (Beedgen et al., 1986); deletion of 2p22 in combination with a reciprocal translation (Webb et al., 1988); trisomy 18 mosaicism (Passarge, 1973); and interstitial deletions of 13q (Kiss and Osztovics, 1989; Lamont et al., 1989; Bottani et al., 1991) and 10q (Martucciello et al., 1992; Luo et al., 1993; Fewtrell et al., 1994).

Familial cases of Hirschsprung's disease have been described. Richardson and Brown (1962) reviewed 54 cases in 21 families, including 1 family in which 5 of 6 sons from the same mother, but with 3 different fathers, had Hirschsprung's disease. Bodian et al., (1951) estimated the probability of producing a second male sibling with the disease at 20%. In a large Texas cohort, Reyna described 6 affected members in a 54 member, five-generation pedigree. He suggested autosomal dominant inheritance with variable expression of the phenotype. The incidence of familial Hirschsprung's disease, however, is only on the order of 3% to 7% of total cases (Reyna, 1994). Klein (1964) suggested that males and females are equally affected with long aganglionic segments,

but males are frequently affected with short-segment aganglionosis. They estimated the probability of a second child with Hirschsprung's disease to be 5% if male, but less than 1% if female, with an overall risk of 4% for short-segment cases. The risk for either sex following birth of a child with long-segment Hirschsprung's disease, however, is 12.5% (Klein, 1964).

Complex segregation analysis performed on multiple families seems to indicate two different patterns of inheritance in Hirschsprung's disease. For families in which there is long-segment aganglionosis extending beyond the sigmoid colon, the mode of inheritance appears to be autosomal dominant, with variable expression of the phenotype. For families affected by short-segment aganglionosis, the inheritance pattern is either multifactorial or due to a recessive gene with very low penetrance (Badner et al., 1990).

Isolated Hirschsprung's disease has complex non-Mendelian inheritance. The major susceptibility genes include the *RET* proto-oncogene, on chromosome band 10q11, the glial cell line–derived neurotrophic factor (GDNF) (Angrist et al., 1993; 1996; Ivanchuk et al., 1996; Solomon et al., 1996), the endothelin-B receptor (EDNRB) and its ligand endothelin-3 (Edery et al., 1996; Hofstra et al., 1996; Puffenberger et al., 1996). These susceptibility genes do not account for the etiology of aganglionosis in many patients, especially sporadic cases. A search continues for other candidate susceptibility genes (Kusafuha and Puri, 1998).

Hirschsprung's disease is considered today to be a sex-modified multifactorial congenital malformation with an overall recurrence risk in siblings of a proband to be 4% (Amiel et al., 2008). A greater risk for recurrence would be expected if the proband is female with long segment Hirschsprung's disease (Edery et al., 1994). As a neurocristopathy, Hirschsprung's disease is associated with a number of other neurocristopathies including multiple endocrine neoplasia type II (MEN2), neuroblastoma, conotruncal heart defects, and Waardenburg syndromes (see Table 75-1).

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76 CHAPTER Imperforate Anus

Key Points

- Incidence is 1 in 5,000 livebirths. Has been linked to maternal diabetes, thalidomide, ethanol, and assisted reproductive technology.
- Imperforate anus is difficult to diagnose by prenatal sonographic studies.
- Sonographic findings that may be due to imperforate anus include transient bowel dilation in first trimester, intraluminal calcifications in the colon, and persistent distal bowel dilation later in gestation.
- Fetal MRI may be an important adjunct to ultrasound examination if anorectal malformation is suspected.
- 50% of anorectal malformations have associated anomalies of the spine, limbs, genitourinary system, trachea, esophagus and the heart. Echocardiogram is indicated.
- Associated with many syndromes and chromosome abnormalities. Amniocentesis is indicated for fetal karyotype.
- Delivery should occur in a tertiary care center with pediatric surgical, radiologic, and genetic expertise available.
- Bowel continence is usually achieved in 90% of patients.

CONDITION

Imperforate anus has been recognized since antiquity, but has only been treatable in all of its forms in the latter half of the past century. The first surgical anoplasty for a low-type of imperforate anus was performed by Amussat in Paris in 1835. The next significant advance did not occur until the work of Stephens, who described a combined sacral and abdominal perineal approach based on cadaveric dissections. This highlighted the importance of the puborectolia sling (Stephens, 1953). The modern approach to reconstruction of imperforate anus was pioneered by deVries and Pena in 1982, with the posterior sagittal approach to the whole spectrum of anorectal malformations using the posterior sagittal anorectoplasty (PSARP) (deVries and Pena, 1982; Pena and deVries, 1982).

Anomalies of the anus and rectum have usually been explained on the basis of an arrest of the caudal descent of the urorectal septum toward the cloacal membrane between 4 and 8 weeks of gestation (Fitzgerald and Fitzgerald, 1994). At 4 to 6 weeks the cloacal membrane becomes partitioned into the anterior urogenital sinus and the posterior anorectum by the cranial to caudal growth of mesoderm-derived urorectal septum. The urorectal septum fuses with the cloacal membrane at what then becomes the perineal body (Paidas and Pena, 1996). The mesoderm-derived urorectal septum is composed of the midline Tournex fold and two lateral Rathke folds. The lower third of the anal canal is derived from the ectoderm of the anal pit. Fusion of the hindgut mesoderm with the ectoderm occurs at the dentate line. Failure of Rathke folds to develop results in arrest of the inferior urorectal septum, resulting in a rectourethral fistula in the male and a persistent cloaca in the female. This arrest in Rathke folds usually occurs just below the paramesonephric duct, but a more caudal arrest in Rathke folds could result in a high rectovaginal fistula in a female. Failure of both Rathke and Tourneaux folds in males results in rectovesicular fistulas at the bladder neck. In the female it is more likely to result in cloacal anomaly or duplicated vagina and uterus (Paidas and Pena, 1996). The malalignment of Tourneaux and Rathke folds may also result in rectourethral fistula in males and vestibular fistula in females. Isolated imperforate anus without a fistula occurs from failure of the anal pit to form, and despite normal descent of Tourneaux and Rathke folds, the lack of an ectodermal anal pit results in imperforate anus. Failure of the anal membrane to resorb or incomplete resorption despite formation of the anal pit results in rectal atresia or stenosis, respectively. Defects in mesoderm at the level of the perineal body are thought to result in perineal fistula.

An alternative theory of the embryologic origin of anorectal malformation focuses on the dorsal cloacal membrane in observations in pigs with anorectal malformations (Van der Putte, 1986; Van der Putte and Neeteson, 1984). Van der Putte suggests that the division of the anal and urogenital systems is the result of a marked alteration in the shape of the cloaca by disproportionately strong growth of the mantle mesenchyme surrounding the urogenital compartment (Van der Putte, 2006).

As many as 50% of cases of anorectal malformations have associated anomalies (Table 76-1). Spinal or skeletal anomalies are present in 50% of cases, genitourinary anomalies in 58%, tracheoesophageal fistula in 10%, and cardiac anomalies in 5% (Sanders, 1996; Stoll et al., 2007). Imperforate anus is part of the VACTERL association and is not uncommon in trisomy 21 (Torres et al., 1998).

INCIDENCE

The incidence of imperforate anus is 1 in 5000 livebirths (Boocock and Donnai, 1987; Cuschieri and EUROCAT Working Group, 2001; Kiely and Pena, 1998; Schwoebel, 1984; Stephens and Smith, 1971). Most reports note a male preponderance of between 55% and 65% of cases (Kiely and Pena, 1998; Stephens, 1953; Weinstein, 1965). Imperforate anus has been linked to maternal diabetes mellitus, thalidomide exposure, ethanol intake, and assisted reproductive technology (Midrio et al., 2006).

SONOGRAPHIC FINDINGS

It is unusual to make a diagnosis of imperforate anus on a prenatal sonographic examination. In a series of 69 cases of imperforate anus, only 11 (15.9%) were diagnosed prenatally (Brantberg et al., 2006). Similarly, Livingston et al. (2006) found that in a series of 95 children diagnosed postnatally with anorectal malformations, the correct diagnosis was made by antenatal sonography in only one child. Sanders (1996) has noted that the anus can be seen in the normal fetus as an echogenic dot on a transverse view at the level of the genitalia. He notes that this dot is absent in cases of imperforate anus. The reliability of the absence of this echogenic dot is unknown. It likely represents the echogenic sphincter complex, which may be present even if there is imperforate anus. More commonly, a dilated distal colon may be observed in the fetal pelvis (Guzman et al., 1995; Taipale et al., 2005) (Figure 76-1). But as Kaponis et al. (2006) have observed, bowel dilatation in anorectal malformations may be transient, occurring only during the first trimester (Gilbert et al., 2006).

Harris et al. (1987) reviewed sonographic features of 12 cases of anorectal atresia and found evidence of bowel dilatation in the distal colon in 5 of the 12 cases. The features of distal bowel obstruction become more obvious as the fetus approaches term. The earliest reported prenatal diagnosis of imperforate anus is 29 weeks of gestation; however, isolated transient bowel dilation which proved to be due to anorectal malformation has been observed as early as 12 weeks of gestation (Gilbert et al., 2006; Kaponis et al., 2006; Lam et al., 2002).

Because of the distal level of obstruction, some authors found it unusual that any degree of bowel dilatation was detectable and blamed the rectourethral or rectovesical fistula as a cause of bowel dilatation (Goldstein, 1994). In cases in which an anorectal malformation is suspected, amniotic fluid levels of digestive enzymes gammaglutamyl transpeptidase, aminopeptidase M, and intestinal alkaline phosphatase were found to be less than the first percentile (Bourdelat et al., 2001).

Several authors have reported intraluminal colonic calcifications in imperforate anus (Bean et al., 1978; Grant et al., 1990; Sholen et al., 1983). This is presumed to be due to urine refluxing via the associated rectourethral fistula and precipitating as calcified meconium. There are a number of sonographically detectable abnormalities that may be seen in association with imperforate anus, including renal agenesis, renal dysplasia, horseshoe kidney, uterine duplications, cardiovascular, central venous system, and gastrointestinal and skeletal system anomalies.

Table 76-1

Anomalies Associated with Anorectal Malformations (ARM)

Syndrome	Prominent Features	Inheritance Pattern
ARM alone		
Isolated imperforate anus	None	Heterogeneous, AR, XLR, and AD
ARM and neurologic anomalies		
Anosacral defect	Anterior sacral meningocele, teratoma, or cyst Macrocephaly, broad forehead, frontal hair upswept, hypotonia, mental retardation	Heterogeneous, AD, XLD, FG, XL
ARM and skeletal anomalies		
Baller–Gerold	Craniosynostosis, radial defect, short stature	AR
IVIC	Radial defects, strabismus, thrombocytopenia, deafness	AD
Jarcho–Levin	Rib and vertebral defects, respiratory failure in infancy	AR
Presacral teratoma	Sacral dysgenesis	AD
Saldino–Noonan	Short ribs, short limbs, postaxial polydactyly, visceral abnormalities, lethality	AR
Say	Preaxial polydactyly, malformed vertebral bodies and ribs (may be the same as PIV syndrome)	Sporadic
Thanatophoric dysplasia	Micromelia, platyspondyly, early death	Sporadic
Townes–Brocks	Deafness, triphalangeal thumb, overfolded helices, flat feet	AD
ARM and chromosomal anomalies		
Cat eye	Ocular coloboma; ear, cardiac, and renal anomalies; variable mental retardation	Extra small marker chromosome derived from 22
Tetrasomy 12p	Coarse face, sparse anterior scalp hair, hypertelorism, epicanthus, hypotonia, hypomelanotic spots, severe mental retardation	Chromosomal anomaly
ARM and cardiovascular anomalies		
Fuhrmann	Polydactyly, heart defect	Uncertain
ARM and urogenital anomalies		
Hypertelorism–hypospadias	Hypertelorism, hypospadias (may be the same as Opitz G syndrome)	XLR
Opitz BBB	Same as Opitz G	
Opitz G	Hypertelorism, hypospadias, swallowing defects	AD
ARM and multiple anomalies		
Ankyloblepharon filiforme	Fused eyelids and normal globe endocardial cushion defects, fused digits, cleft lip and palate, esophageal atresia	AD
Adnatum ASP association	Anal anomalies, sacral defect, presacral mass (teratoma, cyst, or meningomyelocele)	Chromosomal anomaly
Axial mesodermal defect	Sacral dysgenesis; dysfunction of lower limbs, bladder, and bowel; aphalangy; spinal and rib abnormalities	AR
Caudal regression	Dysgenesis of lower spine; variable dysfunction of bladder, bowel, and lower limbs	Heterogeneous, maternal diabetes mellitus in some cases AD

(*continued*)

Table 76-1

Anomalies Associated with Anorectal Malformations (ARM) (*Continued*)

Syndrome	Prominent Features	Inheritance Pattern
ARM and multiple anomalies (*continued*)		
Christian skeletal dysplasia	Metopic ridge, cervical fusion, dysplastic spine, abducens palsy, mental retardation	XLR
Cryptophthalmos	Palate, ear, renal, laryngeal, genital, digital, and eye malformations	AR
Diabetes, maternal	Fetal overgrowth; increased incidence of neural tube defects, cardiac anomalies, caudal dysgenesis, and renal defects	Exposure of abnormal glucose metabolism during pregnancy
Johanson–Blizzard	Hypoplastic alae nasi, exocrine pancreatic insufficiency, deafness, hypothyroidism	AR
Kaufman–McCusick	Congenital heart defects, polydactyly, hydrometrocolpos	AR
Lowe	Sensorineural deafness, nephritis	AD
Meckel	Encephalocele, polydactyly, cystic kidneys	AR
OEIS	Omphalocele, exstrophy of the bladder, imperforate anus, spinal defects	Uncertain, may have vascular cause
Pallister–Hall	Hypophthalmic hemartoblastoma, hypopituitarism, postaxial polydactyly	Sporadic
Pallister: ulnar mammary	Ulnar ray defects, delayed puberty, oligodactyly or polydactyly, hypoplasia of apocrine glands and breasts, genital anomalies	AD
PIV	Polydactyly, imperforate anus, vertebral anomalies	Sporadic
Potter variant	Renal, lung, thymic, parathyroid, dysplasia	AR (?) chromosomal anomaly
Rieger	Ocular anterior chamber anomalies, hypodontia	AD
Sirenomelia	Single, lower limb, renal agenesis, genital agenesis	Sporadic, based on vascular steal
VACTERL	Vertebral, anal, cardiac, tracheoesophageal, renal, and radial limb defects	Sporadic

KEY: AD = autosomal dominant; AR = autosomal recessive; ASP = anal anomalies, sacral defect, presacral mass; IVIC = Instituto Venezolano de Investigaciones Cientificas; OEIS = omphalocele, exstrophy of bladder, imperforate anus, spinal defects; PIV = polydactyly, imperforate anus, vertebral anomalies; XL = X-linked; XLD = X-linked dominant; XLR = X-linked recessive.
Source: Paidas CN, Pena A. Rectum and anus. In: Oldham KT, Columboni P, Folgi RP, eds. Surgery of infants and children: scientific principles and practice. *Philadelphia: Lippincott-Raven, 1996:1330-1331.*

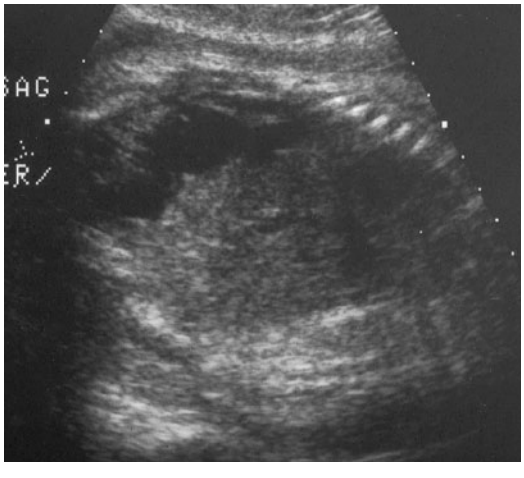

Figure 76-1 Prenatal sonographic image of a fetus who was diagnosed at birth with imperforate anus. Mild colonic distention was noted prenatally.

DIFFERENTIAL DIAGNOSIS

The main differential diagnosis for anorectal atresia includes colonic atresia, Hirschsprung's disease, meconium plug syndrome (Nyberg et al., 1987), distal small-bowel atresia (Vermesch et al., 1986), hydrometrocolpos, ovarian cyst, obstructive uropathy, megacystic-microcolon hypoperistalsis syndrome, urachal cyst, and persistent cloaca (Paidas and Pena, 1996).

Imperforate anus may also occur as part of the VACTERL association. When associated with esophageal atresia, increased amniotic fluid volume and an absent stomach bubble may be noted. Imperforate anus occurs in trisomies 18 and 21; sonographic features of these syndromes should be ruled out (see Chapters 130 and 131). Recently, MRI has become an important adjunct in the prenatal diagnosis of complex malformations including anorectal malformations (Livingston et al., 2006) (Figure 76-2).

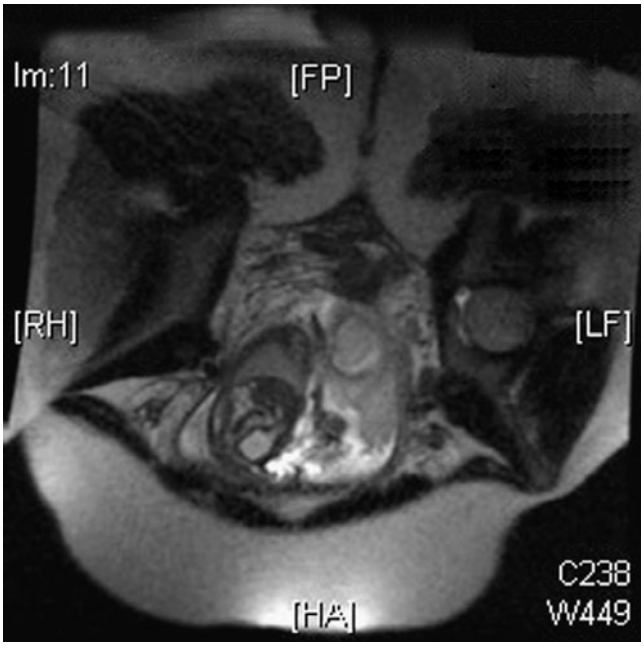

Figure 76-2 Dilated rectum that does not reach the perineum on T2 weighted sagittal image of a fetus with imperforate anus.

ANTENATAL NATURAL HISTORY

Only a few cases of imperforate anus have been prospectively diagnosed prenatally (Bean et al., 1978; Guzman et al., 1995; Harris et al., 1987; Grant et al., 1990; Nyberg et al., 1987). If isolated, the finding of anorectal atresia should not have any direct bearing on the outcome of the pregnancy. If seen as part of the VACTERL association, however, polyhydramnios may appear after 28 weeks of gestation if associated esophageal atresia is present (Greenwood et al., 1975; Smith et al., 1988).

FETAL INTERVENTION

There are no fetal interventions indicated for imperforate anus.

MANAGEMENT OF PREGNANCY

A fetus in which imperforate anus is suspected should undergo a targeted sonographic examination to rule out associated anomalies. In particular, a detailed examination of the genitourinary tract is indicated because of the possibility of associated renal agenesis, renal dysplasia, and horseshoe kidney. Careful examinations of the central nervous system and spine, as well as the gastrointestinal tract, are indicated. Because of the increased risk of structural heart disease, an echocardiogram should be obtained. Because there is also an increased incidence of chromosome abnormalites, such as trisomies 18 and 21, cat eye syndrome, and tetrasomy 12p, amniocentesis for karyotype analysis is recommended. The nature of this anomaly does not alter the indications for delivery. Vaginal delivery should be planned except when standard obstetric indications suggest cesarean delivery. Because the child will require immediate postnatal evaluation and treatment, delivery in a tertiary care center with pediatric radiologists, surgeons, and dysmorphologists available is advisable. Because of the complex nature of this anomaly and the extensive nature of the reconstructive surgery, prenatal consultation with a pediatric surgeon is recommended.

TREATMENT OF THE NEWBORN

The newborn with imperforate anus should be expeditiously evaluated to rule out serious potential associated malformations. Plain chest, abdominal, and pelvic radiographs should be obtained to exclude vertebral anomalies and assess the sacrum, which has a direct bearing on the prognosis in imperforate anus. An abdominal ultrasound examination should be obtained to evaluate the genitourinary tract and the level of the rectal pouch (Willital, 1971).

Once the infant's respiratory status has been assessed, a nasogastric tube should be passed into the stomach to exclude the presence of esophageal atresia. The infant's perineum should be inspected to confirm imperforate anus and look for signs of low imperforate anus, rectoperineal, or rectovestibular fistula (Figure 76-3). The adequacy of the sphincter complex can be evaluated at the bedside by eliciting a reflex contraction by gently scraping the perineum with a swab.

The infant should receive nothing orally and should receive intravenous fluids until the evaluation is complete and a decision is made to proceed with perineal anoplasty (in low lesions) or colostomy (for intermediate and high lesions). An echocardiogram should be obtained, as cardiovascular anomalies are frequently associated with imperforate anus (Boocock and Donnai, 1987; Greenwood et al., 1975; Templeton and Ditesheim, 1985). Duodenal obstruction due to either atresia or to malrotation occurs in 1% to 2% of cases (Greenwood et al., 1975; Partridge and Gough, 1961). Hirschsprung's disease also occurs in association with imperforate anus (Arbell et al., 2006; Kiesewetter et al., 1965; Wangensteen and Rice, 1930).

A flat perineum with missing sacral segments on the pelvic radiograph and poor contraction following perineal scratch suggests a high imperforate anus. In males, passage of meconium via the urethra suggests an intermediate or high lesion. Meconium passing through a perineal fistula suggests a low imperforate anus. After 24 hours, air should have reached the distal rectum. A plain lateral radiograph can be obtained with the body prone and the hips raised, a modification of the so-called invertogram (Narasimharao et al., 1983). A gap of 1 cm or more between the rectum and the skin of the perineum usually represents a high lesion, while a gap of less than 5 mm usually indicates a low lesion.

The infant should remain on prophylactic antibiotics until vesicoureteral reflux is ruled out. Voiding cystourethrography will exclude or confirm vesicoureteral reflux, and may also demonstrate a rectovesical fistula. An ultrasound examination or magnetic resonance imaging (MRI) scan of the

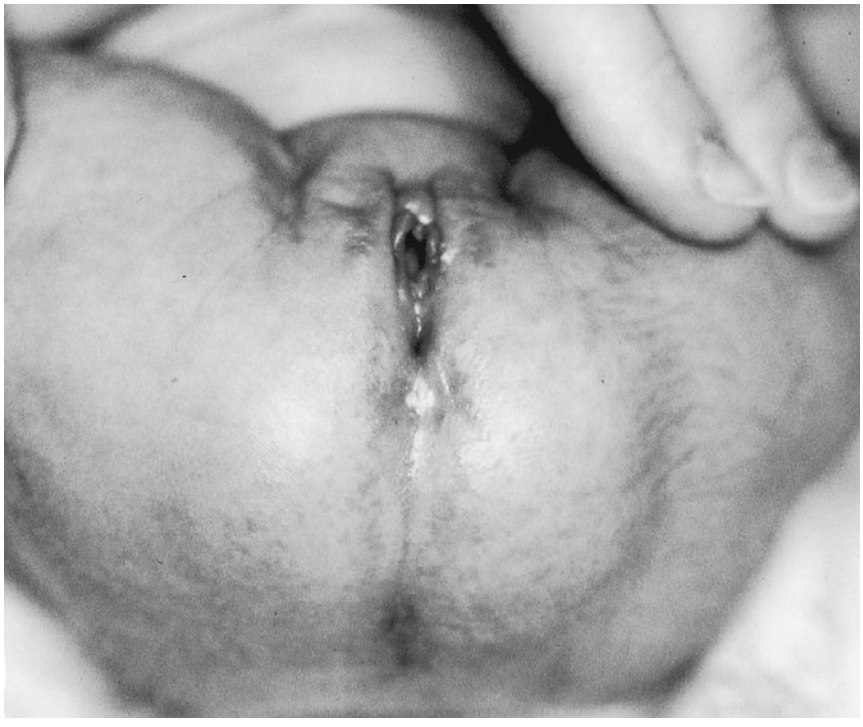

Figure 76-3 Postnatal appearance of the female infant whose prenatal sonographic image is shown in Figure 76-1.

spine should also be obtained to exclude a tethered spinal cord.

SURGICAL TREATMENT

In low imperforate anus several options for management are available. In cases of perineal fistula some form of anal transposition, Y-V anoplasty, or a limited posterior sagittal anorectoplasty are treatment possibilities (Nixon and Puri, 1977; Stone, 1936).

In cases of intermediate and high levels of imperforate anus, a diverting colostomy is performed in the first few days of life. A loop colostomy or colostomy with mucous fistula will allow an antegrade contrast study to determine the level of rectourethral fistula. Anorectal reconstruction can then be carried out at 4 to 8 weeks of age, using the posterior anorectoplasty technique described by deVries and Pena, (1982).

LONG-TERM OUTCOME

The mortality rate associated with imperforate anus is low usually due to associated cardiac or renal abnormalities (Kiely and Pena, 1998). In addition to the usual postoperative complications, voiding dysfunction, stenosis, mucosal prolapse, and constipation may occur. It is uncertain if voiding dysfunction is a consequence of the surgery or reflects a preexisting problem (Kazizoke, 1994; Sheldon, 1991). Anal stenosis may occur in up to 30% of cases but responds to anal dilatations (Nixon and Puri, 1977). Mucosal prolapse may occur after PSARP but requires only trimming the mucosa back in cases that are symptomatic. Constipation is a very common problem in patients following reconstruction for imperforate anus, but this usually responds to medical management.

Continence is usually achieved in about 90% of patients with a low imperforate anus (Matley, 1990; Nixon and Puri, 1977; Rintala et al., 1991). Total continence in high imperforate anus has been disappointing, with rates varying from 0% for cases of bladder neck or vaginal fistula to 26% of cases with a prostatic fistula. Cases of intermediate-level imperforate anus with bulbar or vestibular fistula have continence rates of 34% and 66%, respectively. Voluntary bowel movements occur in cases of intermediate-level imperforate anus at rates of 80% to 93%.

In cases in which continence cannot be achieved, either because of inadequate sphincter complex or inadequate innervation, the Malone antegrade continent enema or MACE procedure may provide a means of staying clean and avoiding a colostomy (Levitt et al., 1997; Malone et al., 1990). In this procedure the appendix is brought out as a catheterizable stoma to deliver daily antegrade enemas to clear the colon and prevent soilage during the day (Squire, 1993).

GENETICS AND RECURRENCE RISK

Imperforate anus occurs in association with a number of syndromes (see Table 76-1). Recurrence risks will depend on whether the anorectal atresia is isolated or syndromic. Most isolated cases are thought to be sporadic, but rare familial cases have been described. Anorectal anomalies may occur as part of a syndrome of multiple malformations (Pinsky, 1978). These patterns of malformations have occurred in clusters, suggesting an autosomal dominant trait that has been transmitted to succeeding generations (Nour et al., 1989; Schwoebel, 1984).

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Echogenic Kidneys

77
CHAPTER

Key Points

- Echogenic kidneys can be a normal variant but are also seen in association with renal dysplasia, chromosomal abnormality, adult and fetal polycystic disease, Pearlman syndrome, Beckwith–Wiedemann syndrome, and CMV infection.
- The incidence of echogenic kidneys has been estimated at 1.6 cases per 1000 sonograms.
- Kidneys are considered echogenic if the reflectivity of the renal parenchyma is greater than the reflectivity of the liver.
- Once diagnosed, other sonographic features of aneuploidy, renal anomalies, and CMC infection should be sought.
- Consider genetic amniocentesis, TORCH titers, and fetal MRI to better evaluate the genitourinary tract and renal parenchyma.

CONDITION

There are some conditions that render the renal parenchyma echogenic on ultrasound examination. While increased renal echogenicity can be a normal variant in children, it has been associated with nephrotic syndrome, glomerulonephritis, and renal dysplasia (Krensky et al., 1983; Brenbridge et al., 1986; Cramer et al., 1986; Kraus et al., 1990). Premature infants also have an increased incidence of increased renal echogenicity (Benacerraf, 1998). While increased echogenicity is a subjective assessment, kidneys that are brighter than liver are considered to be echogenic. This becomes a potential indicator of fetal disease because of the association of this finding with chromosomal abnormality, adult and infantile polycystic kidney disease, Pearlman syndrome, Beckwith–Wiedemann syndrome, and cytomegalovirus infection. The cause of the increased echogenicity of the kidney in these conditions is unknown.

INCIDENCE

Little data are available to estimate a true incidence of echogenic kidneys in the fetus, in either normal fetuses or those with underlying pathology. However, De La Vega and Torres (2005) in a retrospective review of prenatally diagnosed renal disease found 13 cases among 7714 sonographic studies for an incidence of 0.16% or 1.6 cases per 1000 sonograms (Han et al., 2003).

SONOGRAPHIC FINDINGS

The kidneys should be considered to be echogenic if the reflectivity of the renal parenchyma is greater than the reflectivity of the liver (Figure 77-1). Once identified, it is important to note other possible associated findings that would aid in the differential diagnosis. It is important to look for other

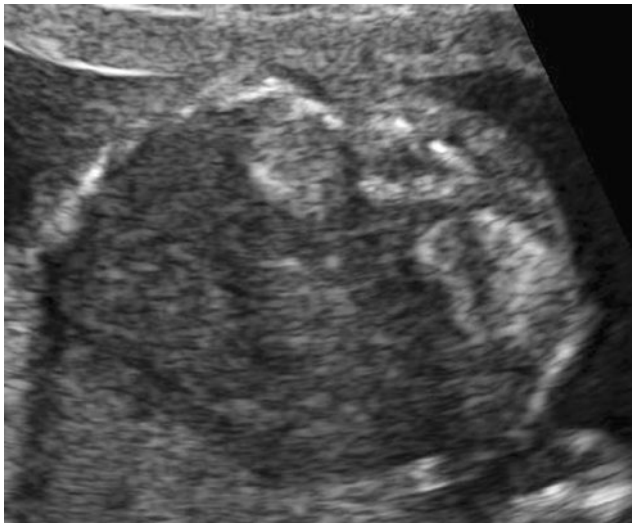

Figure 77-1 Axial image through fetal abdomen demonstrating bilateral echogenic kidneys.

sonographic features that are associated with aneuploidy, especially trisomy 13, including ventriculomegaly, holoprosencephaly, agenesis of the corpus callosum, cleft lip or palate, cyclasia, or microphthalmia. Because of the association of echogenic kidneys with cytomegalovirus infection, attention should be paid to the presence of intracranial calcifications, echogenic bowel, ascites, hydrops, or cardiomegaly (Choong et al., 1993). If the possible renal abnormalities seen with echogenic kidneys (including severe obstructive uropathy at any level from the bladder outlet to the ureteropelvic junction) occur during the second trimester, they can result in increased echogenicity from renal dysplasia. The kidneys in adult and infantile polycystic kidney disease can also be echogenic, but they are usually much larger than normal and may lack normal renal architecture and have severe associated oligohydramnios (see Chapter 79).

DIFFERENTIAL DIAGNOSIS

As noted above, it is important to remember that increased renal echogenicity is a normal variant and there may be no underlying pathology. The differential diagnosis of echogenic kidneys includes cytomegalovirus infection, aneuploidy, particularly trisomy 13, other chromosomal abnormalities such as partial trisomy 10, adult and infantile forms of polycystic kidney disease, and renal dysplasia secondary to obstructive uropathy (see Table 77-1).

ANTENATAL NATURAL HISTORY

What is known about the antenatal natural history of echogenic kidneys is based on two small retrospective reports. Chitty et al. (1991) reported five fetuses with enlarged echogenic kidneys in which the amniotic fluid volume was preserved. The causes of renal echogenicity in their cases included infantile or autosomal recessive polycystic kidney disease, adult or autosomal dominant polycystic kidney disease, trisomy 13, Pearlman syndrome, and cystic renal dysplasia. Estroff et al. (1991) reported their experience with 19 patients with echogenic kidneys in which the process was bilateral in 14 and unilateral in 5 patients. This group excluded cases of renal dysplasia induced by obstructive uropathy as a cause of increased echogenicity. Surprisingly, only 21% of these fetuses proved to be normal at birth. Five fetuses (26%) did not survive because of associated oligohydramnios in cases of infantile polycystic kidney disease or bilateral multicystic dysplastic kidneys. There was a 53% survival rate in this series. However, all infants had abnormalities, including unilateral renal dysplasia, unilateral multicystic dysplastic kidney and hydronephrosis. The most important prognostic factor in this report was the presence or absence of oligohydramnios. If the amniotic fluid volume is preserved and the fetus is otherwise normal except for echogenic kidneys of uncertain cause, the prognosis is good but the infant will be expected to have nonlethal renal disease. In contrast, in cases of echogenic kidneys associated with oligohydramnios the survival rate is dismal (Benacerraf, 1998).

Table 77-1

Differential Diagnosis of Echogenic Kidneys

1. Cystic kidney diseases
   - Autosomal recessive polycystic kidney disease
   - Autosomal positive polycystic kidney disease
   - Multicystic dysplastic kidney disease
2. Kidney neoplasms*
   - Congenital mesoblastic nephroma
   - Wilms tumors
3. Infectious agents
   - Cytomegalovirus infections
   - Candida infections
4. Chromosomal abnormalities
   - Trisomy 9 (nonmosaic)
   - Trisomy 10 (partial)
   - Trisomy 13
   - Trisomy 21
5. Idiopathic echogenic kidney

** Leclair MD, El-Ghoneimi A, Audry G, Ravasse P, Moscovici J, Heloury Y; French Pediatric Urology Study Group. The outcome of prenatally diagnosed renal tumors. J Urol. 2005 Jan;173(1):186-189.*

MANAGEMENT OF PREGNANCY

The sonographic detection of echogenic kidneys indicates the need for a targeted fetal anatomy scan to be performed to

evaluate potentially associated conditions. In particular, it is important to evaluate the amniotic fluid volume and genitourinary tract for signs of obstructive uropathy or features of adult or infantile polycystic kidney disease. In addition, features of cytomegalovirus infection should be sought. Because of reported cases of chromosomal abnormality associated with echogenic kidney, we recommend that a genetic amniocentesis be performed (Chitty et al., 1991; Estroff et al., 1991). Because of the prognostic significance of the development of oligohydramnios in patients with echogenic kidneys, serial scans are indicated. Estroff et al. (1991) noted that echogenic kidneys associated with moderate-to-severe oligohydramnios have an extremely poor postnatal outcome. In contrast, normal amniotic fluid volume in a fetus with echogenic kidney was associated with a good prognosis. The most important aspect of management of a pregnancy in which echogenic kidneys are detected is to appropriately counsel the parents and systematically exclude potential causes. TORCH titers should be obtained. A family history is essential to rule out polycystic kidney disease. In addition, maternal and paternal renal ultrasound examinations should be performed because of the high prevalence of adult polycystic kidney disease in the general population (see Chapter 79). The infantile or recessive form of polycystic kidney disease is more commonly observed prenatally, and a fetus with large echogenic kidneys is more likely to have the infantile form if both parents have normal renal ultrasound examinations.

Decisions regarding mode and site of delivery can be deferred until a definitive diagnosis is made or serial scans have demonstrated oligohydramnios or preserved amniotic fluid volume.

FETAL INTERVENTION

There are no fetal interventions for echogenic kidneys.

TREATMENT OF THE NEWBORN

The newborn noted to have echogenic kidneys in utero should undergo careful postnatal examination to exclude potential underlying causes. If a karyotype has not been obtained prenatally, it should be done postnatally. A renal ultrasound examination should be obtained to assess the size and echogenicity of the kidney. If hydronephrosis of any degree is detected, the infant should also undergo voiding cystoureterography (VCUG) and a diuretic renal scan to assess function and to evaluate for obstruction and vesicoureteral reflux (see Chapters 80, 81, 82, 83). By 36 to 48 hours of postnatal age, the newborn's serum creatinine and blood urea nitrogen levels should reflect the infant's renal function. The newborn's blood pressure should be carefully monitored in cases of adult or autosomal dominant polycystic kidney disease (Cole et al., 1997) (see Chapter 79).

LONG-TERM OUTCOME

Tsatsaris et al. (2002) in a prospective cohort study of 43 cases, prenatally detected isolated bilateral echogenic kidneys and followed them for 34 to 132 months. There were 20 autosomal recessive, 8 autosomal dominant polycystic kidney diseases, 9 other renal disorders, and 6 symptom-free survivors without etiological diagnosis. There were 19 terminations of pregnancy, 5 neonatal deaths, and 19 survivors, of whom 14 had normal renal function 3 had mild and 2 had end-stage renal failure. There were no survivors among those with severe oligohydramnios and enlarged fetal kidneys measuring more than 4 SD above the mean ($n = 14$, 10 terminations and 4 neonatal deaths), whereas of the 17 with normal amniotic fluid volume and kidneys measuring less than 4 SD above the mean, 14 survived of whom 9 were symptom free. As this is a sonographic finding and not a specific etiologic diagnosis, the reader is referred to chapters on the specific underlying diagnoses, including polycystic kidneys (see Chapter 79), hydronephrosis (see Chapters 80, 81, 82, 83), multicystic dysplastic kidneys (see Chapter 78), and trisomy 13 (see Chapter 129).

GENETICS AND RECURRENCE RISK

The risk of recurrence of echogenic kidney depends on whether the underlying cause is sporadic (cytomegalovirus infection, trisomy 13, Beckwith–Wiedemann syndrome) or has a recognized pattern of inheritance. Infantile polycystic kidney disease is inherited as an autosomal recessive condition, and there is a 25% chance that a subsequent pregnancy will be affected, while the adult form of autosomal dominant polycystic kidney disease has a 50% chance of affecting subsequent fetuses. It is not known what percentage of affected fetuses will present in utero with echogenic kidneys in a subsequent pregnancy. However, in autosomal dominant polycystic kidney disease, families should have blood samples collected for DNA analysis prior to a subsequent pregnancy (Breuning et al., 1990). Once a mutation has been identified in a specific family, prenatal DNA diagnosis is available as early as 10 weeks via chorionic villi sampling (see Chapter 79).

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78 CHAPTER Multicystic Dysplastic Kidney

Key Points

- Multicystic dysplastic kidney (MCDK) is a severe renal abnormality associated with atretic ureter and absence of normal renal parenchyma, which is replaced by multiple large noncommunicating cysts.
- MCDK is generally easily diagnosed prenatally, often due to the large size of the kidney and its constituent cysts.
- It is usually unilateral, while the rare cases of bilateral MCDK present as Potters syndrome.
- In almost half of the cases of unilateral MCDK, the contralateral kidney will have associated malformations, the severity of which determines the overall prognosis.
- Management of pregnancy and delivery generally does not need to be changed following the prenatal diagnosis of MCDK.
- While some cases of unilateral MCDK will regress prenatally or in pediatric life, there is no agreement on need for nephrectomy in those cases with persistent MCDK.
- MCDK greater than 6 cm, cases in which the MCDK obstructs the diaphragm or gastrointestinal tract, or cases in which hypertension develops will generally require nephrectomy.

CONDITION

Multicystic dysplastic kidney (MCDK) is the second most common cause of a flank mass in the newborn (Kaplan, 1998). MCDK was first described by Schwartz in a 7-month-old child in 1929 as a "bunch of grapes" replacing the kidney with associated ureteral atresia. Spence (1955) subsequently described MCDK and distinguished it from other cystic renal diseases.

MCDK is an extreme form of dysplasia associated with an atretic ureter. There is often a lack of normal reniform shape, with multiple large cysts and little stroma, giving the "bunch of grapes" appearance. MCDK is typically unilateral, but bilateral MCDKs have been reported in stillborn infants with oligohydramnios and Potter syndrome facies. In unilateral MCDK, the contralateral kidney is normal but at high risk for other abnormalities (Greene et al., 1971; DeKlerk et al., 1977). The contralateral kidney may be affected by

ureteropelvic junction obstruction, vesicoureteral reflux, or obstructive megaureter.

MCDK often presents as an asymptomatic abdominal mass in the neonate (Langino and Martin, 1958). However, currently approximately 85% to 100% of MCDKs are detected by prenatal sonographic examination (Manzoni and Caldamone, 1998; Kuwertz-Broeking et al., 2004). MCDK was often discovered during the course of investigation of other associated congenital anomalies. In particular, esophageal atresia and cardiac anomalies may be associated with MCDK. Other associated nongenitourinary anomalies include anencephaly, hydrocephalus, spina bifida, cleft palate, microphthalmia, duodenal stenosis, tracheoesophageal fistula, and imperforate anus. The pathogenesis of this disorder is poorly understood but is thought to involve failure of the ureteric bud to integrate and branch appropriately into the metanephron during the development of the kidneys (Kitagawa et al., 2000).

INCIDENCE

The incidence of MCDK is estimated at between 1 in 1000 and 1 in 4300 livebirths (Sanders, 1996; Kaplan, 1998). The incidence of bilateral MCDK is estimated at 1 in 10,000 livebirths (Resnick and Vernier, 1981). The male-to-female ratio is 2:1 in contralateral MCDK (Sanders and Hartman, 1984). No estimates are available for the prenatal incidence of MCDK, but it may be more common than the incidence figures above would indicate. It has been also suggested that MCDK is the major cause of apparent unilateral renal agenesis in adults (Aslam and Watson, 2006) as a result of progressive involution.

SONOGRAPHIC FINDINGS

The sonographic features of MCDK include a cystic paraspinal flank mass. The cysts are usually of various sizes, are distributed along the periphery, do not appear to communicate with each other, and are absent of normal renal sinus echos and normal renal parenchyma (Stuck et al., 1982) (Figure 78-1). The large cysts often distort the kidney shape and no normal renal parenchymal tissue is seen (Mahony, 1994). The size and shape of an MCDK may change significantly during the course of gestation (Hashimoto et al., 1986). The cysts may regress or enlarge and then, subsequently, regress in size. Once the condition is identified, the kidney opposite to the MCDK becomes of paramount importance because of the 40% incidence of contralateral anomalies (Kleiner et al., 1986). Preservation of normal amniotic fluid volume suggests normal renal function in the contralateral kidney. However, oligohydramnios and absence of bladder filling suggest a lethal fetal renal disease, which occurs in 30% of fetuses with MCDK. In two-thirds of the cases of oligohydramnios there is bilateral MCDK, and in the remaining third there is renal agenesis.

The development of oligohydramnios in bilateral MCDK may occur as early as 12 weeks of gestation (Stiller et al., 1988). A first trimester ureteropelvic junction obstruction may be observed to progress during the second trimester to MCDK. In approximately 10% of cases of MCDK, the contralateral kidney shows signs of hydronephrosis, often from obstruction at the ureteropelvic junction (Mahony, 1994).

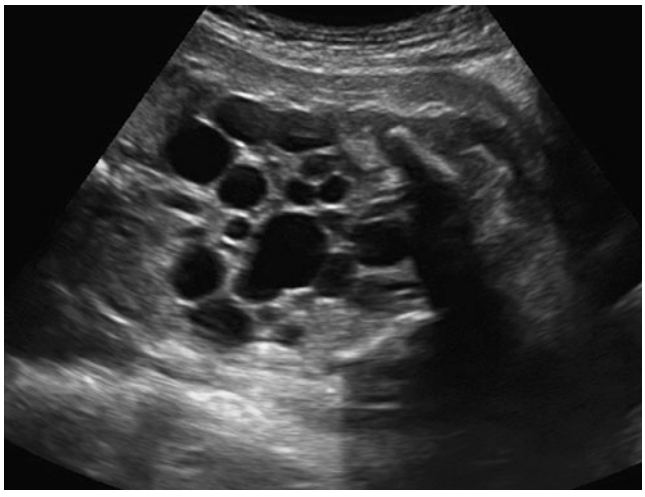

Figure 78-1 Prenatal sonographic image of a fetal kidney in sagittal view demonstrating multiple cysts that do not have a uniform shape and do not communicate, consistent with the diagnosis of multicystic dysplastic kidney.

DIFFERENTIAL DIAGNOSIS

The main differential diagnosis of MCDK includes ureteropelvic junction obstruction, adult or infantile forms of polycystic kidney disease, trisomy 13, and Meckel–Gruber syndrome (D'Alton et al., 1986). Perhaps the most difficult distinction is between ureteropelvic junction obstruction (see Chapter 81) and the hydronephrotic form of MCDK (Rizzo et al., 1987). The sonographic detection of renal parenchymal cysts that communicate with the renal pelvis suggests the diagnosis of ureteropelvic junction obstruction (Romero et al., 1988). In adult polycystic kidney disease (see Chapter 79), the cysts are randomly distributed, in contrast to MCDK, in which the cysts tend to be at the periphery (Sanders, 1996). In Meckel–Gruber syndrome, the cysts are small, uniform, and scattered throughout the kidney. In contrast to MCDK, the kidneys in infantile polycystic kidney disease are very large and echogenic and discrete cysts are not visible (see Chapter 79). In trisomy 13, the kidney is brightly echogenic and has small cysts scattered in the renal parenchyma. The appearance of MCDK should be distinguished from Wilms' tumor or hamartoma, which may have areas of cystic necrosis (Aslam and Watson, 2006).

ANTENATAL NATURAL HISTORY

The natural history of MCDK is becoming better understood, based on studies of serial sonographic examinations of fetuses

with MCDK. Among 64 fetuses diagnosed prenatally with MCDK at the Hospital for Sick Children in London, 33% were diagnosed at 18 to 20 weeks of gestation, 44% between 20 and 30 weeks of gestation, and 33% between 30 and 40 weeks of gestation (Manzoni and Caldamone, 1998). These authors noted that 36% of sonographic examinations were reported as normal on the 18- to 20-week scans, which may indicate that MCDK is easier to diagnose in the latter half of gestation.

In 11% of cases, the MCDK increased in size while in 11% of cases the MCDK disappeared. MCDK can grow to significant proportions, occasionally filling the abdomen. These masses usually regress with time. In cases in which there are bilateral MCDKs, oligohydramnios and absent bladder are observed and this situation is uniformly fatal. In unilateral MCDK, there may be abnormalities in the contralateral system or other nongenitourinary anomalies may be present. However, if renal function is preserved in the contralateral kidney, the prognosis is excellent. One situation that requires careful monitoring is MCDK associated with ureteropelvic junction obstruction in the contralateral kidney. If the obstruction is of high grade, there may be reduced amniotic fluid volume and renal dysplasia may result in the obstructed kidney.

MANAGEMENT OF PREGNANCY

The fetus identified with MCDK should undergo a targeted sonographic examination to evaluate possible associated genitourinary and nongenitourinary anomalies (Table 78-1). Amniocentesis for karyotype analysis should be offered in all cases of MCDK because of the potential for associated chromosomal abnormalities. In cases of bilateral MCDK or unilateral MCDK with contralateral renal agenesis, if diagnosed prior to 24 weeks of gestation, termination of the pregnancy can be considered. If the mother chooses to carry the pregnancy to term, there should be no intervention for fetal distress and neonatologists should be aware of the diagnosis so that no inappropriate attempts at resuscitation are undertaken. In the case of unilateral MCDK, the prognosis depends on other associated abnormalities. Isolated MCDKs have a uniformly good prognosis. It is not necessary to change either the timing or site of delivery in such cases and cesarean delivery should be reserved for standard obstetrical indications. In cases of MCDKs associated with contralateral high-grade ureteropelvic junction obstruction, delivery once lung maturity is likely or decompression in utero may be indicated (see below).

FETAL INTERVENTION

The diagnosis of MCDK does not warrant consideration of fetal intervention except in instances that are associated with high-grade obstructive uropathy, involving either the bladder outlet or the contralateral ureteropelvic junction, with associated oligohydramnios. Under such circumstances, vesicoamniotic shunting for bladder outlet obstruction or pelvic–amniotic shunting for high-grade ureteropelvic junction obstruction can be considered. It should be pointed out that experience with such rare clinical scenarios is limited, and so it may be difficult to recommend such intervention in all cases (Kitagawa et al., 2003).

Table 78-1

Syndromes Associated with MCDK

Meckel-Gruber syndrome*
Short-rib polydactyly syndrome*
Zellweger syndrome*
Roberts syndrome*
Fryns syndrome*
Smith–Lemli–Opitz syndrome*
Apert syndrome†
Brachiootorenal syndrome†
Saldino-Noonan syndrome*
Ivemark syndrome*
Retinal–renal dysplasia*
Majewsky syndrome*

** Autosomal recessive inheritance*
† Autosomal dominant inheritance
Source: Sanders RC. Structured Fetal Abnormalities: The Total Picture. St. Louis, MO: Mosby–Year Book; 1996:100-102.

TREATMENT OF THE NEWBORN

In unilateral MCDKs with a normal contralateral kidney, an excellent prognosis is anticipated and no special measures should be required at delivery. However, if oligohydramnios or a contralateral renal abnormality is present, then newborn resuscitation may be complicated by pulmonary hypoplasia. The newborn should be carefully examined to exclude nongenitourinary abnormalities. The following postnatal studies should be considered for each newborn: renal ultrasound examination to confirm the diagnosis, diuretic renal scan to assess function, and voiding cystourethrography (VCUG) to exclude vesicoureteral reflux. Serum creatinine and blood urea nitrogen levels will begin to reflect newborn renal function

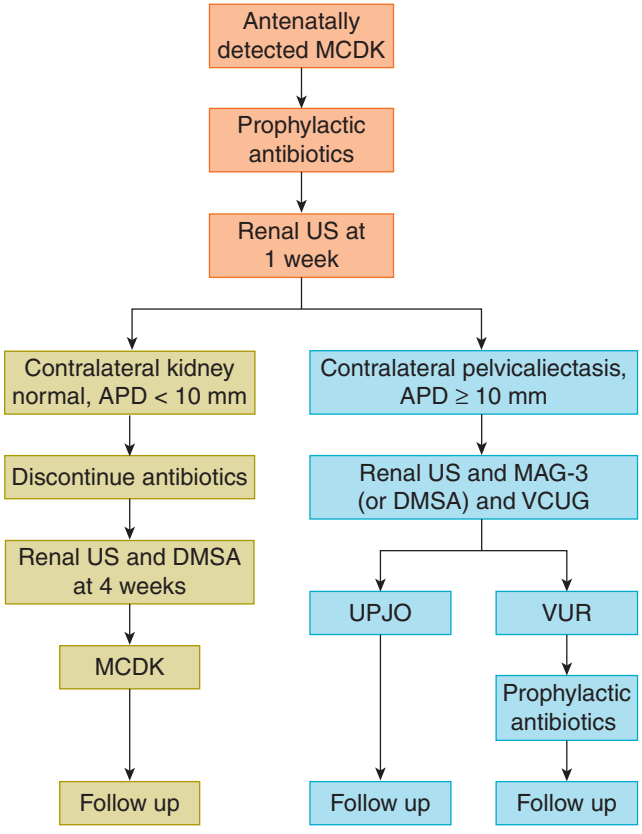

Figure 78-2 Suggested management algorithm for postnatal evaluation of a baby with antenatally detected multicystic dysplasia of the kidney.

after 36 to 48 hours of postnatal age. The infant should be treated with prophylactic antibiotics until vesicoureteral reflux is excluded. Figure 78-2 outlines the management algorithm for postnatal evaluation of a baby with antenatally detected MCDK. If no abnormal pelvic dilation in the contralateral kidney is observed, then follow-up renal ultrasound and DMSA scan should be obtained at 1 month. In contrast, Rabelo et al. reported that spontaneous total involution of MCDKs occurred in 20% and partial involution occurs in 67% (Rabelo et al., 2005). In this study, only those with renal length of ≤62 mm on initial ultrasound had complete involution during follow up (Rabelo et al., 2005). Aslam et al. observed complete involution in 33% during the first 2 years, 47% at 5 years, and 59% at 10 years (Aslam and Watson, 2006).

SURGICAL TREATMENT

See "Long-Term Outcome."

LONG-TERM OUTCOME

Manzoni and Caldamone (1998) compiled the results of 114 patients treated in five series to define the postnatal outcome in MCDKs (Gordon et al., 1988; Rickwood et al., 1992; Gaugh et al., 1995; Webb et al., 1997). Prenatal involution was observed in 6 cases (5%), and there were an additional 16 cases (17.5%) of involution postnatally. Two-thirds of these involutions were observed to occur during the first year of life. Size of the MCDK may influence whether involution occurs. MCDKs less than 5 cm in length will get smaller, disappear, or remain unchanged. Dilation of the contralateral renal pelvis should prompt renal ultrasound, MAG-3 (mercaptoacetyltriglycine-Technetium 99m) or DMSA (technetium dimercaptosuccinic acid), and voiding cystourethrography. If vesicoureteral reflux is found, then the patient should be maintained on prophylactic antibiotics and followed. Similarly, if ureteropelvic junction (UPJ) obstruction is diagnosed, it should be followed closely. Those with MCDK size greater than 6 cm often do not involute. In this study, there was a high incidence of associated genitourinary abnormalities, affecting both the upper and lower urinary tract. Ureteropelvic junction obstruction and megaureter were the most common abnormalities affecting the contralateral kidney. In four cases, renal function in the solitary kidney was already compromised. Hypertension developed in three patients from Manzoni and Caldamone's series, but their blood pressures normalized after nephrectomy. In a review of 29 studies, only 6 cases with MCDK among 1115 cases developed hypertension. Hypertension resolves with nephrectomy in almost all instances (Snodgrass, 2000; Narchi, 2005). The role of nephrectomy in MCDK remains controversial, but for certain indications most authors agree that nephrectomy is warranted. These include cases in which the MCDK represents a large mass that compromises either respiratory or gastrointestinal function (Holloway and Weinstein, 1990). In instances in which the diagnosis of MCDK is in doubt or becomes questionable because of increasing size (Minevich et al., 1996), and in instances in which the MCDK produces symptoms including pain, hematuria, or infection (Ambrose et al., 1982), surgery may be considered. Other authors consider concomitant abdominal surgery reason enough for removal of a MCDK (Hartman et al., 1986). Lastly, maintenance of an observational approach assumes that parents can comply with the long-term follow-up needed to detect hypertension or malignant transformation. If long-term follow-up is in question, nephrectomy should be considered.

The issue of nephrectomy rests on the potential development of hypertension or malignant transformation. In the past 30 years, there have only been 12 cases of malignancy reported in association with MCDK, only 6 of which occurred in children (Raffensperger and Abousleiman, 1968; Oddone et al., 1994; Minevich et al., 1996; Manzoni and Caldamone, 1998). All six pediatric patients had Wilms' tumor, while five adults had renal cell carcinoma and one adult had mesothelioma.

As of 1995, no cases of renal tumor had been described in patients with MCDK reported to the Multicystic Kidney Registry of the Section of Urology of the American Academy of Pediatrics (Wacksman, 1995). Similarly, during the past 30 years there have been only 24 cases of hypertension

reported that arose as a result of MCDK (Susskind et al., 1989; Angermeier et al., 1992; Andretta et al., 1995; Elder et al., 1995; Patterson and Klauber, 1996; Webb et al., 1997; Manzoni and Caldamone, 1998). In 13 of these cases, the hypertension responded to nephrectomy. The long-term data on malignant transformation and hypertension is meager and may not support routine prophylactic nephrectomy, but long-term surveillance is necessary in this group of patients at risk.

GENETICS AND RECURRENCE RISK

Isolated MCDKs are usually sporadic, with no risk of recurrence in subsequent pregnancies. However, there have been familial cases whose defects range from bilateral renal agenesis to hydronephrosis, with an autosomal dominant pattern of inheritance and a 50% chance of a subsequent pregnancy being affected. MCDKs can also be seen as part of numerous syndromes (see Table 78-1). Features of the genetic syndromes should be sought and excluded, as they may be associated with a specific recurrence risk.

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79 CHAPTER

Polycystic Kidney Disease

Key Points

- Autosomal recessive polycystic kidney disease (ARPKD) is characterized by bilaterally enlarged echogenic kidneys.
- Autosomal dominant polycystic kidney disease (ADPKD) is the most common lethal genetic disease inherited as a dominant Mendelian trait.
- ARPKD is less common in the general population because of its early mortality, with an incidence of 1:40,000 births.
- ADPKD has an incidence of 1 in 1000 living individuals with near 100% penetrance.
- The differential diagnosis of PKD includes Bardet–Biedl syndrome, Meckel–Gruber syndrome, Ivemark syndrome, and Jarcho–Levin syndrome.
- In the absence of associated malformations, bilaterally symmetrically enlarged echogenic kidneys with renal cysts and oligohydramnios are most likely due to either ARPKD or ADPKD.
- Renal ultrasound examinations of both parents should be obtained to evaluate for ADPKD.
- Oligohydramnios-induced pulmonary hypoplasia is a leading cause of perinatal mortality in polycystic kidney disease.
- The clinical course for prenatally presenting ADPKD is generally milder than for ARPKD.
- Aggressive neonatal management of infants with ARPKD has led to 1-year survival rates of the order of 82% to 85%.

CONDITION

Polycystic kidney disease (PKD) is an inherited disorder with diffuse involvement of both kidneys. Aside from the presence of the cysts, there is no evidence of renal dysplasia. Multiple renal cysts frequently coexist with lesions in other viscera, especially the liver (Kaplan et al., 1989a). A renal cyst is defined as an enclosed sac or nephron segment lined by epithelial cells dilated to more than 200 μm. A cystic kidney is a kidney with three or more cysts present. Cystic kidney disease is the illness caused by a cystic kidney (Kaplan et al., 1989a).

As early as 1902, it was known that the age distribution of cystic renal disease had two peaks: one close to birth and the other between 30 and 60 years of age (Kaplan et al., 1989b). In general, the use of the term *polycystic kidney disease* is restricted to single-gene disorders: autosomal dominant PKD (traditionally known as adult onset) and recessively inherited PKD (traditionally known as the infantile form). Since the 1970s, physicians have understood that the adult form can also present during infancy. In the recessive form of PKD, generalized dilatation of the collecting tubules exists, whereas in dominant PKD, cysts develop in localized segments of the kidney anywhere along the nephron (Kaplan et al., 1989a).

The dominantly inherited form of PKD (ADPKD) is a highly penetrant nephropathy with variable clinical expression that presents mainly during adulthood, but the disease can also occur at any other time during life. Autosomal dominant polycystic kidney disease is the most common lethal genetic disease inherited as a dominant Mendelian trait (Wilson et al., 2006). Mutations in the *PKD1* on chromosome 16 and *PKD2* on chromosome 4 are responsible for 85% and 15%, respectively, of cases of ADPKD (Harris, 1999). In ADPKD, progressive asymptomatic enlargement of both kidneys occurs with a gradual decline in renal function. Ultrasonography can detect renal cysts in 56% of affected patients during the first decade of life, 80% during the second decade of life, and almost 100% of individuals by the third decade of life (Michaud et al., 1994). The infantile presentation of the adult onset form of PKD was not appreciated until 1971 (Shokeir, 1978).

Bilateral PKD can be attributed to two genetically determined conditions. The so-called infantile form of PKD is inherited as an autosomal recessive condition. The cystic

dilations are fusiform and arranged radially throughout the kidney. The cysts are due to dilations of the distal convoluted tubules and collecting ducts. Concomitant cystic hepatic involvement is observed. Among survivors, hepatic fibrosis, cirrhosis, and portal hypertension occur.

From the perspective of prenatal diagnosis and neonatal presentation, the adult form of PKD is much rarer. It usually presents during the fourth to fifth decade of life. The kidney contains multiple cysts, ranging in size from microscopic to gross, located in both the cortex and the medulla. The intervening areas of the kidney may be normal (Shokeir, 1978).

ADPKD is now considered a systemic disorder. The extrarenal manifestations include liver cysts, cysts of the pancreas, and intracranial aneurysms, which occur in 5% of patients and lead to subarachnoid hemorrhage. There is also an increased prevalence of cardiac valve defects, hernias, and colonic diverticulum (European Polycystic Kidney Disease Consortium, 1994).

The recessively inherited form of polycystic disease (ARPKD) manifests during the neonatal period with respiratory distress or during early infancy with renal insufficiency. There is a wide variation in clinical course (Wisser et al., 1995). The renal involvement in autosomal recessive polycystic kidney disease (ARPKD) is invariably bilateral and largely symmetrical. It is always associated with generalized portal and interstitial fibrosis of the liver (Romero et al., 1984; Zerres et al., 1988). In 1971, Blyth and Ockenden subdivided patients with ARPKD into four groups according to the proportion of dilated renal tubules present. The perinatal classification was associated with the onset of renal failure in utero or at birth and resulted in perinatal or neonatal death. These patients had at least 90% involvement of the renal tubules. The neonatal presentation resulted in a smaller kidney size and mild hepatic fibrosis, but these patients died within 1 year and had 60% of their kidneys affected. The infantile presentation resulted in clinical symptoms by the age of 3 to 6 months, moderate hepatic fibrosis, and hepatosplenomegaly with progressive chronic renal failure, and systemic and portal hypertension. These patients had 25% of their kidneys affected. The latest presentation was the juvenile onset, which occurred between 6 months and 1 year of age and had only 10% of the kidney affected (Blyth and Ockenden, 1971).

INCIDENCE

ADPKD is one of the most common hereditary disorders in humans. It is 10 times more common than sickle cell disease, 15 times more common than cystic fibrosis, and 20 times more common than Huntington disease (Gabow, 1993). The incidence of ADPKD is 1 in 1000 living individuals, with a penetrance rate of 100% (McHugo et al., 1988). Approximately half of the affected patients present during the third to fifth decade of life with hypertension or uremia. ADPKD has been noted to occur in 1 of 500 autopsies (Pretorius et al., 1987). Because of its effect on mortality, ARPKD is less common in the general population, but it is disproportionately increased in the prenatally diagnosed population. The incidence of ARPKD is 1 in 40,000 births (Zerres et al., 1988).

SONOGRAPHIC FINDINGS

Malformations of the urinary tract are detected at a high rate because they are associated with two easily visualized sonographic markers: cystic accumulation of fluid and change in amniotic fluid volume.

Bronshtein et al. (1990) described transvaginal sonographic studies in 1940 in pregnant women at between 10 and 16 weeks of gestation. In the study population, 35 fetuses with renal anomalies were identified (1.8%), and among this group, 2 cases of ARPKD were diagnosed. These authors demonstrated that the fetal kidneys could be imaged as early as the 12th week of gestation, when they appear as hypoechogenic oval masses on both sides of the fetal spine. Indirect evidence of urine production can be inferred by observing emptying of the bladder as early as 18 weeks of gestation. In two cases, the study's authors were able to identify fetal kidneys as early as 9 weeks of gestation. In this report, two types of cystic renal anomalies were described: microcystic, which was defined as the presence of multiple small cysts in the affected kidney, resulting in a spongiform enlarged kidney that comprised most of the fetal abdomen on the longitudinal and transverse scans; macrocystic, in which the sonographic appearance of the affected kidney resembled polycystic ovaries seen in adult women. In the two cases of ARPKD, the amount of amniotic fluid observed was normal. Zerres et al. (1988) described their observations in the prenatal sonographic diagnosis of ARPKD. They noted that increased echogenicity and renal enlargement were the characteristic findings of ARPKD. Oligohydramnios can be present, but it is not required for the diagnosis. These authors thought that the most useful parameter in the prenatal diagnosis of ARPKD in families known to be at risk were repeated sonographic measurements of fetal kidney length. They concluded that prenatal sonographic diagnosis was possible only in severe cases of ARPKD. Oligohydramnios presenting during the first or second trimester carried a very poor prognosis. In a third study, Romero et al. (1984) described their observations in 19 fetuses at risk for ARPKD because of a known family history. Ten (53%) of these fetuses were affected. A definitive antenatal diagnosis of ARPKD was made by the presence of oligohydramnios, an absent urinary bladder, and bilateral renal enlargement, as measured by the kidney circumference to abdominal circumference ratio. The ratio in affected fetuses was >2 standard deviations (SD) above the mean. These authors described a typical hyperechogenic appearance of the kidneys in ARPKD. They had no false-positive diagnoses, but there was one false-negative diagnosis. In contrast, the unaffected neonates had normal bladders, normal amniotic fluid volume, and normal kidney texture. False-negative diagnosis has been reported in

ARPKD. Luthy and Hirsch (1985) described a couple with two previously affected pregnancies with ARPKD. Ultrasound examination performed at 25 weeks of gestation in a subsequent pregnancy revealed oligohydramnios, increased renal parenchymal echogenicity, and a normal renal size and normal bladder. The pregnancy was terminated electively, and at autopsy, the kidneys were shown to be normal.

Okumura et al. reported that ARPKD can be associated with densely echogenic renal pyramids (Okumura et al., 2006). They found on histology that this was due to the ectatic tubules of the pyramids in ARPKD producing multiple reflection interfaces resulting in increased echogenicity. This is a pattern of increased echogenicity that can also be seen in medullary nephrocalcinosis. This appearance has also been observed in a neonate with ARPKD (Herman and Siegel, 1991).

The prenatal diagnosis of ADPKD was first reported by Zerres et al. in 1982, who described enlarged abnormally reflective kidneys with cysts (see Figure 79-1). In a subsequent study, McHugo et al. (1988) described the presence of enlarged fetal kidneys with accentuation of the corticomedullary differentiation but no cysts. These authors thought that this specific finding distinguished between the recessive and dominantly inherited forms of PKD. Of concern in ADPKD is the fact that the sonographic lesions are detected long before the appearance of symptoms. Very few data exist concerning the rate of progression of disease in ADPKD. One report described normalization of fetal renal size in an unaffected fetus (Jeffery et al., 1998). No ultrasonographic criteria exist for clinical staging of this disease except for the presence of oligohydramnios, which carries a poor prognosis (Michaud et al., 1994). One review of 83 reported cases of ADPKD presenting in utero showed a 67% incidence of hypertension in childhood and a 43% incidence of death in the first year of life (MacDermot et al., 1998).

In a study of prenatal diagnosis of ADPKD, Pretorius et al. (1987) described five cases ascertained at their center and combined their clinical information with eight cases reviewed in the medical literature. All 13 fetuses identified had 1 parent affected, but only 5 of the 13 affected parents were aware of their diagnosis prior to pregnancy. Eleven of the 13 affected fetuses with ADPKD had renal enlargement, 10 had increased echogenicity, and 9 had specific echogenicity of the renal parenchyma. Only 6 of 13 had cysts large enough to be detected by antenatal ultrasound examination.

Echogenic kidneys with normal amniotic fluid volume pose a distinct diagnostic challenge. As reported by Mashiach et al., this can be a normal variant, as was the case in one of their seven patients (Mashiach et al., 2005). However, six of the seven patients had significant renal parenchymal disease, four patients had ADPKD, and two patients had multifocal renal dysplasia.

Fetal MRI has been used more frequently to help delineate the etiology of enlarged kidneys because of the limitations of ultrasound examination in the setting of oligohydramnios. Liu et al., described the following MRI findings on single-shot fast spin echo (SSFSE) sequences in ARPKD: hypointensity of the lungs (because of decrease in airway fluid from oligohydramnios), oligohydramnios, symmetrical nephromegaly, and nonvisualization of fluid in the renal pelvis and bladder (Liu et al., 2006). Hawkins et al., found MRI helpful in diagnosing the underlying basis for severe renal anomalies (Hawkins et al., 2008). Similarly, Cassart et al., found MRI to be complementary to ultrasound examination, and in the case of ARPKD, found a hyperintense signal in the pyramids similar to the increased echogenicity observed by sonography by Okumura et al. (Cassart et al., 2004, Okumura et al., 2006).

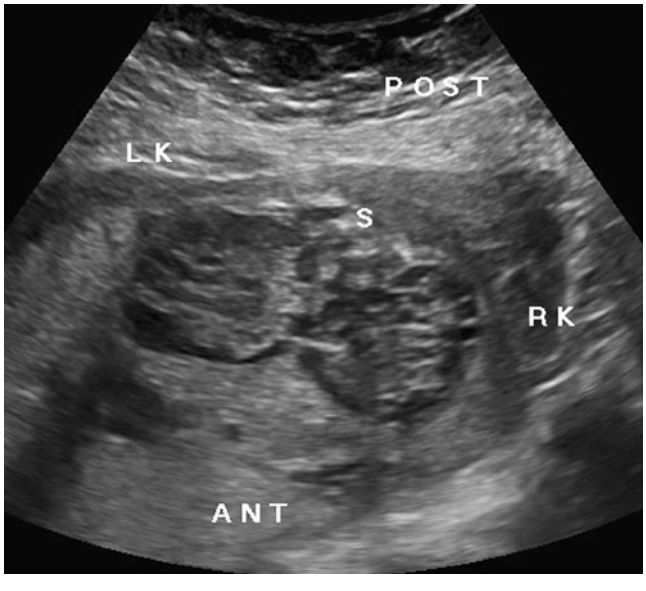

Figure 79-1 Prenatal sonographic image of a fetus with ADPKD. Note the bilateral enlarged kidneys with increased echogenicity. (S, spine; LK, left kidney; RK, right kidney.)

DIFFERENTIAL DIAGNOSIS

When cysts are observed in the fetal kidney, it is important to determine whether they are present in only one kidney or in both. Bilateral presentation is more characteristic of ARPKD. Caution must be observed, however, as ADPKD can be difficult or impossible to prenatally distinguish sonographically from ARPKD (Pretorius et al., 1987). Furthermore, the differential diagnosis of diseases that causes echogenic kidneys in the fetus and newborn differs from that of older pediatric patients (Estroff et al., 1991). Renal cysts can be characteristically found as part of other single-gene disorders, including tuberous sclerosis (Blethyn et al., 1991). It is of interest that one of the genes for tuberous sclerosis maps very closely to one of the genes for ADPKD. Blethyn et al. (1991) described a fetus with a large echogenic kidney diagnosed at 28 weeks of gestation. This infant was later noted to have seizures at 5 weeks of postnatal age, and computed tomographic (CT) scan revealed the presence of cortical tubers. Renal lesions occur in 54% to 100% of patients with tuberous sclerosis. These

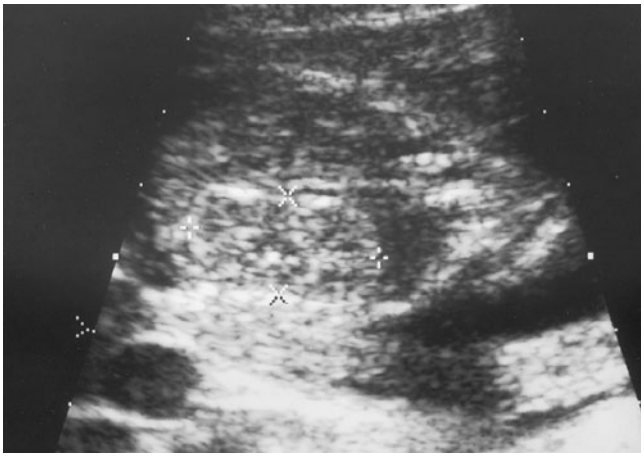

Figure 79-2 Prenatal sonographic image demonstrating increased echogenicity and multiple small cysts in a fetus with Meckel–Gruber syndrome.

consist of angiomyolipomas or renal cysts. Another condition that can present with increased echogenicity of the fetal kidneys and renal enlargement is Beckwith–Wiedemann syndrome. The other condition with bilateral renal enlargement, oligohydramnios, and increased echogenicity that presents prenatally is Meckel–Gruber syndrome (Wapner et al., 1981; Celentano et al., 2006). Sgro et al., have also reported the association of ARPKD and Caroli's disease, which is a rare autosomal recessive condition (Sgro et al., 2004). This fetus was diagnosed at 33 weeks of gestation with dilated intrahepatic bile ducts and enlarged echogenic kidneys (see Figure 79-2). Other conditions that can present with renal cysts are listed in Table 79-1.

When echogenic kidneys are associated with renal cysts, Chaumoitre et al. suggest a differential diagnosis of ADPKD, ARPKD, Bardet–Biedl syndrome, Meckel–Gruber syndrome, Ivemark syndrome, and Jarcho–Levin syndrome, based on their review of 93 fetuses (Chaumoitre et al., 2006). This group found that the key to prenatal diagnosis was the demonstration of associated anomalies that suggested a specific syndrome. In the absence of associated malformations, the main differential is between ARPKD and ADPKD.

ANTENATAL NATURAL HISTORY

The transient embryonic excretory organs—the pronephros and mesonephros—develop around 5 to 7 weeks of gestation. The first fetal urine is formed at approximately 11 weeks of gestation, and this may maintain the patency of the mesonephric duct. At around week 7, the wolffian duct develops a bud from its caudal end that grows medially and dorsally until it meets the caudal end of the nephrogenic cord. This is called the "metanephric blastema," and it induces formation of the definitive kidney. This begins as an interaction between the ureteral bud and metanephros, which results in a series of branching divisions of the ureteral bud, forming

Table 79-1

Conditions Associated with Renal Cysts

Chromosomal abnormalities
Trisomy 8 mosaic
Trisomy 13
Trisomy 18
Triploidy
Turner syndrome (45,X)
Single-gene disorders
Ehlers–Danlos syndrome
Orofacial digital syndrome
Zellweger syndrome
Tuberous sclerosis
Lawrence–Moon–Biedl syndrome
Multiple acyl CoA dehydrogenase defect
Meckel-Gruber syndrome
Acromandibular–renal syndrome
Other
Beckwith–Wiedmann syndrome
Noonan syndrome
Goldenhar syndrome
Lissencephaly

the renal pelvis and major calices around 12 to 14 weeks of gestation. This branching reaches its maximum at 22 weeks of gestation but continues until 34 to 36 weeks of gestation, when the kidney is fully formed (Bronshtein et al., 1990). Pathogenesis of kidney diseases result from one of the six causes (Bronshtein et al., 1990):

1. failure of union between primitive collecting ducts and nephrons;
2. failure of involution of the first generation of nephrons;
3. obstruction of urine flow at the level of the pelvis, urethra, or bladder outlet;
4. intratubular obstruction;
5. abnormalities of the tubular wall and supporting tissues;
6. adrenocortical maternal steroid ingestion.

PKD is characterized by enlargement of renal cysts, interstitial fibrosis, and gradual loss of normal renal tissue in association with progressive deterioration of renal function. In one study, apoptotic DNA fragmentation was detected in polycystic kidneys from five patients with renal failure (Woo, 1995). Apoptotic cells were demonstrated in glomeruli, cyst walls, and both cystic and noncystic tubules of the polycystic kidneys. These authors hypothesize that apoptotic loss of renal tissue may be associated with progressive deterioration of renal function that occurs in patients with PKD. The specific findings in ARPKD, consisting of large, coarsely hyperechoic kidneys, are thought to be secondary to the presence of

innumerable microscopic cortical and medullary cysts. The interfaces of these cysts provide increased echogenicity.

ADPKD is the only form of cystic disease that involves a collecting tubule as well as the nephron. Normal and abnormal nephrons are intermixed (Pretorius et al., 1987). In ADPKD, cysts occur in only 1% to 2% of renal tubules, but it is thought that the affected abnormal nephrons enlarge steadily until they compress and distort the normal parenchyma to the point of causing impaired renal function (Grantham, 1988). Michaud et al. (1994) reported on three cases of ADPKD and performed a literature review. Of 32 affected fetuses, 28 had prenatal sonographic manifestations of disease or siblings with early onset of disease. Pathologic studies demonstrated that the cysts could be found in newly formed nephrons or in more mature nephrons of the deep cortex. The glomeruli were predominantly affected in the fetus. These authors hypothesized that cysts develop in most patients with ADPKD during fetal life and that the rate at which these cysts increase in size determines the clinical severity of the disease (Michaud et al., 1994).

MANAGEMENT OF PREGNANCY

The diagnosis of fetal renal cystic disease mandates complete ascertainment of the family history. It is also recommended that both parents have a renal ultrasound examination performed because of the high prevalence of the ADPKD gene in the general population. Because of the higher prevalence of ARPKD in the prenatally diagnosed population, a fetus with bilateral renal enlargement and echogenicity is more likely to have ARPKD if both parents have normal ultrasound examinations. However, caution must be observed because of the apparent false-positive diagnoses of ARPKD reported in the literature (Lilford et al., 1992). Several authors have described additional diagnostic testing to help with determination of the underlying cause. For example, Tsuda et al. (1994) diagnosed ARPKD in a fetus at risk by measuring hourly fetal urine production. This was reduced in an affected fetus as compared with a normal fetus. Magnetic resonance imaging (MRI) has been performed at 25 weeks of gestation in a fetus diagnosed with bilateral enlarged hyperechogenic kidneys, oligohydramnios, and a small bladder at 22 weeks of gestation. The MRI revealed corticomedullary differentiation but could not demonstrate the presence of renal cysts. The kidneys were noted to be massively increased in size with a very high water content in the renal parenchyma (Nishi et al., 1991). Nicolini et al. (1992) aspirated fetal urine from 21 large cystic renal masses in 18 fetuses diagnosed between 20 and 35 weeks of gestation. They demonstrated that urinary concentrations of sodium, calcium, and phosphate were significantly higher in the multicystic group as compared with the hydronephrotic group. They concluded that reabsorption of phosphate was impaired in multicystic kidneys.

In the absence of the demonstration that one of the parents is affected with ADPKD, counseling regarding expected prognosis can be difficult. Even when one of the parents is known to have ADPKD, the short-, mid-, and long-term prognoses for fetuses in whom renal cysts are demonstrated early in life is unknown (Journel et al., 1981). In the past, fetuses diagnosed with ARPKD were given a dismal prognosis; however, increasing information from the pediatric literature indicates that general health and lifespan for these infants can be better than was previously thought (Guay-Woodford and Desmond, 2003; Beaunoyer et al., 2007). For a presumed diagnosis of ARPKD, the prospective parents should have a complete discussion with a pediatric nephrologist and neonatologist regarding the extent of resuscitation for the affected newborn. Delivery should be planned to occur in a tertiary care center because of the expected problems with respiratory insufficiency due to pulmonary hypoplasia secondary to oligohydramnios and hypertension.

FETAL INTERVENTION

There are no fetal interventions for PKD.

TREATMENT OF THE NEWBORN

Newborns with ARPKD often receive minimal intervention because poor respiratory and renal outcomes are anticipated. In 1995, Bean et al. described two unrelated infants with ARPKD whose respiratory failure was successfully treated with surfactant and mechanical ventilation. Of interest was the fact that the massive kidney size restricted gastrointestinal capacity and limited feeding and growth. In these two cases, unilateral nephrectomy allowed improved feedings. Both patients had their caloric intake supplemented by nightly feedings by gastrostomy tube, to give a caloric equivalent of 120 to 130 kcal per kilogram of body weight per day. Both patients required long-term medications for treatment of hypertension; however, both exhibited normal neurodevelopment for age at 4 years 9 months and 19 months of follow-up. Both of these patients required minimal hospitalization after the neonatal period.

Aggressive neonatal resuscitation was considered to be controversial for ARPKD, but increasing reports have indicated that with ventilatory support, nutrition, and peritoneal dialysis survival rates can be as high as 82% to 85% (Bergmann et al., 2005). Those who survive have hypertension, progressive renal insufficiency, and hepatic fibrosis and will ultimately need renal transplantation (Beaunoyer et al., 2007). All of these issues must be discussed with the prospective parents.

Fetuses affected with ADPKD have far fewer symptoms and are unlikely to present with spontaneous pneumothorax, oligohydramnios, or liver or spleen enlargement (Cole et al., 1997). In the absence of severe oligohydramnios, standard resuscitation and neonatal supportive treatment are appropriate for infants with ADPKD.

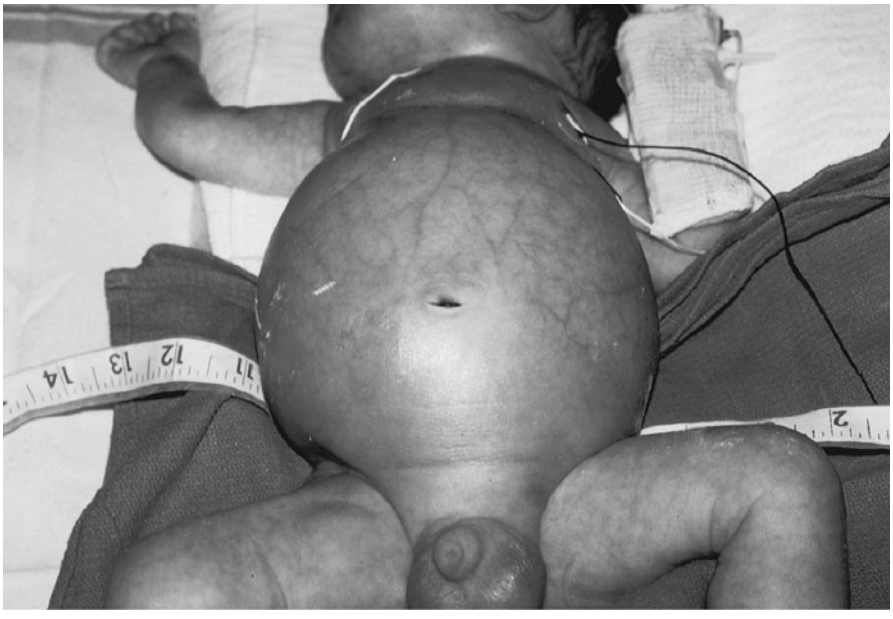

Figure 79-3 A neonate with ARPKD. Massive and rapid enlargement of the right kidney compressed the inferior vena cava, which necessitated emergency nephrectomy.

SURGICAL TREATMENT

The only surgical treatment available for severe PKD is nephrectomy (unilateral or bilateral) or renal transplantation. We have performed unilateral nephrectomy on an emergency basis for an infant with ARPKD because the rapid and massive enlargement of the right kidney compressed the inferior vena cava and seriously impeded venous blood return to the heart (Figures 79-3 and 79-4).

LONG-TERM OUTCOME

A critical milestone for PKD appears to be survival past the first few months of age. Kaplan et al. (1989b) reviewed the clinical features in 55 cases of ARPKD. Of the 24 patients who presented during the neonatal period, 12 (50%) survived beyond 2 years of age. These authors performed an actuarial analysis and showed that once a patient survived beyond 1 year of age, the projected chance of survival beyond 15 years of age was 78%. This data is in agreement with that of Cole et al. (1987), who performed a retrospective survey of 48 patients with PKD who survived the first month and were seen before 1 year of age. These authors indicated that most children diagnosed with PKD who survived the first months of life lived for many years. The majority of all affected children require long-term antihypertensive therapy for persistent problems with high blood pressure.

What is not clearly known, however, is the prognosis for fetuses with the dominant form of PKD who are identified antenatally. In a review of 13 prenatal diagnoses of ADPKD, Pretorius et al. (1987) showed that 10 of 13 infants were alive

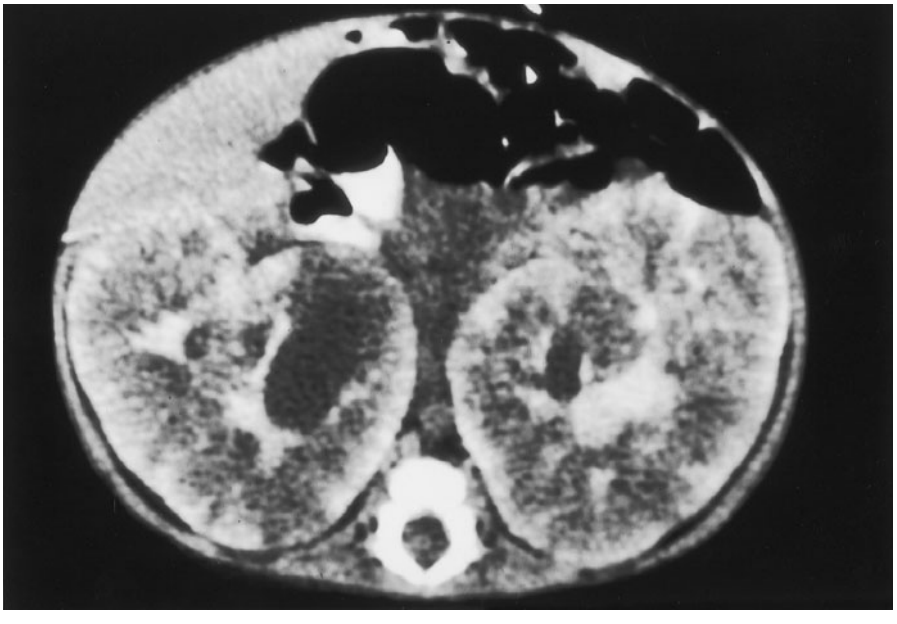

Figure 79-4 Postnatal CT scan from the same infant in Figure 79-3 showing bilateral presence of multiple cysts in enlarged kidneys.

at the time of follow-up. Three were dead because of elective termination of pregnancy, sepsis, or respiratory distress syndrome. Of the 10 surviving children, 8 had normal renal function at the time of follow-up. There is some indication that the neonatal detection of ADPKD correlates with development of hypertension and renal failure in early childhood. However, it is unclear what the fetal presentation of ADPKD implies for future symptoms (Journel et al., 1981).

A review of the literature suggests that fetuses with severe oligohydramnios are unlikely to survive the perinatal period. Improvements in neonatal care permit moderate to severely affected infants with ARPKD to survive the perinatal period. Survival beyond 1 month of life generally indicates the propensity for long-term survival in affected infants with ARPKD. These children require long-term medication and close medical follow-up; however, the literature does not indicate that they spend their entire lives in the hospital. The long-term prognosis for children affected with the dominantly inherited form of PKD is good because in childhood they are more mildly affected. Their clinical situation is also complicated by the fact that in most cases, one of their parents also has the disease, and they may, therefore, be more likely to continue the pregnancy.

GENETICS AND RECURRENCE RISK

Several authors have discussed the difficulties associated with the dual identification of both fetus and parent affected with ADPKD. In Pretorius's study (1987) only 5 of 13 parents were aware of their disease prior to pregnancy. The diagnosis of renal cystic disease in the fetus and young infant should trigger an investigation of the family history. Sonography should be performed on the parents. In ADPKD, however, the severity of parental involvement does not predict either the severity of the child's involvement or the age at onset of symptoms (Michaud et al., 1994). It is well known that difficulties exist in genetic counseling for ADPKD. In one study, 23% of subjects were aware of the hereditary nature of the disease, only 18% had genetic counseling, and 9% had family members examined by sonography (Journel et al., 1981). Fertility is not reduced in ADPKD.

Because it is difficult to distinguish between ADPKD and ARPKD on sonographic examination, and many young parents who have ADPKD are normal on sonographic examination, most geneticists believe that DNA diagnosis is more reliable for prenatal detection of the affected fetus. Fortunately, much recent investigative activity has been directed toward mapping the various genes associated with ARPKD and ADPKD.

ARPKD appears to be genetically homogeneous (Guay-Woodford et al., 1995). ARPKD is caused by a single gene (*PKHD1*) with multiple mutant alleles. This accounts for the relatively high phenotypic concordance within families as well as the broad range of phenotypes evident among different families. The ARPKD gene was mapped to chromosome 6p21-cen in 1994 (Zerres et al., 1994). Most of the families analyzed in this initial report, however, had a milder clinical phenotype compatible with survival beyond infancy. In 1995, Guay-Woodford et al. confirmed and extended Zerres et al.'s findings by performing linkage analysis in families that manifested the severe perinatal lethal form of ARPKD. They narrowed the interval for the gene to 6p21.1-p12 and confirmed that ARPKD results from a single mutant gene.

In contrast, ADPKD is genetically heterogeneous. At least three genes are known to cause ADPKD (Grantham, 1995). ADPKD-1 maps to chromosome 16p13.3 and is responsible for 85% of cases. ADPKD-2 has been mapped to chromosome 4q13-q23 (Peters et al., 1993). It has been postulated that a third gene, ADPKD-3, may be responsible for a small minority of cases, but its chromosomal location is unknown. Spontaneous mutations occur in less than 10% of cases of ADPKD (Gabow, 1993).

DNA linkage analysis in ADPKD was first demonstrated in 1985, when Reeders et al. described a DNA marker located near the α-globin gene cluster on chromosome 16 that was coinherited with ADPKD. The existence of a second gene causing ADPKD was first suspected in 1988 (Kimberling et al., 1988; Romeo et al., 1988). Peters et al. (1993) reported the assignment of a second gene for ADPKD to chromosome 4. Of interest is that patients who do not have ADPKD-1 seem to be diagnosed at an older age, are less likely to have hypertension, live longer, and have fewer renal cysts present at the time of diagnosis. This indicates phenotypic as well as genotypic heterogeneity for ADPKD (Ravine et al., 1992). The first DNA-based prenatal diagnosis of ADPKD was performed in 1986 by Reeders et al.

The *PKD1* gene was cloned and sequenced in 1994 (European Polycystic Kidney Disease Consortium, 1994). It is a very large gene whose protein product is called "polycystin," which is a glycoprotein of approximately 4300 amino acid residues (Harris et al., 1995). Polycystin-1 is a cell–cell matrix interaction protein. It is important for production and maintenance of renal tissue and connective tissue in other organs. It is also expressed in arterial smooth muscle (Griffin et al., 1997). This explains the multisystem nature of the disease. Large sections of the gene are duplicated at separate locations on chromosome 16, and all of these segments of DNA are transcriptionally active. Most *PKD1* mutations have been detected in the single copy 3′ end of the gene, but a group of patients with deletion of *PKD1* and the adjacent tuberous sclerosis 2 gene (with severe infantile PKD) have been characterized (Harris et al., 1995). In the typical patients with adult-onset *PKD1*, small deletions, splicing defects, or a nonsense mutation have been detected in the 3′ end of the gene. In each case, a transcript is produced by the mutant gene. Rarely, large deletions that disrupt, or completely delete, the *PKD1* gene are detected. In every case, these mutations also disrupt the adjacent tuberous sclerosis gene. *PKD2* has also been cloned and sequenced. Both *PKD1* and *PKD2* code for novel proteins (van Adelsberg, 1999). Polycystin-1 is a receptor and similarities between the polycystins and calcium channel subunits suggest that these proteins are subunits of a novel channel.

Families at risk for either ARPKD or ADPKD should have blood samples collected for DNA analysis prior to

contemplating a future pregnancy. For ADPKD, because of the genetically heterogeneous nature of the disorder, there should be enough affected family members tested to determine whether the disease is due to ADPKD-1, ADPKD-2, or other genes (Breuning et al., 1990).

A large review of prenatal DNA analysis in families at risk of ARPKD analyzed 65 diagnoses (Zerres et al., 1998). In the majority of the requesting families, the index child was dead; DNA was extracted from paraffin-embedded tissue. In 4 of the 65 cases, a recombination event occurred between flanking markers and no diagnosis was possible. Forty-three fetuses were diagnosed correctly as unaffected. In 18 fetuses, homozygosity for the disease-associated haplotype was demonstrated. Pathologic changes consistent with ARPKD were seen as early as 13 weeks of gestation in 2 fetuses, both of which were terminated. This study showed that haplotype-based prenatal testing is feasible and reliable in pregnancies at risk for ARPKD (Zerres et al., 1998). Once a mutation has been identified in a specific family, prenatal DNA diagnosis is available as early as 10 weeks of gestation via chorionic villus sampling. DNA diagnosis is recommended for definitive prenatal diagnosis over prenatal sonographic diagnosis, which can be nonspecific. Preimplantation genetic diagnosis is also available for both ARPKD and ADPKD if the familial mutations are known.

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Hydronephrosis: Minimal

80 CHAPTER

Key Points

- Minimal fetal hydronephrosis is defined as anterior posterior renal pelvic diameter >4 mm and <9 mm.
- Minimal fetal hydronephrosis is associated with a slightly increased risk of aneuploidy.
- 90% of cases will resolve on their own.
- Newborns with persistent hydronephrosis should be treated with prophylactic antibiotics until postnatal urologic evaluation.

CONDITION

Hydronephrosis is the most common abnormality reported on prenatal sonographic screening (Thomas, 1990; Blyth et al., 1993). The vast majority of cases are mild, so-called physiologic hydronephrosis, which are of no clinical significance. Numerous theories have been proposed to try to account for this common finding. In the past, one popular theory was that mild fetal hydronephrosis resulted from changes in maternal hydration. However, Hoddick et al. (1985) demonstrated that the degree of maternal hydration had no significant influence on fetal urinary tract dilation.

These findings were subsequently confirmed by Allen et al. (1987). Other potential causes suggested for mild dilation of the fetal urinary tract include transient obstruction, compression by fetal vessels crossing the ureter, vesicoureteral reflux, and natural kinks and folds in the ureter that may occur during development, hyperfiltration of fetal kidneys, or the influence of metabolic or hormonal factors (Homsy et al., 1986; Najmaldin et al., 1990; Zerrin et al., 1993). The hormonal milieu of the fetus may influence the renal pelvic diameter. Maternal hydronephrosis commonly occurs during pregnancy because of the influence of progesterone, a known smooth muscle relaxant. It has been suggested that maternal progesterone may also be responsible for mild fetal upper urinary tract dilation (Cendron et al., 1994).

Distinguishing physiologic fetal renal pelvic distention from significant or pathologic hydronephrosis is a challenge that requires accurate prenatal sonography and follow-up evaluation. Renal pelvic distention may range in anterior/posterior (A-P) diameter from 3 to 11 mm in up to 18% of normal fetuses studied after 24 weeks of gestation (Hoddick et al., 1985). Because fetal hydronephrosis is so common, Arger et al. (1985) proposed criteria to help distinguish abnormal renal pelvic dilation. They suggested that a pelvic diameter of > 10 mm or a ratio of the A-P pelvic diameter to the A-P renal diameter > 0.5 indicated significant fetal hydronephrosis (Figure 80-1A and B). These criteria were subsequently modified by addition of caliectasis as an additional indicator of significant hydronephrosis (Kleiner et al., 1987). This study suggested that caliectasis might be an even more sensitive and reliable indicator for predicting pathologic hydronephrosis than simple pelviectasis (Figure 80-1A). Renal pelvic dilation less than these criteria for pathologic hydronephrosis is considered minimal fetal hydronephrosis. Morin et al. (1996) defined minimal hydronephrosis as renal pelvic dilation > 4 mm but < 10 mm in a fetus that was less than 24 weeks of gestation.

Classification of the degree of renal pelvic dilation is also dependent upon when during gestation it is diagnosed. Fetuses at 15 to 20 weeks of gestation with a renal pelvic diameter of 4–7 mm are considered to have minimal fetal hydronephrosis, while those fetuses with A-P diameter greater than 7 mm are classified as having moderate hydronephrosis. In contrast, after 30 weeks of gestation, the threshold for defining mild, moderate, and severe hydronephrosis is defined as 5–8 mm, 9–15 mm, and over 15 mm, respectively (Pates and Dashe, 2006).

INCIDENCE

Antenatal hydronephrosis is a common finding on antenatal ultrasound with incidence reported from 0.3% to 4.5% with most reports around 1% (Havutcu et al., 2002). When a number of clinical studies are pooled, the calculated incidence of detectable dilation of the fetal urinary tract approaches 1 in 100 pregnancies (Thomas, 1990). However, difficulties in assessing the true incidence of pathologic fetal hydronephrosis stem from the high incidence of physiologic hydronephrosis and the limitations of criteria used to define pathologic urinary tract dilation (Gruppe, 1987). The overall incidence of congenital hydronephrosis in a large-scale maternal–fetal screening program in Sweden was 0.17% (Helin and Persson, 1986). This figure was lower than the one reported (0.76%) in Britain, in a well-designed prospective study using antenatal ultrasonography at a specific time during pregnancy (Livero et al., 1989). In many of these cases, however, a large number of the fetuses displayed what would be considered physiologic hydronephrosis, in other words, minimal pyelectasis. Follow-up studies in patients diagnosed with prenatal hydronephrosis showed that only 1 in 500 fetuses required prenatal or postnatal intervention for hydronephrosis (Thomas, 1990).

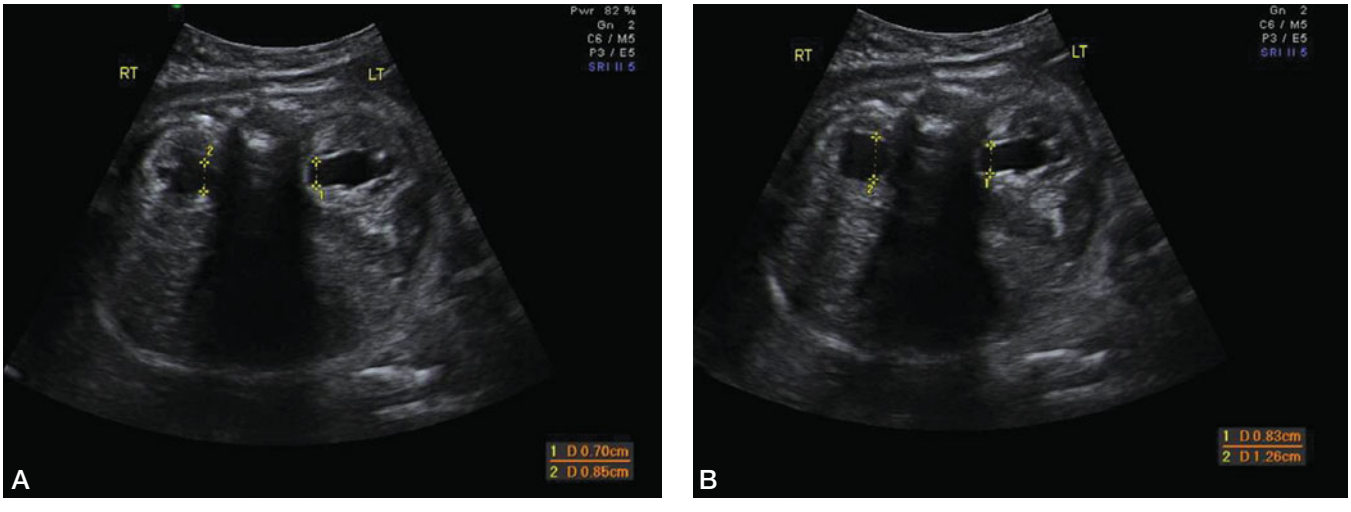

Figure 80-1 **A.** Prenatal sonographic image demonstrating minimal fetal hydronephrosis on the left with an A-P pelvic diameter of 7 mm. The right kidney demonstrates caliectasis even though the A-P pelvic diameter is only 8 mm, which would be considered pathologic. **B.** During bladder contraction there was slight increase on the left in A-P pelvic diameter to 8.3 mm suggesting vesicoureteral reflux.

SONOGRAPHIC FINDINGS

The role of ultrasound examination in the evaluation of the fetal urinary tract is twofold: to monitor the extent of fetal urinary tract dilation and to identify fetuses affected with such severe lesions that intervention or termination of the pregnancy should be considered. Prenatal sonography has irrevocably changed the approach to congenital malformations, particularly those involving the urinary tract (Harrison et al., 1982; Golbus et al., 1983; Mahoney et al., 1984; Harrison and Filly, 1991; D'Alton and DeCherney, 1993). Current diagnostic capabilities allow for the detection of urinary tract anomalies as early as 12 to 14 weeks of gestation (Glazer et al., 1982; Bronshtein et al., 1990; Patten et al., 1990; Blyth et al., 1993). Variables to be considered in the evaluation of fetal hydronephrosis include gestational age at diagnosis, area of urinary tract involved, degree of dilation, and evidence of significant obstruction. Several series have reviewed the accuracy of the diagnosis of hydronephrosis by ultrasound examination of the fetus (Blane et al., 1983; Avni et al., 1985; Watson et al., 1988). Unfortunately, a fairly high rate of false-positive results have been noted, varying between 9% and 22% (Scott and Renwick, 1987; Reznick et al., 1988). It is thought that as our ability to distinguish physiologic from pathologic hydronephrosis becomes more refined, this rate of false-positive scans will be reduced. In order to better define the severity of hydronephrosis, the Society of Fetal Urology has proposed a grading system that uses two parameters: 1) the central renal complex; and 2) renal parenchymal thickness to grade density of the hydronephrosis (see Table 80-1). Most cases of minimal hydronephrosis will fall in the Grade 0 or 1 categories.

Table 80-1

Density of Hydronephrosis

Grade	Central Renal Complex	Renal Parenchymal Thickness
0	Intact	Normal
I	Slight splitting of pelvis and calices	Normal
II	Evident splitting of pelvis and calices	Normal
III	Wide splitting of pelvis and calices	Normal
IV	Further splitting of pelvis and calices	Reduced

Adopted from the Society of Fetal Etiology.

Most authors recommend that all fetuses with an A-P diameter of ≥6 mm should undergo postnatal evaluation (Odibo et al., 2004; Becker and Baum, 2006; Belarmino and Kogan, 2006). Certainly fetuses with an A-P pelvic diameter 10 mm and those who have an A-P pelvic renal cortex ratio >0.5 or with evidence of caliectasis should certainly undergo postnatal evaluation (Cendron et al., 1994).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of minimal fetal hydronephrosis includes extrarenal pelvis, prominent renal veins crossing over the renal pelvis, and vesicoureteral reflux (Table 80-2). The degree of dilation in an extrarenal pelvis can be sufficient to be mistaken for ureteropelvic junction (UPJ) obstruction (see Chapter 81). Color flow Doppler studies should be able to distinguish the crossing renal vein from the true renal pelvis. In vesicoureteral reflux the degree of pelvic dilation will vary over time. In particular, increased renal pelvic diameter may be observed at the time of bladder contractions. Other possibilities include an overlying loop of intestine mistaken for the renal pelvis, a dilated superior pole of a duplex collecting system, and dilated ureter secondary to ureterovesical obstruction. In each of these cases careful sonographic examination should be able to define the fetal anatomy.

ANTENATAL NATURAL HISTORY

Our understanding of the natural history of fetal hydronephrosis is still evolving, especially in cases of hydronephrosis detected before 20 weeks of gestation. In a report describing the use of transvaginal ultrasound screening during the early stages of pregnancy, fetal hydronephrosis was found to vary greatly over the course of gestation (Bronshtein et al., 1990). In fact, of 27 cases of fetal hydronephrosis (renal pelvis >3 mm) diagnosed between 13 and 17 weeks of gestation, only 6 displayed any evidence of hydronephrosis postnatally (Bronshtein et al., 1990). Ten cases of unilateral hydronephrosis gradually disappeared between 15 weeks of gestation and term. The parameters of what constitutes abnormal pelvic distention in fetuses less than 20 weeks of gestation have yet to be clearly established.

In order to better define fetal hydronephrosis and its impact on the developing urinary tract, many ultrasonographic features must be systematically reviewed. The evaluation of the urinary tract should include an assessment of the overall growth and development of the fetus, amniotic fluid index, genitalia, renal parenchymal appearance, extent of dilation of the collecting system, whether involvement is unilateral or bilateral, as well as bladder size, thickness, and emptying. Because of the increased incidence of associated malformations, the fetus should be scanned for extrarenal anomalies. The fetus with hydronephrosis should be evaluated at several points in gestation. In the very early second trimester of pregnancy, a renal pelvic diameter of only 5–8 mm may have functional significance (Blyth et al., 1993). As noted previously, after 20 weeks of gestation, a renal pelvic dilation of

Table 80-2

Differential Diagnosis of Minimal Fetal Hydronephrosis

Cause	Frequency (% of total)
Renal	
Transient HN	48
Physiological HN	15
UPJ obstruction	11
VUR	9
Megaureter	4
MCDK	2
Ureterocele	2
Renal cyst	2
PUV	1
Ectopic ureter	
Prune belly syndrome	
Ureteral atresia	
Urachal cyst	
Not renal	
Ovarian cyst	
Hydrocolpos	
Sacrococcygeal teratoma	
Enteric duplication	
Duodenal atresia	
Meningocele	
Retroperitoneal and/or pelvic masses	

Abbreviations: UPJ, ureteropelvic junction; VUR, vesico-ureteral reflux; MCDK, multicystic dysplastic kidney; PUV, posterior urethral valve.

>6 mm should be considered significant, requiring close prenatal observation and postnatal evaluation. In antenatal hydronephrosis, defined as ≥6 mm A-P renal pelvic diameter, vesicoureteral reflux is the most common cause with ureteropelvic junction obstruction, more often the cause when the renal pelvic diameter is >10 mm (Woodward and Frank, 2002).

Occasionally, progression of physiologic to pathologic hydronephrosis can be seen later in gestation, but the incidence is probably less than 10%. Progression to pathologic hydronephrosis is most often associated with UPJ obstruction and with vesicoureteral reflux (Noe and Magill, 1987; Watson et al., 1988; Zerrin et al., 1993; Morin et al., 1996). Because no criteria are currently available to identify fetuses in which minimal hydronephrosis in the second trimester will progress to pathologic hydronephrosis later in gestation, we currently recommend that a single follow-up sonography be performed at 32 weeks of gestation to rule out progression.

MANAGEMENT OF PREGNANCY

The fetus diagnosed with minimal fetal hydronephrosis prior to 24 weeks of gestation has a 90% chance of complete resolution with no postnatal sequelae. Conversely, 10% of these patients will have worsening of their hydronephrosis (Morin et al., 1996). Because no sonographic criteria discern which fetuses constitute the 10% in which minimal fetal hydronephrosis will progress, we currently recommend that all fetuses with minimal hydronephrosis undergo a repeat ultrasound examination at 32 to 34 weeks to determine which fetuses will require postnatal evaluation. In a review of 127 cases of minimal fetal hydronephrosis, Morin et al. found that 9% had worsening of hydronephrosis during the third trimester and required postnatal evaluation. A retrospective analysis of the sonograms of the fetuses in which minimal hydronephrosis worsened or progressed had one or more of the following features present: caliectasis, in utero progression, or abnormal renal echogenicity. Of the 9% of fetuses with progression of minimal fetal hydronephrosis, four fetuses required postnatal surgery to preserve renal function. This number may be small, but it represents a much larger percentage of pathologic hydronephrosis among fetuses with minimal fetal hydronephrosis than previously described. Of the 23 patients with abnormal findings documented postnatally, 4 were found to have functionally significant UPJ obstruction, 1 had severe vesicoureteral reflux, and all of them required surgical correction of the urologic condition.

Hydronephrosis can be associated with aneuploidy and is a component of several syndromes and the VACTERL association (Benacerraf et al., 1990). A multicenter prospective observational study of unselected fetuses examined between 16 and 26 weeks gestation identified 737 fetuses with mild hydronephrosis in a population of 101,600 births. Of these 737 fetuses, 12 (1.7%) had chromosomal abnormalities (6 trisomy 21, 1 trisomy 13, 1 trisomy 8, 2 Turner's syndrome, 1 unbalanced translocation, and 1 47XXX) (Chudleigh et al., 2001). In this study, the risk of aneuploidy in minimal hydronephrosis was found to be 0.33% and 2.22% in women less than 36 years and greater than or equal to 36 years, respectively. These authors suggested that the presence of hydronephrosis should at least prompt discussion of amniocentesis for karyotype analysis.

Once the fetus is diagnosed sonographically as having progressive minimal fetal hydronephrosis, careful follow-up should be planned to ensure proper postnatal management. At the time of the initial prenatal diagnosis of hydronephrosis, parental counseling is recommended. A multidisciplinary team approach is extremely helpful to inform the parents and to help them understand the implications of this diagnosis.

FETAL INTERVENTION

There is no indication for fetal intervention for minimal fetal hydronephrosis.

TREATMENT OF THE NEWBORN

Every newborn with a prenatal diagnosis of hydronephrosis should undergo a complete physical examination at birth, with specific emphasis on identifying the urethral orifice. Monitoring of the urinary output within the first 24 to 48 hours is unreliable. Failure to void during the first 2 days after birth may reflect normal fluid shifts or may be the first sign of a significant urologic anomaly (Arant, 1992). The differential diagnosis in the neonate who does not void within the first 48 hours includes obstructive uropathy, renal failure, neurogenic bladder, and the effects of maternal medication (Arant, 1992). However, most patients with urinary obstruction will still void, albeit with a weak stream, within the first 2 days of life. Serum electrolyte, blood urea nitrogen, and creatinine levels obtained within the first day of life are a reflection of maternal renal function via placental exchange. It is best to wait at least 24 hours to obtain these values. The most helpful test in the initial evaluation in the newborn with prenatally diagnosed hydronephrosis is an ultrasound examination of the abdomen, including a scan of the bladder. Timing of the ultrasound examination depends on the extent of prenatal hydronephrosis (Dejter and Gibbons, 1989). If severe dilation of the renal pelvis has been detected antenatally, then early ultrasound evaluation within the first 1 to 2 days should be performed to permit early intervention. Otherwise, ultrasound evaluation can be postponed for 3 to 7 days in order to let the physiologic diuresis that occurs during the first 48 hours of life to resolve (Arant, 1992). If the initial postnatal renal ultrasound examination is normal, the evaluation should be pursued with a repeat ultrasound examination in 3 to 4 weeks. The reason for this is that a high incidence of neonates diagnosed with antenatal hydronephrosis have a normal upper urinary tract at the time of their first ultrasound, and are subsequently diagnosed with ureteropelvic obstruction or vesicoureteral reflux (Dejter and Gibbons, 1989).

SURGICAL TREATMENT

Mild cases of hydronephrosis can be observed clinically, and may warrant only one or two ultrasound examinations during the postnatal period. It is rare for mild dilation of the urinary tract to progress. In cases in which additional findings are observed, such as cortical thinning or upper-tract dilation with a normal bladder noted, voiding cystourethrography (VCUG) should be performed to evaluate the presence of vesicoureteral reflux. If vesicoureteral reflux is noted, then a renal nuclear or radionuclide scan, either 99 technetium-diethylenetriaminepentraaccetic acid (DTPA) or mercaptoacetyltriglycine (MAG-3) scans, will be helpful in documenting renal function and degree of obstruction, if present. If no evidence of reflux is noted on VCUG, then a MAG-3 scan with furosemide should be obtained to evaluate the upper renal tract for possible UPJ obstruction (see Chapter 81). If UPJ obstruction is noted, subsequent management is determined by the severity of the obstruction. In severe UPJ obstruction, in which a kidney shows 35% or less function, pyeloplasty should be performed. In the cases in which mild-to-moderate obstruction is noted, and the kidney has more than 35% function, observation alone may be indicated, with a repeat scan in three months. A repeat renal scan will help to assess the changes occurring in renal function. As stated earlier, growing evidence suggests that a mild degree of UPJ obstruction may not be functionally significant and does not warrant surgical intervention (Koff, 1990; Gordon et al., 1991; Duckett, 1993; Woodward and Frank, 2002).

Current recommendations in treatment of the neonate with prenatally diagnosed hydronephrosis include the administration of prophylactic antibiotics, usually a penicillin derivative (Berman and Maizels, 1983). In the past, most patients with hydronephrosis presented with a urinary tract infection later in life. The incidence of urinary tract infection in the setting of prenatally diagnosed hydronephrosis has not been thoroughly evaluated, but a study found that 3% of the patients being evaluated radiologically during the first 6 months of life were found to have a positive urinary culture from a catheterized specimen (Daucher et al., 1992). We currently recommend antibiotic prophylaxis, pending postnatal evaluation, for all neonates with persistent or worsening hydronephrosis diagnosed prenatally. This can be discontinued if no significant urinary tract obstruction or vesicoureteral reflux is noted on the postnatal evaluation.

LONG-TERM OUTCOME

The fetus diagnosed with minimal fetal hydronephrosis who shows no progression at 32 to 34 weeks of gestation requires no postnatal follow-up. Postnatal evaluation is indicated, as discussed above, in fetuses in which there is progression. The long-term outcome is entirely dependent on the diagnosis. In cases of vesicoureteral reflux, complete resolution can often be observed over the first several months of life. Similarly, mild-to-moderate UPJ obstruction, not requiring pyeloplasty, usually has no long-term sequelae. The long-term outcome for specific causes of fetal hydronephrosis is discussed in Chapters 80–83. It is unusual for minimal fetal hydronephrosis that developed during the second trimester to result in renal dysplasia. Good long-term follow-up in these patients is lacking, but we currently do not anticipate late compromise of renal function in these patients. However, recent prospective

studies have found that even mild hydronephrosis that is stable or resolves during pregnancy can redevelop, progress, and may even require surgery later in life (Ismaili et al., 2004; Signorelli et al., 2005).

GENETICS AND RECURRENCE RISK

The risk of recurrence of minimal hydronephrosis with subsequent pregnancies has not been studied. However, given that this condition affects 18% of all pregnancies, chances are at least that high that minimal fetal hydronephrosis will be coincidentally detected in a subsequent pregnancy.

Hydronephrosis can be associated with aneuploidy or syndromes, or the VACTERL association (Benacerraf et al., 1990). Mild hydronephrosis may be associated with a risk of aneuploidy that is slightly higher than age-adjusted risk (Chudleigh et al., 2001).

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Hydronephrosis: Ureteropelvic Junction Obstruction

81 CHAPTER

Key Points

- Ureteropelvic junction obstruction (UPJ) prevents urinary flow from the renal pelvis to the ureter, and is the most common cause of significant neonatal hydronephrosis.
- The timing of onset of obstruction determines the clinical presentation, ranging from multicystic dysplastic kidney to pelvicaliceal dilation for first trimester compared with third trimester obstruction respectively.
- Most cases are unilateral, with bilateral cases, or cases in which the contralateral kidney has multicystic dysplastic changes, having much worse prognosis.
- Pregnancy management is generally unchanged in unilateral UPJ cases, while fetal intervention by means of urinary shunting may be necessary in rare cases of severe bilateral UPJ.
- Management of the neonate usually includes delaying imaging until 3–7 days of life to allow completion of normal physiologic diuresis and initiation of prophylactic antibiotics.
- Indications for surgical intervention include renal function less than 40% expected, worsening hydronephrosis, renal pelvic diameter greater than 5 cm, or febrile morbidity.

CONDITION

Obstruction at the ureteropelvic junction (UPJ) is the most common cause of significant neonatal hydronephrosis (Lebowitz and Griscom, 1986). Because 85% to 90% of affected newborns appear entirely normal on physical examination at birth, prenatal recognition permits treatment of a condition that may otherwise be unrecognized (Grignon et al., 1986). This form of hydronephrosis is characterized by obstruction to the flow of urine from the renal pelvis to the ureter. UPJ obstruction may be classified as either primary or secondary. Primary causes of UPJ obstruction would include intrinsic problems such as intraluminal valves, polyps, congenital mucosal folds, muscular hypertrophy, and functional obstruction and extrinsic causes of obstruction such as aberrant crossing vessels. Secondary causes of UPJ obstruction would include vesicoureteral reflux or more distal obstruction. Among the suggested causes are intrinsic valves at the UPJ, abnormally thickened or oriented muscular bands at the UPJ, high insertion of the ureter on the renal pelvis, anomalous crossing bands or vessels at the UPJ, ischemia, and segmental ureteral dismotility (Williams and Karlaftis, 1966; Kelalis et al., 1971; Johnston et al., 1977; Hendren et al., 1980; Maizels and Stephens, 1980). In the majority of cases, however, a patent UPJ is found at the time of surgical correction. In most cases therefore, the obstruction appears to be more functional than mechanical.

While the pathogenesis of UPJ obstruction is poorly understood, some aspects of the prenatal history are known. Complete obstruction at the UPJ before 8 to 10 weeks of gestation results in severe dysplastic changes in the developing kidney (Scholtmeijer and van der Harten, 1975; Potter, 1976; McGrory, 1980; Sanders and Hartman, 1984). The result is a multicystic dysplastic kidney (see Chapter 78). In contrast, incomplete UPJ obstruction that occurs during the second trimester does not result in multicystic dysplastic kidney but may result in variable degrees of renal dysplasia, in addition to pelvicaliceal dilation. In contrast, UPJ obstruction that occurs during the third trimester may result in marked pelvicaliceal dilation, but usually does not cause renal dysplasia.

Most cases of antenatal hydronephrosis are nonobstructive and will resolve spontaneously in the postnatal period (Belarmino and Kogan, 2006; Becker and Baum, 2006; Hanna, 2006). The diagnosis of UPJ obstruction in the fetus

is based on pelvicaliceal dilation that exceeds proposed criteria for minimal fetal hydronephrosis (see Chapter 80). There is no agreement on the absolute cut-off limit for pathologic antenatal pelvic dilation. Most reports suggest postnatal investigation for pelvic dilation of more than 5 mm (Woodward and Frank, 2002; Becker and Baum, 2006). To distinguish primary UPJ obstructions, an anterior-posterior (AP) pelvic diameter of the renal pelvis $\geq$10 mm or the presence of caliectasis could be used (Arger et al., 1985; Kleiner et al., 1987). To distinguish UPJ obstruction from other causes of obstructive uropathy, there must also be pelvic dilation and an absence of findings suggestive of obstructive uropathy at a lower level, such as ureterectasis, vesicomegaly, ectopic ureterocele, and dilated posterior urethra. Although UPJ obstruction is, in a large part, a diagnosis of exclusion, ultrasound examination has proven reliable in determining the level of obstruction (Kleiner et al., 1987).

INCIDENCE

The overall incidence of genitourinary defects diagnosed by prenatal ultrasound examination has been estimated to be between 0.2% and 0.9%. The incidence of UPJ obstruction is estimated at 0.001% with a male to female ratio of 3:1 (Woodward and Frank, 2002). In newborns the left side is affected in almost two thirds of cases. Bilateral UPJ obstruction is seen postnatally in only 15% of cases (Johnston et al., 1977) but may be more common in prenatally diagnosed cases, as observed by Flake et al. (1986).

SONOGRAPHIC FINDINGS

In unilateral UPJ obstruction the renal pelvis and infundibulum are dilated (Figure 81-1). Dilation of the calices may also

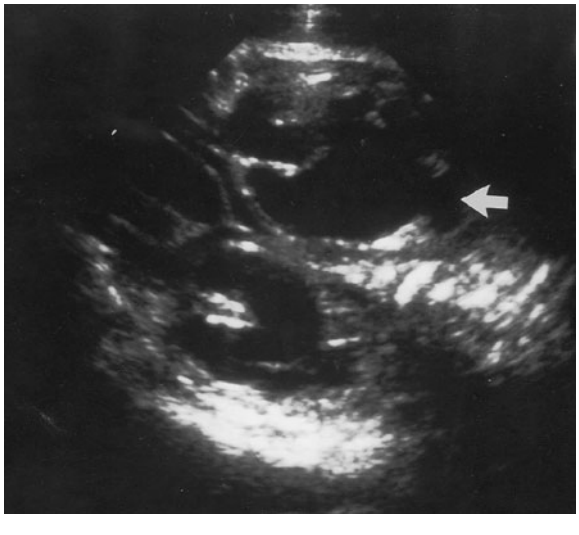

Figure 81-1 Sonogram at 24 weeks of gestation in coronal section of the fetal kidneys demonstrating characteristic features of UPJ obstruction affecting both kidneys with markedly dilated renal pelvis and calices with associated urinary ascites.

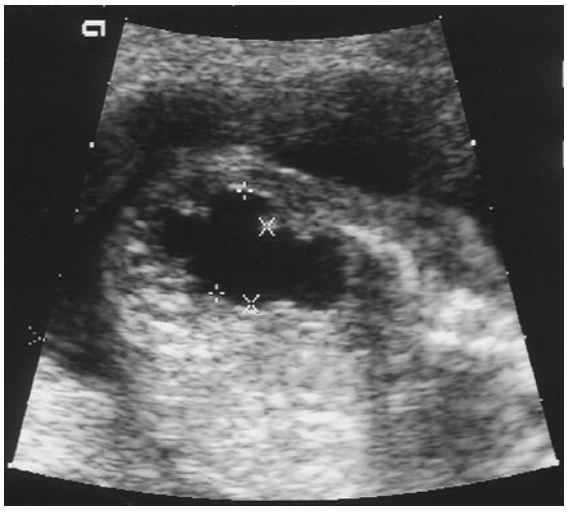

Figure 81-2 Fetal MRI coronal image of the same fetus in Figure 81-1, demonstrating bilateral UPJ obstruction with dilated renal pelvis, caliceal dilation, and urinary ascites.

be seen. The anterior to posterior pelvis to kidney ratio is greater than 50% (Arger et al., 1985). The following findings are not seen in primary UPJ obstruction: dilated ureter, ectopic ureterocele, dilated or thickened urinary bladder, or a dilated posterior urethra. In more severe cases of primary UPJ obstruction only a single fluid-filled structure may be seen, which is the dilated pelvis with only a thin rim of surrounding cortex (Figure 81-2) (Mahony, 1994). In even more severe cases, the renal pelvis may be so dilated that it appears as an abdominal cyst in which not even a rim of renal parenchyma is seen. Such severe UPJ obstructions can reach a significant size, distending the fetal abdomen and elevating the diaphragm (Jaffe et al., 1987). In rare instances, both the infundibulum and the renal pelvis are stenotic and only caliceal dilation is seen (Lucaya et al., 1984). In the most severe form of UPJ obstruction, the collecting system can rupture, with the formation of a perinephric urinoma or urinary ascites. Although some reports suggest it is unusual to have salvageable renal function in a kidney with a perinephric hematoma, in some instances this rupture may be protective (Callen et al., 1983; Friedland et al., 1983; Adzick et al., 1985; Harrison and Filly, 1991). In unilateral UPJ obstruction, the contralateral kidney produces a normal volume of amniotic fluid and the bladder fills and empties normally, even in cases in which the UPJ obstruction has resulted in renal dysplasia. It is important to recognize that UPJ obstruction may be seen frequently in association with contralateral multicystic dysplastic kidney or renal agenesis. Either condition, in association with high-grade UPJ obstruction, may produce profound oligohydramnios and Potters syndrome features (Mahony, 1994).

Bilateral UPJ obstruction is present in 15% to 50% of cases, depending on the series reported (Flake et al., 1986; Kleiner et al., 1987). Fortunately, the involvement is often asymmetric and severe bilateral obstruction is rare. However, as reported by Flake et al. up to 5% mortality can be seen with bilateral UPJ obstruction, which progresses to oligohydramnios and secondary pulmonary hypoplasia. UPJ

obstruction paradoxically results in polyhydramnios in up to 25% of cases (Kleiner et al., 1987). The pathophysiology of the polyhydramnios is uncertain but is thought to be due to hyperfiltration occurring in the partially obstructed kidneys.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of UPJ obstruction includes all other causes of hydronephrosis, including vesicoureteral reflux, megaureter, obstructed duplicated collecting system, and bladder-outlet obstruction (Table 81-1). A detailed sonographic evaluation of the kidneys should differentiate the anatomic level of obstruction causing hydronephrosis. Bladder outlet obstruction, whether due to urethral atresia or posterior urethral valves, should be associated with vesicomegaly with a thick and often trabeculated bladder wall. Cases of ureterovesical obstruction, such as megaureter, are distinguished by the lack of vesicomegaly, with a dilated tortuous ureter extending from the renal pelvis to the ureterovesical junction. A duplex collecting system frequently results in hydronephrosis due to obstruction at the site of the ureteral insertion, often at an ectopic site. This may occur in association with an ureterocele (see Chapter 83). In such cases, the ureter is uniformly dilated up to the superior pole of the kidney, which may have cystic dysplastic changes from long-standing high-grade obstruction.

Vesicoureteral reflux may occur in association with UPJ obstruction and may be difficult to distinguish from UPJ obstruction as a cause of hydronephrosis. One sonographic observation that is helpful in distinguishing between these two diagnoses is observing the degree of pelvic dilation that occurs with bladder emptying. UPJ obstruction is minimally affected by voiding; however, vesicoureteral reflux is usually evidenced by marked fluctuations in the size of the ureter and renal pelvis associated with bladder contraction.

Table 81-1

Differential Diagnosis of Ureteropelvic Junction Obstruction

Bilateral hydronephrosis
Supravesical obstruction
Bilateral UPJ obstruction
Bilateral ureterovesical junction obstruction
Infravesical obstruction
Posterior urethral valves
Urethral atresia
Obstructing ureterocele
Vesicoureteral reflux (bilateral, usually high-grade)
Prune belly syndrome
Megacystis–megaureter complex
Unilateral hydronephrosis
UPJ obstruction
Ureterovesical junction obstruction
Multicystic dysplastic kidney
Megaureter (nonobstructing, nonrefluxing) (may be bilateral)
Renal duplication (may be bilateral)
Dilated loop of bowel

ANTENATAL NATURAL HISTORY

The most important determinants of the outcome of UPJ obstruction in the fetus are the gestational age at onset, severity of obstruction, and whether the UPJ obstruction is unilateral or bilateral. In early gestation, high-grade obstruction at the ureteropelvic junction that occurs during the first trimester results in a multicystic dysplastic kidney. In UPJ obstruction that occurs during the second trimester, the fetal kidneys are at risk for renal dysplasia and compromised renal function at birth. In contrast, UPJ obstruction that occurs during the last trimester rarely causes renal dysplasia, even in cases of high-grade obstruction. This vulnerability of the developing kidney to obstruction-induced dysplasia likely reflects the effect of increased pressure during the nephrogenic phase of renal development between 20 and 30 weeks of gestation (Harrison and Filly, 1991).

Our understanding of the antenatal natural history of UPJ obstruction is still evolving. UPJ obstruction is usually thought to be a benign condition. Flake et al. (1986) challenged this view with their results of a review of 28 fetuses referred to a fetal treatment center with prenatally diagnosed UPJ obstruction in 44 kidneys. This series was unusual, in that over half the cases were bilateral, as compared with the usually quoted lower rates of 5% to 20% (Williams and Karlaftis, 1966; Kelalis et al., 1971; Johnston et al., 1977; Hendren et al., 1980). In some cases, pelvicaliceal dilation due to UPJ obstruction resolves during gestation. In the series reported by Flake et al. (1986), 2 cases resolved. All but five newborns required surgical intervention postnatally, ranging from nephrostomy to pyeloplasty, ureteroureterostomy, or nephrectomy. Nongenitourinary anomalies were noted in 5 of the 28 fetuses. There was a 5% mortality rate in this series, with all deaths occurring in cases of bilateral UPJ obstruction (Flake et al., 1986).

Antenatal progression in the degree of hydronephrosis in cases of UPJ obstruction is a reliable predictor of the need for postnatal surgical decompression. Harrison and Filly (1991) felt that progression was more likely in bilateral UPJ obstruction. However, the degree of hydronephrosis seen in utero does not always correlate with postnatal parenchymal function.

Polyhydramnios may be seen in 25% to 33% of cases of UPJ obstruction (Flake et al., 1986; Kleiner et al., 1987). Polyhydramnios has been described in association with impaired renal function and bilateral obstruction (Henderson et al., 1980; Hadlock et al., 1981; Laing et al., 1984). It has been suggested that polyhydramnios occurring in UPJ obstruction is due to impaired renal concentrating ability, resulting in higher urine output (Harrison and Filly, 1991).

While the prognosis in unilateral UPJ obstruction is usually excellent, there is a high incidence of genitourinary abnormalities in the contralateral side. These abnormalities may range from multicystic dysplasia to vesicoureteral reflux. However, because there is usually a normally functioning kidney on the contralateral side, amniotic fluid volume is maintained, and there is no adverse affect on outcome of pregnancy and neonatal survival. Even in cases in which renal dysplasia complicates UPJ obstruction, there is often a compensatory increase in renal mass and function in the contralateral kidney (Sauer et al., 1986).

The prognosis in bilateral UPJ obstruction is somewhat more guarded. There is a 5% mortality associated with high-grade bilateral UPJ obstruction (Flake et al., 1986). In addition, fetuses with bilateral UPJ obstruction are at increased risk for polyhydramnios, progression in the degree of obstruction, and oligohydramnios in the most severe cases. While unilateral UPJ obstruction is an indication for postnatal genitourinary evaluation, it usually has few implications for the management of the pregnancy. In contrast, fetuses with bilateral UPJ obstruction should undergo serial sonographic assessments of the degree of dilation, renal parenchymal changes, and amniotic fluid volume.

In the series by Flake et al. (1986), oligohydramnios developed in 4 fetuses with bilateral UPJ obstruction, prompting early delivery. All 4 were delivered at 32 to 35 weeks of gestation and underwent pyeloplasty during the neonatal period, with normal renal function after repair. Nineteen of the 23 patients underwent pyeloplasty. Seven pyeloplasties were performed in cases of unilateral UPJ obstruction, with evidence of impaired function in the kidney. All had improved or stable function following pyeloplasty. Twelve pyeloplasties were performed in 9 patients with bilateral UPJ obstruction. In 5 of the 9, renal function was abnormal but became normal after pyeloplasty. An indication of the severity of UPJ obstruction in this group of patients is the 9 nephrectomies performed, either for multicystic dysplastic kidneys, perinephric urinomas, or kidneys with no demonstrable renal function on preoperative diuretic renal scan.

MANAGEMENT OF PREGNANCY

The fetus diagnosed with UPJ obstruction should have a prompt referral for detailed sonographic assessment to confirm the diagnosis, evaluate associated genitourinary abnormalities, and possible associated nongenitourinary abnormalities. There is an overall increased incidence of chromosomal abnormalities in cases of obstructive uropathy, and consideration should be given to amniocentesis for karyotype analysis. It is important to perform a detailed fetal anatomical scan to exclude other associated renal and extrarenal anomalies such as horseshoe kidney, multicystic dysplastic kidney, as well as diaphragmatic hernia, hydrocephalus, and congenital cystic adenomatoid malformation (Harrison and Filly, 1991).

Pregnant women carrying a fetus suspected of having UPJ obstruction should be referred to a pediatric surgeon or pediatric urologist for prenatal consultation. In cases of isolated UPJ obstruction, a favorable prognosis can be anticipated, and routine obstetric care can be performed with planned postnatal genitourinary evaluation. In cases of bilateral UPJ obstruction or unilateral UPJ obstruction associated with either multicystic dysplastic kidney or renal agenesis, serial sonographic examinations at least every 2 to 3 weeks should be performed to evaluate progression in obstruction and development of oligohydramnios or polyhydramnios.

FETAL INTERVENTION

In unilateral UPJ obstruction there is no indication for fetal intervention. However, in high-grade bilateral UPJ obstruction or unilateral UPJ obstruction associated with a contralateral multicystic dysplastic or renal agenesis, consideration may be given to fetal intervention. In such cases presenting after 30 weeks of gestation, consideration should be given to steroid administration and early delivery (Flake et al., 1986; Harrison and Filly, 1991). Cases that present prior to 30 weeks of gestation may be candidates for evaluation for fetal intervention. Prognostic evaluation consists of direct sampling of fetal urine from the renal pelvis in bilateral UPJ or from the bladder in unilateral UPJ with associated MCDK or renal agenesis. Laboratory values associated with a good prognosis include a fetal urine sodium of less than 100 meq per liter, chloride of less than 90 meq per liter, osmolarity of less than 210 mOsm per liter, and a β_2-microglobulin of less than 4 mg per liter (Crombleholme et al., 1990; Mandelbrot et al., 1991; Cendron et al., 1994). Laboratory values for fetal urine electrolytes above these limits may prompt serial fetal urinary sampling in order to be certain that the elevated values accurately reflect renal function.

Fetuses with bilateral high-grade UPJ obstruction, complicated by oligohydramnios, in which a good prognostic profile was obtained by direct renal pelvic tap for fetal urine electrolyte analysis, may be candidates for intervention. Placement of a Harrison catheter into the renal pelvis under ultrasound guidance has been rarely done but may restore amniotic fluid volume and prevent ongoing damage to the obstructed kidney.

TREATMENT OF THE NEWBORN

Once a fetus has been found on prenatal ultrasound examination to have a significant degree of hydronephrosis, careful follow-up should be planned to ensure proper postnatal treatment. At the time of the initial prenatal diagnosis of hydronephrosis, parental counseling is recommended. A team approach is extremely helpful to inform the parents and to help them understand the implications of this prenatal diagnosis (Cendron et al., 1994).

Every newborn with a prenatal diagnosis of hydronephrosis should undergo a detailed physical examination at birth for signs of sequelae from obstructive uropathy. Monitoring of the urinary output within the first 24 to 48 hours is unreliable. Failure to void during the first 2 days after birth may reflect normal fluid shifts or may be the first sign of a significant functional urologic abnormality (Arant, 1992). The differential diagnosis in the neonate who does not void within the first 48 hours includes obstructive uropathy, renal failure, neurogenic bladder, and the effects of maternal medication (Arant, 1992). However, most patients with an obstruction will void, albeit with a weak stream, within the first 2 days of life. Serum electrolytes, blood urea nitrogen, and creatinine levels measured within the first day of life are a reflection of maternal renal function via placental exchange. It is therefore best to wait at least 24 hours to measure these values. The most helpful test in the initial evaluation of the newborn with prenatally diagnosed hydronephrosis is an ultrasound examination of the abdomen, including the bladder. Timing of the postnatal ultrasound examination depends on the degree of prenatal hydronephrosis (Dejter and Gibbons, 1989). If severe dilation of the renal pelvis has been detected antenatally then early ultrasound evaluation should be performed so as to permit early intervention. Otherwise, ultrasound examination can be postponed for 3 to 7 days in order to let the physiologic diuresis that usually occurs in the first 48 hours of life to resolve (Arant, 1992). If the initial postnatal renal ultrasound examination is normal, the evaluation should be pursued with a repeat study in 3 to 4 weeks. Fifty percent of neonates with UPJ and vesicoureteral reflux who were diagnosed antenatally with hydronephrosis have a normal upper urinary tract at the time of the first postnatal ultrasound examination (Dejter and Gibbons, 1989).

Mild cases of hydronephrosis can be treated conservatively with observation, and may warrant only one or two ultrasound examinations during the postnatal period. It is rare for mild dilation of the upper urinary tract to progress. In cases in which other findings are seen, such as cortical thinning or upper tract dilation with a normal bladder, voiding cystourethrography (VCUG) should be performed to evaluate for the presence of vesicoureteral reflux (VUR). If VUR is noted, then a renal nuclear medicine scan using 99 technetiumdiethylenetriaminepentaacetic (DTPA) or preferably mercaptoacetyltriglycine (MAG-3) will be helpful in documenting function of the kidneys (Ismaili et al., 2004). MR urography is an alternative imaging study that provides both anatomic and functional information in children with UPJ obstruction in a single test that does not expose the child to ionizing radiation. Anatomic evaluation combined with renal transit time classification provides a reliable parameter for the identification of obstruction. However, sophisticated software, technical expertise, and cost are limitations of MR urography (McDaniel et al., 2005). If no evidence of reflux is noted on VCUG, then a MAG-3 with furosemide should be obtained to evaluate the upper urinary tract for a possible UPJ obstruction. If UPJ obstruction is noted, treatment is determined by the severity of the obstruction. There is no unanimity of opinion on the indications for surgical treatment of UPJ obstruction. Among the more commonly agreed indications some include reduced renal function to less than 40%, deterioration in differential renal function of more than 5%, persistent or worsening hydronephrosis, unilateral gross hydronephrosis of more than 5 cm renal pelvic A-P diameter, severe hydronephrosis in a solitary kidney, severe bilateral hydronephrosis of more than 3 cm renal pelvic A-P diameter, and febrile breakthrough infection. In severe UPJ obstruction, in which a kidney shows 40% or less function, pyeloplasty should be considered. In the cases in which mild-to-moderate obstruction is noted, and the kidney has more than 40% function, observation alone may be indicated, with a repeat ultrasound examination in three months. A repeat renal scan will help to assess changes in renal function. As stated earlier, there is growing evidence to suggest that a mild degree of UPJ obstruction may not be functionally significant and does not warrant surgical intervention (Koff, 1990; Gordon et al., 1991; Duckett, 1993).

If prenatal ultrasound examination shows a multicystic dysplastic kidney, a VCUG and a renal scan should be obtained. These studies can confirm the lack of function in the affected kidney and rule out any abnormalities in the contralateral kidney (Flack and Bellinger, 1993).

Surgical intervention at birth is required in cases in which a severe obstruction will jeopardize renal function. This applies most often to cases of posterior urethral valves, obstructing ureterocele, and severe UPJ obstruction affecting a solitary kidney. Emergency surgical treatment is seldom warranted. Reconstruction of the urinary tract should not be attempted until the newborn has stabilized from a medical standpoint and has been fully evaluated. Temporary decompression of the urinary tract in cases of severe UPJ obstruction can be achieved by placement of a nephrostomy tube until definitive repair of the urinary tract can be accomplished. In the presence of a solitary kidney, every attempt should be made to ensure adequate drainage so as to not further jeopardize renal function.

Finally, current recommendations for treating the neonate with prenatally diagnosed hydronephrosis include the administration of prophylactic antibiotics, usually a penicillin derivative (Woodward and Frank, 2002; Becker and Baum, 2006; Belarmino and Kogan, 2006; Hanna, 2006). In the past, most patients with hydronephrosis presented with a urinary tract infection later in life. The incidence of urinary tract infection in the setting of prenatally diagnosed hydronephrosis has not been thoroughly evaluated, but one study found that 3% of patients being evaluated radiologically during the first 6 months of life were found to have a positive culture from a catheterized specimen (Dacher et al., 1992).

LONG-TERM OUTCOME

Most pediatric urologists manage the majority of severe fetal hydronephrosis cases due to UPJ obstruction with observation and reserve surgery for patients with deterioration

in renal function or clinical symptoms. No prospective randomized studies comparing operative to nonoperative management of UPJ obstruction have been conducted. There are, however, longitudinal follow-up studies with conversion from observation to surgery when renal function deteriorated by 10% or symptoms occurred (Ransley et al., 1990; Cartwright et al., 1992; Koff and Campbell, 1994). Chertin et al., recently reported that among children diagnosed prenatally with UPJ obstruction that did not appear to need pyeloplasty in infancy, 50% went on to pyeloplasty by 16 years of age (Chertin et al., 2006). The long-term outcome of UPJ obstruction depends on whether it is unilateral or bilateral and if there is an underlying renal dysplasia. In the absence of renal dysplasia, renal function often returns to baseline levels following pyeloplasty. In cases in which UPJ obstruction has caused dysplastic changes, compensatory hypertrophy in the normal contralateral kidney ensures an excellent prognosis. However, in cases of contralateral multicystic dysplastic kidney or renal agenesis, renal dysplasia induced by UPJ obstruction will lead to progressive renal insufficiency and ultimately renal failure necessitating renal transplantation. This latter group of patients requires follow-up with a pediatric nephrologist as well as a pediatric urologist.

GENETICS AND RECURRENCE RISK

In general, VUR has a high familial incidence. It is thought to be an autosomal dominant condition with reduced penetrance (Devriendt et al., 1998). Although UPJ obstruction is a common entity, it is usually sporadic. It is important to note that UPJ obstruction can remain clinically stable for years only to present in adult life with symptoms such as stone formation, pain, or infection. The natural history of antenatal UPJ obstruction may take 30 or more years to fully evolve. Multiple case reports suggest inheritance of a gene that specifically predisposes to UPJ obstruction. These include affected identical twin females, a mother and two children, and multiple siblings in different families (Cohen et al., 1978; Sidebottom and Sadlowski, 1984; Buscemi et al., 1985; Dabra et al., 2003). In one report, histocompatibility typing of a family with 15 members and a history of UPJ stenosis suggested that the renal malformation and histocompatibility haplotype were linked (Senger et al., 1979). More recently, study of a large affected kindred using DNA linkage markers on the short arm of chromosome 6 concluded that there was no linkage between the presence of ureteral abnormalities and the HLA genes (Klemme et al., 1998).

Whether inheritance of UPJ obstruction is dominant or multifactorial, it is clear that siblings are at increased risk for uropathology. In one study, 37 siblings of 20 probands with UPJ obstruction were evaluated with intravenous pyelography and VCUG. Fourteen of the 37 (38%) had some form of uropathology that required subsequent therapy (Dwoskin, 1979). We recommended that siblings of children with UPJ obstruction be investigated for uropathology regardless of age or sex.

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Hydronephrosis: Bladder Outlet Obstruction

82 CHAPTER

Key Points

- Posterior urethral valves (PUVs) are the most common cause of bladder outlet obstruction in males.
- PUVs account for 10% of all urologic anomalies detected by prenatal ultrasound.
- PUVs have a broad range of severity from completely asymptomatic to complete obstruction, oligohydramnios, pulmonary hypoplasia, and renal dysplasia.
- Oligohydramnios due to a PUV, if untreated, is associated with nearly uniform neonatal mortality due to pulmonary hypoplasia.
- Sonographic prognostic criteria predicting poor outcome include presence of subcortical cysts and increased echogenicity of the kidneys, which are associated with renal dysplasia.

Key Points (cont.)

- Fetal urine electrolytes (Na <100, Cl <90, Osm <210, β_2-microglobulin <6) are associated with preserved renal function and favorable prognosis with treatment.
- Fetal urine electrolytes are only valid for fetuses at 20 weeks of gestation or later.
- Treatment options include vesicoamniotic shunt placement, fetoscopic ablation of PUV, and open fetal surgery for vesicostomy.
- Fifty percent of successfully treated fetuses with PUV develop growth failure and chronic renal failure requiring dialysis and/or transplantation.

CONDITION

Unlike obstruction of the urinary tract at other levels, bladder outlet obstruction has the potential to affect the development of the whole urinary tract as well as the lungs. In males, the most common cause of bladder outlet obstruction is posterior urethral valves (PUVs) (Atwell, 1983). In contrast, in females the most common cause of bladder outlet obstruction is urethral atresia. As in many other congenital anomalies, there is a broad range of severity, with bladder outlet obstruction ranging from completely asymptomatic to the infant who presents at delivery with respiratory insufficiency due to pulmonary hypoplasia caused by long-standing oligohydramnios and renal failure from renal dysplasia.

PUVs are thought to be embryologically derived from mullerian duct remnants or remnants of the cloacal membrane dating back to between the 7th and 11th weeks of gestation (Dewan et al., 1992, 1995). Young et al. (1919) described a classification scheme for PUVs. In type I, the valves are sail-like leaflets that arise from the crista-urethralis distal to the verumontanum. These valves may cover only the lower half of the urethra or may encircle the urethra and cause complete obstruction. Type II valves are nonobstructing folds of the superficial muscle and mucosa that extend from the verumontanum to the bladder neck (Cuckow, 1998). Type III valves usually cause a diaphragm-like obstruction at the level of the verumontanum, but can be seen at the level of the anterior urethra distal to the external urethral sphincter (Hendren, 1971).

The characteristic prenatal presentation of bladder outlet obstruction is that of a dilated bladder and bilateral hydroureteronephrosis. The severity of prenatal bladder outlet obstruction ranges from mild to severe as is seen postnatally. At the better end of the spectrum, the fetus may have obstructive uropathy with preservation of amniotic fluid volume, minimal changes in the bladder and ureters, and no dysplastic changes in the kidneys. At the severe end of the spectrum are fetuses with profound oligohydramnios, distended bladder, and ureters with cystic dysplastic changes in the kidneys. The longstanding oligohydramnios results in pulmonary hypoplasia, which leads to severe respiratory insufficiency at birth and is a leading cause of death during the neonatal period. Fetuses with obstructive uropathy can also have other associated nongenitourinary anomalies, chromosomal abnormalities, and deformations related to oligohydramnios, emphasizing the importance of careful prenatal evaluation. In cases of isolated bladder outlet obstruction due to PUVs, vesicoamniotic shunting may be lifesaving.

INCIDENCE

The figures reported for the incidence of bladder outlet obstruction vary widely, reflecting the spectrum of severity seen in obstructive uropathy. In PUVs, the most common cause, the range in severity extends from fetuses presenting with oligohydramnios, renal dysplasia, and pulmonary hypoplasia to asymptomatic octogenarians noted to have PUVs at the time of cytoscopy for benign prostatic hypertrophy. The incidence of PUVs has been reported to be between 1 in 5000 and 1 in 25,000 births (Atwell, 1983). PUVs account for 10% of all urologic anomalies detected by prenatal ultrasound, which occur as frequently as 1 in 800 livebirths (Thomas and Gordon, 1989; Hutton et al., 1994). Prenatal ultrasound picks up 50% of new cases of PUVs, suggesting an incidence of 1 in 4000 livebirths (Cuckow, 1998). Recently, there has been increased awareness of PUVs, and Richmond and Atkins reported an increase in apparent prevalence from 1.9 per 10,000 births to 2.4 per 10,000 births (Richmond and Atkins, 2005). This estimate does not take into account cases of intrauterine fetal death, loss to pregnancy termination, stillbirths, or the asymptomatic cases that present later in life with voiding difficulty (Hendren, 1971; Pieretti, 1993).

SONOGRAPHIC FINDINGS

Urinary tract obstruction at the level of the bladder outlet is usually due to PUVs in male fetuses and urethral atresia in females. The cardinal features of bladder outlet obstruction include marked and persistent dilation of the urinary bladder with a thickened, often trabeculated, bladder wall (Glick et al., 1984; Mahony et al., 1985). The posterior urethra is dilated in urethral obstruction due to PUVs. This dilated proximal urethra resembles a keyhole, extending from the bladder toward the fetal perineum (Figure 82-1). The dilated bladder can become quite large, filling both fetal pelvis and abdomen. The mural thickness of the normal bladder is quite thin and bladder wall thickness greater than 2 mm is pathologic. In cases of severe bladder outlet obstruction, the nondilated

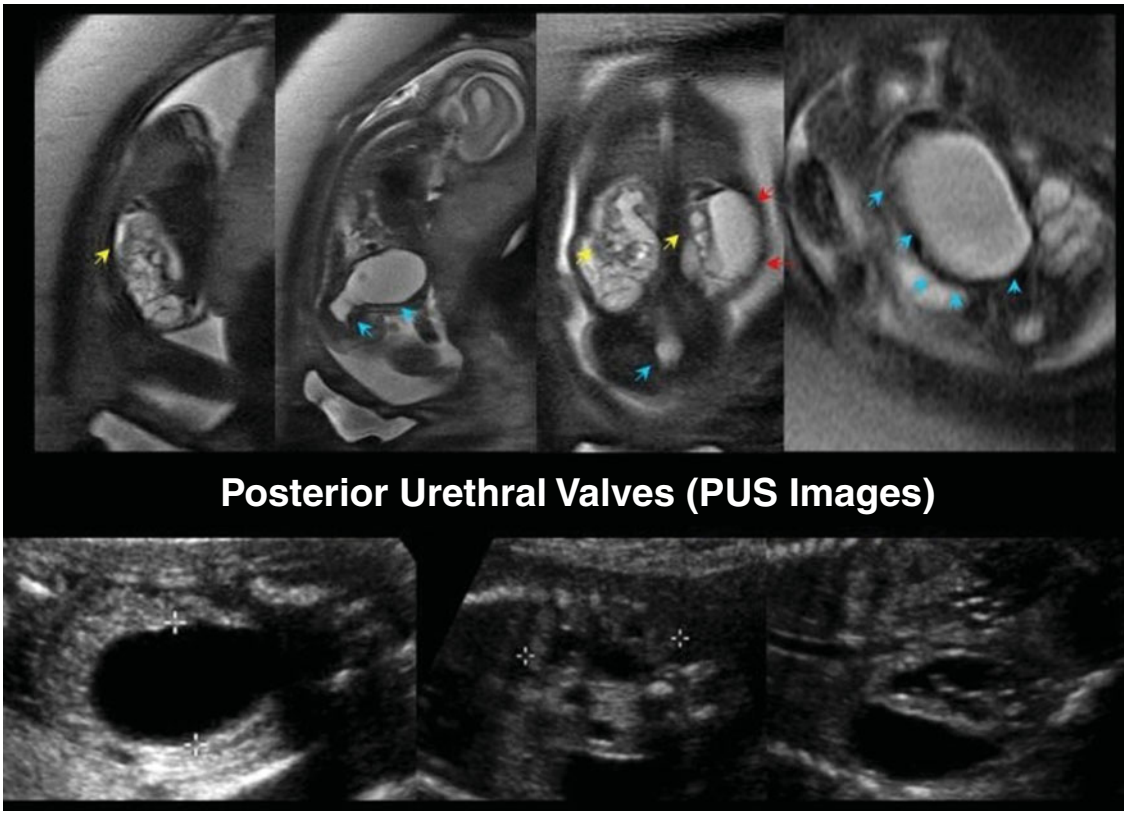

Figure 82-1 The upper panel shows four MRI images of the same fetus. The panel at the left shows a small perinephric urinoma (*small yellow arrow*). The second panel shows the dilated bladder and posterior urethra. The third panel shows in coronal section the dilated urethra and hydronephrosis and calyceal dilatation. The blue arrow points out the dilated posterior urethra. The panel on the right shows the very dilated bladder with thickened walls.

Lower panel demonstrates characteristic findings on ultrasound in posterior urethral valves in a fetus at 21 weeks of gestation. The left panel shows the dilated thick-walled bladder in sagittal plane. The middle panel shows the hydronephrotic kidney with calyceal dilatation. The right panel demonstrates the dilated tortuous ureter. (*Courtesy of Pramod Reddy, MD, Pediatric Urology, Fetal Care Center of Cincinnati)*

bladder (either following bladder tap or spontaneous voiding) can be as thick as 10 to 15 mm (Mahony, 1994). Often, severe bladder outlet obstruction will result in ureterectasis and caliectasis due to vesicoureteral reflux induced by high intravesical pressure. However, the absence of these features does not preclude the diagnosis of bladder outlet obstruction because only 40% of fetuses will demonstrate ureterectasis and pyelectasis in bladder outlet obstruction (Mahony, 1994). In high-grade bladder outlet obstruction, the urinary bladder may spontaneously decompress through rupture of the urinary tract, resulting in either fetal urinary ascites or perinephric urinoma (Callen et al., 1983; Mahony et al., 1984). The end-stage effects of early gestation high-grade bladder outlet obstruction is often bilateral renal dysplasia. This may be sonographically evident from markedly increased renal parenchymal echogenicity and, most specifically, from the presence of subcortical cysts (Mahony et al., 1984; Crombleholme et al., 1991). Paradoxically, the lack of caliectasis in the otherwise obstructed urinary tract may suggest the presence of renal dysplasia and reflects the lack of urine production by severely damaged kidneys. Oligohydramnios is indicative of high-grade obstruction and, if long-standing, may result in deformations including Potter facies and clubfeet.

Fetal MRI has been found to be a useful adjunctive imaging modality in the evaluation of the fetus with obstructive uropathy (Caire et al., 2003). MRI may be more sensitive in defining subcortical cysts, suggesting renal dysplasia. In addition, fetal MRI may provide anatomic detail on pelvic structures not available with ultrasound, particularly in the setting of bladder outlet obstruction presenting prior to 16 weeks of gestation. In these early cases, persistent cloaca may be more clearly diagnosed by MRI than by ultrasound alone.

The functional capacity of the fetal kidney affected by obstructive uropathy depends on the extent and severity of renal dysplasia caused by the obstruction. The dysplastic fetal kidney is characterized by the presence of disorganized metanephric structures surrounded by fibrous tissue which, in addition, may have cortical cysts (Rubenstein et al., 1961; Beck, 1971; Potter, 1972; Risdon, 1975; Bernstein, 1976). More than 90% of dysplastic kidneys with cortical cysts are associated with obstruction during nephrogenesis (Rubenstein et al., 1961; Bernstein, 1976). Detection of cortical cysts

sonographically implies the presence of severe renal dysplasia and irreversible renal damage, excluding the patient from intervention. A normal kidney will display an echotexture similar to that of the liver, with an internal architecture showing a differentiation between cortex and medulla. The medulla containing tubules and fluid will appear darker. A dysplastic kidney, however, will show no internal architecture and may display an increased echogenicity due to a disruption in the normal renal histology. Renal dysplasia may be associated with cystic formation with the parenchyma (Harrison et al., 1982a; Risdon, 1975). Features of multicystic dysplasia of the kidney (MCDK) include the presence of multiple noncommunicating cysts of variable sizes, interfaces between the cysts (presence of echogenic areas within the renal parenchyma), nonmedial location of the largest cyst, and absence of an organized parenchyma (see Chapter 78) (Fong et al., 1986; Kleiner et al., 1986). Multicystic dysplasia of the kidney is most often seen unilaterally and is associated with a high incidence of contralateral urologic anomalies that will warrant postnatal evaluation by a pediatric urologist (Thomas, 1990). Cystic dysplasia should not be confused with severe hydronephrosis.

Mahony et al. (1984) studied the kidneys of 49 fetuses with obstructive uropathy and found that the presence of cortical cysts had a positive predictive value of 100% for the presence of renal dysplasia. Sonography was also 100% specific as no fetus without dysplasia had detectable cortical cysts. The presence of cortical cysts reliably predicts the presence of renal dysplasia and irreversible renal damage, but the absence of cortical cysts cannot ensure the absence of renal dysplasia. Of the kidneys without cortical cysts in the study by Mahony et al., only 44% were free of dysplastic changes. Renal dysplasia may be present without cysts, or the diameter of the cysts may be below the resolution of ultrasound. Technical factors may also limit the ability of the sonographer to adequately image the fetal kidneys, including shadowing from the adjacent spine and oligohydramnios, which often accompanies obstructive uropathy.

In the dysplastic kidney, there is abundant fibrous tissue that may increase the echogenicity of the renal parenchyma. It has been suggested that increased echogenicity at the renal cortex may be a sign of renal dysplasia. However, when this sonographic sign was evaluated, it was shown to be less specific and to have a lower positive predictive value than the presence of cortical cysts (Mahony et al., 1985). The evaluation of renal echogenicity is also a more subjective assessment with inherent interobserver variability, which further limits its utility.

Ultrasonographic examination of the fetal kidneys may provide prognostic information if cortical cysts and increased echogenicity are detected, but is less specific in their absence (Mahony et al., 1985; Crombleholme et al., 1991). Similarly, the volume of amniotic fluid is not a useful prognostic indicator except at the extremes (Harrison et al., 1981a, 1982a, 1987; Glick et al., 1985). Zaccara et al. found that amniotic fluid index remains a reliable predictor of renal function in cases of obstructive uropathy (Zaccara et al., 2005). Preserved amniotic fluid almost always predicts normal renal function at long-term evaluation. Fetuses with bilateral hydronephrosis and normal amniotic fluid may not require intervention. Similarly, fetuses with bilateral hydronephrosis, severe oligohydramnios, and severely dysplastic renal cortex as seen on ultrasound are unlikely to benefit from in utero therapy. It is for the fetuses between these two extremes that prognostic criteria are most important. Assessment of residual fetal renal function by indirect methods such as ultrasound determination of bladder filling and emptying or furosemide stimulation of urine production have not proven reliable (Campbell et al., 1973; Wladimiroff, 1975; Chamberlain et al., 1985). A more sensitive means of assessing fetal renal function is essential for the appropriate selection of fetuses with obstructive uropathy for treatment.

An evaluation of the fetal urinary tract should include an assessment of the overall growth and development of the fetus, amniotic fluid index, gender, renal parenchymal appearance, extent of dilatation of the collecting system, unilateral or bilateral involvement, and bladder size, thickness, and emptying (Cendron et al., 1994). Because of the increased incidence of associated malformations, the fetus should be scanned for extrarenal anomalies. Serial sonographic evaluation is also essential to evaluate for progression of these sonographic features.

DIFFERENTIAL DIAGNOSIS

The sex of the fetus will help narrow the differential diagnosis. Sonographic demonstration of male external genitalia in the setting of bladder outlet obstruction strongly suggests the diagnosis of PUVs. In a female fetus, one should consider the diagnosis of urethral atresia, persistent cloaca, caudal regression anomaly, or megacystis-microcolon–intestinal hypoperistalsis syndrome (Table 82-1). An unusual cause of bladder outlet obstruction that can occur in either sex is prolapse of an ectopic ureterocele from a duplex collecting

Table 82-1

Causes of Bilateral Hydronephrosis

Supravesical obstruction Bilateral ureteropelvic junction obstruction Bilateral ureterovesicular junction obstruction
Infravesical obstruction Posterior urethral valves Urethral atresia Obstructing ureterocele
Vesicoureteral reflux (bilateral, usually high-grade)
Prune belly syndrome
Megacystis-microcolon–hypoperistalsis syndrome

system. In distinguishing urethral atresia in a female fetus, the oligohydramnios is profound and long standing. Particularly when diagnosed prior to 16 weeks of gestation, a dilated "bladder" on ultrasound should raise the possibility of persistent cloaca. The presence of a persistent cloaca may be suspected from the anatomy of the "bladder" and the presence of debris in the cloaca from the intestinal communication. Intraluminal calcifications within bowel loops suggest a communication between intestinal and genitourinary tracts. Caudal regression should be evident from images of the fetal spine. In the megacystis-microcolon–intestinal hypoperistalsis syndrome, the bladder is very dilated but with a thin wall even after decompression, as opposed to the pressure-induced hypertrophy observed in bladder outlet obstruction from PUVs. This is a rare, usually lethal, anomaly in which 80% of affected fetuses are females (Winter and Knowles, 1986). Other features that are clues to this diagnosis include small-bowel dilation, a microcolon with malrotation, and polyhydramnios in the third trimester (Stramm et al., 1991). This is inherited as an autosomal recessive condition and therefore has implications for future pregnancies.

ANTENATAL NATURAL HISTORY

A thorough understanding of the pathophysiology of fetal obstructive uropathy and its sequelae in the developing fetus is essential in formulating a rational approach to clinical management. It is important to understand why obstructive uropathy results in pulmonary hypoplasia, renal dysplasia, and associated malformations and whether or not these changes can be reversed by decompression in utero.

Obstruction of the urethra during the latter half of gestation results in dilatation and hypertrophy of the bladder and megaureter and bilateral hydronephrosis. But obstruction that starts this late in gestation does not usually produce the dysplastic changes in the renal parenchyma seen in human fetuses. Some have argued that dysplasia is caused by an abnormal interaction between the ureteric bud and the metanephric mesenchyme and is only incidentally associated with obstruction. Experiments in a fetal chick in which ureteric buds were denuded of metanephric mesenchyme formed primitive ducts, suggesting that in the chick, dysplasia may be due to nonobstructive causes. These studies have questionable relevance to the pathogenesis in higher animals and humans.

The proponents of obstruction-induced dysplasia argue that after 8 to 10 weeks of gestation, when the kidney begins to make urine, obstruction results in back pressure into the developing nephrons. Potter demonstrated that the collecting tubules of the nephrogenic kidney are straight and short and may be more susceptible to injury from back pressure than the mature nephron. Chevalier (1993) confirmed that early in development, renal injury from ureteral obstruction occurs more frequently than in the adult kidney. It follows that in order to preserve renal function in the face of an obstruction, early recognition and prompt decompression may be necessary. Early obstruction will cause the development of dysplastic changes in the kidney, but further impairment in renal function may occur not so much as a result of nephron loss from a pressure-mediated mechanism, but by a vasoconstrictive effect mediated by an overactivation of the renin–angiotensin system (Chevalier, 1993).

In humans, oligohydramnios, because of obstructive uropathy, renal agenesis, or prolonged amniotic fluid leak, results in severe pulmonary hypoplasia (Kemper and Mueller-Wiefel, 2007). The lungs of infants affected by obstructive uropathy show decreased airway branches from segmental bronchi, reflecting compromised development during the first half of gestation (pseudoglandular stage, 5 to 16 weeks). Although the lung made hypoplastic by compression during the pseudoglandular stage would not be expected to develop new airway branches, it would retain the capacity to make new alveoli and intra-acinar arteries. To evaluate the effect of obstructive uropathy on pulmonary development in an early gestation model, Adzick et al. (1987) performed bilateral ureteral ligation at 60 days of gestation, during the pseudoglandular stage of lung development (60–80 days of gestation), on lambs. Morphometric analysis of the lungs at birth revealed significant reduction of lung volume, radial alveolar count, and mean linear intercept (an indicator of airspace size) in the lambs with bilateral ureteral ligation as compared with the controls (Adzick et al., 1987). In addition, muscularization of the intra-acinar arteries was greater in lambs with bilateral ureteral ligation, indicating increased peripheral pulmonary arteriolar muscularization. These morphometric findings were the same as those in human infants who died from oligohydramnios-induced pulmonary hypoplasia from obstructive uropathy (Potter, 1972; Hislop et al., 1979). These experimental models replicated both the renal dysplastic changes and the pulmonary hypoplasia that are observed in human fetuses who die from severe obstructive uropathy and oligohydramnios.

The mechanism by which oligohydramnios causes pulmonary hypoplasia is uncertain. Several possible contributing factors include the small uterine cavity, which causes thoracic compression and limited intrathoracic space. Fetal breathing movements may be limited by uterine compression of the fetal chest and abdomen. Fetal respiration is thought to be an important factor in lung growth (Wigglesworth and Desai, 1982). Ablation of fetal breathing by cord transection, curare-induced paralysis, or damping fetal breathing movements by thoracoplasty—all result in pulmonary hypoplasia (Liggins et al., 1979; Wigglesworth and Desai, 1979; Moessinger, 1983). Oligohydramnios may also increase the loss of lung fluid, with decreased lung fluid volume within the airway (Lanman et al., 1971). Chronic fetal tracheal drainage of lung fluid results in pulmonary hypoplasia. The amniotic fluid may also act as a hydraulic stent. Increases in amniotic pressure are transmitted to the fluid in the fetal airway and prevent increases in transthoracic pressure, which might restrict lung growth from chest compression. Another possibility is the loss of a growth factor produced by the kidneys (Lanman et al., 1971).

These studies form the basis for in utero intervention to decompress the urinary tract and restore amniotic fluid dynamics to prevent neonatal death due to pulmonary hypoplasia and renal dysplasia.

MANAGEMENT OF PREGNANCY

A fetus with suspected bladder outlet obstruction should undergo a detailed sonographic survey to detect nongenitourinary anomalies. In particular, sonographic features of trisomies 13, 18, and 21 should be ruled out because chromosomal abnormalities can be seen in bladder outlet obstruction in as many as 12% of cases (Crombleholme et al., 1991; Cusick et al., 1995). Deformations due to oligohydramnios such as clubfoot and Potter facies should be ruled out. A sonographic evaluation of the urinary tract should include the sex of the fetus, amniotic fluid volume, presence or absence of ascites, and a detailed examination of the urinary tract itself. Not only the presence of the keyhole sign, but the size of the bladder and evidence of bladder wall hypertrophy should be noted. The presence or absence of an ureterocele should be sought, and the bladder should be observed during voiding for evidence of vesicoureteral reflux. The degree of ureteral dilation, hydronephrosis, and/or caliectasis may increase with voiding in the presence of vesicoureteral reflux. All fetuses with bladder outlet obstruction should have a genetic consultation and should consider amniocentesis. Echocardiography should be performed to rule out structural heart disease. In less severe cases of bladder outlet obstruction, in which amniotic fluid volume is preserved, there should be no adverse effects on pulmonary development and the site, timing, and mode of delivery should be unaffected. In severe cases in which oligohydramnios has occurred, either a decision should be made not to aggressively resuscitate the infant, or the baby should be delivered in a tertiary care setting. In the case of severe long-standing bladder outlet obstruction associated with oligohydramnios and renal dysplasia, there should be no intervention for nonreassuring fetal testing or attempts at resuscitation because these infants have severe pulmonary hypoplasia and renal dysplasia that are incompatible with life. Prenatal consultation with pediatric specialists in urology, nephrology, and neonatology may be helpful in counseling parents about the options for treatment and long-term outcome. The approach to the fetus with bladder outlet obstruction is outlined in the algorithm in Figure 82-2.

It is important to stress that the appearance of the fetus with bladder outlet obstruction may evolve during gestation. The fetus with complete or high-grade bladder outlet obstruction associated with oligohydramnios may spontaneously evolve with development of less-severe outlet obstruction and restoration of amniotic fluid volume. Conversely, the fetus with high-grade partial bladder outlet obstruction but preserved amniotic fluid volume may progress during pregnancy, with the kidneys becoming more echogenic and demonstrating subcortical cysts consistent with the development of dysplasia. Serial sonographic surveillance should be a part of a prenatal management plan of all fetuses with bladder outlet obstruction.

FETAL INTERVENTION

During the past decades, much has been learned about the natural history of obstructive uropathy, and the pathophysiology has been replicated in animal models (Glick et al., 1984; Harrison et al., 1985, 1987; Nakayama et al., 1986; Bronshtein et al., 1990; Crombleholme et al., 1988b, 1991; Mandell et al., 1992; D'Alton and DeCherney, 1993). It has been demonstrated experimentally that bladder decompression in utero can prevent the progression of dysplastic changes seen in obstructive uropathy (Glick et al., 1983, 1984). There are those who question whether animal models accurately replicate the pathophysiology in humans (Berman and Maizels, 1982; Lissauer et al., 2007). A major problem in management is the proper selection of fetuses with bilateral hydronephrosis who might be candidates for intervention, i.e., fetuses with obstruction severe enough to compromise renal and pulmonary development, but not so severe that renal damage is irreversible even if the obstruction is relieved. Several methods have been suggested to assess the functional capacity of the kidneys in a fetus with obstructive uropathy, including the sonographic appearance of the kidneys, amniotic fluid volume, and various fetal urine electrolytes and proteins.

In the 13th week of gestation, the fetus begins to make urine, which is best characterized as an ultrafiltrate of fetal serum (McCance and Widdowson, 1953; Alexander and Nixon, 1961; McGrory, 1972; Mellor and Slatter, 1972; Hill and Lumbers, 1988). The urine is hypotonic because of selective tubular resorption of Na and Cl in excess of free water (Glick et al., 1985). The urine composition normally becomes progressively hypotonic between 16 and 21 weeks and may become even slightly more hypotonic late in gestation as a result of tubular maturation and increased fetal glomerular filtration rate (Glick et al., 1985; Nicolini et al., 1992). Glick et al. (1985) observed that fetuses with congenital hydronephrosis and normal renal function after birth had hypotonic urine but those with poor function produced urine that was isotonic. Similar observations were made in fetuses with hydronephrosis but good renal and pulmonary function was evaluated postnatally by Weinstein and McFaydon and their colleagues (Weinstein et al., 1982; McFaydon et al., 1983).

It is uncertain why the fetus produces isotonic urine in the presence of long-standing obstruction. It has been suggested that dysplastic changes may alter tubular function sufficiently to prevent the resorption of Na and Cl. Rappaport et al. (1960) suggested that the stagnant urine may equilibrate with serum. The fluid aspirated from the fetus with severe obstructive uropathy may also present fluid produced by bladder urothelium.

In order to develop more sensitive fetal renal function tests, Glick et al. (1985) used bladder catheterization to evaluate 20 fetuses with obstructive uropathy. The fetuses who

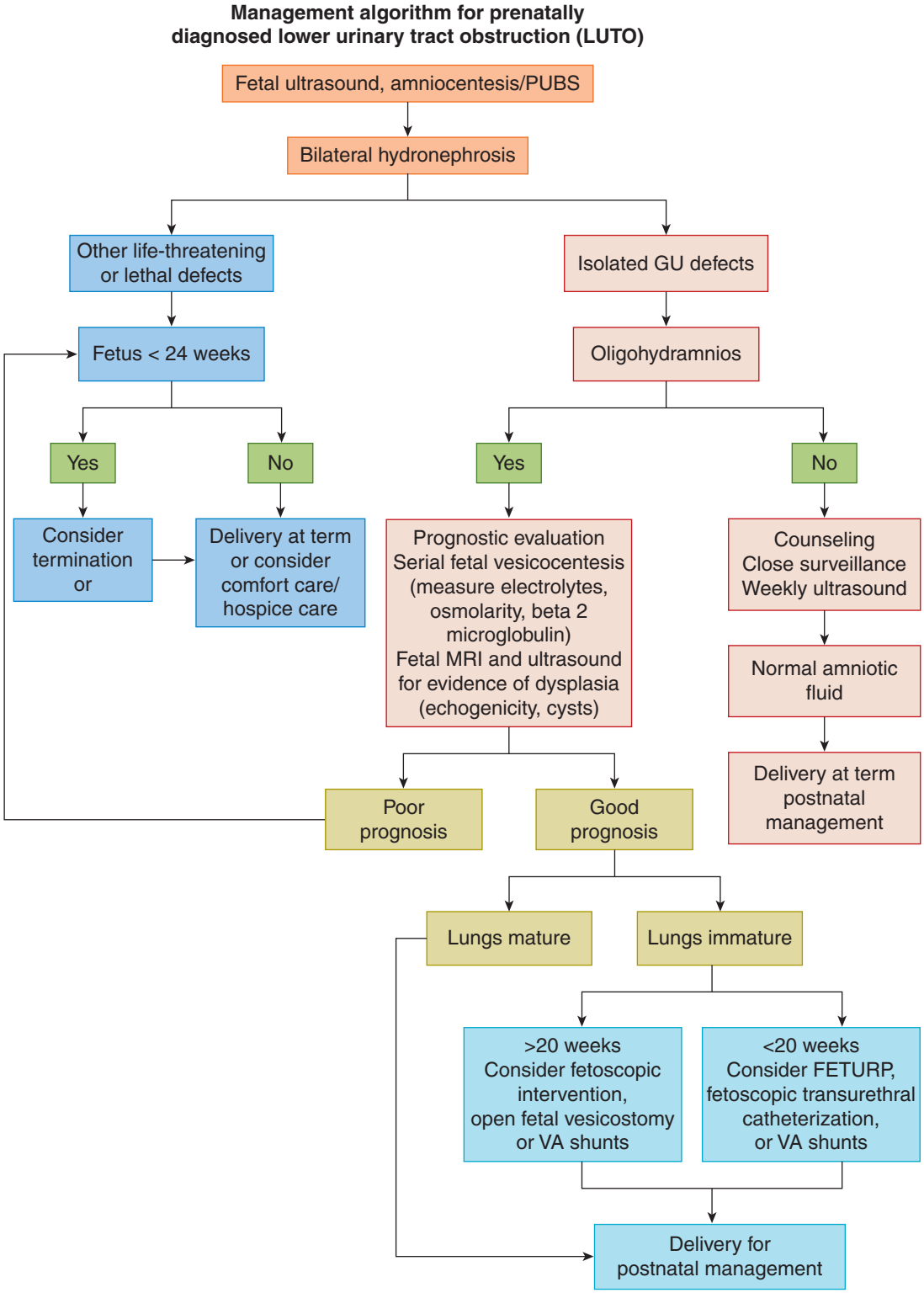

Figure 82-2 Algorithm for prenatal and perinatal management of the fetus with bladder outlet obstruction. VA, vesicoamniotic; GU, genitourinary; FETURP, fetoscopic transuterine release of posterior urethral valves; PUBS, percutaneous umbilical blood sampling. *(Lim FY, Crombleholme TM. In: Mattei P, ed. Surgical Directives: Pediatric Surgery. 2nd ed. In Press.)*

Table 82-2

Prognostic Criteria in Obstructive Uropathy

Sonography	No Cortical Cyst, Normal Echogenicity
Na	<100 mEq per liter
Cl	<90 mEq per liter
Osm	<210 mEq per liter
Ca	<2 mmol per liter
PO_4	<2 mmol per liter
β_2-microglobulin	<2 mg per liter

subsequently had a poor outcome were all "salt wasters" and those who had a good outcome had hypotonic urine. On the basis of this study, prognostic criteria for renal function in congenital hydronephrosis were proposed (Table 82-2). These results were questioned by other groups, who reported that these prognostic criteria did not accurately predict the renal function at birth. Wilkins et al. (1987) reported results using these prognostic criteria in nine cases of fetal obstructive uropathy. The criteria were accurate in predicting a poor outcome, as all four patients died and three of these four had evidence of renal dysplasia. In the fetuses with a predicted good prognosis, four of the five had poor renal function and the only patient with a good outcome underwent in utero decompression with a vesicoamniotic shunt.

The reports questioning the utility of fetal urine electrolyte levels as prognostic criteria prompted a reevaluation in a series of 40 fetuses with bilateral hydronephrosis. Crombleholme et al. (1991) retrospectively assigned fetuses to a good prognostic group only if they had a Na <100, Cl <90, osmolarity <210, and there was no sonographic evidence of dysplasia (Figure 82-3). Fetuses were assigned to a poor-prognosis group if even one of these criteria was not met. There was a statistically significant difference in survival in the good versus the poor-prognosis group (81% vs. 12.5%) even after excluding pregnancy terminations (87% vs. 30%). These prognostic criteria were intended as a means to select fetuses for in utero intervention. They accurately select the fetuses that have sufficient renal function to have a favorable outcome if decompressed in utero. If the fetal obstruction is unrelieved, however, the renal function is likely to deteriorate despite a favorable prognostic profile. Fetal obstructive uropathy is a dynamic process, and experimental studies in fetal lambs have demonstrated that the severity of renal damage from obstruction depends on the timing, duration, and severity of the obstruction (Harrison et al., 1981a, 1983; Glick et al., 1983, 1984). The fetal urine electrolytes obtained at 20 to 24 weeks of gestation may only reflect the renal function at the time they are assayed. In fact, Nicolini et al. (1992) have demonstrated by serial fetal bladder aspirations the worsening urinary electrolyte profile and renal function in fetuses with obstructive uropathy in which the obstruction was untreated. In the report from Wilkins et al. (1987), the fetuses in the favorable group had unrelieved obstruction and progression in their renal deterioration. The one fetus that was successfully decompressed in utero had a good outcome.

These prognostic criteria for in utero intervention in obstructive uropathy have become widely used and are being more appropriately applied as selection criteria for intervention. However, Nicolini et al. (1992) have pointed out that one potential problem with these criteria is that they fail to take into account the gestational age of the fetus and that threshold values were established in fetuses with obstructive uropathy and not normal fetuses. The effect of gestational age on fetal urine electrolytes is most marked prior to 21 weeks of gestation, becoming progressively more hypotonic and then remaining relatively stable throughout the remainder of gestation. The criteria proposed by Glick et al. (1985) were selected to establish the threshold for a poor prognosis as 2 SD from the mean value of the patients with a good prognosis. This does skew the criteria toward including potentially compromised fetuses into the good-prognosis group. But as the results reported by Crombleholme et al. (1991) confirm, this has not resulted in the treatment of fetuses with irrevocably compromised renal function. In fact, overly stringent selection criteria for intervention as proposed by Nicolini et al. (1992) may exclude many potentially salvageable fetuses from treatment. There are, however, no established fetal urine electrolyte parameters for fetuses less than 20 weeks of gestation.

In addition to the use of fetal urine Na, Cl, and osmolarity, other groups have suggested the addition of urine Ca^{2+}, PO_4, and β_2-microglobulin to assess fetal renal function. Nicolini et al. (1992) studied fetal urine creatinine, urea, and electrolytes, notably Ca^{2+}, Na, and PO_4 in a group of 24 fetuses with obstructive uropathy and 26 normal controls. They found that the urinary Ca^{2+} and Na were significantly higher in fetuses with renal dysplasia as compared with those with lower urinary tract obstruction but normal renal histology or normal clinical outcome. Urinary Ca^{2+} levels were found to be the most sensitive (100%) indicator of renal dysplasia but lacked specificity (60%). Urinary Na was slightly less sensitive (87%) but was found to be the most specific (80%). Urinary PO_4, creatinine, and urea were not significantly different in fetuses with dysplastic kidneys versus those without dysplasia.

The predictive value of fetal urine electrolytes in bladder outlet obstruction has been found to be enhanced by serial bladder taps (Johnson et al., 1995). Johnson et al. have recommended complete bladder drainage at 24-hour intervals for a minimum of three taps to best establish a clear pattern of increasing or decreasing urinary hypertonicity. While values clearly in the normal range on initial bladder tap may not require additional bladder taps to establish a prognosis, a

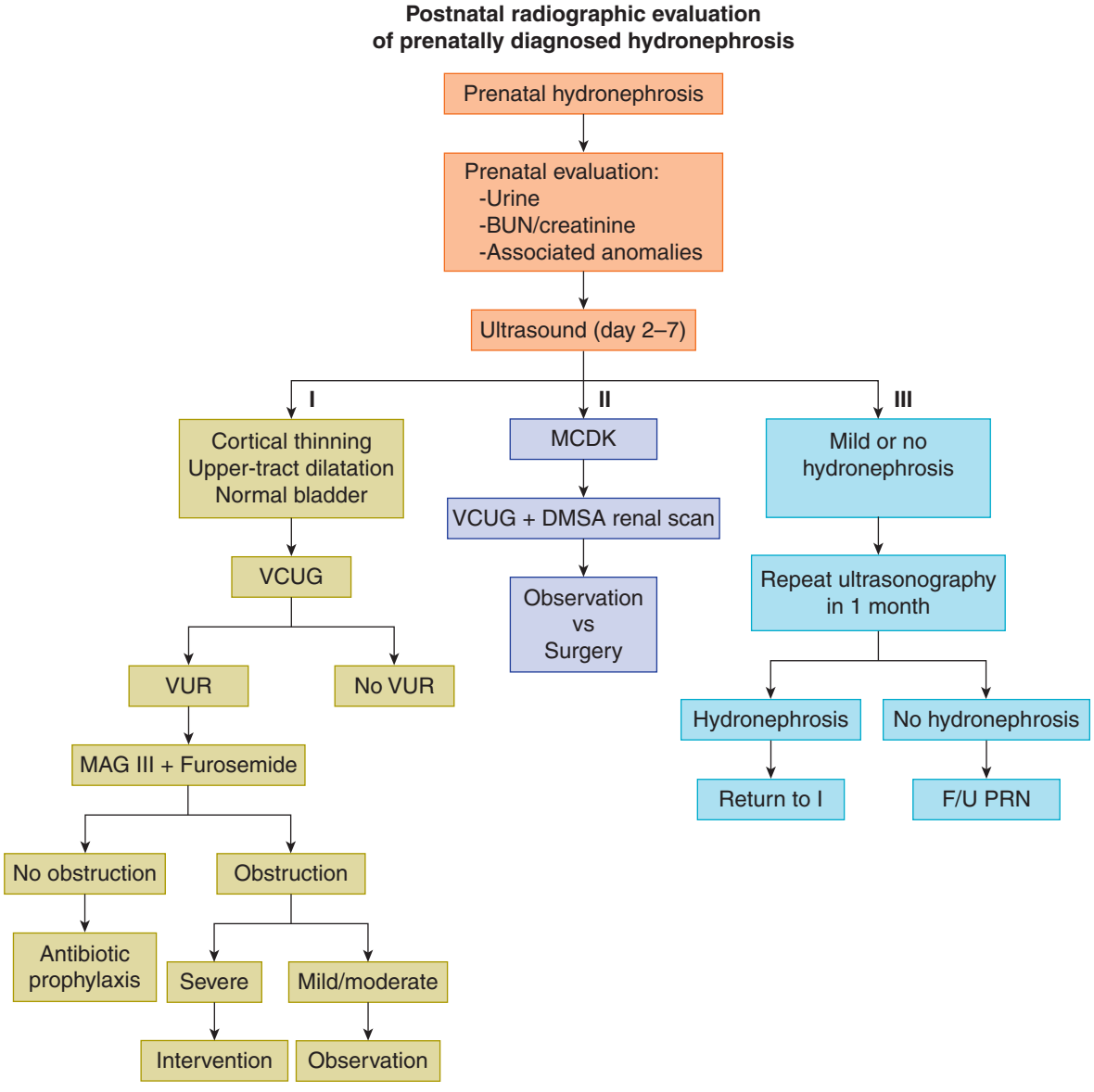

Figure 82-3 Algorithm for the postnatal evaluation of fetal hydronephrosis. MCDK, multicystic dysplastic kidney; VUR, vesicoureteral reflux; VCUG, voiding cystourethrography; F/U PRN, follow up as needed.

fetus with elevated values may show a clear trend of improving electrolyte values with sequential taps. The sequential taps are thought to clear stagnant urine that may not accurately reflect renal function (Qureshi et al., 1996).

It has been observed that obstructive uropathy due to PUVs has a long natural history (Parkhouse et al., 1988; Harrison and Adzick, 1991). Renal failure may not develop for years in a newborn with PUVs. A fetus with obstructive uropathy, a favorable prognostic profile, and normal amniotic fluid is currently not considered a candidate for in utero decompression. A small number of fetuses diagnosed with hydronephrosis were observed to have findings consistent with obstructive uropathy, a favorable prognostic profile, and normal amounts of amniotic fluid, but progressive renal insufficiency subsequently developed during infancy despite good renal function initially. We, thus, have lacked criteria that allow us to identify a fetus with obstructive uropathy and a good prognostic profile that, despite the presence of normal amniotic fluid volume, is at risk for ongoing renal damage. Muller et al. (1993) reported the use of fetal urinary β_2-microglobulin as a predictor of postnatal renal function at 1 year of age. They reported that 17 of 40 patients with normal amniotic fluid volume and a good prognostic profile had a creatinine level of >0.56 mg/L at 1 year of age. This value was selected as the threshold since it was 2 SD from the mean creatinine of normal 1-year-old infants. In this group of patients, the β_2-microglobulin was found to be significantly elevated as compared with patients with the same prognostic profile but with a creatinine of <0.56 mg/L at 1 year of age. β_2-Microglobulin may allow us to identify fetuses at risk for renal damage by unrelieved obstruction even though their amniotic fluid has not diminished.

Our current approach to in utero treatment for obstructive uropathy is to intervene in fetuses with a good prognostic profile only for decreasing amniotic fluid or frank oligohydramnios (Crombleholme et al., 1991; Cendron et al., 1994) (see Figure 82-3). Fetal therapy of obstructive uropathy up to now has been aimed at restoration of amniotic fluid volume to allow pulmonary development, averting neonatal death from pulmonary hypoplasia. The potential utility of β_2-microglobulin is that it may allow us to select for in utero therapy among fetuses with a good prognostic profile those at risk for ongoing renal damage. The goal of this treatment would be preservation of renal function as opposed to prevention of pulmonary hypoplasia. This would significantly expand the indications for fetal intervention in obstructive uropathy. However, this report is preliminary, and longer follow-up of these children as well as confirmation by other investigators will be necessary to define the role of fetal intervention in the setting of an elevated urinary β_2-microglobulin in fetuses with good prognostic profiles and normal amniotic fluid volume.

One major question that is difficult to address in fetal treatment of obstructive uropathy is assessing the efficacy of prenatal decompression. In a report of a large experience with vesicoamniotic shunts at a single institution, Johnson et al. (1995) described the outcome in 55 fetuses that underwent shunt placement. Unfortunately, this was a heterogeneous group of patients with good- and poor-prognosis patients with a range of diagnoses including PUVs, prune belly, urethral atresia, and a variety of other anomalies. In the group with PUVs, the postnatal survival was 60%. Of note is that the incidence of an elevated nadir creatinine level >1 mg/dL in the first year of life was 33%. Coplen et al. (1996) in a review of prenatal intervention for lower urinary tract obstruction from five reported series found an overall survival rate of only 48% and a catheter-related complication rate of 45%. In the report by Crombleholme et al. (1991), in both the good-prognosis and poor-prognosis groups, survival was greater in fetuses who were decompressed in utero as opposed to those who were not decompressed. In the group of 10 fetuses with a poor prognosis, 3 were electively terminated, 4 neonatal deaths were from pulmonary hypoplasia or renal dysplasia, and 3 had survived. All three survivors had restoration of normal amniotic fluid levels, but renal failure developed in two of the three survivors and they have since undergone renal transplantation. Among the 14 patients with no intervention, there were no survivors (11 terminations and 3 neonatal deaths from pulmonary hypoplasia).

In the good-prognosis group of nine fetuses, one was electively terminated, and there were no deaths, leaving eight neonatal survivors. One infant died at 9 months of age from unrelated causes, with normal renal function. Of the seven patients in the good-prognosis group who were not treated, five survived and two died after birth. Renal failure later developed in two of the survivors. The incidence of oligohydramnios in the good-prognosis group was 7 out of 16. All six patients with oligohydramnios who had fetal intervention survived. One patient with oligohydramnios that was untreated died at birth from pulmonary hypoplasia.

When in utero intervention restores amniotic fluid volume, neonatal death from pulmonary hypoplasia is averted. When oligohydramnios develops during the canalicular stage of lung development (16–24 weeks) the fetus usually has pulmonary hypoplasia precluding survival. In the group of fetuses reported by Crombleholme et al. (1991), there was a preponderance of oligohydramnios in the poor-prognosis group (23 of 24 as compared with 7 of 16 in the good-prognosis group). Fetuses from the good-prognosis group appear to survive as a result of fetal treatment in the face of variable rates of oligohydramnios. In the good-prognosis group, six of the seven fetuses with oligohydramnios had intervention and all six survived with normal renal function. However, the seventh patient with oligohydramnios, who was not treated, died at birth from pulmonary hypoplasia. Uncorrected oligohydramnios was associated with a 100% neonatal mortality. Normal or restored amniotic fluid volume was associated with a 94% survival (Crombleholme et al., 1991).

In utero decompression appears to prevent neonatal death from pulmonary hypoplasia, but the effect on renal function is less clear. The development of postnatal renal failure in two infants who were not treated because amniotic fluid volume remained normal raises a question about treating obstructed fetuses before oligohydramnios develops. Because renal development or maldevelopment is complete at birth, relief of obstruction in infancy or childhood may not prevent the progression to end-stage renal failure (Warshaw et al., 1982).

The severity of renal dysplasia at birth depends on the timing and severity of obstruction before birth (Glick et al., 1984; Adzick et al., 1987). Experimental work suggests that relief of obstruction during the most active phase of nephrogenesis (20–30 weeks of gestation) may obviate further damage and allow normal nephrogenesis to proceed (Bronshtein et al., 1990; Patten et al., 1990; Thomas, 1990; Blyth et al., 1993). One fetus in this series evaluated at 18 weeks of gestation had a favorable prognostic profile, but because the amniotic fluid level was normal, it was not a candidate for intervention. While the sonographic appearance of the kidneys was normal at 18 weeks of gestation, postnatal sonography suggested renal dysplasia and development of chronic renal insufficiency.

The maternal morbidity of vesicoamniotic shunts was minimal, but there was a high incidence of chorioamnionitis, in 3 of 21 procedures. However, all cases of chorioamnionitis were early in this particular study experience, before the routine use of prophylactic antibiotics and during a period when long-term (4–16 hours) bladder catheterization rather than aspiration was used for fetal urine sampling (Glick et al., 1985; Crombleholme et al., 1991). Among the five open cases of fetal surgery, there was no fetal morbidity or mortality, but preterm labor was observed in each mother requiring aggressive tocolytic therapy (Crombleholme et al., 1988a).

Harrison et al. (1981a, 1981b) first proposed the concept of in utero decompression in a report of poor outcome

Figure 82-4 Newborn with iatrogenic gastroschisis due to herniation of viscera through the abdominal wall defect created by attempted vesicoamniotic shunt placement. *(Courtesy of Burton Harris, MD)*

in 13 fetuses with obstructive uropathy. This same group subsequently reported the first case of vesicoamniotic shunting for obstructive uropathy using a "Harrison" double pig-tail catheter. Other groups quickly followed suit, and in a 1986 report of the International Fetal Surgery Registry, 62 fetuses had been treated by percutaneous vesicoamniotic shunts (Manning et al., 1986). The overall survival was only 48%; the survival rate was 76% in cases due to PUVs. The procedure-related mortality rate in the registry was 3%. There were several problems with this early experience with vesicoamniotic shunts. Many fetuses were treated inappropriately prior to the development of selection criteria. Secondly, many cases were assessed by indwelling fetal bladder catheters for several hours, which along with the lack of prophylactic antibiotics, predisposed to chorioamnionitis. In addition, as noted by Glick et al. (1985), multiple shunt insertions are often necessary because of shunt occlusion, or dislodgment. Iatrogenic "gastroschisis" has also been reported when trocars used for insertion lacerated the abdominal wall during placement of vesicoamniotic shunts (Manning et al., 1986) (Figure 82-4). Rodeck has reported experience with the KCH catheter, which appears to function better than the Harrison catheter (Rodeck et al., 1988). The utility of vesicoamniotic shunts is limited, however, by the brief duration of decompression, risk of infection, catheter obstruction or dislodgment, fetal injury during placement, and potentially inadequate decompression of the fetal urinary tract. These factors make vesicoamniotic shunting inappropriate for early gestation decompression of the urinary tract. It is not clear that vesicoamniotic shunting has any benefit beyond restoring amniotic fluid volume. Both the Harrison catheter as well as the KCH catheter have a small diameter and are relatively long. According to Poiseuilles's law, very high intravesical pressures are necessary to force urine through the shunt from the bladder to the amniotic cavity. In most cases of high-grade bladder outlet obstruction, there is incompetence of the vesicoureteral junction and intravesical pressure is transmitted to the developing kidney. Despite restoring amniotic fluid volume, vesicoamniotic shunts do not completely decompress the genitourinary tract and do not protect the developing kidneys. This view is consistent with the poor long-term renal outcomes of fetuses successfully treated by vesicoamniotic shunting. Freedman et al., found that 50% of successfully treated fetuses had severely compromised growth and 55% had renal insufficiency or chronic renal failure requiring dialysis or transplantation (Freedman et al., 1999). Biard et al., reported similar growth problems but slightly better renal outcomes in PUV versus urethral atresia. Another underappreciated complication of vesicoamniotic shunts is subsequent severe bladder dysfunction, which may be sufficiently severe to preclude kidney transplantation (Biard et al., 2005).

The presence of oligohydramnios in the second-trimester fetus with bilateral hydronephrosis due to bladder outlet obstruction is uniformly fatal if untreated (Glick et al., 1985; Crombleholme et al., 1991). Complete decompression of the genitourinary tract and elimination of high intravesical pressure can only be achieved by vesicostomy. Vesicoamniotic shunts are inadequate to completely decompress the genitourinary tract and protect the bladder and kidneys from high intravesical pressures, and Harrison et al. have reported their experience with open fetal surgery in eight cases (Crombleholme et al., 1988a, 1991; Harrison et al., 1991). Six of the eight treated were delivered by cesarean section at 32 to 35 weeks of gestation. Four of the six had restoration of amniotic fluid levels by the procedure and had no evidence of pulmonary hypoplasia. The other two fetuses died postnatally of severe pulmonary hypoplasia because of persistent oligohydramnios due to renal dysplasia. They displayed long-standing oligohydramnios prior to treatment and suffered pulmonary hypoplasia despite intervention. These cases would be excluded from treatment by current selection criteria. There were two stillbirths; one pregnancy was

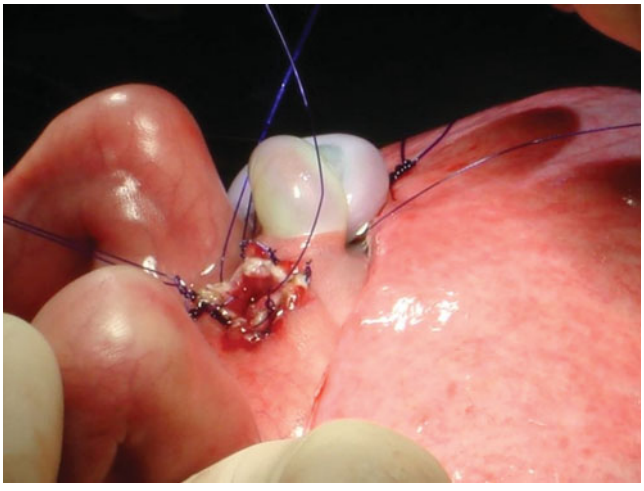

Figure 82-5 Intraoperative photograph taken during open fetal surgery for vesicostomy creation in a 19-week gestation fetus with bladder outlet obstruction due to posterior urethral valves.

terminated (by parental request) because of cloacal anomaly and the other when the mother discontinued tocolytic therapy. Three of the four survivors have had no evidence of renal insufficiency during follow-up of up to 8 years. Progressive renal insufficiency developed in the fourth patient, requiring renal transplantation at 5 years of age; the child was doing well 4 years after transplantation.

Recently, Crombleholme et al. have reintroduced open fetal surgery for vesicostomy in bladder outlet obstruction due to PUVs (T. M. Crombleholme, personal oral communication, 2010) (Figure 82-5). Preliminary experience with this approach suggests that open vesicostomy successfully decompresses the genitourinary tract and preserves renal function and bladder function. No maternal complications have occurred in these patients. However, prematurity with deliveries from 29 to 35 weeks of gestation have been observed. Long-term follow-up will be necessary to accurately assess renal function and bladder function. Open fetal surgery for fetal vesicostomy to relieve bladder outlet obstruction is technically feasible and has been successful in restoring amniotic fluid dynamics and preventing death from pulmonary hypoplasia. However, this is achieved at potentially significant risk to mother and fetus in the form of preterm labor precipitated by hysterotomy. Fetal cystoscopic treatment of bladder outlet obstruction offers the appeal of a minimally invasive approach that can be performed under local anesthesia (Quintero et al., 1998; Agarwal et al., 1999). Fetal cystoscopy can be used to disrupt the valves by hydroablation, guide-wire passage, or laser ablation (Quintero et al., 1995a, 1995b, 2000; Welsh et al., 2003). Clifton et al., have recently reported success with antegrade passage of a transurethral stent, not only restoring amniotic fluid but with normal renal function out to 2 years (Clifton et al., 2008). A limitation of all fetoscopic approaches is the angulation of the posterior urethra, which increases at 20 weeks of gestation, making this approach technically more difficult.

It has been recognized that there is a paucity of high-quality evidence to inform counseling and decision-making regarding fetal therapy (Clark et al., 2003). As a result, a randomized controlled trial of percutaneous shunting in lower urinary tract obstruction (PLUTO trial) is underway (funded by Wellbeing for Women). Even if shunting proves not to be efficacious, other interventions such as fetoscopic techniques and open fetal surgery will still need to be evaluated. (Lissauer et al., 2007).

TREATMENT OF THE NEWBORN

A team approach is extremely helpful to inform the parents and to help them understand and cope with the diagnosis and understand the postnatal evaluation (see Figure 82-2).

Any newborn with a prenatal diagnosis of hydronephrosis should undergo a physical examination at birth. Monitoring of the urinary output within the first 24 to 48 hours is unreliable. Failure to void during the first 2 days after birth may reflect normal fluid shifts or may be the first sign of a significant urologic anomaly. In the neonate who does not void within the first 48 hours, the differential diagnosis of anuria includes obstructive uropathy, renal failure, urogenic bladder, and the effects of maternal medication. However, most patients with an obstructive process will void, albeit with a weak stream, within the first 2 days of life. Serum electrolytes, blood urea nitrogen, and creatinine levels measured within the first day of life are a reflection of maternal renal function via placental exchange. It is best to wait for 24 hours to measure these levels. The most helpful test in the initial evaluation of the newborn with prenatally diagnosed hydronephrosis is ultrasonography of the abdomen including a scan of the bladder. Timing of the ultrasonography depends on the degree of prenatal hydronephrosis. If severe dilatation of the renal pelvis has been detected antenatally, then early ultrasound evaluation should be performed so as to permit early intervention. Otherwise, ultrasound examination can be postponed for 3 to 7 days in order to let the diuresis that occurs during the first 48 hours of life to resolve (Arant, 1992). If the initial postnatal renal ultrasound is normal, the evaluation should be pursued, with a repeat ultrasound in 3 to 4 weeks. There is a high incidence (50%) of additional lesions, such as ureteropelvic junction obstruction (UPJ) and vesicoureteral reflux, diagnosed in neonates with antenatal diagnosis of hydronephrosis that have a normal upper urinary tract at the time of the first ultrasound (Detjer and Gibbons, 1989).

Mild cases of hydronephrosis can be watched and may warrant only one or two ultrasounds during the postnatal period (see Figure 82-2). It is rare for mild dilatation of the upper urinary tract to progress. In cases in which other findings are seen (such as cortical thinning, upper tract dilatation, and a normal bladder) voiding cystorurethrography (VCUG) should be performed. If there is reflux, then a renal scan with 99 technetium diethylenetriaminepentaacetic acid (DTPA) or mercaptoacetyltriglycine (MAG-3) will be

helpful in documenting function within each kidney. If no evidence of reflux is noted by VCUG, then a MAG-3 scan with furosemide should be obtained to evaluate possible UPJ obstruction. If UPJ obstruction is noted, treatment is determined by the severity of the obstruction. In severe UPJ obstruction, in which a kidney shows 35% or less function, pyeloplasty should be performed. In cases in which mild-to-moderate obstruction is noted and the kidney has more than 35% function, observation alone may be indicated, with repeat ultrasonography in 3 months. A repeat renal scan will help to assess changes in renal function. As stated earlier, there is growing evidence to suggest that a mild degree of UPJ obstruction may resolve and may not warrant surgical intervention (see Chapter 81).

If prenatal ultrasound reveals a multicystic dysplastic kidney, a VCUG and renal scan should be obtained. These studies confirm the lack of function in the affected kidney and rule out any abnormalities in the contralateral kidney (Flack and Bellinger, 1993).

SURGICAL TREATMENT

Surgical intervention at birth is required in cases when a severe obstruction will jeopardize renal function. This applies most often to cases of PUVs, obstructing ureterocele, and severe UPJ obstruction affecting a solitary kidney. Emergency surgical treatment is seldom warranted. Reconstruction of the urinary tract should not be attempted until the newborn has stabilized from a medical standpoint and has been fully evaluated. Drainage of the urinary tract can provide decompression by placement of either a urethral catheter, suprapubic catheter, or a nephrostomy tube until definitive repair of the urinary tract can be accomplished.

PUVs and obstructing ureterocele are amenable to early endoscopic treatment but may require further surgical intervention once the child has stabilized and grown. In the presence of a solitary kidney, every attempt should be made to ensure adequate drainage so as to not further jeopardize renal function.

LONG-TERM OUTCOME

Reports in the urologic literature in the late 1970s and early 1980s reviewing experience with PUVs in newborns were notable for the lack of respiratory problems encountered. In contrast, Nakayama et al. (1986) reported 11 cases of PUVs, clinically evident at birth, in which five of the infants died. Three died within hours of birth as a result of respiratory insufficiency and two survived their respiratory insufficiency only to die from renal failure within 3 weeks. Of the six survivors, four had severe respiratory problems requiring prolonged ventilatory support. In addition to the two infants who died early from renal failure, three others developed renal failure despite urinary diversion. Only two of the patients in this series had normal renal function after reconstruction of their urinary tracts.

Clinical experience suggests that the pulmonary and renal consequences of bladder obstruction will vary with the severity of the obstruction. The degree of obstruction will determine the volume of amniotic fluid, the extent of pulmonary hypoplasia, and the dysplastic effects of obstruction on the developing kidney. High-grade bladder outlet obstruction causes megacystis, bilateral hydronephrosis, and oligohydramnios, which results in pulmonary hypoplasia and postnatal respiratory insufficiency. In addition to pulmonary hypoplasia and renal dysplasia, fetal urethral obstruction produces a wide variety of deformations, including Potter facies, limb abnormalities such as clubfoot and hip dislocation, and abnormal abdominal wall muscular development (prune belly). Less severe obstruction may permit enough urine output to allow sufficient pulmonary development for survival. Despite adequate pulmonary development for survival, partial high-grade obstruction may result in renal dysplasia, bladder dysfunction, and irreversible renal failure. Milder forms of obstruction may have normal pulmonary development and mild renal insufficiency or normal renal function. This broad spectrum of severity of fetal obstructive uropathy presents a diagnostic and therapeutic challenge: which cases are severe enough to warrant prenatal intervention, which should be delivered early to prevent ongoing renal damage, and which are best managed postnatally at term?

Freedman et al. (1987) have reported on the long-term outcome of 14 patients who underwent vesicoamniotic shunting for obstructive uropathy. This was a mixed group of patients, with seven cases of prune belly, four cases of PUVs, and one case each of urethral atresia, megacystis–microcolon syndrome, and bilateral vesicoureteral reflux. Growth was observed to be below the 5th percentile in 7 and below the 25th percentile in 12. Four of the patients required ventilatory support at birth; two required it for up to a month. Two children had reactive airway disease and four had chronic bronchitis. Eight of the fourteen void spontaneously, four catheterize in addition to voiding, and the remaining two catheterize only. Bladder augmentation was required in three of the four patients with PUVs. Renal function was normal in six, renal insufficiency in three, and the remaining five had end-stage renal disease and had undergone renal transplantation. Biard et al., reported only slightly better outcomes in the setting of PUVs (Biard et al., 2005).

Sexual function may be impaired because of a much higher incidence of undescended testes, impaired ejaculatory mechanism, and effects of renal failure on potency. The incidence of undescended testes is 12% in patients with PUVs as compared with 0.8% in the normal population (Kruegar et al., 1980). Woodhouse et al. (1989) reported that half of 21 adult patients aged 19 to 37 years with PUVs had dry, slow, or retrograde ejaculations. In addition, one patient had poor erections and another was impotent as a result of renal failure and dialysis. Despite these problems, semen analysis revealed all to be potentially fertile, and 3 of the 21 had fathered children.

GENETICS AND RECURRENCE RISK

In most cases, bladder outlet obstruction due to PUVs is a sporadic event, with no risk of recurrence. However, if associated with chromosomal abnormality, there may be an increased risk of having an affected fetus, depending on the nature of the abnormality. The megacystis–microcolon–intestinal hypoperistalsis syndrome is a rare cause of bladder outlet obstruction that may be difficult to distinguish from other causes. This is an important distinction, as this syndrome has an autosomal recessive inheritance pattern with a 25% risk of affecting a subsequent pregnancy.

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83 CHAPTER Hydronephrosis: Ectopic Ureterocele

Key Points

- Ectopic ureteroceles are associated with duplex collecting systems and are more common in females.
- An ectopic ureterocele can be stenotic or refluxing.
- Ectopic ureteocele can result in dysplastic changes in the superior pole of ipsilateral kidney.
- Ectopic ureteroceles can be challenging to diagnose as they intermittently decompress.
- Ectopic ureteroceles are a rare cause of bladder outlet obstruction.

CONDITION

A ureterocele is a cystic dilatation that occurs at the distal end of the ureter at its junction with the bladder. Simple ureteroceles are those that are located in the normal location of the ureteral orifice in the trigone of the bladder. Simple ureteroceles are more commonly detected in adults and usually are associated with a single collecting system. Simple ureteroceles are rarely associated with the upper pole ureter of a complete duplication of the collecting system. Simple ureteroceles may be associated with a varying degree of obstruction, but this is not significant in most patients. In contrast, with an ectopic ureterocele the ureteral orifice is located in an ectopic position, usually distal to the trigone, and this form is typically associated with a duplex collecting system. Ectopic ureterocele is also associated with an increased incidence of duplication in the contralateral kidney. The ureterocele may vary in size, from a tiny cystic lesion within the submucosal ureter, to that of a large cystic balloonlike structure that fills the bladder. The size of the ureterocele may fluctuate from one examination to the next. Histologically, the ureterocele is covered by the mucosa of the bladder and lined by the mucosa of the ureter, with varying degrees of attenuated smooth muscle bundles and connective tissue between the two layers of mucosa.

Several theories have been proposed to account for the embryonic development of a ureterocele. In one theory, a membrane covering the ureteral orifice persists for a long period, leading to the development of the ureterocele (Chwalle, 1927). In another theory, a ureterocele forms as a result of a stimulus to an expansion that transforms the bladder into a globular cap, creating an expanded thin-walled distal ureter (Stephens, 1971). Lastly, a localized embryonic arrest has been hypothesized as the cause of the ureterocele (Tokunaka et al., 1981).

Ectopic ureterocele has been classified anatomically by Stephens (1958, 1983). In this classification scheme, stenotic ectopic ureterocele is characterized by a small stenotic orifice and accounts for approximately 40% of cases. In sphincteric ectopic ureterocele, the orifice of the ureterocele is within the internal sphincter and accounts for an additional 40% of cases. In sphincteric ectopic ureterocele the ureteral orifice may be of normal caliber or may be enlarged and may open either in the posterior urethra in males or distal to the external sphincter in females. Sphincterostenotic ectopic ureterocele accounts for approximately 5% of cases. The stenotic orifice of this type of ectopic ureterocele is located within the urethral floor. There are other rarer types of ectopic ureterocele, including cecoureterocele, in which the lumen extends distal to the level of the orifice as a long tongue or cecum; blind ectopic ureterocele, in which there is no orifice so that the ureter is completely obstructed; and nonobstructive ectopic ureterocele, in which the orifice is enlarged within the bladder.

In complete ureteral duplication, the ureter draining the upper pole moiety usually opens caudal and medial to the ureter draining the lower pole moiety. This upper pole moiety ureter is commonly associated with ureterocele. When a duplex system is found to be present on one side, there is contralateral duplication in approximately 50% of the cases. This occurs far more frequently in females and can potentially result in bladder outlet obstruction if the ureterocele is sufficiently large. The orifice of the ureterocele is usually

obstructed either by stenosis or because it opens at the level of the urogenital diaphragm and is obstructed by the closed bladder neck. Not only can the ureterocele cause obstruction of the ureter from which it arises, but the ureterocele can also result in obstruction of the ureter draining the lower pole moiety, placing the entire kidney at risk. In ectopic ureterocele the upper pole moiety is commonly dysplastic and has poor or no function because of long-standing high-grade obstruction. The ectopic ureterocele may also affect the contralateral ureter and renal unit. Large ectopic ureteroceles may obstruct the ipsilateral lower pole moiety and, if extensive enough, they may even obstruct the contralateral side or induce vesicoureteral reflux (Koyanagi et al., 1980; Harrison and Filly, 1991).

INCIDENCE

The incidence of ureterocele is estimated to be 1 in 4000 autopsies in children (Brock and Kaplan, 1978). Ureteroceles are far more common in whites than in blacks. Ureteroceles are also five times more common among girls than among boys (Brock and Kaplan, 1978). Approximately 80% of ureteroceles are associated with a duplex collecting system. No information is available about the prenatal incidence of ectopic ureteroceles.

SONOGRAPHIC FINDINGS

The common mode of presentation for a fetus with ectopic ureterocele is unilateral hydronephrosis. The dilated upper pole of a duplex collecting system and a normal-appearing lower pole collecting system are key features that permit an accurate sonographic diagnosis of an obstructed duplex collecting system (Mahony, 1994). The dilated upper pole moiety may enlarge sufficiently so that it displaces the nondilated lower pole of the kidney inferiorly and laterally. Sonographic detection of two distinct ureters may be quite difficult in utero. It is important to search for a thin-walled fluid-filled ectopic ureterocele within the bladder (Figure 83-1). This may be very challenging, as the ureterocele may expand and decompress with ureteral peristalsis and bladder emptying. The ureterocele may also prolapse into the urethra if intravesical pressure exceeds intraurethral pressure. The ureterocele will initially collapse then subsequently prolapse or herniate into the urethra (Cremin et al., 1977; Fitzsimmons et al., 1986). Ultrasonographers should be mindful of this potential diagnostic pitfall, especially since ultrasonographic urinary bladder examinations with a full bladder are the very condition most likely to cause difficulty in identifying ureteroceles because of the flattening or intraurethral prolapse it causes. In every patient in whom hydronephrosis is antenatally diagnosed, a detailed examination of the fetal bladder should be performed to look for an intravesical cystic structure or the appearance of an extravesical diverticulum due to the intraurethral prolapse of the ureterocele during micturition (Fitzsimmons et al., 1986).

Antenatal recognition of the ectopic ureterocele and associated duplex collecting system can be exceedingly difficult. While upper pole hydronephrosis may be diagnosed, its cause is often missed. In a series reported by Winters and Lebowitz (1990), of 40 cases of hydronephrosis, prenatal diagnosis of duplex system with upper pole hydronephrosis was suggested in only one-third and only 1 of 19 ureteroceles were correctly diagnosed. This low specificity is thought to be due to the fact that many prenatal sonographers are unfamiliar with this entity. In addition, the duplex collecting system associated with ectopic ureterocele is difficult to diagnose even postnatally. The ureterocele can be mistaken for a bladder if the bladder is empty, or the full bladder can result in effacement

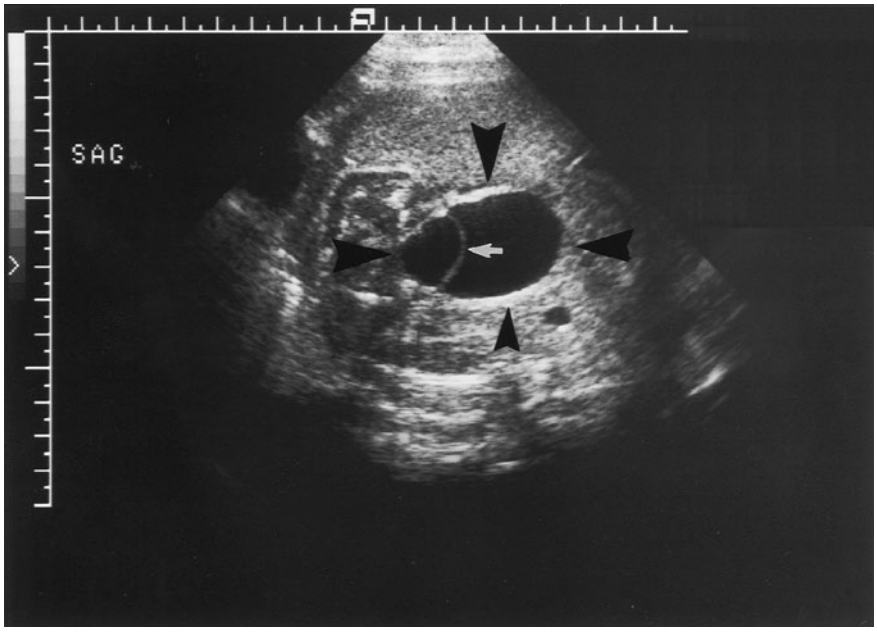

Figure 83-1 Prenatal sonographic image of a fetus that presented with unilateral hydronephrosis and was found to have a large ectopic ureterocele filling the bladder. This sagittal section through the bladder (*black arrowheads*) demonstrates the crescentic membrane (*white arrow*) of the ureterocele filling the bladder. *(Reprinted, with permission, from Cendron M, D'Alton ME, Crombleholme TM. Prenatal diagnosis and management of the fetus with hydronephrosis. Semin Perinol. 1994;18:163-181.)*

of the ureterocele (Lebowitz and Griscom, 1980). Another sonographic pitfall is the recognition of an ectopic ureterocele that on subsequent examinations is not visualized and therefore is thought to have resolved. As noted by Garmel et al. (1996) the "vanishing ureterocele" may be missed as a result of this same phenomenon, either by dilation in an empty bladder or effacement by a full bladder. It is important to recognize that a ureterocele will persist despite failure to demonstrate it on follow-up sonographic examinations. In some cases, the diagnosis may be facilitated by the use of a fetal MRI. As noted by Sozubir et al. (2003) fetal MRI can be an important adjunct to ultrasound enabling the diagnosis, in this case, of ectopic ureterocele with prolapse through the urethra onto the perineum in a female fetus (Sozubir et al., 2003).

DIFFERENTIAL DIAGNOSIS

The presenting sonographic features determine the differential diagnosis. If the most prominent feature is the cystic dilatation of the superior pole moiety of the kidney, then ureteropelvic junction obstruction, adrenal cyst, and mesenteric cyst are part of the differential diagnosis. Megaureter is also considered if a tortuous dilated ureter draining the upper pole moiety is a prominent feature. If the ureterocele prolapses into the urethra and causes bladder outlet obstruction, the fetus may present with a dilated bladder and bilateral hydronephrosis. This needs to be distinguished from posterior urethral valves, urethral atresia, and megacystis–microcolon. In addition, with ureteral dilatation of one or both sides, an ectopic ureterocele should be distinguished from vesicoureteral reflux. This can often be differentiated by the increase in ureteral size noted during fetal bladder contraction. However, the sonographic appearance of the crescentic membrane within the bladder is pathognomonic for ectopic ureterocele and narrows the differential diagnosis to this one condition (Figure 83-1).

ANTENATAL NATURAL HISTORY

Ureterocele is the third most common structural cause of congenital hydronephrosis (Chinn and Filly, 1982). The prenatal history of this condition is usually benign. In most instances the ectopic ureterocele is associated with some degree of obstruction, which, because of its long-standing nature, results in cystic dysplastic changes of the upper pole moiety (Cendron et al., 1994). The presence of the duplex collecting system and the ectopic ureterocele, however, places the ipsilateral kidney at some risk. If the ureter draining the lower pole moiety becomes obstructed this lower pole moiety is also at risk for renal dysplasia. Extremely large ureteroceles or ureteroceles that prolapse through the urethra may present as bladder outlet obstruction. It is only with careful sonographic evaluation that the true nature of the condition can be distinguished from other causes of bladder outlet obstruction. The prolapse of the ureterocele through the urethra results in vesicomegaly and bilateral hydronephrosis. This is the one instance in which ectopic ureterocele must be followed closely because its potential consequences for amniotic fluid volume and dysplastic renal changes in both kidneys are essentially equivalent to other causes of bladder outlet obstruction, such as posterior urethral valves. In most instances, however, the fluctuation in the size of the ectopic ureterocele allows adequate bladder emptying and maintenance of amniotic fluid volume. All fetuses with this form of ectopic ureterocele should be followed closely with serial sonography to exclude the possibility that a more significant degree of bladder outlet obstruction is compromising amniotic fluid volume or that there is an error in diagnosis and another form of bladder outlet obstruction exists.

The most important aspect of prenatal diagnosis of ectopic ureterocele is the prevention of postnatal urosepsis and loss of renal function (Caione et al., 1989). The vast majority of patients with ectopic ureterocele who present postnatally present with urosepsis, a decrease in renal function, or failure to thrive. It has been suggested by some authors that prenatal diagnosis of ectopic ureterocele identifies a group of patients who would otherwise be entirely asymptomatic and for whom a less aggressive approach to their postnatal treatment is indicated. While it may be true that the need for surgery remains to be defined in this group of patients, the identification of such patients warrants immediate initiation of prophylactic antibiotics to prevent reflux associated upper tract infections and secondary decrease in renal function.

MANAGEMENT OF PREGNANCY

The diagnosis of an ectopic ureterocele should prompt a detailed sonographic assessment of the contralateral kidney and exclusion of potential associated nongenitourinary anomalies. All fetuses with suspected ectopic ureterocele should be evaluated by a pediatric surgeon or pediatric urologist. In most instances, the presence of the ureterocele will have no effect on the pregnancy and should not have an impact on the clinical site, mode, or timing of delivery. The only exceptions are ureteroceles that cause bladder outlet obstruction, either because of their very large size or because they prolapse into the urethra. In these cases serial ultrasound examinations are warranted to observe amniotic fluid volume, which may be compromised. Decreasing amniotic fluid volume or oligohydramnios may require intervention. If a fetus is beyond 32 weeks of gestation, consideration should be given to steroid administration and early delivery.

FETAL INTERVENTION

At present there is no indication for fetal intervention following the prenatal diagnosis of an ectopic ureterocele.

TREATMENT OF THE NEWBORN

Chertin et al., have shown that prenatal diagnosis of ectopic ureterocele and associated duplex collecting system leads to fewer urinary tract infections and earlier endoscopic treatment (Chertin et al., 2005). All newborns with suspected duplex collecting systems and associated ectopic ureteroceles should undergo a complete urologic evaluation. It is prudent to wait 72 hours from the time of birth to obtain a postnatal sonogram so that an accurate assessment of the upper tract anatomy can be made. It is not uncommon in patients diagnosed prenatally with hydronephrosis, without a more specific etiologic diagnosis, to have a duplex collecting system with an ectopic ureterocele as the cause of hydronephrosis postnatally. If there is some doubt as to the cause of the hydronephrosis, the most useful test for defining the anatomy is voiding cystourethrography (VCUG). Function of the affected upper pole moiety can best be assessed by a technetium-99m DMSA renal scan.

The management of ectopic ureteroceles is controversial as there are several options for treatment (Rickwood et al., 1992). Churchill et al. (1992) have suggested an approach based on the function of the upper pole moiety. In cases in which there is nonfunctioning of the upper pole and only grade I vesicoureteral reflux, an upper pole nephroureterectomy can be performed in association with cystoscopic ureterocele drainage. If upper pole nonfunction is associated with grade II or III vesicoureteral reflux, then the upper pole nephrectomy can be combined with ureterocele excision and lower pole moiety ureteral reimplantation. If the function of the upper pole moiety is indeterminate, then endoscopic incision of the ureterocele can be performed and the subsequent degree of vesicoureteral reflux and function can be reassessed. In cases in which function of the upper pole moiety is preserved and there is only grade I vesicoureteral reflux, ureteropyelostomy and cystoscopic ureterocele drainage is indicated. If there is associated grade II or grade III reflux in these cases then ureteropyelostomy, ureterocele excision, and ureteral reimplantation are indicated.

Other groups have suggested a more conservative approach to management with initially only a transurethral incision of the ureterocele (Castagnetti et al., 2004). Transurethral incision of the ureterocele is effective in most patients with only a 5% rate of vesicoureteral reflux requiring reimplantation of the incised moiety. Other secondary surgery may be necessary in up to 50% of cases usually due to pre-existing vesicoureteral reflux in either the lower pole moiety or the contralateral system.

LONG-TERM OUTCOME

In general, the long-term outcome in ectopic ureterocele is excellent. Prenatal diagnosis allows initiation of prophylactic antibiotics at birth to prevent urosepsis. The presence or absence of upper pole dysplasia and vesicoureteral reflux will determine the surgical approach taken. The prospects for preservation of renal function and avoiding urosepsis are excellent. It is not uncommon for ectopic ureterocele to be difficult to diagnose postnatally; therefore, persistence is necessary. Ultrasound examination, voiding cystourethrography, and even cystoscopy may be necessary to make the diagnosis. These efforts are rewarded by the avoidance of urinary tract infection and preservation of upper pole renal function if dysplasia has not already developed.

GENETICS AND RECURRENCE RISK

Ectopic ureterocele is a sporadically occurring genitourinary anomaly without a known association with chromosomal abnormality or an increased risk for recurrence in subsequent pregnancies or offspring of an affected patient.

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84 CHAPTER

Ambiguous Genitalia

Key Points

- Incidence is 1 in 5,000 livebirths. Most common cause is congenital adrenal hyperplasia (CAH), resulting in a virilized genetic female. This autosomal recessive condition has an incidence of 1 in 14,000 livebirths.
- Prenatal classification of ambiguous genitalia is based on cause. Fetuses can be virilized genetic females, undervirilized genetic males, or true hermaphrodites with both ovarian and testicular tissue present.
- Sonographic prenatal diagnosis of ambiguous genitalia is more accurate in males. Clitoromegaly is associated with false-positive diagnosis in females. The presence of a normal fetal uterus after 19 weeks is strongly predictive of a virilized genetic female.
- Differential diagnosis in a virilized female includes androgen exposure due to CAH or maternal tumors. An undervirilized male may be due to defects in the synthesis of testosterone or its precursor, androgen insensitivity, chromosome abnormalities, or true hermaphroditism. Single-gene disorders, such as Smith–Lemli–Opitz syndrome, should be considered.
- Prenatal management should include fetal karyotype and testing of 7-dehydrocholesterol (7-DHC) levels in the amniotic fluid. Delivery should occur at a tertiary center.
- Fetal treatment is available for CAH and Smith–Lemli–Opitz syndrome.
- Infant sex assignment should occur after birth using a team approach.
- The role of genital surgery in children with ambiguous genitalia is controversial.
- Recurrence risk depends on the etiology of the ambiguous genitalia.

CONDITION

Although the genotype of a fetus is determined at conception, sexual differentiation does not occur until 6 to 7 weeks of gestation (McGillivray, 1992). Before that point, the embryo has bilateral undifferentiated gonads and both müllerian and wolffian duct systems. Fetuses with a Y chromosome containing the gene for the testis-determining factor *(SRY)* will convert the undifferentiated gonad to a testis, which involves the formation of seminiferous tubules that surround the primitive germ cells. As shown in Figure 84-1, Leydig cells begin to produce testosterone, which acts on the wolffian ducts to produce male internal genitalia. Sertoli cells produce antimüllerian hormone (AMH), also known as müllerian duct inhibiting substance (MIS), which causes regression of the müllerian system (McGillivray, 1992).

At 6–7 weeks of gestation, the external genitalia are undifferentiated and consist of a genital tubercle, genital folds, and swellings. During male embryogenesis, masculinization of the common primordia is induced by the activity of dihydrotestosterone (DHT). DHT is formed from testosterone via the enzyme 5α-reductase. The urogenital tubercle then differentiates into the glans. The urogenital folds differentiate into the shaft of the penis and a male type of urethra by 12 to 14 weeks of gestation. The urogenital swellings fuse at the midline into the scrotum. Without testosterone, the müllerian duct develops into the fallopian tubes, uterus, and upper vagina. The genital tubercle becomes the clitoris, and the genital folds and swellings become the labia. Two X chromosomes are needed to maintain the ovaries and germ cells.

Most fetuses with genital ambiguity are otherwise well formed, although malformations of the sex organs sometimes

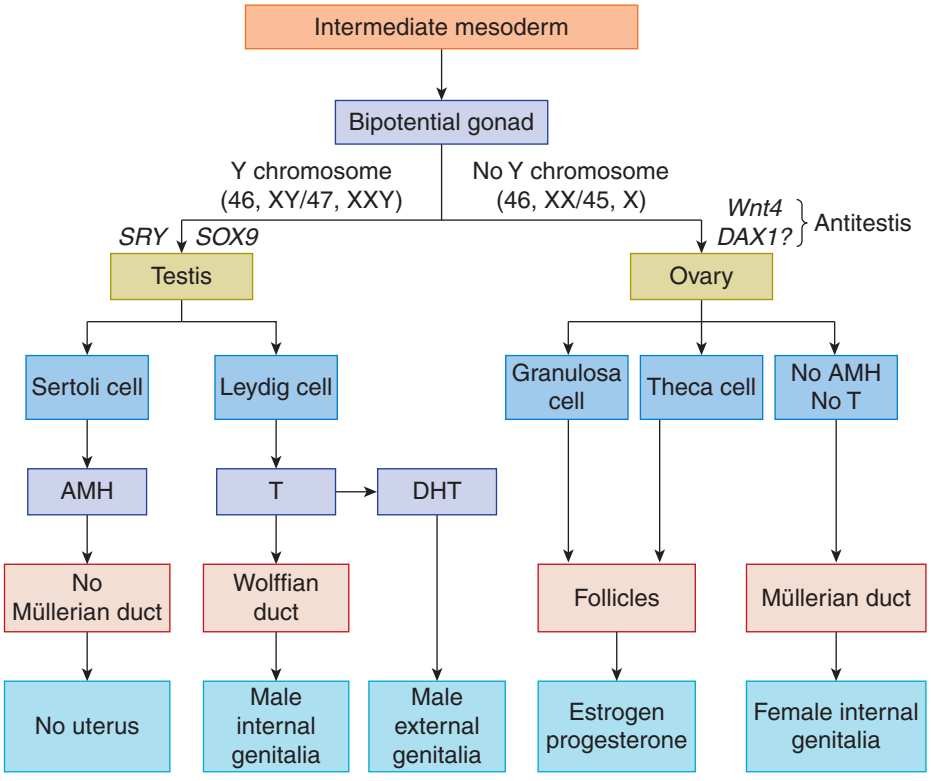

Figure 84-1 Development of genitalia in male and female fetuses. Normal sexual differentiation. SRY: sex determining region on Y chromosome; AMH: anti-Müllerian hormone; T: testosterone; DHT: dihydrotestosterone; Wnt4: Wnt = a group of secreted signaling molecules that regulate cell to cell interactions during embryogenesis; DAX1: DSS-AHC critical region of the X chromosome. *(Reprinted with permission from, Ogilvy-Stuart AL, Brain CE. Early assessment of ambiguous genitalia.* Arch Dis Child. *2004;89:401-407.)*

combine with malformations of the urinary tract (Aarskog, 1992). Abnormalities of sexual differentiation can be classified into disorders of chromosomal sex, gonadal sex, or phenotypic sex. One system of classification is based on the actual gonad found at surgical exploration. This classification divides infants with ambiguous genitalia into five subgroups:

1. Only an ovary is present (female pseudohermaphroditism).
2. Ovary and testis are present (true hermaphroditism).
3. Only a testis is present (male pseudohermaphroditism).
4. Testis and gonadal streak are present (mixed gonadal dysgenesis).
5. Only a gonadal streak is present (pure gonadal dysgenesis).

Unfortunately, this system is not practical to use in the prenatal context.

The more practical classification to use prenatally is based on cause. Three categories can be delineated:

1. True hermaphrodite—these fetuses have both ovarian and testicular tissue present.
2. Female pseudohermaphrodites—these are virilized females.
3. Male pseudohermaphrodites with and without müllerian structures—these are undervirilized males.

Female pseudohermaphrodites have a normal female karyotype (46, XX) and have ovarian gonadal tissue present. They have normal müllerian duct structures (uterus, fallopian tubes, and upper vagina) and no wolffian duct structures (epididymis, vas deferens, seminal vesicles). The female fetus becomes virilized because of exposure to androgens in utero. The causes for this include congenital adrenal hyperplasia (CAH), ingestion of androgens by the mother, and maternal virilizing tumors. Male pseudohermaphrodites with a normal 46, XY karyotype have only testicular tissue present. The Sertoli cells produce anti-müllerian hormone, but the undervirilization is due to inadequate synthesis of testosterone or dihydrotestosterone (see Figure 84-1), or the presence of an androgen receptor defect. Male pseudohermaphrodites with müllerian structures usually have a mixture of cell lines, with at least one cell line having a Y chromosome present, but no cells having two X chromosomes. The gonadal tissue in these cases is either normal testis or a streak gonad.

INCIDENCE

The incidence of ambiguous genitalia is 1 in 5000 livebirths (Kutteh et al., 1995). Hypospadias occurs in 2.5 to 8.2 per 1000 live male births (Bronshtein et al., 1995). Ambiguous

genitalia due to CAH occurs in 1 in 14,000 newborns (Hurtig, 1992).

SONOGRAPHIC FINDINGS

Axial scans often provide optimal visualization of the perineum and external genitalia when the fetal lower extremities are held in flexion. Sagittal scans of the perineum may be helpful to demonstrate the penis. When the fetus is male, testes can be identified within the scrotum after 28 weeks of gestation. de Elejalde et al. (1985) described the sonographic determination of fetal gender in 722 fetuses between 13 and 35 weeks of gestation. They compared their prediction with fetal karyotype, and all of these patients were studied prior to amniocentesis. These authors stated that the fetal genitalia could be imaged in 60.5% of fetuses examined before 18 weeks of gestation and 100% of those examined later than 20 weeks of gestation. In 3% of the cases, an error in sex assignment occurred, but these fetuses were all at less than 24 weeks of gestation. In female fetuses, the labia majora, labia minora, and occasionally the clitoris were visualized. In male fetuses, the scrotum was visualized in coronal and transverse planes. The transverse scan was useful for recognizing the penis. These authors stated that a fetal erection could be seen in utero by 20 weeks of gestation (de Elejalde et al., 1985). In an even larger study, Natsuyama (1984) determined fetal sex in 1879 pregnant women between 12 and 40 weeks of gestation. These authors used transverse, frontal, and sagittal scans of the fetal lower pelvic region. They were able to image 97.1% of cases and stated 99.9% accuracy in fetal gender assignment. These authors confirmed their findings postnatally. The most helpful findings were that between 12 and 23 weeks of gestation, the penis was pointed anteriorly toward the amniotic cavity but the clitoris was turned inferiorly. Another difference was the distance between the anal and genital regions. Males were noted to have a longer distance than females at later than 10 weeks of gestation (Natsuyama, 1984). Other authors described the "dome" sign, which was the sonographic visualization of the fetal scrotum and cranially directed phallus. In females, the diagnostic criterion is the presence of two or four parallel lines representing labial folds and a caudally directed clitoris. Some authors use the length of the phallus as a diagnostic criterion for gender assignment and some do not (Bronshtein et al., 1995). Benacerraf et al. (1989) have stated that sonographic visualization of the fetal genitalia is accomplished 80% to 90% of the time, with a correct sex assignment given 92% to 100% of the time. Fetal cephalic presentation is more favorable than breech for gender determination (Ali, 1992). Subsequent studies have established normal reference ranges for both penile length (Johnson and Maxwell, 2000; Zalel et al., 2001) and uterine development (Soriano et al., 1999).

In a pregnant woman with a positive family history of prior affected children with CAH, ambiguous genitalia were documented by the presence of two angulated lines representing labia and the presence of a central, domelike structure representing an apparent "scrotum" (Sivan et al., 1995) (Figure 84-2). In a follow-up study of 17 fetuses with genital malformations, 12 were raised as males, 4 were raised as females, and 1 genetic male was raised as a female due to congenital absence of a penis. In all cases an extremely small fetal phallus was observed, with undescended gonads (Figure 84-3). Four of the 17 fetuses had a sonographically abnormal phallus. The underlying diagnosis in 3 of the 4 fetuses with an abnormal phallus was congenital adrenal hyperplasia; 1 case was due to panhypopituitarism. The other underlying

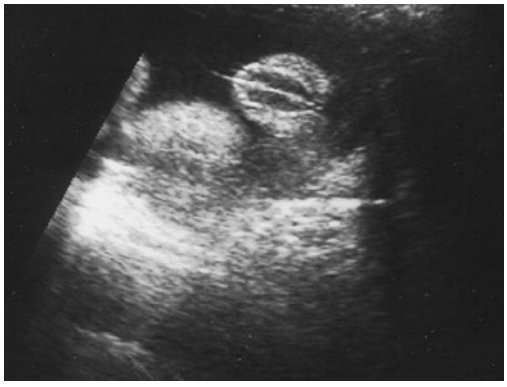

Figure 84-2 Prenatal sonographic study from a fetus with ambiguous genitalia at 27 weeks of gestation. This fetus had apparent fusion of the labia minora and a straight (as opposed to curved) clitoris/phallus. Fetal karyotype was 46, XX and the underlying cause of the masculinization was congenital adrenal hyperplasia.

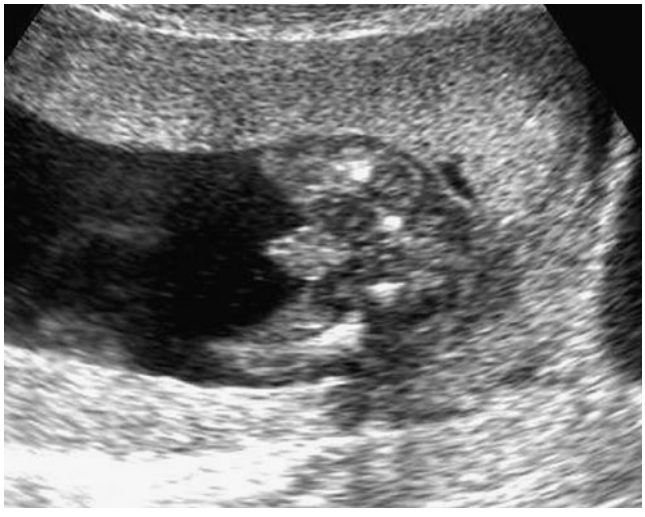

Figure 84-3 Fetoscopic view of a fetus at 20 weeks of gestation undergoing selective fetoscopic laser photocoagulation for twin-to-twin transfusion syndrome. This fetus was found to have ambiguous genitalia by preoperative ultrasound examination and MRI. This fetoscopic view demonstrates the virilized genitalia of a 46, XX female fetus with 21-hydroxylase deficiency. Note the elongated downward curving phallus and vaginal introitus still visible beneath the clitoris.

diagnoses in the remaining 13 cases included 2 cases of male pseudohermaphroditism, 3 cases of severe hypospadias with chordee, 2 cases of microphallus, 2 cases of cloacal anomaly, 2 cases of penoscrotal transposition, 1 case of intra-abdominal testes, 1 case of megaureter, and 1 case of cloacal exstrophy (Mandell et al., 1995).

The accuracy of the sonographic prenatal diagnosis of ambiguous genitalia was addressed by Cheikhelard et al. (2000). In this study, 34/43 cases were accurately diagnosed prenatally. The diagnoses were 100% correct when the fetus was diagnosed as an undervirilized male, but only 46% correct when the fetus was diagnosed as a virilized female. The authors diagnosed clitoromegaly when the clitoris measured more that 5 mm beyond the labia majora. This finding was clearly over diagnosed.

The use of three dimensional (3-D) sonography has been reported to improve visualization of a male fetus with ambiguous genitalia (Naylor et al., 2001). There have been no reports of prenatal use of MRI to diagnose ambiguous genitalia. However, a postnatal study compared 10 children with intersex disorders and found MRI and sonography to be equally sensitive (Biswas et al., 2004). For external detection of the gonads, MRI was marginally more sensitive.

Pinhas-Hamiel et al. (2002) identified 16 fetuses with ambiguous genitalia amongst their practice experience of over 10,000 fetuses. These affected fetuses underwent a full evaluation, including (1) repeated sonographic studies, (2) metaphase karyotype and FISH for *SRY*, and (3) hormonal assays of amniotic fluid. Twelve of the sixteen fetuses were referred because of an abnormal sonogram and 4 had a karyotype discrepancy. The underlying diagnoses were the following: 5 were virilized female fetuses (3 cases of CAH, 2 of urorectal septum malformation), 4 were undervirilized male fetuses (1 steroid sulfatase deficiency, 1 campomelic dysplasia, 2 unknown cause), 5 had chromosome abnormalities, and 2 were 46, XX, *SRY*+ males. These authors concluded that a screening ultrasound examination at 13 to 15 weeks was not sufficiently sensitive or specific to rule out ambiguous genitalia, and that the size and structures of the reproductive tract evolve throughout gestation. Importantly, after 19 weeks the sonographic presence of a normal uterus was strongly predictive of a virilized genetic female.

DIFFERENTIAL DIAGNOSIS

Ambiguous genitalia are either noted as a primary finding on sonographic examination, or as a secondary finding when karyotype and external genitalia are discordant. The key considerations in the differential diagnosis include determining whether the fetus is a virilized female or an undervirilized male (Table 84-1). The important diagnostic considerations include an inborn error of metabolism due to a single gene (mendelian) defect, an underlying chromosomal disorder, or a multiple malformation syndrome. Furthermore, the umbilical cord can be misinterpreted as a penis. Careful attention should be paid to distinguishing between the umbilical cord on longitudinal section and the genitalia (Ali, 1992). The most common cause of virilization of a female fetus is CAH, due primarily to the enzyme 21-hydroxylase deficiency (see Figures 84-2 and 84-3). In this disorder, 17-hydroxyprogesterone is not converted to 11-deoxycortisol. Cortisol is not synthesized and ACTH levels rise due to the lack of negative feedback. Subsequently, the levels of androgenic precursors rise, exposing the female embryo to androgen excess. In the severe form, limited secretion of cortisol as well as aldosterone leads to increased plasma renin activity and ultimately to hyponatremic dehydration and vascular collapse after birth. Other, rarer causes of CAH include 11β-hydroxylase deficiency and 3β-hydroxysteroid dehydrogenase deficiency.

Undervirilized males can occur due to a testosterone synthetic defect (Figures 84-4 and 84-5). The various causes of inadequate synthesis of testosterone are listed in Table 84-1. Testosterone is normally converted to dihydrotestosterone by the action of the enzyme 5α-reductase. Deficiency of 5α-reductase is also known as pseudovaginal perineoscrotal hypospadias. Affected subjects have ambiguous genitalia with hypospadias and a clitoris-like phallus. They also have a bifid scrotum and a blind vaginal pouch. The wolffian structures are normally differentiated, and the müllerian derivatives are fully regressed (al-Attia et al., 1993). Affected infants are usually assigned as female at birth but they virilize selectively at puberty. Because the fetal brain is exposed to a normal level of testosterone in utero and after birth, these patients usually take on the male gender at puberty. Another cause of undermasculinization of a male is the testicular feminization syndrome. The term Reifenstein syndrome has been applied to several disorders that were formerly thought to be separate entities. They are now known collectively to be mutations of the same androgen receptor gene present on the X chromosome and to cause familial partial androgen insensitivity. Affected children present with micropenis, small testes, and genital abnormalities, including hypospadias, bifid scrotum, and vaginal pouch remnants. Most affected patients are reared as males; however, in the setting of complete androgen insensitivity, female gender assignment may be most appropriate (Griffin, 1992; Lumbroso et al., 1994). At puberty, gynecomastia develops and virilization is poor. Considerable phenotypic variability has been reported depending on the molecular basis for the disorder.

A variety of multiple malformation syndromes have ambiguous genitalia as one component, primarily undermasculinization of affected male fetuses. These include Robinow syndrome, which consists of short stature, short arms, and a characteristic facies. The males have micropenis and the females have hypoplastic clitoris and labia minora. Opitz syndrome is characterized by hypertelorism and hypospadias. Affected females are normal. Aarskog syndrome is an X-linked disorder with short stature, hypertelorism, short nose, anteverted nostrils, a long philtrum, and genital dysplasia. There is a characteristic scrotal fold that extends

Table 84-1

Approach to the Fetus with Ambiguous Genitalia

Fetus with ambiguous genitalia or discordance between karyotype and external genitalia

↓

Karyotype

↓ 46, XX	↓ 46, XY	↓ Other abnormality/other chromosomal cause
Masculinized due to androgen exposure	Undermasculinized due to synthetic or receptor defect	Partial or full gonadal dysgenesis
		True hermaphrodite 46, XX/69, XXY
Congenital adrenal hyperplasia:	Inadequate synthesis of	
21-hydroxylase	T:20,22-desmolase	
11β-hydroxylase	3-β hydroxysteroid dehydrogenase	
3β-hydroxysteroid dehydrogenase deficiency	17β-hydrolase	
	17,20-desmolase	
	17α-hydroxylase deficiency	
	17β-hydroxysteroid deficiencies	
Maternal androgen	Leydig-cell hypoplasia	
Virilizing tumors	Inadequate synthesis of dihydrotestosterone:	
	5α-reductase deficiency	
	Receptor defect:	
	Reifenstein (androgen insensitivity) syndrome	
	Testicular feminization	

dorsally around the base of the penis (Aarskog, 1992). Other reasonably common multiple malformation syndromes that include ambiguous genitalia as a component include Smith–Lemli–Opitz syndrome, which is due to an inherited defect in 7-deoxycholesterol (see Figure 84-4). Affected fetuses have intrauterine growth restriction and may have a variety of other malformations, including holoprosencephaly and cleft palate. Patients with Prader–Willi syndrome may have micropenis. Patients with WAGR (Wilms tumor, aniridia, growth restriction, and genital anomalies) may have ambiguous genitalia. This disorder can be associated with a deletion on the short arm of chromosome 11. Other chromosomal abnormalities can also be associated with ambiguous genitalia. The urorectal septum malformation, a lethal condition, consists of ambiguous genitalia with absence of perineal and anal openings (Wheeler et al., 1997).

ANTENATAL NATURAL HISTORY

In the normal scenario, at less than 8 weeks of gestation the male and female genitalia appear identical. Normal female structures form in the absence of testicular hormones. Testosterone is needed by 8 weeks of gestation to induce normal male differentiation. Male differentiation occurs rapidly over 8 to 10 weeks of gestation. By 14 to 16 weeks of gestation, a normal penile urethra has formed. At over 20 weeks of gestation, the androgen levels in male and female fetuses are similar; by this time, the urethral and introital positions are fixed. Testicular descent into the scrotum occurs between 20 and 30 weeks of gestation in 62% of males and in 93% of males by 32 weeks of gestation (Cooper et al., 1985).

In cases of ambiguous genitalia, between 8 and 12 weeks of gestation, increased androgen levels in the female produce clitoromegaly, labial fusion, and persistence of the urogenital sinus. Decreased androgen levels in male fetuses may result in microphallus, incomplete fusion of the penile urethra (hypospadias), cryptorchidism, inadequate scrotal fusion, and the presence of a vaginal pouch (Meyers-Seifer and Charest, 1992).

MANAGEMENT OF PREGNANCY

When ambiguous genitalia is identified in a fetus, the pregnant woman should be asked whether there is any possibility

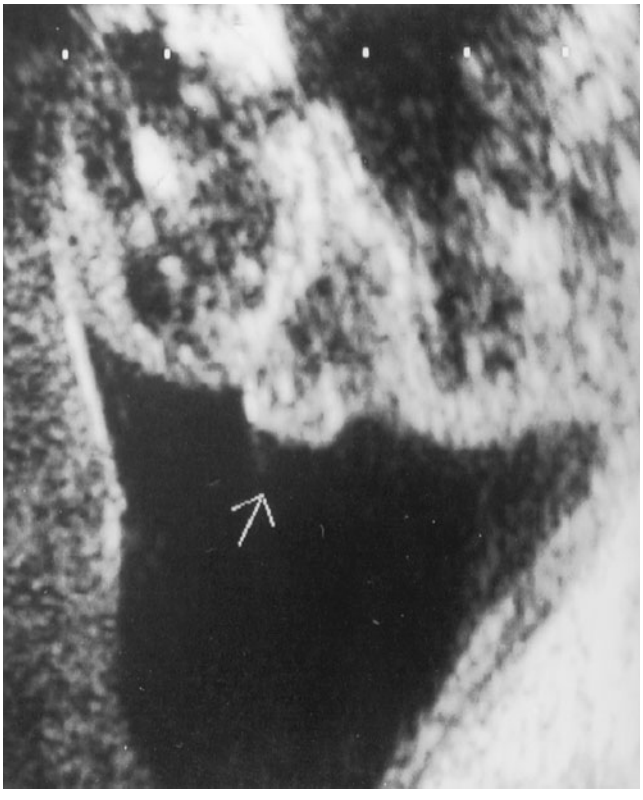

Figure 84-4 Prenatal sonographic study from an undermasculinized male fetus. The arrow indicates an enlarged clitoris rather than a small phallus. No definite testicles are seen lateral to this structure. This image is from a fetus with Smith–Lemli–Opitz syndrome.

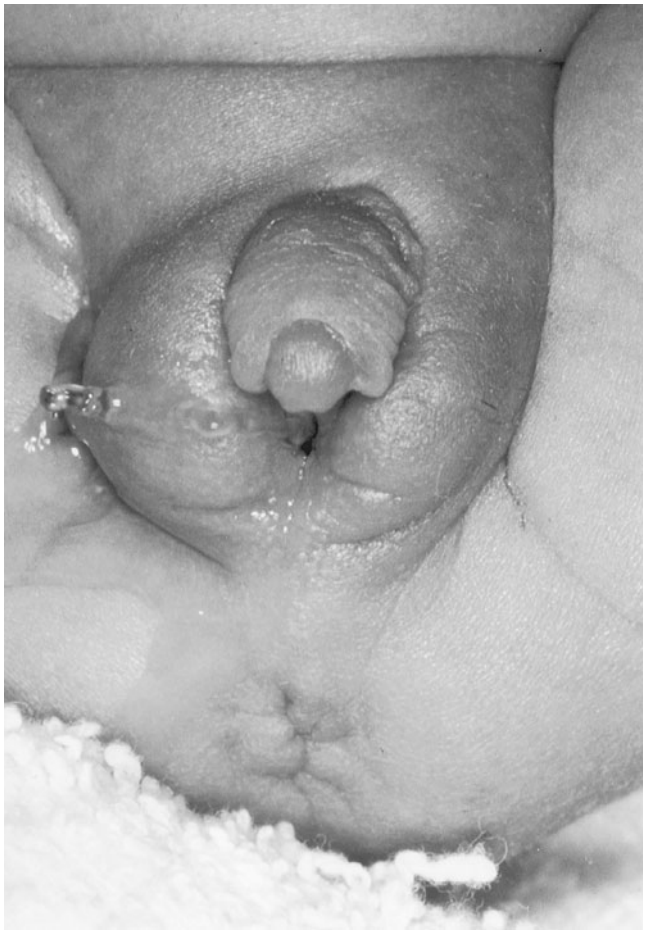

Figure 84-5 Postnatal photograph of an infant with ambiguous genitalia. Note small phallus, split foreskin, urethral opening at base of penis and split scrotum. Urine is streaming out of the urethral opening.

that she ingested medications, such as progesterone for threatened miscarriage or androgens for endometriosis during the first trimester. The pregnant woman should be examined for signs of androgen overproduction, such as acne, a deep voice, or the development of hirsutism during pregnancy. A complete family history should be obtained, with specific questions asked regarding history of infertility in family members, prior cases of ambiguous genitalia, neonatal deaths, or consanguinity (Meyers-Seifer and Charest, 1992). Antenatal workup and treatment of the fetus with ambiguous genitalia is best performed in the setting of a multidisciplinary team that includes specialists in pediatric endocrinology, genetics, neonatology, pediatric urology and surgery, and psychology. It is recommended, however, that only one member of the team communicate with the family. We recommend that a prenatal karyotype be offered to determine the genetic sex, as well as to rule out the presence of associated chromosomal abnormalities. If the parents decline an invasive procedure, such as amniocentesis, noninvasive fetal gender testing may be performed using cell-free fetal DNA in maternal blood (Pajkrt and Chitty, 2004). If a Y chromosome sequence is present the fetus is a genetic male. However, the parents should be informed that definitive gender assignment may not be possible until 2 to 3 days after birth. We recommend that fetuses with ambiguous genitalia be delivered in a tertiary care center to avoid confusion on the admitting papers and birth certificate because when the sex of rearing differs from the sex assignment at birth, parents experience a lot of difficulties with changing medical records and the birth certificate. We also recommend admitting the baby to the newborn intensive care unit or special care nursery as "baby," not "baby boy" or "baby girl."

At the time of amniocentesis (if performed), amniotic fluid should be analyzed for the presence of 7-dehydrocholesterol (7-DHC). This metabolite is normally quite low in amniotic fluid; elevated levels are strongly suggestive of Smith–Lemli–Opitz syndrome (Kratz and Kelley, 1999). Measurement of 7-DHC in amniotic fluid is rapid and straightforward. Furthermore, there is a strong correlation between the level of amniotic fluid 7-DHC and clinical severity of the affected fetus. Amniocytes should also be saved as a source of DNA for mutation analysis of the 21-hydroxylase gene.

FETAL INTERVENTION

In families known to be at risk for affected fetuses with congenital adrenal hyperplasia (CAH), prenatal diagnosis for chromosomal sex and DNA analysis can be performed as early as 10 weeks of gestation by chorionic villus sampling (CVS). If the fetus is diagnosed as female and affected with congenital adrenal hyperplasia, consideration can be given to administering dexamethasone to the pregnant woman as early as 5 to 7 weeks of gestation in order to minimize the effect of androgens, not only on the genitalia but also the developing fetal brain. Once the genotype is known, dexamethasone can be discontinued in fetuses found to be 46, XY. Some groups are using analysis of cell-free fetal DNA in maternal blood in the first trimester to noninvasively determine fetal gender (Rijnders et al., 2001). If the fetus is male, maternal steroids are not indicated.

Later in gestation, while consideration must be given to the potential maternal side effects of dexamethasone treatment, we recommend steroid treatment to arrest the growth of the clitoris and limit the severity of virilization that will be present by the time of birth. This may reduce or potentially eliminate the need for clitoral recession and feminizing genitoplasty. In addition, successful prenatal treatment of an affected female with CAH due to 11β-hydroxylase deficiency has also been described (Cerame et al., 1999).

A review of 403 at-risk pregnancies evaluated at the New York Cornell Medical Center diagnosed 84 fetuses with classical 21-hydroxylase deficiency (21-OHD) (Carlson et al., 1999). Of these 52 were female. In 23 affected female fetuses, dexamethasone administered to the mother at or before 10 weeks of gestation was effective in reducing virilization. No significant or permanent side effects were noted in the mothers or the fetuses, indicating that dexamethasone treatment is safe. Treated newborns did not differ in weight, length, or head circumference from untreated affected newborns (Carlson et al., 1999).

Smith–Lemli–Opitz syndrome, a disorder of cholesterol metabolism, can present in utero with growth restriction and ambiguous genitalia. Postnatal treatment with cholesterol supplementation improves plasma sterol levels and enhances growth and development. In one reported case, antenatal treatment of a fetus with Smith–Lemli–Opitz syndrome by administration of fresh frozen plasma (cholesterol level = 219 mg/dl) via repeated transfusions resulted in improved fetal cholesterol levels and increased fetal red cell volume (Irons et al., 1999).

TREATMENT OF THE NEWBORN

Parents of an affected fetus or infant with ambiguous genitalia should be told that their infant has a sex that is incompletely developed and has yet to be determined (Izquierdo and Glassberg, 1993). The major considerations in the treatment of the newborn include: (1) to rule out life-threatening processes, (2) to determine the sex of rearing and gender identity, (3) to plan for surgery if necessary, (4) to plan for as normal pubertal development and fertility as possible, and (5) to provide genetic counseling. The affected newborn with ambiguous genitalia should be admitted to a tertiary care nursery capable of providing diagnostic tests and treatment. The infant's blood pressure should be closely monitored. Physical examination of the genital area should include a measurement of the phallus length as precisely as possible along the dorsum of the stretched penis from the pubic ramus to the tip of the glans (a measurement of 2.5 cm is 2.5 SD below the mean at term) (Meyers-Seifer and Charest, 1992). Although the clitoris reaches a term size at 27 weeks of gestation, the penis continues to grow until full term. On physical examination, an attempt should be made to palpate gonads. If they are palpable, are they symmetric, and is the position above or below the inguinal ring? The infant should be specifically examined for the presence of hypospadias and/or chordee. An assessment should be made of the labioscrotal folds for the degree of fusion (see Figure 84-4). The perineum should be examined for the presence of a urethra, vagina, vaginal pouch, or urogenital sinus. A rectal examination should be performed to try to palpate the uterus (Meyers-Seifer and Charest, 1992). A complete physical examination should be obtained to look for the presence of other abnormalities. A clinical geneticist can help in this regard.

After physical examination of the external genitalia the infant can be classified as having one of Prader's five stages. Stage 1 is isolated clitoral hypertrophy. Stage 2 is clitoral hypertrophy with visibly separate urethral and vaginal openings. Stage 3 is clitoral hypertrophy with a single urogenital sinus opening. Stage 4 is a micropenis with hypospadias. Stage 5 includes the findings of Stage 4 plus cryptorchidism (Sultan et al., 2002).

The initial blood work recommended includes serum electrolytes, glucose, and cholesterol, serum 17-hydroxyketosteroids, and a chromosome analysis, if it was not performed antenatally. The use of the buccal smear is no longer recommended. Fluorescence *in situ* hybridization (FISH) studies using X- and Y-chromosome–specific probes on nondividing cells is equally rapid and more accurate.

Additional studies that can be performed during the newborn period include urogenital sinography, which will outline the urethral and vaginal anatomy, magnetic resonance imaging of the pelvic region, and abdominal sonography. Kutteh et al. (1995) studied 100 term infants with the external genitalia covered. A neonatal uterus was identified in 47 of 50 female infants (sensitivity, 94%). The absence of the uterus correctly predicted 49 of 50 male infants (specificity, 98%). Most of the time the neonatal uterus demonstrated the typical linear echo of the endometrial cavity. The only false-positive was a distended bowel that was incorrectly identified as a uterus. These authors recommended that the bedside determination of the presence of the uterus was

important in the initial studies regarding gender assignment, as infants who have a uterus will almost always be assigned as a female.

Infants with ambiguous genitalia who require medical treatment during the newborn period include those with CAH, who are treated with adrenogenital steroids. This prevents potentially life-threatening urinary salt wasting and dehydration. In addition, it arrests virilization and permits normal growth and development of normal female secondary sex characteristics, menstruation, and fertility. In males who are undermasculinized due to 5α-reductase deficiency, an elevated plasma testosterone:dihydrotestosterone ratio is seen after human chorionic gonadatropin (hCG) stimulation. The diagnostic test is the presence of diminished 5α-reductase activity in skin fibroblasts, usually in the setting of a positive family history. Infants affected with 5α-reductase deficiency who are 46, XY should be assigned as male and given topical dihydrotestosterone therapy. This will enlarge the phallus and allow eventual repair of the hypospadias (al-Attia et al., 1993).

It is beyond the scope of this chapter to thoroughly discuss all of the underlying enzyme abnormalities that can cause ambiguous genitalia. However, female pseudohermaphrodites with 21-hydroxylase deficiency and 3β-hydroxysteroid dehydrogenase deficiency will have hyperkalemia and hyponatremia. Male pseudohermaphrodites with cholesterol side-chain cleavage defects and 3β-hydroxysteroid dehydrogenase defects will also have hyperkalemia and hyponatremia. Female pseudohermaphrodites with 11β-hydroxylase deficiency and male pseudohermaphrodites with 17α-hydroxylase deficiency will have hypokalemia. Diagnoses of most of these inborn errors of metabolism rely on the demonstration of the elevated immediate precursor in the affected infant's serum.

SURGICAL TREATMENT

The role of genital surgery in the management of ambiguous genitalia is becoming increasingly controversial (Creighton, 2004; Crouch and Creighton, 2004; Diamond et al., 2006). In theory, for the virilized female, clitoral recession, labioscrotal reduction, and vaginoplasty can all be performed between 2 and 5 months of age. Undervirilized males who are assigned a female gender can undergo a clitoral reduction, vaginoplasty, gonadectomy, and removal of wolffian ducts if surgery is elected. These patients will require estrogen at puberty (Izquierdo and Glassberg, 1993). Pseudohermaphrodites who are assigned as male can undergo correction of the hypospadias at about 1 year of age. At this time, if indicated, the testes can be placed into the scrotum. Some of these patients will require hCG stimulation during the newborn period and testosterone therapy at puberty. In patients with gonadal dysgenesis, the dysgenetic gonads are prone to neoplasia and should be removed. For patients who are true hermaphrodites, it is recommended that the tissue that is contrary to the sex of rearing be removed. For example, in patients being raised as female, testes and wolffian duct structures should be removed.

In practice, a recent survey of 185 members of the Pediatric Urology section of the American Academy of Pediatrics demonstrated a distinct shift in recommendations (Diamond et al., 2006). These physicians were given two clinical scenarios with photographs. One infant was a severely virilized female with CAH. All respondents favored a female sex assignment to preserve potential fertility. The other infant was a genetic male with phallic disruption due to cloacal exstrophy. Two-thirds of respondents recommended a sex assignment as male due to androgen brain imprinting, but the other third wanted to assign as female due to the difficulty of creating a functional penis. All respondents agreed that a team approach was needed, that parents should be actively involved, and that surgery, if performed, should occur at less than 18 months of age.

Others advocate for a need to re-evaluate "automatic progression" to surgery, especially for feminizing genitoplasty (Creighton, 2004; Crouch and Creighton, 2004). In feminizing genitoplasty some of the clitoris is removed and a vagina or vaginal opening is constructed. The main complication of genitoplasty is vaginal stenosis, which occurs in 30%–100% of cases and necessitates revision in adolescence. Most authors agree that there is a paucity of objective long-term outcome data. In one study, using objective criteria, 66% of patients had good outcomes if their surgery was performed by a surgeon with specific experience in the treatment of children with intersex disorders (Lean et al., 2005).

LONG-TERM OUTCOME

Increasing attention is being paid to the long-term psychological difficulties experienced by adults who encountered a conflict between the appearance of their surgically reconstructed external genitalia and their sexual identity (Reiner, 1999). Furthermore, several groups of adult patients currently advocate that genitalia should be left ambiguous permanently. Support groups such as the Intersex Society of North America and the Androgen Insensitivity Support Group can serve as clearinghouses of information for prospective parents (Warne et al., 1998).

GENETICS AND RECURRENCE RISK

The genes involved in gonadal differentiation are given in Table 84-2. CAH is inherited as an autosomal recessive condition. Partial androgen insensitivity is familial and is now known as Reifenstein syndrome. The androgen receptor gene has been mapped to Xq11–12. Defects in the androgen receptor are responsible for approximately 50%–70% of males with pseudohermaphroditism (Lumbroso et al., 1994). With molecular analysis, it is now known that the main mechanism

Table 84-2

Consequences of Mutations/Deletions and Duplications/Translocations of Genes Involved in Gonadal Differentiation

	Chromosome Location	Gonadal Development	Associated Disorder	Sex Reversal / Genital Ambiguity	Müllerian Development
Gene mutations or deletion (loss of function)					
WTI	11p13	Dysgenesis (♀ & ♂)	WAGR syndrome	Genital ambiguity (♂)	Variable (♂)
			Denys–Drash syndrome	Sex reversal or genital ambiguity (♂)	Variable (♂)
			Frasier syndrome	Sex reversal (♂)	Yes (♂)
SF1	9q33	Dysgenesis (♂)	Adrenal failure	Sex reversal (♂)	Yes (♂)
SRY	Yp11.3	♂ → ovary		Sex reversal or genital ambiguity (♂)	♂ (variable)
DAX1	Xp21	♂ Dysgenesis	Adrenal failure and hypogonadotrophic hypogonadism/ impaired spermatogenesis	No	No
SOX9	17q24.3–25.1	♂ Dysgenesis or ovary/ovotestis	Campomelic dysplasia	Sex reversal or genital ambiguity (♂)	Variable
AMH	19p13.3–13.2	Normal			Yes (♂)
Gene duplication or translocation (gain of function)					
SRY Y fragment translocation	Yp11.3	♀ → testis		Sex reversal or genital ambiguity (♀)	No
DAX1 duplication	dupXp21	♂ Dysgenesis or ovary/ovotestis		Sex reversal or genital ambiguity (♂)	Variable
Wnt4 duplication	dup 1p35	♂ Dysgenesis		Genital ambiguity (♂)	Yes
SOX9 duplication	dup17q24.3–25.1	♀ → Testis		Genital ambiguity (♀)	No

WAGR: Wilms' tumor, aniridia, genitourinary anomalies, mental retardation; Denys–Drash (exonic mutations): WT, diffuse mesangial sclerosis; Frasier (intronic mutations): no WT, focal segmental glomerulosclerosis. Other abbreviations as for Figure 84–1.
Reprinted with, permission from, Ogilvy-Stuart AL, Brian CE. Early assessment of ambiguous genitalia. Arch Dis Child. *2004;89:401-407.*

that causes androgen insensitivity syndrome is a single nucleotide change that introduces a premature stop codon or an amino acid substitution into the coding sequence of the androgen receptor gene. Over 100 point mutations have been reported in this gene (Lobaccaro et al., 1994).

It is of interest that the gene abnormality in the 5α-reductase deficiency, inherited as an autosomal recessive disorder, causes abnormal sexual development only in 46, XY homozygotes. Heterozygous 46, XY males are apparently completely normal. In addition, 46, XX homozygotes with 5α-reductase deficiency are completely normal and fertile (al-Attia et al., 1993). Several Santo Domingan families have been described in the literature with this condition (al-Attia et al., 1993). All of the chromosomal disorders that are the underlying basis for gonadal dysgenesis are generally sporadic.

It is important to make an accurate diagnosis of the underlying cause of the ambiguous genitalia, as the genetic bases for many of these conditions are known and prenatal diagnosis is available for subsequent pregnancies. In particular, prenatal diagnosis and treatment options are available for CAH and Smith–Lemli–Opitz syndrome. Therefore, it is important to rule out these diagnoses in the family of a fetus that presents with ambiguous genitalia.

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85 CHAPTER

Persistent Cloaca

Key Points

- Persistent cloaca refers to the continuation of the early embryological stage of a common opening for the rectum, vagina, and urinary tract.
- This is an extremely rare abnormality, being seen in only 1 in 50,000 births.
- Fetal abdominal cystic masses are the most typical prenatal diagnostic features, usually due to hydrocolpos and associated bladder outlet obstruction.
- Following the prenatal diagnosis, targeted fetal ultrasound, amniocentesis, and fetal MRI are helpful in accurately delineating the fetal anatomy.
- Postnatal surgical reconstruction is complex and should be undertaken only by a multidisciplinary pediatric surgical team after complete neonatal radiological and endoscopic anatomic evaluation.
- Long-term outcome appears favorable after surgical correction with the majority of patients being continent of urine and feces and several having successfully delivered children.

CONDITION

Cloaca, the Latin word for sewer, is aptly named as it represents the persistence of a developmental phase (typically in a female fetus) in which the rectum, vagina, and urinary tract share a common channel. In normal human development, there is a stage during which the cloaca forms from the confluence of the allantois and hindgut (Stephens and Smith, 1971). At 4 to 6 weeks of development, the urorectal septum descends, separating the allantois from the hindgut. Failure of this urorectal septum to descend results in persistent cloaca (Figure 85-1). The infant with persistent cloaca usually presents at birth with abdominal distention and an abnormal perineum. Typically, these children have only a single perineal opening without an anus or a vaginal introitus. The genitalia are ambiguous, often with a hooded phalluslike structure suggesting a masculinized gender, yet their chromosomes are consistently 46,XX and they have two normal ovaries. The length of the common channel to the perineum may vary, from 1 to 12 cm (Canning et al., 1998, Pena et al., 2004). In cases with a common channel <3 cm, there is usually a well-developed sacrum and sphincter complex. In contrast, longer common channels are more likely to have an abnormal sacrum and a poor sphincter complex, and these are usually more complex defects. In more than 50% of cases, there is hydrocolpos due to partial obstruction of the entry of the vagina into the common channel. The hydrocolpos can compress the trigone of the bladder, with resulting bladder outlet obstruction and hydroureteronephrosis. The prenatal sonographic detection of hydronephrosis may be the only indication of cloacal malformation. Duplicated vagina and uterus didelphys are commonly seen in persistent cloaca (Figure 85-2).

In 90% of cases of persistent cloaca, there are other associated urogenital anomalies (Rich et al., 1988). There is also a high incidence of nongenitourinary anomalies associated with persistent cloaca, including esophageal atresia, duodenal atresia, diaphragmatic hernia, vertebral anomalies, congenital heart disease (particularly tetralogy of Fallot), spina bifida, and caudal regression syndrome.

INCIDENCE

Persistent cloaca occurs in approximately 1 in 50,000 live-births (Gray and Skandalakis, 1972). Because of the rarity of prenatal diagnosis of persistent cloaca, no data are available on its prenatal incidence.

SONOGRAPHIC FINDINGS

The prenatal sonographic features of persistent cloaca are often secondary effects of the anomaly. A septated or bilateral

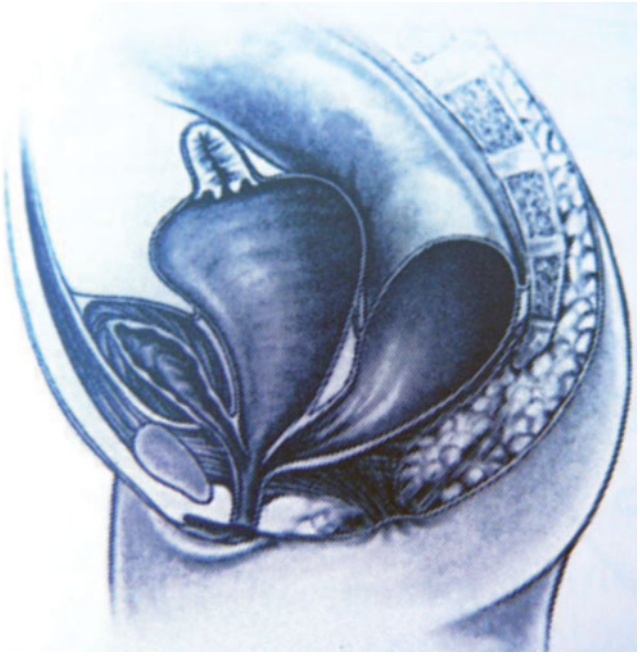

Figure 85-1 Line drawing depicting the anatomic relations typically observed in persistent cloaca with dilated rectum and, in this case, hydrocolpos. (*From Pena A. Atlas of Surgical Management of Anorectal Malformations. New York: Springer-Verlag; 1990:60. Lois Barnes Medical Illustrator. Used with permission.*)

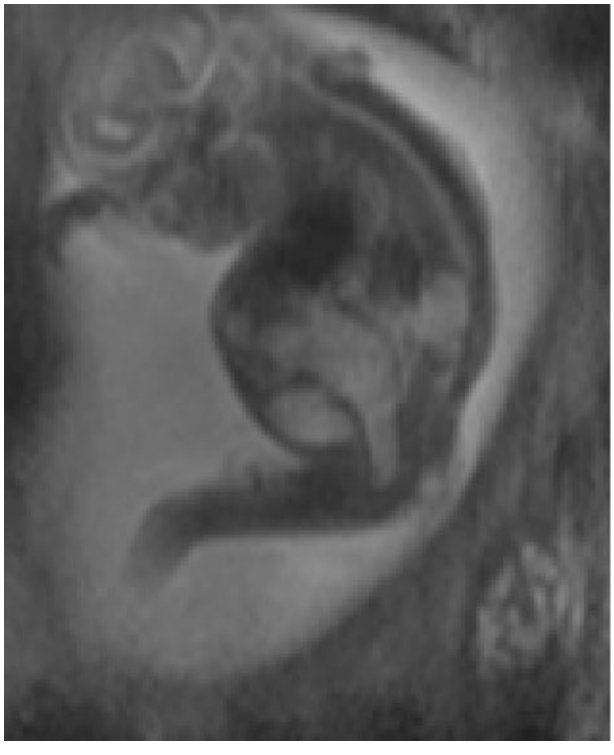

Figure 85-2 Fetal MRI image in saggittal view of a fetus with cloaca demonstrating hydronephrosis, hydrocolpos, and dilated rectum. *(Provided by Marc Levitt, MD, Colorectal Center for Children, Cincinnati Children's Hospital.)*

cystic pelvic mass may be observed. In as many as 50% of cases, hydrocolpos may be present and may be the most striking feature. This may also partially obstruct the trigone of the bladder, with resulting vesicomegaly and hydroureteronephrosis. The distinction between hydrocolpos and a distended bladder may be very difficult to make. We have had one patient who presented with a dilated cystic pelvic mass (Figure 85-3) due to hydrocolpos and vesicomegaly. It was notable that mucus or meconium from the vagina or colon had refluxed into the bladder, forming a sediment in the trigone of the bladder. With passage of urine from the ureters to the bladder, a striking swirling of this sediment could be observed sonographically. We believe this to be a specific sonographic sign of communication between the urinary tract and either the vagina or colon. This can be seen in either persistent cloaca or, perhaps, a persistent urogenital sinus. The presence of calcifications within the lumen of the bowel should raise the possibility of either imperforate anus and rectourethral fistula or a cloaca, as urine mixing with meconium will create luminal calcifications.

In addition to the cloacal anomaly, the presence of other associated genitourinary anomalies should be sought, including hydronephrosis and horseshoe kidney. The combination of hydronephrosis and sacral anomalies should raise the possibility of a cloacal malformation. In cases of VACTERL (vertebral, anus, cardiac tracheal, esophagus, renal, limbs), cloaca can be seen in association with absent radius, cardiac abnormalities, or esophageal atresia with polyhydramnios and absent stomach. Spinal abnormalities and neural tube defects, such as sacral agenesis, have been reported in association with persistent cloaca.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses to be considered when confronted with a fetus with a cystic pelvic mass, in addition to cloaca, should include urethral atresia, imperforate anus, presacral meningocele, ovarian cyst, bladder duplication, and imperforate hymen with hydrometrocolpos.

ANTENATAL NATURAL HISTORY

There are few reported cases of prenatally diagnosed persistent cloaca, and there is scant information available about its natural history (Cilento et al., 1994, Geipel et al., 2001).

MANAGEMENT OF PREGNANCY

Any fetus suspected of having a persistent cloaca should have a targeted ultrasound, not only to define the genitourinary anatomy but also to exclude potential associated anomalies. An echocardiogram should be obtained because of the increased incidence of congenital heart disease, especially

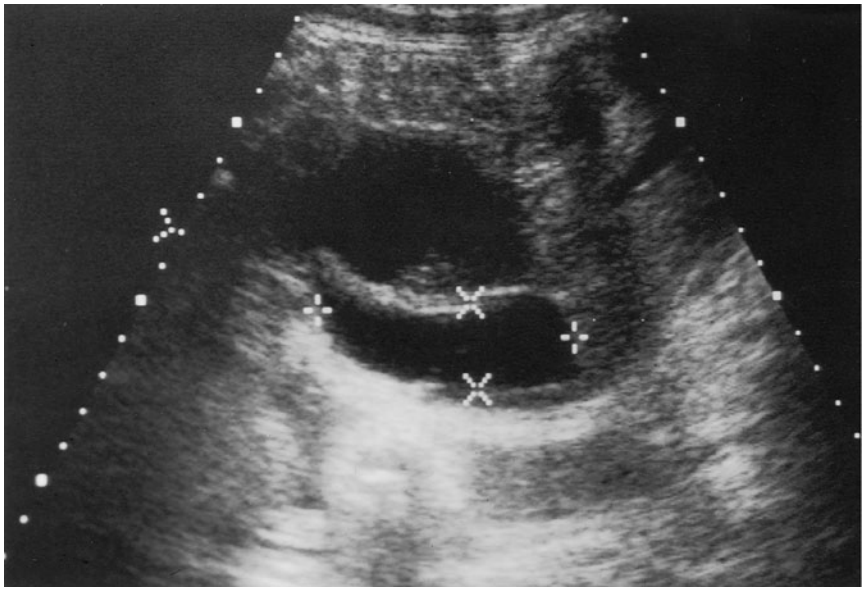

Figure 85-3 Prenatal sonographic image of a fetus at 24 weeks of gestation referred for evaluation of hydronephrosis. This fetus was found to have ambiguous genitalia and an unusual dilated pelvic cystic structure. A layer of sediment can be appreciated in the more anterior cystic space, which is the bladder. The more posterior space is the hydrocolpos outlined by "×" and "+" signs. Dilated colon was not appreciated at this gestational age. In the real-time study of the urine draining from the ureters to the bladder, the sediment was noted to "swirl" in the bladder.

tetralogy of Fallot in persistent cloaca. An amniocentesis should be performed to determine genotype. Ultrafast fetal magnetic resonance imaging (MRI) may be extremely helpful in confirming the diagnosis and defining the anatomy of the cloaca (Hubbard and Pena, 1997). Extensive prenatal counseling should be initiated to not only explain the complex nature of the anomaly but also explain the reconstruction. Consultation with a pediatric surgeon, pediatric urologist, and geneticist may be extremely helpful. The delivery should be in a center with pediatric surgeons and pediatric radiologists who are capable of evaluating an infant with persistent cloaca and can initiate treatment once the anatomy has been defined (Levitt and Pena, 2005). There is no reason to alter the delivery plan, and cesarean section should be reserved for standard obstetric indications.

FETAL INTERVENTION

There is only a single reported case of fetal intervention for cloaca reported by Shimada et al. (Shimada et al., 2001). These cases were decompressed in utero by vesicoamniotic shunt when the diagnosis was presumed to be bladder outlet obstruction. However, in general, most experts consider the presence of an obstructed cloacal anomaly a contraindication to shunt placement. This is because there are no data to demonstrate that the prognosis can be improved in these fetuses by in utero decompression. While decompression may be considered in cases associated with oligohydramnios and evidence of obstruction, evidence of preserved renal function should be demonstrated by fetal urine electrolyte analysis. In addition, the anatomy should be clearly defined by ultrafast fetal MRI. Lastly, parents considering fetal intervention should be extensively counseled about the implications of this diagnosis and have the opportunity to meet with a pediatric surgeon to discuss the extensive reconstructive procedures that may be necessary and the quality of life that the children with this anomaly may expect. Termination of pregnancy should be included in the options available to the parents when a diagnosis of fetal cloaca is made.

TREATMENT OF THE NEWBORN

The first priority in treating a newborn with persistent cloaca is to define the anatomy and to exclude other anomalies. A nasogastric tube should be passed to exclude esophageal atresia. Plain chest, abdominal, and pelvic radiographs should be obtained to exclude vertebral anomalies, especially involving the sacrum. The anatomy of the cloaca can best be defined by a combination of retrograde contrast studies through the single perineal opening and panendoscopy. Typically, the vagina is markedly distended with urine and vaginal secretions (Figure 85-4) (Pena and Levett, 2003). Only after a complete understanding of the anatomy has been achieved should treatment be undertaken (Hendren, 1998). In unusual cases, the entry of the rectum is low in the urogenital sinus, which may be amenable to perineal anoplasty (Hendren, 1980). More commonly, the level of entry of the rectum into the urogenital sinus is above the level of the levators, and this type is best managed by a diverting (as opposed to a loop) colostomy with a rectal pull-through procedure later. The adequacy of urinary tract decompression should be assessed to determine if a perineal cutback procedure is necessary to relieve obstruction.

Cystoscopic examination of the urogenital sinus may simultaneously allow dilation of the vaginal opening into the urogenital sinus to provide decompression of the hydrocolpos. Catheterization via the urogenital sinus preferentially goes to the vagina and not the bladder, allowing catheter decompression. Hydrocolpos, if present, may need to be drained with a tube vaginostomy if these other methods are not successful. In rare circumstances, if drainage of the hydrocolpos fails to improve the associated hydronephrosis, a vesicostomy

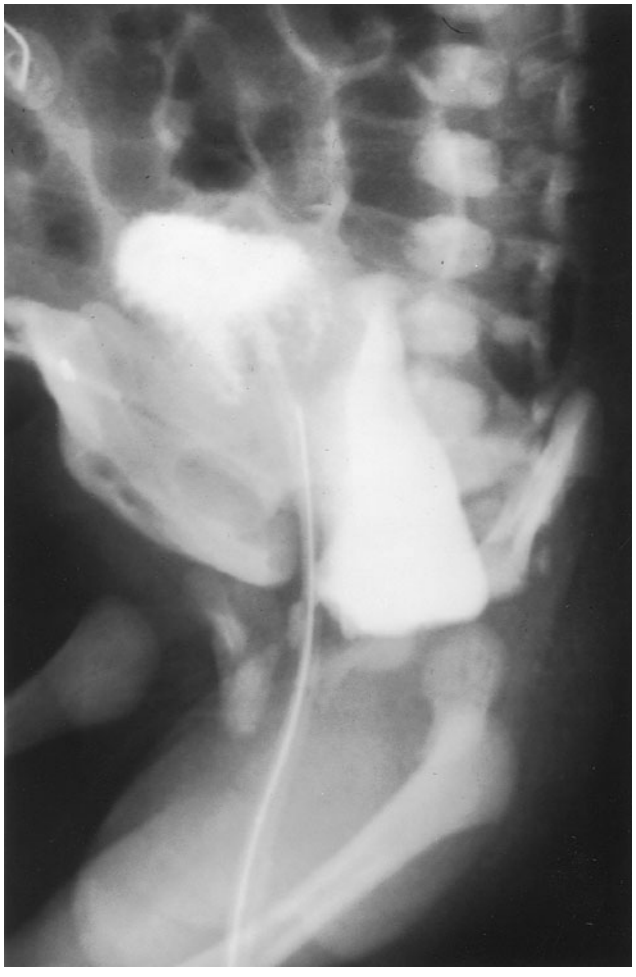

Figure 85-4 Postnatal study demonstrating the cloacal anatomy. A catheter has been passed into the urogenital sinus and contrast medium opacifies the bladder anteriorly and the rectum posteriorly.

may be needed to drain the urinary tract. A complete reconstruction by a posterior sagittal anorectovaginourethroplasty can then be performed at approximately 6 months of age (deVries and Pena, 1982). The diverting colostomy should be performed with an end colostomy to prevent contaminating the urinary tract. The downstream mucous fistula allows evaluation to the distal rectum and defines its entry into the urogenital sinus. Our practice is to obtain an MRI scan prior to reconstruction to define adequacy of the musculature, which will aid in planning the surgery and may provide prognostic information about the likelihood of eventual continence. In addition, one-third of these infants will have a tethered spinal cord, which MRI can help in defining (Sato et al., 1988).

SURGICAL TREATMENT

In reconstructing persistent cloaca, a posterior sagittal anorectovaginourethroplasty is performed (Pena and deVries, 1982; Pena et al., 2004). The muscle fibers are separated in the midline via a posterior sagittal incision from the coccyx to the center of the sphincter complex as defined by electrical stimulation. The rectum is identified and the urogenital sinus is opened posteriorly up to the confluence with rectum and vagina. The rectum is dissected free from the vagina. If there is a common channel of less than 4 cm, the urogenital sinus can be mobilized as a unit (Pena, 1997). If the length of the urogenital sinus is greater than 4 cm, a form of vaginal interposition may be necessary. This can be achieved using a segment of small intestine on its mesentery to bridge the gap between the vagina and perineum. The rectum is then mobilized to create a neo-anus within the sphincter complex, with or without a tapering rectoplasty. The new vaginal and anorectal passages are routinely dilated by parents, using a Hegar dilator of appropriate size, beginning several weeks after reconstruction. The colostomy closure is performed 4 to 6 weeks later as long as there is no stricture formation in the new anorectum and an urethrovaginal fistula is ruled out by endoscopy.

LONG-TERM OUTCOME

Hendren's (1998) series of 154 patients and Pena's (2004) series of 339 patients with persistent cloaca are the largest reported experiences of individual surgeons. In Hendren's series, voluntary bowel movements with satisfactory continence were achieved in 82 of 141 individuals (58%). An additional 38 patients were on an enema program and were focally continent; 9 patients had a permanent colostomy; 7 young children continued to soil and their parents had elected further treatment; 5 had undergone surgery too recently to evaluate. In Pena's experience, 203 of 339 (60%) had voluntary bowel movements and the remaining 135 (40%) were fecally incontinent, but all patients were clean with a specifically designed bowel management program.

In terms of urinary continence, in Hendren's series 83 of 141 patients voided spontaneously, 40 of 141 needed to catheterize to empty their bladders, 4 had urinary diversions, and 1 had a continent diversion. Five other patients had urinary incontinence and required further surgery. Eight patients had undergone surgery too recently to judge urinary continence. In Pena's series, when the urogenital sinus was less than 3 cm, 72% were continent of urine and 28% required intermittent catheterization. In those patients who had a urogenital sinus of more than 3 cm, 22% were continent and 78% required intermittent catheterization.

In Hendren's series, 24 patients were adults, of whom 14 were married, 17 had had coitus, and 6 had had children. Five adult women delivered their children by cesarean section and one by vaginal delivery (Greenberg and Hendren, 1997).

GENETICS AND RECURRENCE RISK

Persistent cloaca is a complex embryologic anomaly that is sporadic, with no increased risk of recurrence.

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Renal Agenesis

86 CHAPTER

Key Points

- Developmental anomaly that occurs at 4 to 6 weeks of embryonic life.
- Incidence of bilateral renal agenesis is 1 in 3000 livebirths; for unilateral renal agenesis it is 1 in 500–1300 livebirths and higher in twins.
- Sonographic findings are severe oligohydramnios or anhydramnios occurring after 14 to 16 weeks in bilateral renal agenesis. In unilateral cases, the remaining kidney may be >95% in length for gestational age.
- Syndromes associated with bilateral renal agenesis are sirenomelia, caudal regression, branchio-oto-renal, cerebro-oculo-facial, Fraser, and Rokitansky–Kuster–Hauser. DiGeorge syndrome is also associated with unilateral renal agenesis.
- Consider amnioinfusion to obtain a karyotype.
- Most hereditary cases are inherited as an autosomal dominant condition with variable expressivity.
- Sonographic screening of the parental kidneys is recommended.
- Outcome is uniformly fatal for bilateral renal agenesis.
- For unilateral renal agenesis consider postnatal radionucleide scan, voiding cystourethrography, and prophylactic antibiotics.

CONDITION

Renal agenesis is the congenital absence of one or both kidneys as a result of the complete failure of the kidney to form. The sequence of renal agenesis, severe oligohydramnios, amnion nodosum, flattened face, low set and floppy ears, bilateral pulmonary hypoplasia, and perinatal death was first described by Potter in 1946.

Renal agenesis is a developmental anomaly that occurs at 4 to 6 weeks of embryonic life (Kaffe et al., 1977). Normal

renal embryogenesis requires that three events take place: the ureteric buds must arise bilaterally from mesonephric (wolffian) ducts; subsequently, bilateral metanephric blastema must form from mesoderm in the caudal region of the nephrogenic cord; and finally, ureteric buds must grow, contact, and invaginate the metanephric blastema, thereby inducing differentiation of the blastema into two mature kidneys (Wax et al., 1994). Failure of the metanephros to develop results in complete absence of the kidney. This can be due to either nonexistence of the ureteral bud or failure of the ureteral bud to develop from the wolffian duct.

In unilateral renal agenesis, there is complete absence of the kidney on one side, with compensatory hypertrophy on the contralateral side. Most cases of unilateral renal agenesis are due to lack of induction of the metanephric blastema by the ureteral bud, but some cases of absent kidney may be due to in utero regression of a multicystic dysplastic kidney (see Chapter 78) (Mesrobian et al., 1993). In cases of unilateral renal agenesis, compensatory hypertrophy of the remaining kidney occurs prenatally (Zalel et al., 2002). This has been demonstrated by Hartshorne et al. (1991), who performed a retrospective analysis of 20 fetuses who died with unilateral renal agenesis. Total renal mass was measured and was shown to comprise 82.7% of the weight of both kidneys removed from control fetuses at the same gestational age. Had prenatal compensatory hypertrophy not occurred, the total renal mass would have been only 50% of control values (Hartshorne et al., 1991). It is of biologic interest that in unilateral renal agenesis, symmetrical hypertrophy of all nephron components occurs during prenatal life, when the placenta clears all metabolic waste products. These authors hypothesized that it is the change in renal mass, rather than abnormality in function, that triggers compensatory growth of the contralateral kidney. This may be due to an as yet uncharacterized renotropic humoral growth factor (Hartshorne et al., 1991).

INCIDENCE

The incidence of bilateral renal agenesis is 1 in 3000 livebirths (Cardwell, 1988; Droste et al., 1990) and 1 in 240 stillbirths (Whitehouse and Mountrose, 1973). A recent ultrasound study performed in 12 European countries by the EUROSCAN group demonstrated a prevalence of 95 cases of bilateral renal agenesis in 709,030 pregnancies (Weisel et al., 2005). The antenatal detection rate was 91% at a mean gestational age of 21.2 weeks. Bilateral renal agenesis is 2.5 times more common in males than in females. Bilateral renal agenesis is also more common in twins as compared with singletons. Some authors have postulated a common cause for twinning and the development of renal agenesis (Roodhooft et al., 1984). An increased incidence of bilateral renal agenesis is not associated with advanced maternal age or maternal illness.

Unilateral renal agenesis occurs in 1 in 500 to 1 in 1300 livebirths, although many cases are clinically silent (Bronshtein et al., 1995). In the EUROSCAN study, unilateral renal agenesis was found in 58 of 709,030 studied pregnancies (Weisel et al., 2005). The antenatal detection rate was 62% at a mean gestational age of 28.6 weeks. In one study, the missing kidney was nearly always the left one (Hartshorne et al., 1991), but in another study of 46 consecutive cases of unilateral renal agenesis, the right kidney was absent in 19 of 46 individuals (Cascio et al., 1999). The true incidence of unilateral agenesis is likely to be even greater because this abnormality can be asymptomatic throughout life.

SONOGRAPHIC FINDINGS

The sonographic criterion for the diagnosis of bilateral renal agenesis is the presence of severe oligohydramnios or anhydramnios occurring after 14 to 16 weeks of gestation with failure to visualize the fetal urinary bladder and both kidneys (Droste et al., 1990). Prior to the 16th week of gestation, the fetal kidneys contribute relatively little to the amniotic fluid volume. After 28 weeks, premature rupture of the membranes or placental dysfunction may reduce amniotic fluid volume (Dubbins et al., 1981). The accuracy of the diagnosis of renal agenesis was addressed in one study, in which three groups of patients were analyzed (Romero et al., 1985). In the first group, 16 patients who had a positive family history of bilateral renal agenesis were studied. In the second group, an additional 3 patients were diagnosed with possible renal agenesis during a routine anatomic scan. In the last group, 30 patients were studied who had a previously abnormal level 1 scan that was highly suspicious for renal agenesis. In the overall study, 19 truly affected fetuses were present and of these 18 were correctly diagnosed. Seven cases were correctly diagnosed at <24 weeks of gestation. One case was a false-negative due to difficulty in imaging the kidneys at 36 weeks of gestation in a fetus with massive hydrocephaly and oligohydramnios. There were no false-positive diagnoses. In the 19 affected fetuses, no bladder was visualized in 18 of them. All 19 fetuses had oligohydramnios. These authors concluded that an absent fetal bladder diagnosed after 16 weeks of gestation should prompt further investigation for bilateral renal agenesis (Romero et al., 1985). This study demonstrated that sonographic diagnosis of renal agenesis was highly accurate in the second or third trimester (Table 86-1). Figure 86-1 demonstrates the sonographic findings in a case of unilateral renal agenesis.

Other reports of false-negative diagnoses in cases of bilateral renal agenesis have been attributed to the sonographic misidentification of apparently enlarged fetal adrenal glands as fetal kidneys. To answer the question about whether the adrenals were really enlarged, autopsy records were reviewed from 11 affected fetuses with bilateral renal agenesis. These authors compared normal values on 240 fetuses at the same gestational age. They established regression curves for adrenal weights versus foot and crown-to-rump length as an indicator of gestational age. The adrenal weights from the 11 patients

Table 86-1

Diagnostic Accuracy of Ultrasound in the Antenatal Diagnosis of Bilateral Renal Agenesis

		Diagnosis			
Study Group	**No. of Cases**	***True Positive***	***True Negative***	***False-Positive***	***False-Negative***
Family history of bilateral renal agenesis	16	3*	13	0	0
Incidental finding on routine scan	4949	3	†	0	†
Previous suspicious scan in level I facility	30	12	17	0	1

** In one case the diagnosis was delayed until the third trimester.*
† Precise figures not available as not all perinatal deaths underwent autopsy.
Source: Romero R, Cullen M, Grannum P, Jeanty P, Reece EA, Venus I, Hobbins JC. Antenatal diagnosis of renal agenesis with ultrasound. Am J Obstet Gynecol. *1985;151:38-43.*

with bilateral renal agenesis were all within the normal limits. Therefore, these authors concluded that adrenal hypertrophy was not a common finding in renal agenesis and that the false-negative diagnosis of renal agenesis was due to a change in the normal adrenal shape rather than an increase in adrenal mass (Figure 86-2) (Droste et al., 1990). In approximately 10% of patients with unilateral renal agenesis, the ipsilateral adrenal gland is also absent (Fortune 1927; Ashley and Mostofi, 1960).

First trimester diagnosis of bilateral renal agenesis is complicated by the fact that at that point in gestation, amniotic fluid volume is not significantly reduced. Bronshtein et al. (1994) identified 9 of 13,252 fetuses with bilateral renal agenesis by transvaginal sonography between 12 and 18 weeks of gestation. The fetal kidneys can be visualized from 10 weeks of gestation by transvaginal sonography, and they appear as bilateral echogenic masses with the same density as fetal lungs. In contrast, the adrenal glands are relatively hypoechogenic. Diagnosis of renal agenesis consists of demonstration of oval bilateral hypoechogenic masses in the renal bed interpreted as adrenal glands. In this study, one false-positive diagnosis was made in a fetus with hypoplastic kidneys due to trisomy 22. These authors noted that the early second trimester sonographic findings in fetuses with bilateral renal agenesis consisted of three different presentations: (1) absence of any masses in the fetal flanks without sonographic evidence of ectopic kidneys, (2) the presence of bilateral hypoechogenic masses in the fetal flanks with no sonographic evidence of a fetal bladder and positive evidence of oligohydramnios at <17 weeks of gestation, and (3) bilateral hypoechogenic masses demonstrated in the fetal flanks with a small bladder present and a normal amount of amniotic fluid (Bronshtein et al., 1994).

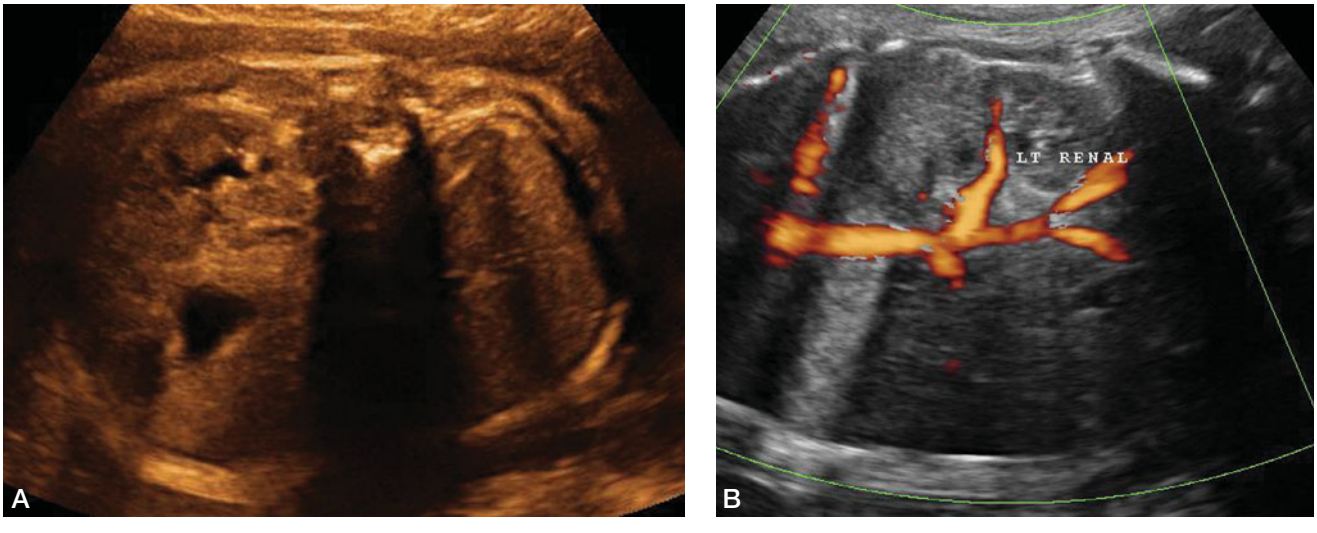

Figure 86-1 Axial image demonstrating normal left kidney with empty right renal fossa suggestive of unilateral renal agenesis **(A)** and coronal image of the same fetus using color Doppler to demonstrate the presence of a normal left renal artery and absence of the right renal artery **(B)**.

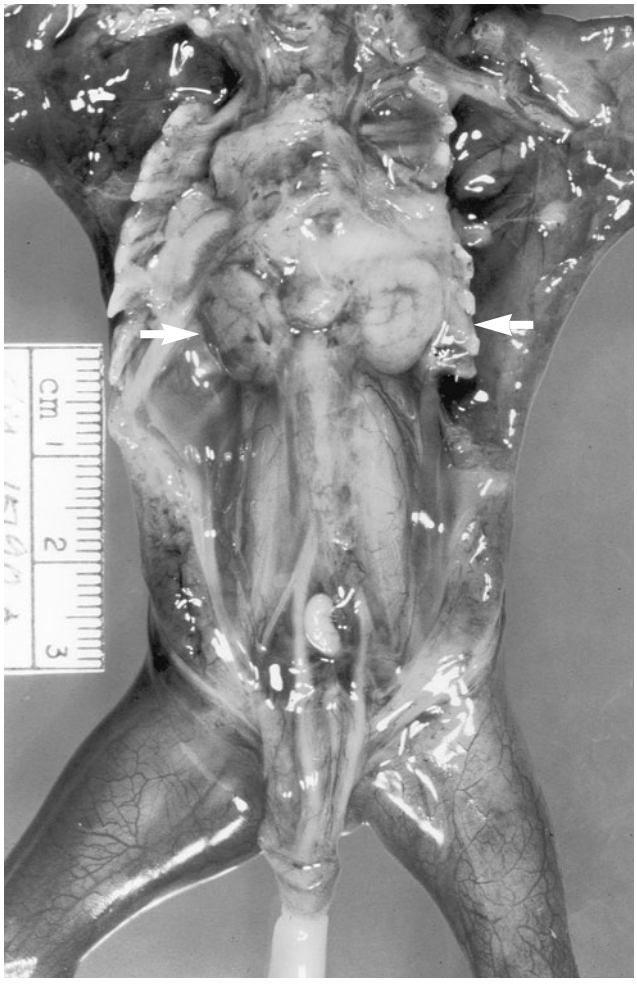

Figure 86-2 Postmortem photograph of a fetus at 17 weeks of gestation. This fetus had multiple congenital anomalies, including bilateral renal agenesis, absent ureters, absent bladder, absent uterus, absent fallopian tubes, and vaginal atresia. The arrows indicate the discoid-shaped adrenal glands. The centrally placed beanlike structure is a dysmorphic ovary. *(Courtesy of Dr. Joseph Semple.)*

Because oligohydramnios can impair visualization of the fetal kidneys and bladder, color Doppler sonography is recommended as an adjunct to the diagnosis of bilateral renal agenesis (Figure 86-3) (Sepulveda et al., 1998). In one study of 33 consecutive second trimester pregnancies complicated by severe oligohydramnios, high-resolution color Doppler ultrasonography was used to establish the presence or absence of renal arteries. The results showed that neither renal artery was visualized in eight fetuses; postmortem examination confirmed bilateral renal agenesis in seven fetuses and unilateral renal agenesis with a contralateral atrophic multicystic kidney in one fetus. In three cases, only one renal artery was visualized; postmortem examination confirmed unilateral renal agenesis in two fetuses and bilateral multicystic dysplastic kidneys in one fetus. When both renal arteries were identified prenatally (22 cases), postnatal or postmortem evaluation confirmed the presence of both kidneys (Sepulveda et al., 1995). Nomograms exist that predict the location of the renal arteries (distance from the bifurcation of the iliac arteries), using the fetal femur length as a reference (DeVore, 1995). In cases in which uncertainty remains after ultrasound, MRI is a useful adjunct to identify fetal kidneys or confirm unilateral or bilateral renal agenesis.

Late second- and third trimester fetuses with bilateral renal agenesis may also have intrauterine growth restriction. Affected infants have an increased incidence of associated malformations, most commonly of the genital system, cardiovascular system, vertebral bodies, or imperforate anus (Roodhooft et al., 1984). In the study by Bronshtein et al. (1994), six of the eight fetuses with renal agenesis had associated malformations. In five of the six affected fetuses, cardiac malformations were demonstrated.

Nomograms exist for kidney length from 13 to 22 weeks of gestation (Zalel et al., 2002). In one study, four cases with unilateral renal agenesis had a single kidney with a length greater than 95% (Zalel et al., 2002). In a postnatal study,

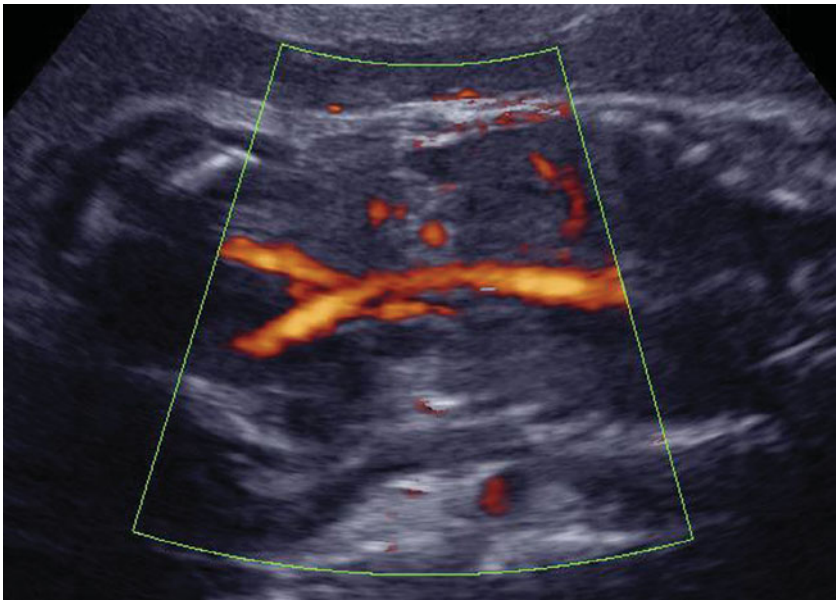

Figure 86-3 Coronal image with power Doppler demonstrating absence of both the right and left renal artery in a fetus with bilateral renal agenesis.

nearly half of the patients with unilateral renal agenesis had associated urological abnormalities, including vesicoureteral reflux, ureterovesical junction obstruction, and uteropelvic junction obstruction in the remaining kidney (Cascio et al., 1999).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of bilateral renal agenesis includes sirenomelia (see Chapter 87), caudal regression syndrome, and other nonanatomic causes for severe oligohydramnios, such as placental insufficiency. Sirenomelia is almost always associated with bilateral renal agenesis. Syndromes that are associated with renal agenesis include branchio-oto-renal syndrome, which is inherited as an autosomal dominant trait. This syndrome consists of preauricular pits, hearing loss, cervical fistulae, and renal abnormalities (Fitch, 1977). In one study, 6% of affected infants born to a parent with branchio-oto-renal syndrome were demonstrated to have severe renal anomalies (Greenberg et al., 1988). An additional syndrome that can present with renal agenesis is the cerebro-oculo-facial syndrome, which is inherited as an autosomal recessive trait. Affected infants with this condition have a dysmorphic face, micrognathia, flexion contractures, and severe renal anomalies. Unilateral and bilateral renal agenesis are often associated with bicornuate uterus and atresia of the vagina in females (also known as Rokitansky–Kuster–Hauser syndrome) and absence of the seminal vesicles and vas deferens in males (Holmes, 1989; Intaraprasert and Benchakan, 1985). Fraser syndrome is a rare autosomal recessive disorder that presents with cryptophthalmos, syndactyly, and renal anomalies. Bilateral renal agenesis is present in 47% of cases and unilateral renal agenesis in 37% (Wellesley and Howe, 2001). Bilateral renal agenesis should also be considered in twin gestations where one twin appears "stuck" due to severe oligohydramnios (Kuller et al., 1994). The differential diagnosis for unilateral renal agenesis includes renal aplasia, multicystic dysplastic kidney (see Chapter 78), crossed and double-crossed renal ectopia, and DiGeorge syndrome (22q11.2 microdeletion) (see Chapter 139) (Stewart et al., 1999).

ANTENATAL NATURAL HISTORY

As many as 33% of affected fetuses with bilateral renal agenesis are stillborn (Droste et al., 1990). It is becoming increasingly appreciated that a multicystic dysplastic kidney may result in the apparent absence of a kidney on sonography. The presence of microscopic residual renal tissue in these cases indicates that renal aplasia, not renal agenesis, is present. Family studies, however, suggest a relationship between renal agenesis and renal dysgenesis (Holmes, 1989). In one study, nine neonates who were previously known by prenatal sonography to have renal abnormalities were subsequently shown on postnatal studies to have unilateral renal absence (Hitchcock and Burge, 1994). Five of these infants had multicystic dysplastic kidney, and two had hydronephrosis noted antenatally. Unilateral renal absence may represent the prenatal involution of a multicystic dysplastic kidney, although this is controversial.

Unilateral renal agenesis is associated with genital anomalies in 12% of males and 40% of females (Heaney et al., 1987). In males, cysts of the seminal vesicle occur because of the common embryologic origin of the ureteral bud and the seminal vesicle from the mesonephric duct at 12 weeks of gestation (Heaney et al., 1987). In 68% of cases of seminal vesicle cysts, ipsilateral renal agenesis exists (Carvalho et al., 1986). In females, bicornuate or unicornuate uterus are common coexisting abnormalities. Also, ipsilateral blind vaginas and müllerian duplications are caused by lesions of the mesonephric duct. These lesions result in a closed urogenital sinus, which is due to the absent upward migration of the ureteral bud toward the metanephric blastema. This prevents the normal subsequent development of the kidney (Acien et al., 1991).

MANAGEMENT OF PREGNANCY

Further management of pregnancy when bilateral renal agenesis has been diagnosed will depend on the indication for the initial sonography and time of gestation. Serial sonography with color Doppler flow studies or MRI can be helpful when any doubt exists regarding the diagnosis. Attempts to diagnose bilateral renal agenesis in the first trimester are complicated by the fact that the renal contribution to amniotic fluid is minimal before 17 weeks of gestation and oligohydramnios is not necessarily present. Bronshtein et al. (1994) showed that an apparent urinary bladder may be seen during the first trimester in cases of bilateral renal agenesis due to retrograde filling or a small urachal cyst. Diagnosis at 13 to 16 weeks of gestation by transvaginal sonography can be made by demonstrating the presence of bilateral hypoechogenic structures that are clearly visualized in the renal bed without evidence of ectopic kidneys in the pelvis. These authors recommend at least a 60-minute period of observation to monitor filling of the bladder. If no bladder is visualized, a presumptive diagnosis of renal agenesis may be made, and the parents should be offered the opportunity to terminate the pregnancy. If, however, minimal amniotic fluid is present and a cystic structure is detected within the pelvis, these authors recommended fetal karyotyping, with follow-up sonography occurring at 17 to 19 weeks of gestation.

Sonographic diagnosis of bilateral renal agenesis can be complicated by poor fetal imaging due to lack of amniotic fluid. Intra-amniotic instillation of physiologic fluids can improve visualization of the fetus in cases of severe oligohydramnios. Cameron et al., recommend a single amnioinfusion, if needed, for sonographic diagnosis of renal agenesis. The amnioinfusion also permits fetal karyotyping. Another option

to visualize fetal anatomy is to perform magnetic resonance imaging (MRI) of the fetal abdomen, although there has been at least one case report of a false diagnosis of renal agenesis on MRI (Sgro et al., 2005). In practice, however, MRI is rarely needed to make the diagnosis.

In one study, pregnancies complicated by known lethal fetal renal anomalies were shown to have higher rates of antepartum complications (such as bleeding) and intrapartum complications (such as breech presentation) that led to statistically and significantly higher rates of primary cesarean section delivery (Carpenter et al., 2000). For fetuses with bilateral renal agenesis, there is no indication for a cesarean section. In cases of unilateral renal agenesis, routine obstetric management should prevail.

FETAL INTERVENTION

In one case report, a fetus with bilateral renal agenesis was presented. Serial amnioinfusions were performed to attempt to prevent pulmonary hypoplasia because the parents insisted that all therapeutic options be maintained. This infant was delivered at 33 weeks of gestation because of chorioamnionitis following multiple amnioinfusions. The infant had no clinical symptoms of pulmonary hypoplasia and no compressive effects on the face and limbs. Aggressive neonatal treatment was undertaken to achieve a goal of eventual renal transplantation. Peritoneal dialysis was initiated, but it ultimately proved unsuccessful. Cameron et al. (1994) strongly discourage this aggressive type of treatment of fetuses with bilateral renal agenesis. While it is possible to achieve survival without pulmonary hypoplasia in some cases with serial amnioinfusion, the family should be well informed regarding the postnatal challenges these infants face. Peritoneal dialysis is difficult to maintain in infants and allow growth to 10 kg, the usual minimal weight required for renal transplantation. In addition, previous experience with neonatal dialysis was associated with significant neurodevelopmental delay later in life. While management of neonatal dialysis has improved, parents should be aware of uncertain neurodevelopmental outcomes, difficulty in getting children to grow to 10 kg and the scarcity of appropriate infant donor kidneys.

TREATMENT OF THE NEWBORN

If the sonographic diagnosis is absolutely certain, no resuscitation of the newborn is indicated. However, if any question exists regarding the diagnosis, a neonatologist should be present at the delivery to confirm the presence of Potter-like features and clinical evidence of pulmonary hypoplasia. Bilateral renal agenesis is considered a lethal diagnosis. Intubation and mechanical ventilation of the newborn, however, may be considered appropriate in the setting of an unknown diagnosis. Once it has been confirmed postnatally that the infant lacks both kidneys, withdrawal of life support systems is appropriate.

Most newborns with bilateral renal agenesis die from pulmonary insufficiency resulting from severe oligohydramnios. In one study, a detailed quantitative analysis of the lungs of eight infants who died from bilateral renal agenesis or dysplasia was described (Hislop et al., 1979). The total lung volume and number of airway generations were reduced. This implied an interference with normal pulmonary development when the amniotic fluid volume was normal. Even at 12 to 16 weeks of gestation, the alveoli were reduced in size and number. These authors hypothesized that factors other than the oligohydramnios affected early lung growth. This was possibly due to the decreased production of proline, which is normally manufactured by the kidneys. Cases of bilateral renal agenesis have the lowest ratio of lung weight to body weight as compared with other types of kidney anomalies (Hislop et al., 1979).

In most newborns, unilateral renal agenesis is clinically silent. For fetuses that have been identified antenatally as having unilateral renal agenesis, a physical examination with palpation of the kidneys is indicated as well as postnatal abdominal sonography. Consideration should also be given to a radionucleide scan of the remaining kidney to document renal function. Because of the increased incidence of vesicoureteral reflux in the remaining kidney, voiding cystourethrography is also recommended. Prophylactic antibiotics are recommended in all cases of unilateral renal agenesis until vesicoureteral reflux has been ruled out.

SURGICAL TREATMENT

There are no surgical treatments for renal agenesis.

LONG-TERM OUTCOME

The longest surviving baby with bilateral renal agenesis was 39 days old (Whitehouse and Mountrose, 1973). Effectively, there is no long-term outcome for infants with bilateral renal agenesis.

In cases of unilateral renal agenesis, the infant may be asymptomatic, but patients with this diagnosis are at increased risk for proteinuria, hypertension, and renal insufficiency. Thirty percent of patients with unilateral renal agenesis have contralateral vesicoureteral reflux (Atiyeh et al., 1993).

GENETICS AND RECURRENCE RISK

Genetic counseling for renal agenesis is complicated by the fact that etiologic heterogeneity exists for this condition.

Many, but not all, cases of renal agenesis are inherited as multifactorial traits. The recurrence risk for an affected fetus or infant with isolated bilateral renal agenesis and a negative family history is in the order of 3% to 4% (Roodhooft et al., 1984; Holmes, 1989). If the renal agenesis is part of a complex of multiple abnormalities, the recurrence rate for siblings is 8% (Holmes, 1989). Chromosomal abnormalities, X-linked inheritance, autosomal dominant and autosomal recessive inheritance have all been reported for this condition. The chromosomal abnormalities most commonly seen in cases of bilateral renal agenesis include trisomy 22 (Bronshtein et al., 1994; Van Buggenhout et al., 1995), microdeletion of 22q11 (Stewart et al., 1999), trisomy 21 (Cardwell, 1988), trisomy 7, trisomy 10 (Schwarzler et al., 1999), 45, X/46, XY (Wax et al., 1994), 45, X/47, XXX (Roodhooft et al., 1984), and double aneuploidy for chromosomes 7 and X (Biri et al., 2005). An association between XYY and renal agenesis may also exist (Rudnik-Schoneborn et al., 1996). Fetuses with renal agenesis and other anomalies may have an underlying syndrome (see "Differential Diagnosis").

As stated earlier, the incidence of renal agenesis is higher in twin pregnancies than in singleton pregnancies. Monozygotic twins can either be concordant (Yates et al., 1984) or discordant (Cilento et al., 1994). Cilento et al. described a monoamniotic twin gestation with normal renal function that provided enough amniotic fluid to avoid the extrarenal manifestations of Potter syndrome. The twin with bilateral renal agenesis had no pulmonary abnormalities because there was enough urine being produced by the other twin. There is an increased incidence of recurrent renal agenesis in families, especially in those affected by hereditary hydronephrosis (Finn and Carruthers, 1974). Several families have been reported with two or more siblings of the same sex who were born with bilateral renal agenesis (Kaffe et al., 1977).

In one report, 9% of parents or siblings of patients with bilateral renal agenesis or dysgenesis had asymptomatic renal malformations (Roodhooft et al., 1984). In this study, 71 parents and 40 siblings of 41 index cases with bilateral renal agenesis, unilateral renal agenesis with dysgenesis of the other kidney, and bilateral severe dysgenesis were studied. Ten of these 111 relatives had an asymptomatic renal malformation. Most commonly, this was unilateral renal agenesis. The incidence of unilateral renal agenesis was 4.5% in the relatives of affected individuals with bilateral renal agenesis versus 0.3% in control adults. The malformation seen in the relatives included a double ureter, hydronephrosis, multicystic kidney, and multiple renal cysts. In addition, 2 of 37 mothers studied had a bicornuate uterus. These authors recommended sonographic screening for parents and siblings of affected fetuses or infants (Roodhooft et al., 1984). In families in which there is evidence of both unilateral and bilateral renal agenesis, the term "hereditary renal adysplasia" has been used. In most cases, this is due to a single gene inherited in an autosomal dominant pattern with variable expression (Pallotta et al., 2004).

To date, specific genes have not been identified in association with bilateral renal agenesis. Prenatal diagnosis in subsequent pregnancies should consist of serial sonographic examinations.

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87 CHAPTER

Sirenomelia

Key Points

- Incidence is 1 in 60,000 livebirths.
- Results from localized injury or insult to caudal end of developing embryo between days 13 and 22.
- Classified into 7 types according to the number of long bones present in the lower extremity.
- Associated with monozygotic twinning.
- First trimester sonographic findings include fused lower limb and increased nuchal translucency.
- Second trimester sonographic findings include single umbilical artery, bilateral renal agenesis, oligohydramnios, and growth restriction.
- Differential diagnosis includes bilateral renal agenesis and caudal regression syndrome.
- Chromosomes are usually normal.
- Prognosis is extremely poor for extrauterine survival.

CONDITION

Sirenomelia, also known as "mermaid syndrome," has been noted since the Greco-Roman period. Initially described in the medical literature by Rocheus in 1542 (Murphy et al., 1992), the condition is characterized by a single lower extremity, with the concomitant presence of severe anomalies of the urogenital and gastrointestinal system. Although historical and mythological accounts portray sirens and mermaids as females, the majority of patients with sirenomelia are male (deJonge et al., 1984). In all likelihood, the confusion originated as a result of the fact that most patients with sirenomelia had no obvious external genitalia.

It is often stated that sirenomelia is characterized by apparent fusion of the lower limbs. This terminology is embryologically incorrect because *fusion* refers to two processes joining after breakdown of intervening epithelia. *Merging* is the more correct term, because it does not imply intervening breakdown of epithelium. Sirenomelia, therefore, is a syndrome of merging, malrotation, and dysgenesis of the lower extremities (Kapur et al., 1991).

In 1865, Förster classified sirenomelia into three groups according to the number of feet present (van Zalen-Sprock et al., 1995). In symelia apus, the most common of the three conditions, both legs are merged completely into a single lower extremity. Both feet are absent or rudimentary. On radiographic studies, only one femur is present; there are no fibulae and one or two tibulae. In symelia unipus, 1 foot is present and up to 10 toes also may be seen (see Figure 87-1). In this type of sirenomelia, two femora, two tibia, and two fibulae are present. In symelia dipus, two distinct feet are present, although generally they are malrotated, and often give the appearance of fins. Stocker and Heifetz (1987) further classified sirenomelia according to seven types. In type I, all thigh and leg bones are present. In type II, there is a single fibula. In type III, there is an absent fibula. In type IV, the femurs are

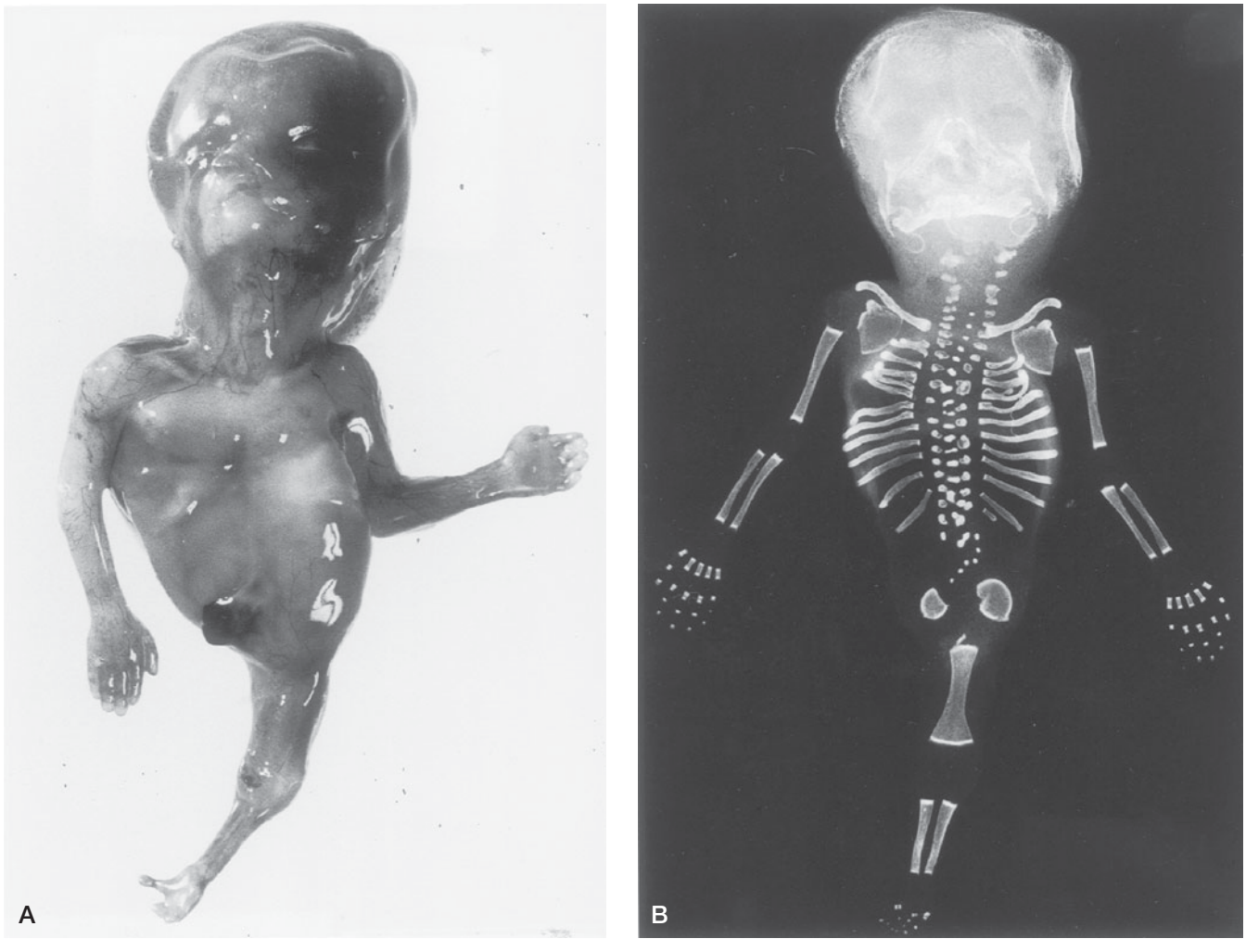

Figure 87-1 **A.** Fetus with symelia apus, demonstrating a single lower extremity and a single foot with four toes. **B.** Radiograph of a fetus with sirenomelia, demonstrating a single femur with broad metaphyses, paired tibiae, scoliosis, hemivertebrae, and minimal ossification of the lumbosacral spine. *(Reprinted, with permission, from Van Zalen-Sprock MM, Van Vugt JMG, Van Der Harten JJ, Van Geijn HP. Early second trimester diagnosis of sirenomelia.* Prenat Diagn. *1995;15:171-177.)*

partially fused and the fibulae are fused. In type V, the femurs are partially fused. In type VI, there is a single femur and a single tibia. In type VII, there is a single femur and an absent tibia.

In 1961, Duhamel coined the term *caudal regression syndrome* and first recognized an association between caudal regression and lower extremity abnormalities. He noted the presence of additional associated anomalies in sirenomelia, including sacral agenesis, anorectal atresia, renal agenesis, single umbilical artery, and ambiguous genitalia (Duhamel, 1961).

The cause of sirenomelia is still debated. Most agree that the site of injury to the embryo is the caudal mesoderm (Murphy et al., 1992). Sirenomelia probably results from a localized insult to the caudal end of the developing embryo between days 13 and 22 of development (Hoyme, 1988). By 23 days of embryonic age, the prospective limb bud regions normally assume a lateral position, separated by allantoic structures. If the lower extremity remains unipodal, the insult must have occurred prior to this point in gestation (Stevenson et al., 1986). Two theories have been developed to explain the occurrence of sirenomelia: vascular and caudal injury. In 1927, Kampmeier reviewed 52 cases of sirenomelia and was the first to note the constant finding of a single umbilical artery. He postulated that the single umbilical artery was very important in the etiology of the sirenomelia and that a vascular abnormality would affect the allantoic circulation with subsequent abnormal development of caudal elements. More recently, Talamo et al. (1982) performed postmortem arteriography on an infant with sirenomelia and documented a persistent vitelline artery and a dorsal hypoplastic distal aorta. They demonstrated that the femoral arteries ran anteriorly and posteriorly along the single femur, rather than in the normal orientation of right and left. They thought that this demonstrated a failure of rotation during early embryonic life and supported the pathogenetic concept of limb bud merging and malrotation after damage to the posterior axis mesoderm. Stevenson et al. (1986) dissected the abdominal vasculature in 11 cases of sirenomelia and documented the common feature of a single large artery arising from high in the abdominal cavity, which they thought diverted nutrients from the caudal end of the embryo in a vascular "steal" phenomenon. The steal vessel was a derivative from the vitelline artery complex, an early embryonic vascular network important in supplying nutrients to the yolk sac. They showed that the fetal arteries below the level of this steal vessel were underdeveloped; the tissues dependent on the normal vasculature for supply of nutrients subsequently failed to develop. This study demonstrated that in sirenomelia, the celiac and superior mesenteric arteries are usually present and normal in size. The inferior mesenteric artery may be missing. If present, it is very small and supplies the distal colon, which usually ends blindly in sirenomelia. In all the cases described by Stevenson et al. (1986), the major abdominal artery was a derivative of the vitelline artery complex; this was the primary artery carrying blood from the fetus to the placenta. Of note, the abdominal aorta distal to the origin of the vitelline artery gave off no tributaries. However, there were renal or inferior mesenteric arteries present proximal to the aortic bifurcation into the iliac arteries. These authors stated that the presence of the vitelline artery alone did not predispose to sirenomelia; rather, it was the stealing of nutrients normally intended for the caudal structures of the body that increased the risk for development of sirenomelia. While single umbilical artery is quite common and occurs in 1% of all livebirths (see Chapter 109), it was the unique point of origin of this single umbilical artery just distal to the celiac axis that predisposed to the caudal steal (Stevenson et al., 1986).

Any hypothesis regarding sirenomelia must also explain the association between this condition and monozygotic twinning (Young et al., 1986). Vascular abnormalities are common in monozygotic twin gestations; thus, development of a vascular steal sequence could be related to abnormalities in development of the placenta occurring in early monozygotic twinning. Alternatively, an abnormal division of the embryo could potentially result in a deficiency of caudal determinants in one of the embryos (Kapur et al., 1991).

INCIDENCE

The incidence of sirenomelia is 1 in 60,000 livebirths (deJonge et al., 1984). A male predominance exists, with a male-to-female ratio of 2.7:1. A strong association between sirenomelia and all caudal regression defects has been noted with maternal diabetes (Kucera, 1971; van Zalen-Sprock et al., 1995). As previously noted, there is a 100- to 150-fold increase in the incidence of sirenomelia in monozygotic twins as opposed to singletons (Smith et al., 1976; Wright and Christopher, 1982; Di Lorenzo et al., 1991; McCoy et al., 1994). In all cases of sirenomelia, 8% to 15% are associated with monozygotic twinning (Stocker and Heifetz, 1987). The association might be even more common than suspected, as at least one case of sirenomelia with a vanishing twin has been reported (Kapur et al., 1991). One case has been described in association with an in vitro fertilization triplet gestation and early intrauterine death of one of the triplets (Drossou-Agakidou et al., 2004). Sarpong and Headings (1992) reported two cases of sirenomelia associated with a history of cocaine exposure during the first trimester, as well as an 18-fold higher than normal incidence of sirenomelia in a cocaine-exposed population. A case of partial sirenomelia has been reported in which the mother took large amounts of vitamins A and E during the periconceptual period (Von Lennep et al., 1985).

SONOGRAPHIC FINDINGS

The diagnosis of sirenomelia may be easier to make in the first trimester as the amniotic fluid volume is relatively normal. The earliest reported diagnosis was made at 9 weeks of gestation in which an intra-abdominal cystic structure was observed (Schiesser et al., 2003). Subsequent scans at 11 and

Table 87-1

Characteristic Anomalies in Sirenomelia

Lower limb	Fusion, flexion, external rotation
Vertebral	Sacral agenesis
Anorectal	Imperforate anus, blind-ending colon
Urinary tract	Bilateral renal agenesis, ureteral, vesical, urethral agenesis
Genital	Absent or rudimentary external genitalia, gonads present
Craniofacial	Potter facies
Pulmonary	Hypoplastic lungs secondary to severe oligohydramnios

13 weeks demonstrated fusion of the lower limbs. In another report, two cases of sirenomelia diagnosed in the first trimester were associated with increased nuchal translucency measurement (Monteagudo et al., 2002).

Later in pregnancy, sonographic diagnosis of sirenomelia may be obscured by severe oligohydramnios. Oligohydramnios, intrauterine growth restriction, a large single umbilical artery, and bilateral renal agenesis are the second- and third trimester hallmarks of the diagnosis. Other findings characteristic of this condition are listed in Table 87-1 (Mok, 1990; Chenoweth et al., 1991). A more subtle finding may be the defective movement of the single lower limb with medially positioned fibulae. In symelia apus, the presence of a single femur may alert the sonographer to the correct diagnosis. When more than one femorae are present, the diagnosis is more challenging, particularly in the setting of little amniotic fluid. van Zalen-Sprock et al. (1995) described two cases at 14 and 16 weeks of gestation detected by transvaginal sonography (Figures 87-2 and 87-3). These cases were notable for the fact that despite the presence of bilateral renal agenesis, the amniotic fluid volume was only slightly decreased as compared with normal fetuses at the same gestational age. A larger series of 11 cases of sirenomelia diagnosed prenatally noted oligohydramnios as a universal finding. In only 5 of 11 cases (45%) was the correct diagnosis made prenatally. The remaining cases were diagnosed as bilateral renal agenesis. Significant additional anomalies noted included cardiovascular defects (36%), abdominal wall defects (36%), severe scoliosis (45%), and other skeletal deformities (90%) (Sirtori et al., 1989). Sonographic features that permit the correct antenatal diagnosis of sirenomelia include consideration of the diagnosis whenever bilateral renal agenesis is demonstrated, demonstration of persistently opposed lower extremities, and observation of a single hypoplastic foot with absent fibulae (Kapur et al., 1991).

Three-dimensional sonography has been used to further characterize the abnormalities in cases of sirenomelia (Monteagudo et al., 2002). The dynamic "live 3D" mode demonstrates the lack of normal fetal leg movement in this condition (Blaicher et al., 2001). Color flow and power Doppler studies may be of benefit in imaging the renal arteries when bilateral renal agenesis is suspected (Sepulveda et al., 1998) and to document abnormal vascular anatomy (Patel and Suchet, 2004). Magnetic resonance imaging has also been suggested as a helpful adjunct to characterize sirenomelia in the setting of oligohydramnios (Fitzmorris-Glass et al., 1989; Twickler et al., 1993).

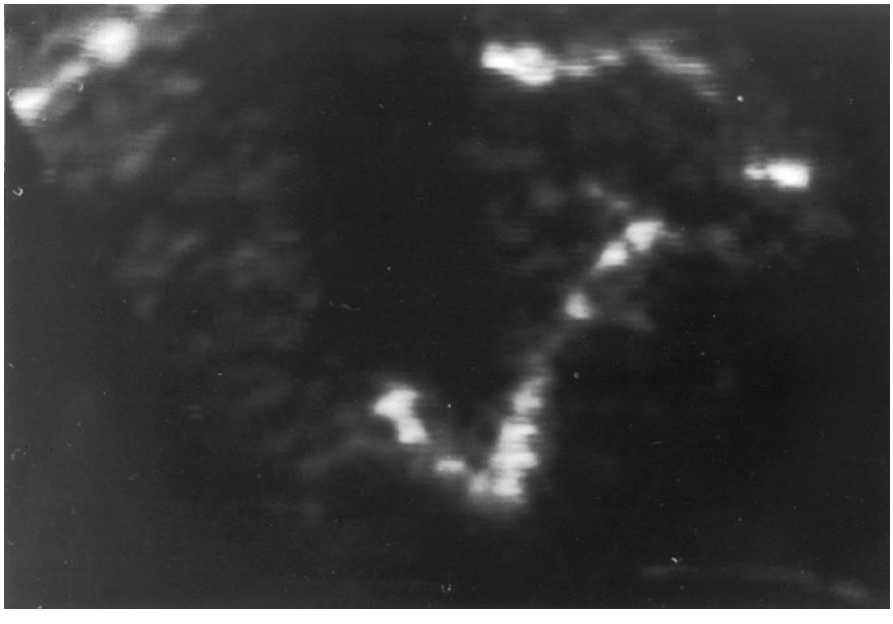

Figure 87-2 Sonographic image of a single midline femur with two iliac bones. (*Reprinted, with permission, from Van Zalen-Sprock MM, Van Vugt JMG, Van Der Harten JJ, Van Geijn HP. Early second trimester diagnosis of sirenomelia.* Prenat Diagn. *1995;15: 171-177.*)

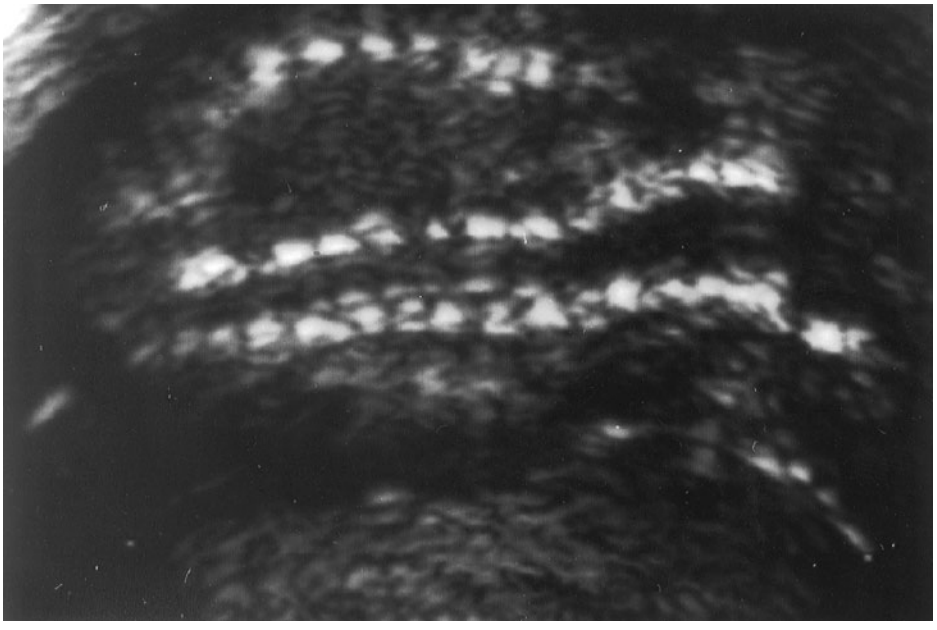

Figure 87-3 Sonographic image of scoliosis and abnormal vertebrae seen in a case of sirenomelia. This antenatally obtained image corresponds to the radiograph shown in Figure 87-1B. *(Reprinted, with permission, from Van Zalen-Sprock MM, Van Vugt JMG, Van Der Harten JJ, Van Geijn HP. Early second trimester diagnosis of sirenomelia.* Prenat Diagn. *1995;15:171-177.)*

DIFFERENTIAL DIAGNOSIS

Sirenomelia should be considered when the fetus has severe oligohydramnios. The differential diagnosis for sirenomelia includes isolated bilateral renal agenesis, which is 11 times more common than sirenomelia (Wright and Christopher, 1982), and caudal regression syndrome, which is generally associated with normal amniotic fluid volume.

ANTENATAL NATURAL HISTORY

Most patients with sirenomelia have bilateral renal agenesis. Consequently, oligohydramnios begins during the second trimester, when the kidneys would normally be producing fetal urine. Uterine size may be smaller than the gestational dates indicate. The consequences of severe oligohydramnios eventually manifest during the third trimester and include pulmonary hypoplasia and Potter facies. There is an increased risk of spontaneous pregnancy loss with this condition. Sirenomelia occurs in 4 in 1000 pregnancies that are spontaneously lost (Malinger et al., 1987).

MANAGEMENT OF PREGNANCY

When sirenomelia is suspected antenatally, consideration should be given to obtaining a fetal radiograph to look for the bony abnormalities seen in the lower merged extremity (Wright and Christopher, 1982) (see Figure 87-1B). If there is concern about inability to visualize the fetal bladder, amnioinfusion should be considered (Langer et al., 1996). Maternal furosemide administration is no longer recommended because of the high incidence of false-positive results. In the setting of severe oligohydramnios, chromosome studies from amniocytes may be very difficult to obtain and their indication is debatable. More than 300 cases of sirenomelia have been reported in the literature and the majority have had normal chromosome studies. Only two cases of chromosomal abnormalities have been reported, and in each case the abnormal chromosomes were obtained from specific organ tissue. In one case, chromosome studies were performed on pericardial tissue; they revealed mosaicism for a tandem duplication of the long arm of chromosome 1–46, XX/46, XX, dir dup (1) (q12 → qter) (Stevenson et al., 1986). In the other case, a fibroblast culture was obtained from the abnormal lower limb of an infant with sirenomelia. Metaphase spreads from this culture had a 6-fold increase in chromosomal breaks and a 23-fold increase in abnormal chromosome associations. There were multiple quadriradials observed that involved nonhomologous chromosomes. In contrast, fibroblasts obtained from a skin biopsy from the normal upper limb of the same patient had a normal karyotype (Sprague et al., 1970). Despite these intriguing findings, postnatal karyotyping in a confirmed case of sirenomelia is not indicated.

FETAL INTERVENTION

There are no fetal interventions indicated for sirenomelia.

TREATMENT OF THE NEWBORN

In the past, sirenomelia was considered uniformly fatal due to the known association with other major anomalies, including bilateral renal agenesis. Since 1989, however, there have been two reports of survivors with this condition. Lethality in this condition is due to the associated visceral anomalies that determine prognosis. If adequate renal function is present, survival outside the womb is possible. Savader et al. (1989) described the first survivor with this condition. This patient was noted to have fusion of the lower extremity to the level of the heels with a normal anus and kidneys, a normal heart, and single umbilical artery and transposition of the external genitalia and urethral opening. Postnatal magnetic resonance imaging confirmed the presence of distinct epiphyseal ossification centers and well-developed normal anatomic muscle groups that would permit future separation of the lower extremities. Subsequently, Murphy et al. (1992) described a patient who was diagnosed at 29 weeks of gestation and not expected to survive. Cesarean delivery was performed at term. The infant weighed 2.38 kg and had Apgar scores of 8 and 9. Her physical examination was notable for a fused lower extremity, an imperforate anus, colonic atresia, bilaterally fused pelvic kidneys, a preauricular skin tag, and posterior fusion of two ribs. She did not require aggressive support in the newborn intensive care unit. Because of her stable clinical status, a laparotomy was performed on the second day of life and revealed a malrotation with a blind-ending colon. A colostomy was performed and she was discharged to home. She was reported again at 3 months of age by Clarke et al. (1993), where she was described as neurologically normal. Her only medical problem has been prolapse of the colostomy. Tissue expanders were placed to facilitate a planned reconstruction of her lower limbs.

SURGICAL TREATMENT

The rare survivor with sirenomelia will need postnatal assessment of the genitourinary and gastrointestinal systems. Most patients will have imperforate anus, so a colostomy will be necessary. Postnatal renal imaging and functional studies will be necessary to determine the extent of renal function. Ultimately, there will be significant surgical issues related to appearance of the external genitalia and ambulation.

LONG-TERM OUTCOME

The long-term outcome is currently unknown, as there are only two examples of long-term survivors with sirenomelia that have been reported in the medical literature (Savader et al., 1989; Murphy et al., 1992; Clarke et al., 1993).

GENETICS AND RECURRENCE RISK

Sirenomelia is a developmental abnormality related to early embryogenesis. For most humans, it does not appear to be inherited as a single-gene defect (Gellis et al., 1973). In mice, however, a "sirenomelic syndrome" has been described that is inherited as an autosomal recessive gene (Orr et al., 1982). One family presented with a spectrum of four cases of renal anomalies, including a case of sirenomelia. The inheritance pattern in this family suggests that there is an autosomal dominant gene mutation present that affects renal development (Selig et al., 1993). Sirenomelia is associated with the monozygotic twinning process. Families at risk for increased incidence of monozygotic twins may also have an increased risk of sirenomelia. In general, chromosomal abnormalities have not been described in the etiology of this condition.

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Hemivertebrae

88
CHAPTER

Key Points

- Hemivertebrae are a major cause of congenital scoliosis and kyphoscoliosis.
- Incidence is 0.3 to 1 per 1000 livebirths. More common in females.
- Vertebral anomalies develop during first 6 weeks of gestation.
- Hemivertebrae act as a wedge within the vertebral column, causing curvature away from side of defect.
- Prognosis for isolated hemivertebra(e) is good.
- Can be associated with neural tube defects, occult intraspinal defects, renal anomalies, tracheoesophageal atresia/fistula.
- Associated syndromes in the differential diagnosis include: Goldenhar, Jarcho–Levin, Poland, Robinow, chondrodysplasia punctat, Alagille, and Pallister–Hall.

CONDITION

Hemivertebrae are vertebral anomalies that can be detected sonographically by the second trimester of pregnancy. These anomalies develop during the first 6 weeks of gestation, when the future anatomical pattern of the spine is formed in mesenchyme. Once the mesenchymal pattern is established in the embryo, subsequent cartilaginous and osseous stages follow (McMaster and Ohtsuka, 1982). At approximately 6 weeks of gestation, a chondrification center appears for each mesenchymal vertebra. Each vertebral body has a dorsal and ventral primary ossification center. These centers fuse, resulting in three primary centers of ossification, which can be visualized sonographically as early as 12 weeks of gestation, but histologically as early as 8 weeks of gestation (Zelop et al., 1993). Abnormalities of the vertebral bodies result from either failure of formation or failure of segmentation (Abrams and Filly, 1985). Abnormalities in vertebral segmentation result in bar or block vertebrae, whereas abnormalities in formation result in hemivertebrae (McMaster and Ohtsuka, 1982). Nasca et al. (1975) classified hemivertebrae by their morphologic appearance and described six different types: single supernumerary hemivertebrae, single wedge-shaped hemivertebrae, multiple hemivertebrae, multiple hemivertebrae with a unilateral bar defect on the contralateral side, balanced hemivertebrae, and posterior hemivertebrae. This latter defect occurs when the anterior part of the vertebral body fails to develop. Clinically this results in a kyphosis rather than a scoliosis. The medical significance of hemivertebrae is that they act as a wedge within the vertebral column, causing a curvature away from the side of the defect (Zelop et al., 1993). The abnormal vertebral body elongates the convex side of the spine. When growth occurs on the affected side, it causes compression of the superior and inferior vertebral end plates, resulting in decreased growth on the concave side (Nasca et al., 1975).

Hemivertebrae are a major cause of congenital scoliosis and kyphoscoliosis. Prenatal detection of this abnormality

has become possible only within the past few years, so relatively little is known about the clinical significance of isolated asymptomatic vertebral defects.

INCIDENCE

In a study of more than 15,000 chest radiographs, the incidence of congenital scoliosis due to vertebral anomalies was 0.5 in 1000 livebirths (Wynne-Davies, 1975). This estimate of vertebral anomalies is low, as only thoracic abnormalities were included in this study. The probable incidence of hemivertebrae is more on the order of 1 in 1000 livebirths (Wynne-Davies, 1975). All vertebral defects are more common in females. The male to female ratio for patients with multiple vertebral anomalies is 0.31 and 0.68 for patients with single vertebral anomalies (Wynne-Davies, 1975). In a retrospective study over a 17-year period (1985–2001) performed in Israel, 26 cases of hemivertebra(e) were identified among 78,500 liveborn infants (Goldstein et al., 2005). Seventeen cases had a single hemivertebra and 9 had multiple vertebral defects.

SONOGRAPHIC FINDINGS

Examination of the fetal spine should include views in three planes: sagittal, coronal, and transverse (de Elejalde and de Elejalde, 1985). Figures 88-1 and 88-2 demonstrate transverse and sagittal views. The sonographic criterion for hemivertebrae is a disruption in the alignment of one or more vertebral body ossification centers on a coronal section of the fetal spine obtained at 15 weeks of gestation or later. Benacerraf et al. (1986) initially described three cases of hemivertebrae identified sonographically between 17 and 28 weeks of gestation. In a study of 27 fetuses with sonographically detected vertebral anomalies, Zelop et al. (1993) described irregularities along the parallel line formed by vertebral body ossification centers and/or the two posterior neural arch ossification centers on either side (Figure 88-2). In another study, Harrison et al. (1992) described 20 cases of fetal scoliosis. In their study, all fetal spines were examined in the transverse and longitudinal planes for normal vertebral body configuration and curvature. Abnormal spinal curvature was defined as any focal, fixed kyphosis or a fixed curvature of the spine that persisted despite fetal movement. In this latter study, only one case of isolated hemivertebrae accounted for the fetal spinal curvatures. The remaining patients had various associated anomalies. Neural tube defects were the most common, described in 12 of the 20 fetuses studied. This study noted a poor outcome for the fetuses with scoliosis. Only 3 of the 20 infants survived and of these 2 had myelomeningoceles. Twelve of the remaining fetuses were electively terminated, 3 were stillborn, and 2 died on the first day of life.

Zelop et al.'s (1993) study is more relevant to the issue of diagnosis and management of the fetus with hemivertebrae. She and her colleagues described 27 fetuses with abnormalities in the spinal ossification centers visualized during the second and third trimesters. Of the 27 patients studied, 11 (41%) had hemivertebrae as the only anomaly documented. The hemivertebrae were distributed all along the spinal column: four were present in the thoracic region, two were present in the thoracolumbar region, and five were lumbar. All of the patients with isolated hemivertebrae had normal karyotypes. Nine of these 11 fetuses were born alive; 1 was electively terminated and 1 died at 32 weeks of gestation after premature

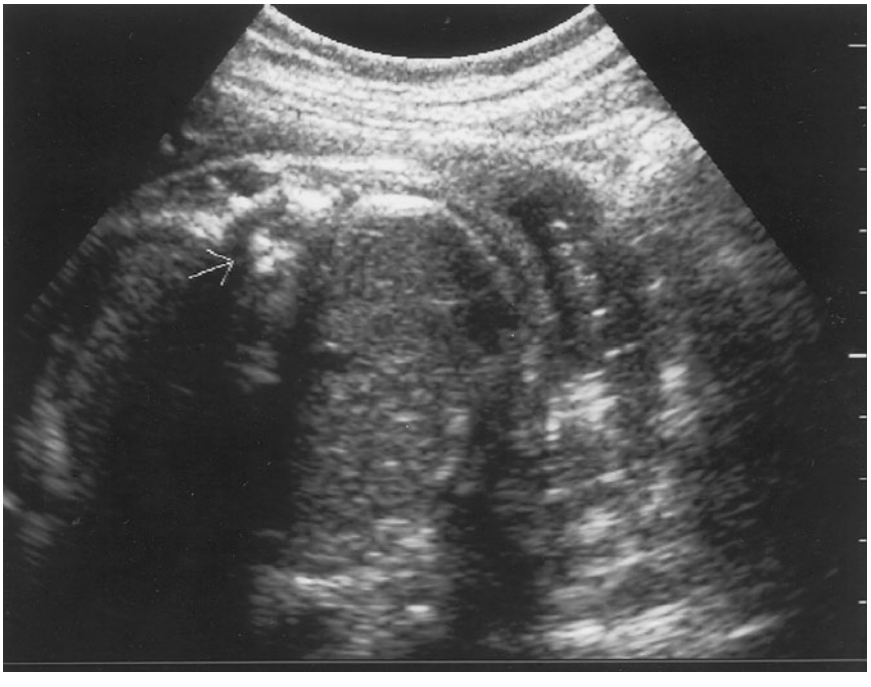

Figure 88-1 Transverse section demonstrating disruption of the vertebrae. The arrow indicates a cleft in the vertebral body.

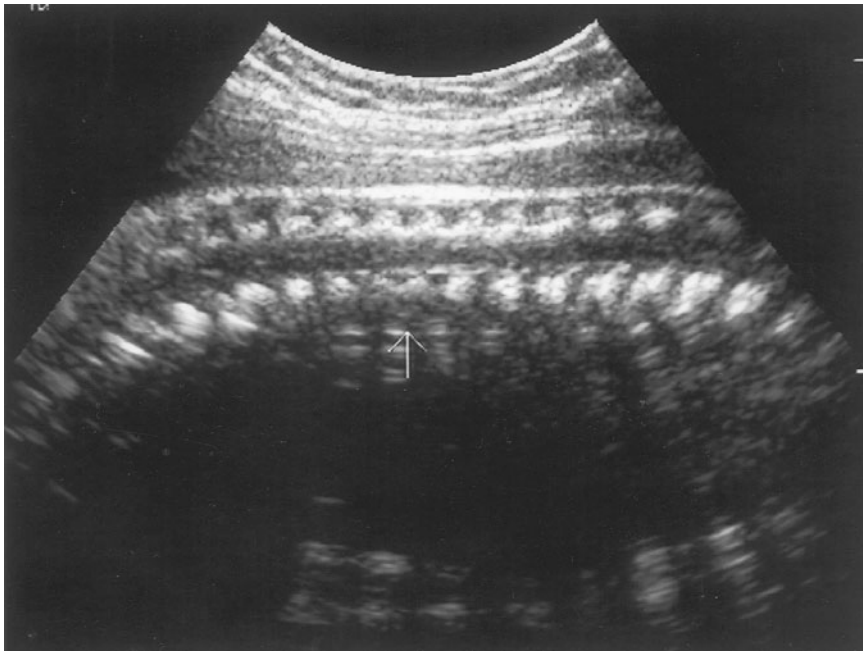

Figure 88-2 Sonographic scan in sagittal plane. The arrow indicates an irregularity in the anterior aspect of the vertebral body.

rupture of the membranes with sepsis. Of the nine liveborn infants, two required spinal surgery during infancy. The others remained well. In the other 16 cases that comprised this report, multiple additional defects were noted. The following abnormalities were noted: renal in 11 cases, gastrointestinal in 6 cases, cardiac in 4 cases, facial in 4 cases, extremity in 2 cases, cranial in 2 cases, and chest in 1 case. Seven of the fetuses had renal dysgenesis and severe oligohydramnios, consistent with Potter sequence. Four of the patients had polyhydramnios. Of the fetal patients with additional anomalies, seven had a chromosome analysis performed and all had normal karyotypes. Of the 16 patients with additional anomalies, 5 of the 16 survived postnatally, an additional 5 died during the newborn period, and 6 were terminated electively. The study concluded that the prognosis for a fetus with isolated hemivertebrae was good. Of note, however, more than half of the patients with hemivertebrae had significant additional anomalies that affected the prognosis.

DIFFERENTIAL DIAGNOSIS

The main consideration in the differential diagnosis of hemivertebrae is to determine whether the anomaly is isolated or part of a syndrome or association. The anatomic location of the hemivertebrae will also affect the differential diagnosis. For example, hemivertebrae in the cervical region are more likely to be part of the Klippel–Feil syndrome or be one manifestation of oculoauriculovertebral dysplasia (Goldenhar syndrome) (Anderson and David, 2005). Hemivertebrae that are present in the sacral region may suggest caudal regression syndrome. Vertebral abnormalities are also significantly associated with neural tube defects. Therefore, demonstration of hemivertebrae or other spinal abnormalities mandates exclusion of myelomeningocele (see Chapter 19). Approximately 2% of cases of esophageal atresia with tracheoesophageal fistula have associated vertebral anomalies (see Chapter 40) (Stevenson, 1972). Thus, a diagnosis of vertebral anomalies, particularly in the thoracic region, requires demonstration of a normal stomach bubble. Vertebral anomalies and tracheoesophageal anomalies are commonly seen as part of the VACTERL association.

Hemivertebrae are a prominent abnormality in the Jarcho–Levin and Robinow syndromes. Jarcho–Levin syndrome (see Chapter 96) is a single-gene disorder that presents with multiple vertebral anomalies at all levels of the spine and rib malformations (Jarcho and Levin, 1938; del Rio Holgado et al., 2005). Robinow syndrome is a recessively inherited disorder that includes mesomelic brachymelia, hemivertebrae, micropenis, a flat facial profile, and midline cleft lip (Vera-Roman, 1973; Wadlington et al., 1973).

There are also individual case reports of families that have constellations of abnormalities, including hemivertebrae, aphalangy, and urogenital and intestinal dysgeneses (Johnson and Munson, 1990). Other disorders in which hemivertebrae infrequently are part of the phenotypic spectrum include: oculoauriculovertebral dysplasia (see Chapter 24); chondrodysplasia punctata, Conradi–Hünermann type (see Chapter 99); Alagille syndrome (arteriohepatic dysplasia), which includes neonatal jaundice, peripheral pulmonic stenosis, and an unusual face; Noonan syndrome; Marfan syndrome; and Pallister–Hall syndrome, a disorder that includes hypothalamic hamartoblastoma, hypopituitarism, imperforate anus, and postaxial polydactyly. Vertebral anomalies are also associated with bladder and cloacal exstrophy (Loder and Dayioglu, 1990). More recently, a fetus with Poland syndrome (unilateral chest wall hypoplasia, ipsilateral hand abnormalities, and hemivertebrae) has been described in the literature (Paladini et al., 2004).

ANTENATAL NATURAL HISTORY

The antenatal natural history for fetuses with hemivertebrae is based primarily on the studies of Zelop et al. (1993) and Harrison et al. (1992). In both of these reports, comprising a total of 47 fetuses, there was no evidence for increased in utero mortality. However, 18 of the fetuses were electively terminated. Harrison's group of patients had severe scoliosis and were presumably more severely affected than the cases described by Zelop. Both studies noted a strong association with extraspinal anomalies, which affect the overall prognosis for the fetus. In Harrison et al.'s study, neural tube defects were the most common finding, whereas in Zelop et al.'s study 41% of fetuses had renal anomalies. The strong association with the renal malformations has been documented in a postnatal study of 231 children with congenital scoliosis (Macewen et al., 1972). Of this group, 42 of the 231 (18%) had an asymptomatic urologic abnormality. The most common finding was unilateral renal agenesis, which was documented in 6.5% of the total cases. This is significantly increased as compared with the 0.2% incidence of unilateral renal agenesis observed in pediatric autopsies. The second most common abnormality demonstrated was a duplication of the kidney or ureter, seen in 4% of total cases. This is also increased as compared with the general pediatric autopsy population, in which a duplication of the kidney or the ureter was seen in 0.7% of cases. Obstructive uropathy, unsuspected clinically, was demonstrated in 6 of 42 cases of congenital scoliosis. In addition, renal ectopia was seen in another six cases. Postnatal studies have also documented a very high association of occult intraspinal anomalies with vertebral defects (McMaster, 1984).

MANAGEMENT OF PREGNANCY

When a fetal hemivertebra has been diagnosed, a detailed anatomic scan should be performed to rule out associated abnormalities. Special attention should be paid to the presence of either oligohydramnios or polyhydramnios. If the vertebral defect is isolated, there is no evidence that there is an increased risk for an abnormal fetal karyotype. All of the patients in Zelop et al.'s study had normal chromosomes. If a vertebral anomaly is seen in association with another anatomic abnormality, we recommend offering an amniocentesis to document the fetal chromosome constitution.

Hypoplastic vertebrae, hemivertebrae, and vertebral coronal clefts have been noted in patients with microdeletions of chromosome 22q11 (see Chapter 139) (Ming et al., 1997). Thus, if congenital heart malformations and/or renal anomalies are noted, fluorescence in situ hybridization studies using a probe for 22q11.2 should be considered.

In the setting of an isolated fetal vertebral defect, there is no indication for delivery in a tertiary care center or for cesarean delivery. Recommendations for delivery of fetuses with hemivertebrae and associated anomalies should be guided by the nature and severity of the anomalies. Antenatal consultation with a pediatric orthopedic surgeon may be warranted to reassure the parents.

FETAL INTERVENTION

There are no fetal interventions for hemivertebrae.

TREATMENT OF THE NEWBORN

When a fetal vertebral defect has been identified antenatally, a detailed and thorough physical examination of the newborn is indicated to specifically rule out congenital scoliosis. Postnatal radiography is indicated to confirm the prenatal sonographic finding and to more specifically delineate the vertebral defect. If scoliosis is absent at birth, the infant can be observed and followed conservatively by a pediatric orthopedic surgeon. If scoliosis is present, approximately one-fourth of cases will progress rapidly, half will progress slowly, and one-fourth will not progress at all (Zelop et al., 1993). Infants with scoliosis need close follow-up by a pediatric orthopedic surgeon. If adequate views of the fetal renal anatomy were not obtained antenatally, consideration should be given to documentation of renal anatomy during the newborn period either by ultrasonography or by intravenous pyelogram. As previously noted, infants with vertebral anomalies have a high incidence of associated renal abnormalities (18% of cases) (Macewen et al., 1972). In addition, in one large study of 251 patients with congenital scoliosis, 18% had occult intraspinal abnormalities. The most frequent abnormality was diastematomyelia, which is a partial or complete sagittal split in a localized segment of either the spinal cord or cauda equina (McMaster, 1984). The problem with diastematomyelia is that an osseous or fibrocartilaginous spur projects backward into the midline from the posterior aspect of one or more adjacent vertebral bodies. This spur invaginates the dura and causes neurologic abnormalities. It is very important to identify diastematomyelia because sensory deficits, bowel or bladder incontinence, muscle weakness, or shortening of one lower extremity can result if the condition is left untreated. In McMaster's study, other occult intraspinal abnormalities were noted, including neurenteric cysts, epidermoid or dermoid cysts, teratoma, lipofibroma, absence of nerve roots, fibrous bands, or a tight filum terminale (McMaster, 1984). Occult neurologic defects are frequently missed because the skin overlying the dura usually appears normal, although some cases of hairy patches have been documented. Thus, newborns with congenital scoliosis due to hemivertebrae should undergo postnatal studies of their spinal cords by magnetic resonance imaging (MRI).

SURGICAL TREATMENT

As indicated above, most newborns are treated nonoperatively. The infant is generally followed with clinical examination and radiography for the development or progression of scoliosis. The indications for surgery include rigid decompensation of the spine, progression of the scoliotic curve, pain, desire for improvement of appearance, or development of dyspnea on exertion due to a restrictive pulmonary disease. Surgery is generally not performed during the newborn period, but the optimal age for surgical treatment has not yet been determined (Holte et al., 1995). In Zelop et al.'s (1993) report, of the nine patients with isolated hemivertebrae, only two required surgery during the first few years of life. Holte et al. (1995) described their experience with 37 patients treated with anterior and posterior wedge resection of hemivertebrae. All of their patients required a cast or brace for a period of 4 to 6 months, and most had to remain on bed rest for a period of more than 2 months. The average age at the time of these spinal operations was 12 years. Postoperatively, the curve containing the hemivertebrae was reduced from 55 to 33 degrees in all the patients. In approximately half of the patients, a measurable improvement in balance was achieved and maintained. This type of treatment is recommended only for patients with the most severe types of scoliosis. More recently, Deviren et al. (2001) described 10 consecutive patients (mean age, 13 years) who underwent excision of thoracic or thoracolumbar hemivertebrae. The mean preoperative coronal curve was 78.2 degrees. This was corrected to 33.9 degrees. There were no major complications and no neurological damage.

LONG-TERM OUTCOME

For fetuses and infants identified with isolated hemivertebrae, the long-term outcome is expected to be good. For patients identified with associated anomalies, the long-term outcome will be related to the underlying cause for the multiple malformations.

GENETICS AND RECURRENCE RISK

As noted in the "Differential Diagnosis" section, many syndromes exist that include hemivertebrae as one component. Recurrence risk would depend upon the particular syndromic diagnosis. In addition, a three-generation pedigree has been described with isolated hemivertebrae, inherited as an autosomal dominant trait (Ishida and Taute, 1973). There is, however, likely an environmental component to the development of hemivertebrae, as many sets of monozygotic twins have been described that are discordant for hemivertebrae (Peterson and Peterson, 1967; Wynne-Davies, 1975). The recurrence risk for isolated vertebral anomalies is on the order of 2% to 3% (Wynne-Davies, 1975). Significantly, an additional increased risk (on the order of 4%) for neural tube defects has been identified for siblings of children with isolated hemivertebrae (Connor et al., 1987). Thus, in subsequent pregnancies, women whose previous children have had hemivertebrae should have detailed scanning for sonographic abnormalities consistent with neural tube defects.

PAX1 is under investigation as a candidate gene for vertebral malformations (Giampetro et al., 2005).

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89

CHAPTER

Achondroplasia

Key Points

- Most common form of short-limbed dwarfism.
- Incidence is 1 in 26,000 livebirths.
- Most consistent sonographic finding is shortening of long bones between 21 and 27 weeks. Additional findings include macrocrania, frontal bossing, trident-shaped hand.
- Differential diagnosis includes diastrophic dysplasia, achondrogenesis, Ellis–van Creveld syndrome, hypochondroplasia.
- Condition is due to mutations in fibroblast growth factor receptor 3 (*FGFR3*) gene, which is a negative regulator of chondrocyte proliferation. Mutations activate the receptor and cause gain of function.
- Pregnant women affected by achondroplasia need baseline pulmonary function tests and cesarean section delivery.
- Prenatal diagnosis can be performed by sonography or by DNA analysis.
- Major pediatric complications include short stature, foramen magnum compression, hydrocephalus, spinal stenosis, restrictive pulmonary disease, hypotonia, and recurrent ear infections. IQ is normal.
- Inherited as an autosomal dominant condition, but 80% of cases are new mutations that always derive from the father and are associated with advanced paternal age.

CONDITION

Achondroplasia is the most common form of short-limbed dwarfism. The condition has been recognized since ancient times. Dwarfs were accepted socially in ancient Egypt, and their daily activities, recorded through art, suggest not only assimilation into daily life, but also in some cases, a high-ranking position in society (Kozma, 2006). The term achondroplasia, meaning total absence of cartilage, was first used by Parrot in 1878 (Scott, 1976). Although this is not correct in a pathologic sense, the designation is commonly accepted.

INCIDENCE

The incidence of achondroplasia is 1 in 26,000 livebirths (Oberklaid et al., 1979). Earlier studies that indicated an incidence of as high as 1 in 10,000 births probably included other causes of short-limbed dwarfism. More than 80% of cases are due to new mutations (Shiang et al., 1994). Advanced paternal age was initially thought to be correlated with an increased incidence of new mutations resulting in achondroplasia (Murdoch et al., 1970). However, more recent observations have led to the alternative theory that sperms bearing the fibroblast growth factor receptor 3 (*FGFR3*) mutation that

causes achondroplasia have a selective advantage over sperms without this mutation (Horton et al., 2007).

SONOGRAPHIC FINDINGS

Virtually all of the bones in the body are affected by achondroplasia. Postnatal radiographic studies of the lumbar spine, pelvis, and cranial regions permit definitive diagnosis (Figure 89-1). Antenatally, diagnosis is complicated by a relatively normal appearance until the early second trimester. The most consistent sonographic finding is shortening of the long bones, particularly the femur, occurring between 21 and 27 weeks of gestation (Figure 89-2) (Kurtz et al., 1986). The overall shape of the femurs is within normal limits. Initially, a normal relationship of biparietal diameter to femur is present, but these measurements become progressively asynchronous over time (Filly et al., 1981). Additional findings that have been described during the second trimester include large head (macrocrania), abnormal facial profile due to frontal bossing (Figure 89-3), protuberant abdomen, and trident-shaped hand (Figure 89-4) (Cordone et al., 1993).

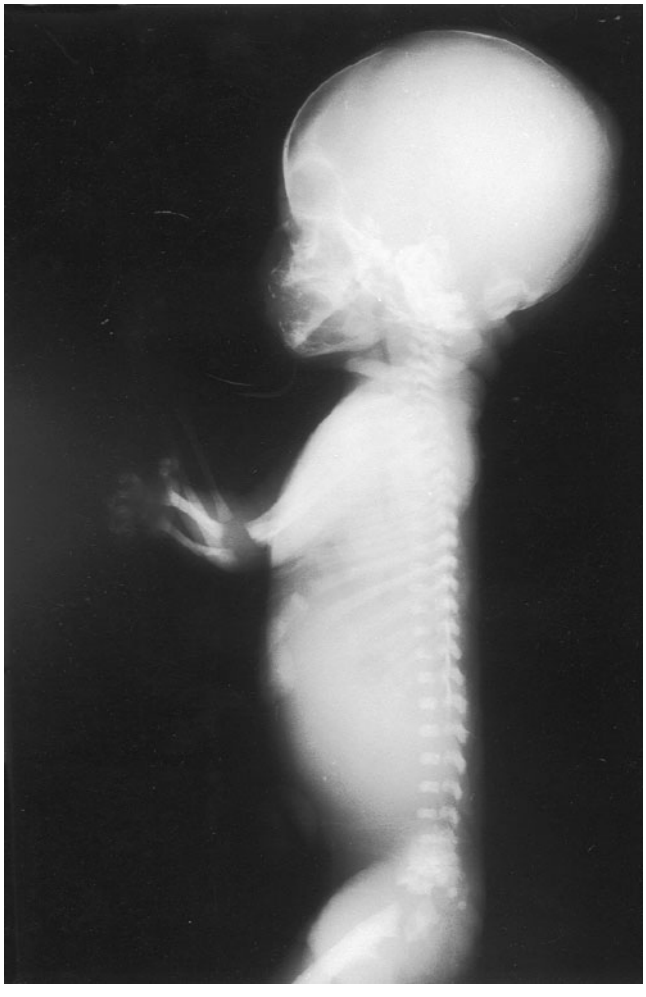

Figure 89-1 Postnatal radiograph of a patient with achondroplasia demonstrating flattened vertebral bodies with increased intervertebral space, cupped anterior ends to ribs, and hypoplastic midfacial bones. (*Reprinted, with permission, from Cordone M, Lituania M, Bocchino G, Passamonti U, Toma P, Camera G. Ultrasonographic features in a case of heterozygous achondroplasia at 25 weeks' gestation.* Prenat Diagn. *1993;13:400. Copyright 1993 John Wiley & Sons, Ltd. Reprinted, with permission, of John Wiley & Sons, Ltd.*)

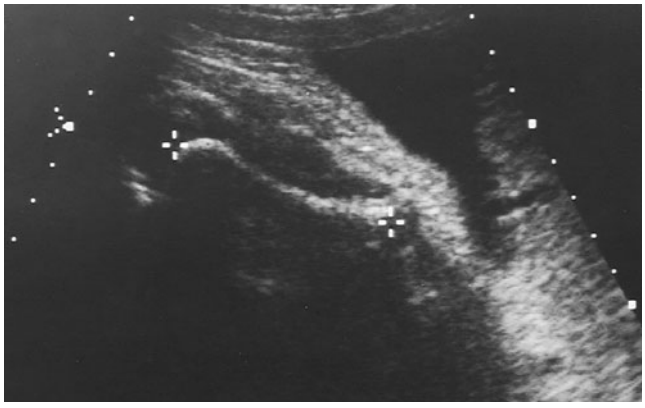

Figure 89-2 Shortening (<5%) and bowing of the femur in a fetus at 29 weeks of gestation with heterozygous achondroplasia.

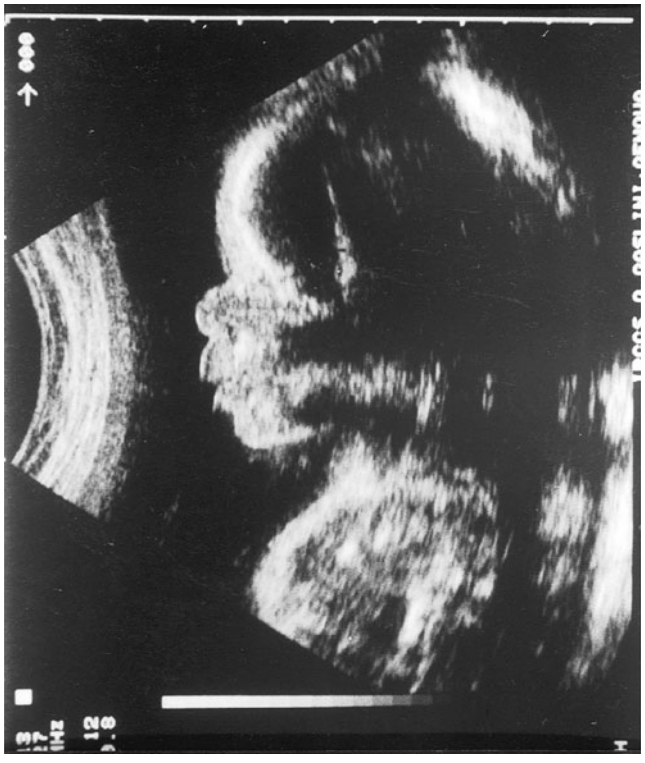

Figure 89-3 Antenatal facial profile of the fetus in Figure 89-4 and the infant in Figure 89-1, demonstrating frontal bossing, depressed nasal bridge, and an elongated philtrum. (*Reprinted, with permission, from Cordone M, Lituania M, Bocchino G, Passamonti U, Toma P, Camera G. Ultrasonographic features in a case of heterozygous achondroplasia at 25 weeks' gestation.* Prenat Diagn. *1993;13:398. Copyright 1993 John Wiley & Sons, Ltd. Reprinted, with permission, of John Wiley & Sons, Ltd.*)

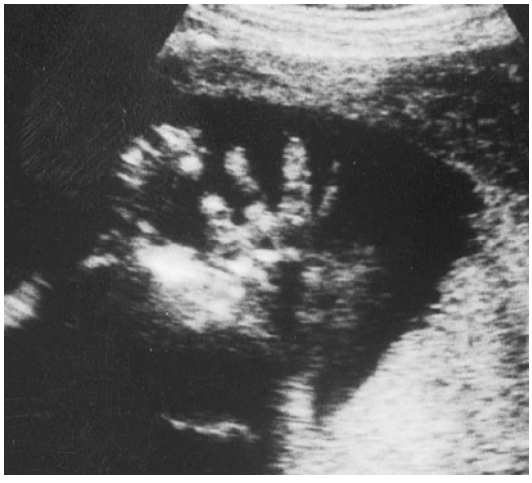

Figure 89-4 Prenatal sonogram of fetal hand at 25 weeks of gestation demonstrating relatively short phalanges and tridentlike appearance. (*Reprinted, with permission, from Cordone M, Lituania M, Bocchino G, Passamonti U, Toma P, Camera G. Ultrasonographic features in a case of heterozygous achondroplasia at 25 weeks' gestation.* Prenat Diagn. *1993;13:397. Copyright 1993 John Wiley & Sons, Ltd. Reprinted, with permission, of John Wiley & Sons, Ltd.*)

For prenatal diagnosis in the setting of one parent affected with achondroplasia, the fetus is considered to be affected if the length of the long bones is less than the third percentile or if polyhydramnios is present (Lattanzi and Harger, 1982; Elejalde et al., 1983). If both parents are affected by achondroplasia, the fetus is at 25% risk of inheriting both mutant alleles. In a retrospective review of 15 fetuses at 25% risk of homozygous achondroplasia, Patel and Filly (1995) demonstrated that fetal femoral length dropped below the third percentile at a mean of 15.6 weeks and 21.5 weeks in fetuses with homozygous and heterozygous achondroplasia, respectively.

If both parents are unaffected, prenatal diagnosis is more challenging. A fetus in which long bone growth is initially normal but then drops below the 10th percentile during the third trimester needs to be serially evaluated for the possibility of achondroplasia or hypochondroplasia. Hypochondroplasia is considered to be an allele of achondroplasia, with less severe clinical manifestations.

Krakow et al. (2003) compared 2D and 3D imaging in the diagnosis of skeletal anomalies. In a case of achondroplasia, 3D imaging captured the trident hands and more clearly delineated the disproportionate aspects of the limbs. For example, the left arm raised to the fetal forehead demonstrated that the level of the elbow was at the chin instead of the nose due to foreshortening of the proximal part of the arm (rhizomelia).

In one case report, an increased nuchal translucency measurement was noted in a fetus that was subsequently confirmed by molecular diagnosis to have achondroplasia. Rhizomelia, narrow thorax, and macrocrania were not observed until 18 weeks (Tonni et al., 2005).

DIFFERENTIAL DIAGNOSIS

The most likely diagnosis for a fetus with shortened long bones is that the fetus is normal or has intrauterine growth restriction that is not due to a skeletal dysplasia. However, the differential diagnosis includes chromosomal abnormalities as well as other types of dwarfism, some of which may be lethal at birth. An important prenatal finding that distinguishes heterozygous achondroplasia from some of the other skeletal dysplasias is the initially normal first and second trimester long bone measurements.

Other considerations in the differential diagnosis include diastrophic dysplasia, a recessively inherited form of short-limbed dwarfism, with the additional findings of thickening of the external ear and the characteristic "hitch-hiker" thumbs (see Chapter 93). In achondrogenesis, a lethal, recessively inherited condition, there is deficient ossification of the vertebral bodies. As compared with achondroplasia, a greater discrepancy between head size and trunk exists in achondrogenesis (see Chapter 97). In chondroectodermal dysplasia (Ellis–van Creveld syndrome), progressive distal shortening of the extremities and postaxial polydactyly are present (see Chapter 94). In addition, congenital heart malformations are present in 50% of cases. In hypochondroplasia, the major findings are short stature and an increased upper-to-lower body segment ratio. The facial features are within normal limits.

ANTENATAL NATURAL HISTORY

Achondroplasia is due to mutations in the fibroblast growth factor receptor 3 (*FGFR3*) gene. *FGFR3* is a negative regulator of chondrocyte proliferation and differentiation in the growth plate. Mutations in the gene therefore activate the receptor and cause a gain of function (Horton, 2006). They predominantly affect bones that develop by endochondral ossification (Kurtz et al., 1986; Horton, 2006). Membranous bone formation occurs at a normal rate (Murdoch et al., 1970). The abnormality in achondroplasia is confined to cartilage, and consists of a failure of interstitial cells to proliferate. Bones that are initially formed from cartilage, such as the long bones of the extremities, bones at the base of the skull, and vertebral bodies are affected by this condition.

In histologic studies of bone and cartilage from patients with achondroplasia, morphology is normal (Rimoin et al., 1976). The arrangement of rows and columns of cells is regular and well organized. The rate of endochondral ossification is reduced and this contrasts with the normal periosteal ossification. This disparity results in periosteal bone extending beyond the growth plate and gives the appearance of short squat bones with cupped ends. Ultrastructural studies are also generally normal. The only abnormalities demonstrated have been a relative increase in the number of dead cells surrounded by microscars that contain focal aggregations of collagen fibrils (Rimoin et al., 1976).

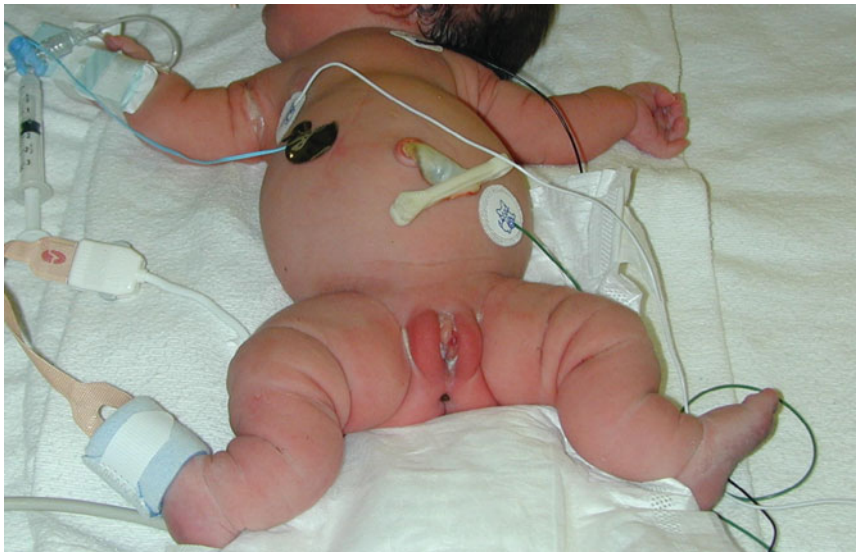

Figure 89-5 Postnatal photograph of an infant with homozygous achondroplasia, demonstrating the narrow chest and short, malformed bones. Homozygous achondroplasia is nearly uniformly fatal.

MANAGEMENT OF PREGNANCY

For an unaffected pregnant woman, the antenatal course for this condition is usually benign. When achondroplasia is suspected, serial sonography may be useful to determine if macrocrania is developing, which may necessitate cesarean delivery.

For the pregnant woman affected with achondroplasia, special problems include increased incidence of fetal loss, preeclampsia, and respiratory compromise in the third trimester (Trotter et al., 2005). Baseline pulmonary function studies should be performed. Cesarean delivery is mandatory for cephalopelvic disproportion secondary to marked pelvic contracture (Lattanzi and Harger, 1982; Allanson and Hall, 1986).

The identification of the gene responsible for achondroplasia, *FGFR3* (Shiang et al., 1994), allows DNA-based prenatal diagnosis. This is especially important for couples in which both partners are affected. In this situation, there is a 25% chance that the fetus will inherit the two mutant genes, resulting in homozygous achondroplasia that is associated with a very high incidence of fetal and neonatal death (Figure 89-5). In one report, first trimester DNA diagnosis has been described in a couple at risk for homozygous achondroplasia (Bellus et al., 1994).

In recent years, fetal chromosome analysis has been increasingly performed for short fetal bones due to the concerns of possible trisomy 21 (see Chapter 131). In the setting of a fetus with short bones and a normal karyotype, amniotic fluid cells may be used as a source of fetal DNA to test for *FGFR3* mutations. If an *FGFR3* mutation is found, this is diagnostic.

FETAL INTERVENTION

There is no fetal intervention for achondroplasia.

TREATMENT OF THE NEWBORN

Most newborn infants with achondroplasia do not require special medical treatment and can be cared for in the regular nursery. In fact, many cases of achondroplasia are missed at birth. According to one study, even at 1 year of age, only 60% of cases are diagnosed (Saleh and Burton, 1991). Due to increased use of prenatal sonography in more recent studies it is estimated that approximately 20% of cases are missed at birth (Horton, 2006). For infants with achondroplasia, the main issues are definitive diagnosis and coordination of subspecialty care. All infants with a suspected diagnosis of achondroplasia should have radiographs taken of their long bones.

The salient clinical findings of achondroplasia in the newborn include short stature of the rhizomelic type. This means that the proximal arms and legs are relatively more shortened than the distal segments of the extremities. However, the short stature may be mild or even absent. Horton et al. (1978) showed that the range of birth length in newborns with achondroplasia overlaps the normal population. Mean growth velocity is also normal during the first year of life. It is after the first year that growth velocity drops significantly. Other features of achondroplasia during the newborn period may include macrocrania, frontal bossing, and midface hypoplasia with coarsened facial features. The lumbar lordosis that is apparent later in life is rarely appreciated at birth. Cognitive development, socialization, speech, and language milestones are achieved normally, but initial gross motor milestones may be delayed (Scott, 1976). The muscular hypotonia responsible for delayed motor development disappears spontaneously at 4 to 6 years of age. The general pediatric recommendations for health supervision for children with achondroplasia have been summarized and updated (Trotter et al., 2005).

A serious potential problem in achondroplasia is cervicomedullary junction compression due to a small foramen

magnum. The foramen magnum is narrowed in a transverse direction (Hecht et al., 1989). This can result in occipitocervical pain, ataxia, incontinence, or the more serious complication of apnea and sudden infant death (Pauli et al., 1984). Magnetic resonance imaging (MRI) studies in five affected patients have demonstrated the discrepancy between the size of the brainstem and the foramen magnum (Thomas et al., 1988). In addition, hydrocephalus is frequently found due to anatomic abnormalities in the occipital bone that produce intracranial venous hypertension. It has been hypothesized that obstruction at the jugular foramen elevates intracranial venous pressure, resulting in decreased absorption of cerebrospinal fluid into the sagittal sinus, producing a communicating hydrocephalus (Thomas et al., 1988). Approximately 5% of affected children require placement of a shunt (Haga, 2004).

Approximately 10% of patients with achondroplasia have respiratory complications due to foramen magnum compression (Stokes et al., 1983; Thomas et al., 1988). It is recommended that computed tomographic (CT) or MRI be performed in conjunction with somatosensory evoked potentials to screen for this problem (Reid et al., 1987). Although posterior fossa decompression and atlantal laminectomy represent major surgical intervention, symptoms have been reported to improve postoperatively (Ryken and Menezes, 1994). The increased mortality seen in achondroplasia (Hecht et al., 1987) is due to this brainstem compression and it primarily affects children younger than 4 years old.

SURGICAL TREATMENT

Cervicomedullary compressive surgery is indicated for individuals with symptoms of foramen magnum compression (Ho et al., 2004). This surgery can treat central apnea that may result in death, and/or relieve neurologic complications secondary to spinal cord damage. In one study, the quality of life and morbidity of individuals with achondroplasia who underwent cervicomedullary decompression surgery was indistinguishable from age and gender matched controls (Ho et al., 2004).

The orthopedic deformities in achondroplasia consist of bowing of the legs, hyperlordosis, and spinal stenosis. In approximately 25% of cases, the bowing of the legs is treated with corrective osteotomies of the tibia. This surgery is usually performed between 3 and 10 years of age. Although spinal stenosis is universal, only in relatively few cases does it cause cauda equina syndrome, which manifests as a lower motor neuron flaccid paralysis. This becomes evident during very late adolescence or adulthood and requires a decompressive laminectomy. The most severe but least common orthopedic problem is thoracolumbar kyphosis, which can cause paraplegia earlier in childhood. This requires aggressive spinal surgery.

Surgical therapies currently being optimized may also significantly improve the cosmetic aspects of achondroplasia. Craniofacial surgery is possible to advance midfacial bones and correct severe dental malocclusion (Denny et al., 1992).

Leg lengthening has received much attention as a means of improving height and appearance for patients with achondroplasia (Figure 89-6). This has been utilized more commonly outside of North America. The surgery is painful; it should be performed on only adolescents; and it may take up to 2 years to complete (Saleh and Burton, 1991). Aldegheri and Dall'Oca (2001) reviewed their experience in performing limb lengthening on 80 achondroplastic individuals. Ten of these individuals also underwent humeral lengthening to improve ability to independently attend to matters of personal

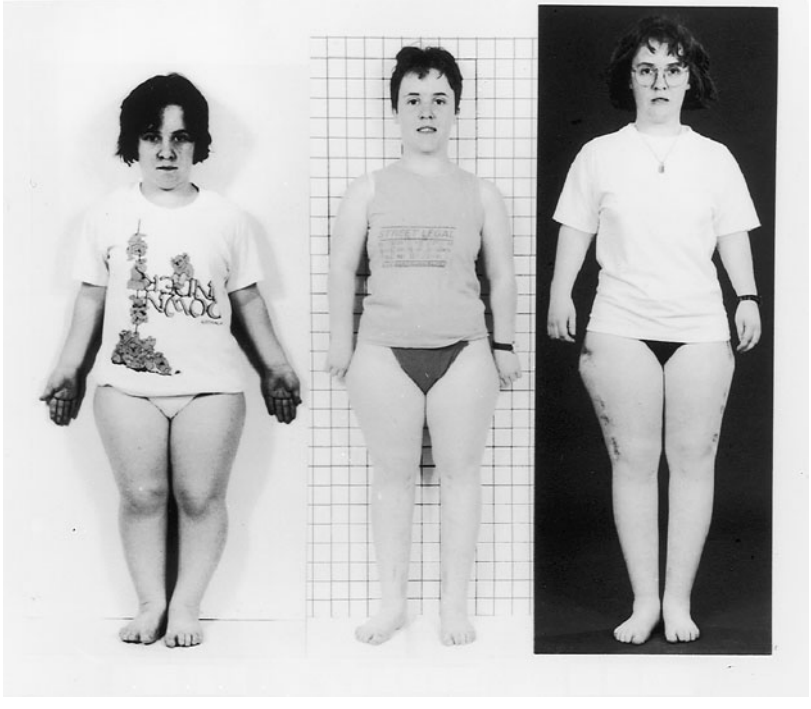

Figure 89-6 Patient with achondroplasia demonstrating cosmetic effects of multiple leg-lengthening operations over an almost 4-year period. (*Courtesy of Professor Michael Saleh, Sheffield Children's Hospital, Sheffield, United Kingdom.*)

hygiene. Patients gained an average of 20.5 cm in height but 39% of them had complications. The treatment time required was approximately 33 months. Limb lengthening surgery is invasive, complex, and potentially dangerous.

LONG-TERM OUTCOME

The long-term consequences of achondroplasia are cervicomedullary compression, hydrocephalus, spinal stenosis, restrictive and obstructive lung disease, otitis media, and thoracolumbar kyphosis (Hunter et al., 1998; Trotter et al., 2005). Mental development is generally normal.

Standard growth curves exist to assess normal growth for children with achondroplasia (Horton et al., 1978). The average adult height for an affected male is 52 inches (129 cm) and an affected female 48.6 inches (122 cm). The average adult weight for a male is 120 lb (55kg) and a female 100 lb (45kg) (Murdoch et al., 1970; Scott, 1976). Obesity is common (Hecht et al., 1988). In sporadic cases, parental height does not significantly influence the adult height of affected offspring (Murdoch et al., 1970; Scott, 1976).

In an initial clinical trial, recombinant human growth hormone given to patients with achondroplasia at doses of 0.3 mg per kilogram of body weight per week moderately increased overall height velocity, particularly in the short term. There were no untoward effects, particularly with regard to worsening of the degree of spinal stenosis (Horton et al., 1992). Further clinical trials have not shown a clear long-term benefit. Currently, most experts do not recommend growth hormone for achondroplasia (Horton et al., 2007).

Further medical problems for children with achondroplasia include recurrent ear infections (in 90% of children) and conductive and sensorineural hearing loss. Patients with achondroplasia have specific structural changes of the temporal bone, although it is unclear how these changes relate to hearing loss (Shohat et al., 1993). Approximately half of the affected children undergo placement of ventilation tubes in the tympanic membrane (Haga, 2004). For many patients, dental crowding necessitates orthodontic treatment.

Intelligence quotient (IQ) is normal for individuals with achondroplasia. One study compared 20 adults affected with achondroplasia with siblings of the same sex and found that the mean number of years of formal education was comparable for each group. Females, more than males, have a significantly lower occupational level as compared with their same-sex siblings (Roizen et al., 1990). It was questioned whether this was due to a self-esteem problem that was more profound in females. The psychiatric aspects of achondroplasia have also been studied. In general, patients with achondroplasia had achieved satisfactory life adjustment and had secure identities as "little people" (Brust et al., 1976). The functional health status of adults with achondroplasia is not drastically reduced in comparison with the general United States population (Mahomed et al., 1998).

Looking toward the future, novel therapies will be directed toward countering the effects of the overactive *FGFR3* (Horton, 2006, Horton et al., 2007). Chemical inhibitors that downregulate the tyrosine kinase activity of *FGFR3* might be used in a manner analogous to the treatment of chronic lymphocytic leukemia with inhibitors to *Bcr-abl* tyrosine kinase. Alternatively, antibodies could be used to interfere with the binding of FGF ligands to *FGFR3*. The molecular mechanism responsible for achondroplasia is the same as in many cancers. Also, C-type natriuretic peptide (CNP) downregulates FGF-induced activation of MAP kinase signaling pathways in growth plate chondrocytes. It has been suggested as a treatment for achondroplasia because of therapeutic effects observed in mouse models (Horton, 2006).

GENETICS AND RECURRENCE RISK

Achondroplasia is inherited as an autosomal dominant condition. Fifty percent of an affected parent's offspring will also have achondroplasia. The phenotype is 100% penetrant, which means that all offspring who carry the gene will express the full clinical appearance of achondroplasia. If both parents are affected, there is a 50% chance of having a child with heterozygous achondroplasia, a 25% chance of having a child with homozygous achondroplasia, and a 25% chance of having a child with normal stature.

As stated earlier, the majority of cases (80%) are due to new mutations. Murdoch et al. (1970) studied 148 patients with achondroplasia. Thirty-one (21%) had one or both parents affected, whereas 117 cases (79%) had no family history of the condition. Although a case has been described of one family in which normal parents gave birth to multiple affected children (Fryns et al., 1983), a larger Canadian study that examined the risk of recurrence due to parental gonadal mosaicism found only 1 case in 443 full siblings of children with achondroplasia (Mettler and Fraser, 2000). Thus the recurrence risk if the parents are normal is only 0.02%.

The gene involved in achondroplasia was localized to chromosome 4 band p16.3 in 1994 (LeMerrer et al., 1994). The disease is caused by mutations in the coding sequences for *FGFR3*. At least nine different heparin-binding fibroblast growth factors are known. All of them have pleiotropic effects on different cell types and have quite different patterns of expression during development. Evidence that the *FGFR3* gene was a good "candidate" gene for achondroplasia included the fact that *FGFR3* mRNA is found in the central nervous system and all of the prebone cartilage structures of the mouse (Shiang et al., 1994).

In a landmark study, Shiang et al. (1994) demonstrated point mutations in the DNA of 15 of 16 individuals studied with achondroplasia. The mutations all occurred at nucleotide 1138, and resulted in the substitution of an arginine residue for a glycine at position 380 of the mature protein, which is in the transmembrane domain of *FGFR3*. This work has been validated and extended by other investigators, who have also shown that all achondroplasia mutations studied result in the same substitutions at the same amino acid of the transmembrane domain of the *FGFR3* protein

(Bellus et al., 1994; Rousseau et al., 1994). The homogeneous nature of these mutations in achondroplasia is unprecedented for an autosomal dominant disorder. This may explain the phenotypic similarity between all patients with achondroplasia. *FGFR3* has subsequently been shown to be one of the most mutable genes in the human genome (Vajo et al., 2000).

Based on these results, rapid polymerase chain reaction-based prenatal diagnosis is available for the condition (Bellus et al., 1994). DNA testing is relatively straightforward because the mutations involved are minimal in number, and they create new recognition sites for restriction endonucleases (Francomano, 1995). In sporadic cases of achondroplasia, the *FGFR3* mutation arises during spermatogenesis and is associated with advanced paternal age (Wilkin et al., 1998; Vajo et al., 2000).

It is now known that achondroplasia is one of six diseases caused by mutations in the *FGFR3* gene. Four are associated with skeletal dysplasias and two are associated with craniosynostosis. The other three skeletal dysplasias are hypochondroplasia, thanatophoric dysplasia (see Chapter 90), and severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN) (Bonaventure et al., 1996; Bellus et al., 1999). *FGFR3* mutations also cause Muenke coronal craniosynostosis and Crouzon syndrome with acanthosis nigricans (Vajo et al., 2000) (see Chapter 10).

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90 CHAPTER

Thanatophoric Dysplasia

Key Points

- Most common of the lethal skeletal dysplasias. Presents in the second trimester.
- Two subtypes exist: TD I has short curved femurs with or without a cloverleaf skull; TD II has straight, longer femurs and generally a more severe cloverleaf skull.
- Sporadic inheritance with extremely small recurrence risk associated with advanced paternal age (>35 years).
- Mutations in fibroblast growth factor receptor 3 (*FGFR3*) are the underlying basis for the disorder. There is a strong genotype–phenotype correlation. DNA diagnosis is highly accurate.
- *FGFR3* is also expressed in the brain. Rare survivors are uniformly severely developmentally delayed.

CONDITION

Thanatophoric dysplasia, a lethal chondrodysplasia, was first recognized as a unique clinical entity in 1967 (Maroteaux et al., 1967). *Thanatophoric* is Greek for "death bearing". The classic clinical features include micromelic limbs, short ribs, narrow thorax, relative macrocephaly, frontal bossing, midface hypoplasia, reduced height of the vertebral bodies, and central nervous system abnormalities (Figure 90-1). It is the most common form of lethal dwarfism in the human.

Fetuses and infants affected with thanatophoric dysplasia have been classified according to radiographic differences, such as the presence or absence of a cloverleaf skull and whether the femurs are curved or straight. At one time, the two subtypes of thanatophoric dysplasia (TD), TD I and TD II, were thought to be two separate entities, with possibly two different patterns of inheritance (Young et al., 1989). As of 1995, however, it was demonstrated that mutations in the fibroblast growth factor receptor 3 (*FGFR3*) gene were the underlying basis for both conditions (Tavormina et al., 1995). Mutation analysis of the DNA of affected patients has revealed that individuals with TD type I have short curved femurs with or without a cloverleaf skull deformity, whereas patients with TD type II have straight, somewhat longer femurs and severe cloverleaf skull (Tavormina et al., 1995). In the developing mouse and human fetus, the highest levels of

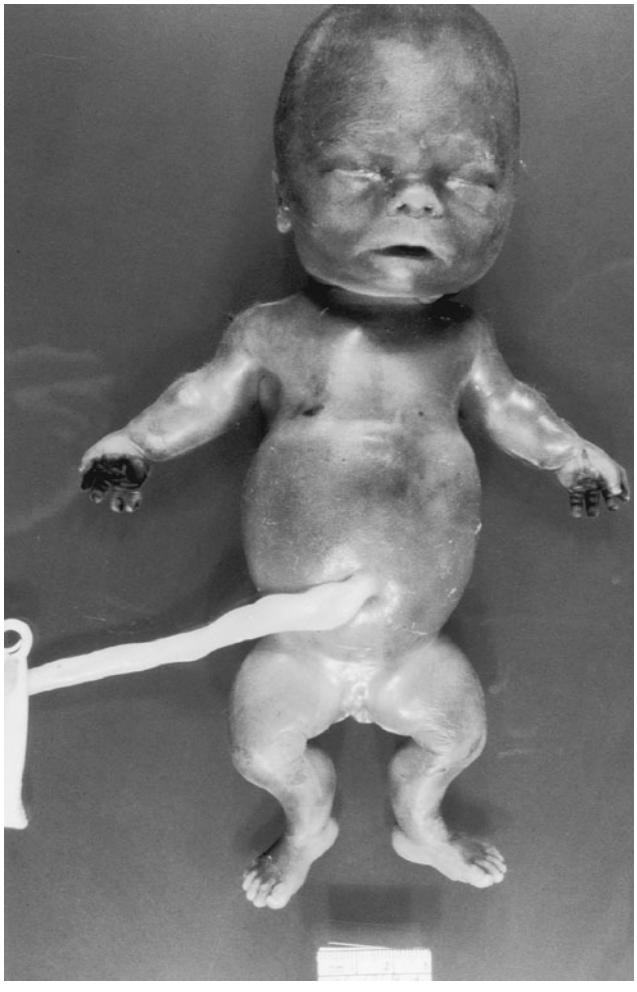

Figure 90-1 Fetus at 21 weeks of gestation with thanatophoric dysplasia, demonstrating severe micromelia, narrow chest, and prominent abdomen. (*Courtesy of Dr. Joseph Semple.*)

FGFR3 expression are in the skeleton and the central nervous system (Tavormina et al., 1995).

Mutations in FGFR3 are also the underlying basis for achondroplasia (Bonaventure et al., 1996) (see Chapter 89). Both TD and achondroplasia exhibit poor cellular proliferation in the growth plate of the long bone, although heterozygous achondroplasia is clinically less severe than TD. It is of interest that patients with homozygous achondroplasia manifest a more severe clinical phenotype than patients with heterozygous achondroplasia. The features in homozygous achondroplasia clearly resemble TD and result in neonatal lethality (Tavormina et al., 1995).

INCIDENCE

The incidence of TD ranges from 0.27 in 10,000 to 0.4 in 10,000 livebirths (Martínez-Frías et al., 1988; Rasmussen et al., 1996). In a large series of 126,000 deliveries occurring at one institution, TD was the most common osteochondrodysplasia observed (Rasmussen et al., 1996).

In individuals affected with TD, the mean paternal age is elevated as compared with unaffected controls (Martínez-Frías et al., 1988; Orioli et al., 1995). In 50% of cases of TD, the father is >35 years of age (Orioli et al., 1995). There is approximately a threefold increased risk for having a fetus with TD when the father is between the ages of 35 and 39 (Martínez-Frías et al., 1988).

To date, most cases of TD have occurred sporadically. The small number of familial cases reported reveals a paucity of well-documented sibling pairs, except in the case of monozygous twins. There is no evidence for parental consanguinity in affected fetuses (Martínez-Frías et al., 1988).

SONOGRAPHIC FINDINGS

The sonographic findings in cases affected by TD include severe micromelia with limited limb mobility and narrow chest (Figure 90-2A to 90-2C). Although the femur is classically described as curved and resembling a telephone receiver (Figure 90-3), affected fetuses can also have straight femurs. Additional sonographic findings include short, broad ribs, a narrowed chest circumference with consequent pulmonary hypoplasia, and hypoplastic vertebral bodies. The pelvic bones are characteristically small. Polyhydramnios is frequently present (Burrows et al., 1984; Stamm et al., 1987). In one report, an associated cardiac abnormality consisting of an atrioseptal defect and a bicuspid aortic valve was also described (Isaacson et al., 1983).

The *kleeblattschädel* (cloverleaf) deformity was first described in 1960 (Holtermüller and Wiedemann, 1960). This cloverleaf shape of the skull is due to early fusion of the lambdoidal and coronal sutures. This results in a towering calvarium and lateral bulges of the temporal lobes, which form three leaves of the cloverleaf when the head is viewed from the face (Figure 90-4). Because the lambdoidal and coronal sutures are fused, subsequent brain growth results in bulging in the regions of least resistance (Isaacson et al., 1983). The cloverleaf skull is present in only 14% of cases of TD (Iannaccone and Gerlini, 1974). Hydrocephalus is frequently associated with the cloverleaf skull (Shaff et al., 1980; Isaacson et al., 1983). To diagnose the cloverleaf skull deformity, a coronal scan that shows the temporal lobes is recommended (Stamm et al., 1987).

In the literature, multiple reports exist of the second trimester diagnosis of TD on the basis of the severe micromelia (Camera et al., 1984; de Elejalde and de Elejalde, 1985; Loong, 1987; Meizner et al., 1990; Schild et al., 1996). More recent studies report on the molecular diagnostic findings as well (De Biasio et al., 2000; Chen et al., 2001). These reports all describe fetuses with a long bone length of less than the third percentile for gestational age, an extremely narrow chest, a protruberant abdomen, and vertebral bodies of reduced height.

First trimester diagnosis has also been reported (Benacerraf et al., 1988). Benacerraf et al. described a

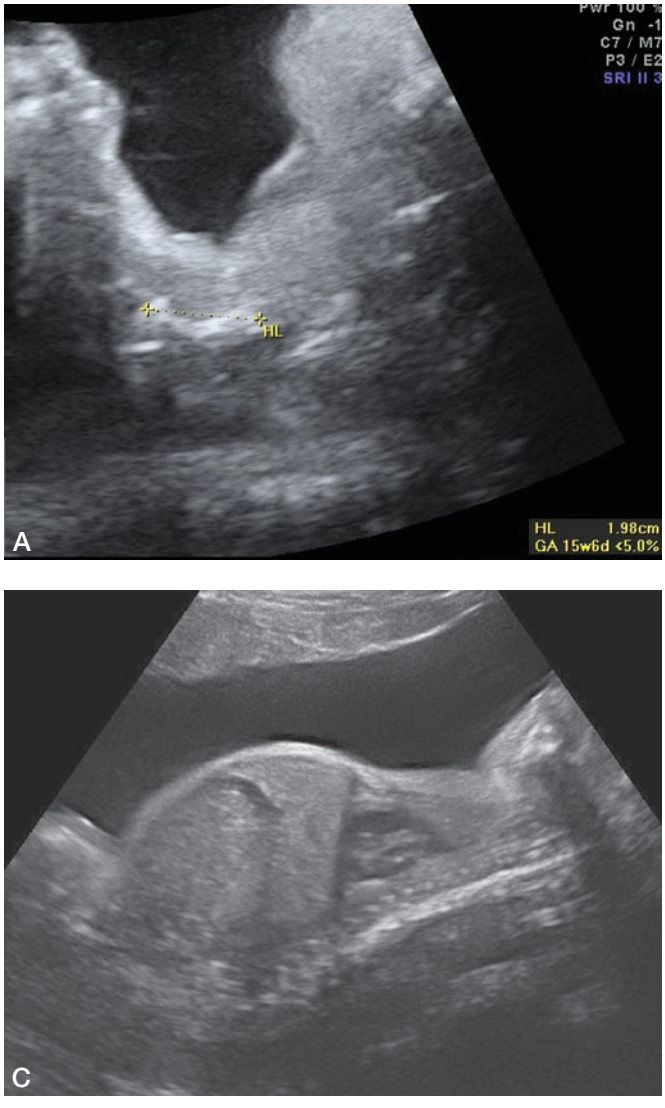

Figure 90-2 Prenatal ultrasound images of a 30-week fetus with thanatophoric dysplasia. (**A**) demonstrates short curved humerus (15-week size); (**B**) demonstrates 15-week size radius and ulna; (**C**) shows sagittal view of narrow chest with normal abdomen.

13-week-old fetus with a narrow chest and foreshortened and bowed femurs. A repeat sonographic examination performed at 15 weeks again demonstrated the abnormalities. The pregnancy was electively terminated. In contrast, another group has described a fetus that appeared normal at 15 weeks of gestation and was subsequently diagnosed at 32 weeks of gestation with TD (Macken et al., 1991). Three-dimensional sonography is considered to be advantageous for evaluation of the midface hypoplasia that is seen in TD (Krakow et al., 2003).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes other skeletal dysplasias that manifest as severe micromelia, such as campomelic dysplasia (see Chapter 92), Ellis van–Creveld syndrome (see Chapter 94), and short-rib polydactyly syndrome (see Chapter 95). Polydactyly is absent in TD. In achondrogenesis, the bones are usually less mineralized than in TD.

The cloverleaf skull is occasionally mistaken for an encephalocele (Chervenak et al., 1983; Mahony et al., 1985; Weiner et al., 1986; Stamm et al., 1987). Any soft tissue bulge in the head or neck must be evaluated for its exact position. Encephalocele and cystic hygroma occur in the midline and most often are posterior. The cloverleaf skull is bilateral, with enlargement of the temporal lobes. The standard teaching that the skull is not intact in encephalocele is not helpful to distinguish between encephalocele and cloverleaf skull. This is because the bony calvarium may be expanded, thinned, or partially absent in the cloverleaf skull deformity, and conversely, in cases of encephalocele, the osseous defect in the skull may be very small (Stamm et al., 1987). A cloverleaf skull may also be noted in Apert, Carpenter, Crouzon, and Pfeiffer syndromes as well as in homozygous achondroplasia.

ANTENATAL NATURAL HISTORY

The underlying defect in TD is in the formation of bone from a cartilage model. There is generalized disruption and decrease

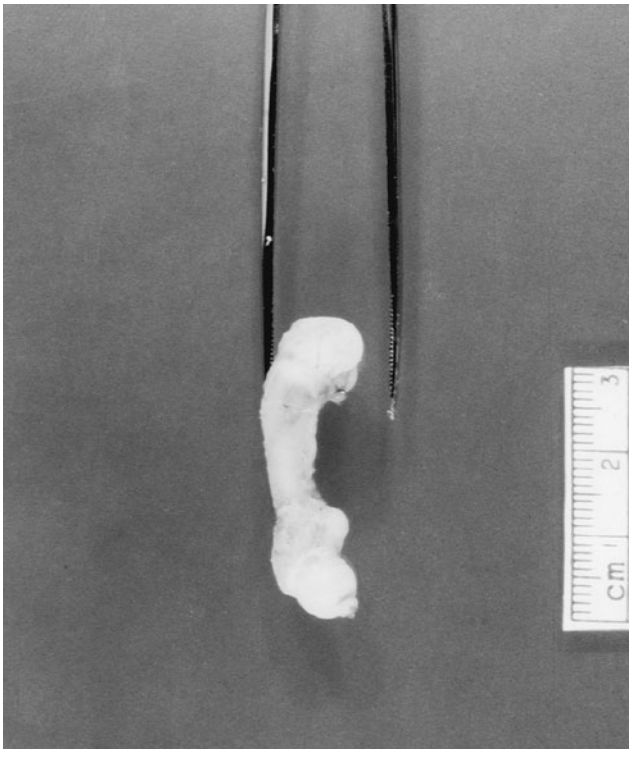

Figure 90-3 Postmortem photograph of an isolated femur from a fetus with thanatophoric dysplasia at 21 weeks of gestation, demonstrating its resemblance to a telephone receiver. (*Courtesy of Dr. Joseph Semple.*)

in endochondral ossification, with membranous ossification being less affected (Lemyre et al., 1999). Fetuses affected with TD show a progressive decrease in the growth rate of the long bones throughout gestation. While sometimes early in the second trimester, the femur length can be in the normal range, the bones become progressively shortened and curved (Burrows et al., 1984).

The function of *FGFR3* can be deduced from the *FGFR3* −/− knockout mouse, which is overgrown with excessively long femurs and elongated vertebrae (Cohen, 2002). The normal function of *FGFR3* is to regulate endochondral ossification by controlling growth. Mutations in FGFR3 result in abnormally early maturation of the skeletal and cranial bones (Cohen, 2002).

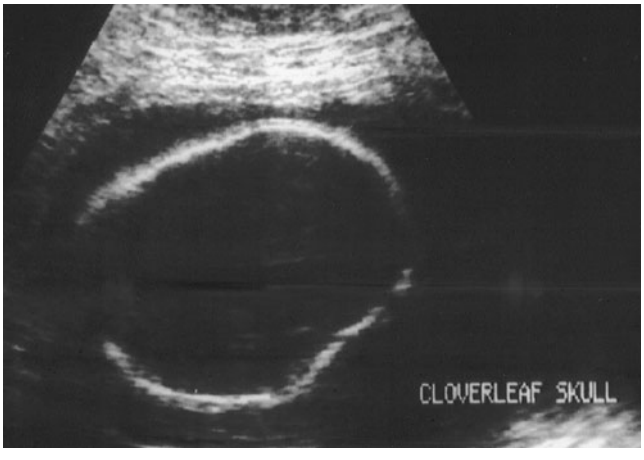

Figure 90-4 Antenatal sonogram demonstrating cloverleaf skull. (*Courtesy of Dr. Marjorie C. Treadwell.*)

The histologic abnormalities in TD include the presence of abnormal mineralizing tissue at the growth plate. In the region normally occupied by growth plate cartilage, cells and matrix have morphologic characteristics of epiphyseal cartilage, and the chondrocytes are not organized into columns or clusters. In addition, there are pyramidal areas of cartilage that resemble a shortened but normal growth plate, but the most characteristic finding is tufts of fibrous tissue scattered randomly along the growth plate. These have been termed "ossification tufts" (Horton et al., 1988). It is unclear whether these ossification tufts represent a primary phenomenon that disrupts endochondral bone growth or a secondary response to defective endochondral ossification. Marked abnormalities in endochondral and perichondral bone structures have been demonstrated by xeroradiography in a 20-week-old fetus (de Elejalde and de Elejalde, 1985).

Increasing evidence exists that the brain is seriously involved in patients affected with TD. This is not surprising given that *FGFR3* expression is very high in the developing central nervous system (Tavormina et al., 1995). In a neuropathologic study of seven affected individuals, Wongmongkolrit et al. (1983) reported that all brains in TD patients were larger than normal and demonstrated maldevelopment of the temporal lobes, characterized by extensive gyration and deep sulcation. The predominant findings were megencephaly, abnormal gyration, polymicrogyria in the temporal cortex, lateral displacement of the basal ganglia, reduced fiber tracts, and dysplasia of several nuclei. Ventricular dilation was present without evidence of obstruction. The most characteristic abnormality was the malformation of the temporal lobe with a pattern of disorganization that was distinctly different from any other condition. These investigators hypothesized that there was a relative vascular hypoperfusion of the developing temporal lobe, which resulted in polymicrogyria. In some cases, partial agenesis of the corpus callosum was also observed.

MANAGEMENT OF PREGNANCY

If it is suspected that a pregnant woman is carrying a fetus with a severe skeletal dysplasia such as TD, she should be evaluated at a center capable of performing a detailed fetal anatomic scan. Specific attention should be paid to measurement of the long bones and the chest circumference, as well as noting the presence or absence of polyhydramnios. There is no indication for a fetal karyotype, as the chromosomes are usually normal in TD. In addition, amniotic fluid α-fetoprotein and cholinesterase are also normal (de Elejalde and de Elejalde, 1985). However, an amniocentesis should be performed to obtain amniotic fluid cells for DNA analysis of

FGFR3, which will provide a definitive diagnosis (Sawai et al., 1999). If the diagnosis is made prior to 24 weeks of gestation, the parents should be counseled regarding the extremely poor prognosis and be given the opportunity to terminate the pregnancy. Pregnancies with fetuses with TD are frequently complicated by polyhydramnios, prematurity, malpresentation, and cephalopelvic disproportion. The presence of the cloverleaf deformity and hydrocephalus may necessitate cephalocentesis and assisted delivery. Vaginal breech deliveries are sometimes complicated by an extended short and rigid neck that may hinder the passage of the fetal head (Loong, 1987). A cesarean section may sometimes be necessary to safely deliver the fetus, although it will not alter the otherwise grim prognosis for fetal survival (Wongmongkolrit et al., 1983).

FETAL INTERVENTION

There are no fetal interventions for TD.

TREATMENT OF THE NEWBORN

Infants affected with TD uniformly experience respiratory distress at birth. Potential explanations for the respiratory distress include the narrow chest with associated pulmonary hypoplasia, abnormalities of the bronchial cartilage, compression of brainstem respiratory centers, and altered pulmonary phospholipids (Isaacson et al., 1983). If the diagnosis is known from antenatal studies, the parents may have the opportunity to request that no newborn resuscitation occurs.

Infants who are delivered with a severe skeletal dysplasia but without antenatal knowledge of the diagnosis may initially require resuscitation until a precise diagnosis can be made. A complete physical examination of the newborn is indicated, which will demonstrate the presence of a bulging forehead, prominent eyes, flattened nasal bridge, narrow chest, and severely shortened extremities (Figure 90-5). Radiographs should be obtained, which will show the severe micromelia and femurs possibly shaped like telephone receivers (Figure 90-6). The chest radiograph will also indicate the presence of short ribs, flat vertebral bodies that are H-shaped in the frontal projection, widened intervertebral disk spaces, a short pelvis with a small sacroiliac notch, and a possible cloverleaf skull deformity (Andersen, 1989). The most important differential radiologic features include the markedly flattened vertebral bodies with widened intervetebral spaces, the shortened bowed extremities, and the irregularly flared metaphyses (Campbell, 1971).

Once the diagnosis of TD has been confirmed, respiratory support may be electively withdrawn, given the nearly uniform neonatal lethality and poor outcome for the rare long-term survivors with this condition (MacDonald et al., 1989). If the diagnosis was not made prenatally, a postmortem skin biopsy should be performed, and a fibroblast line should be established to facilitate DNA mutation studies of the *FGFR3* gene to confirm the diagnosis.

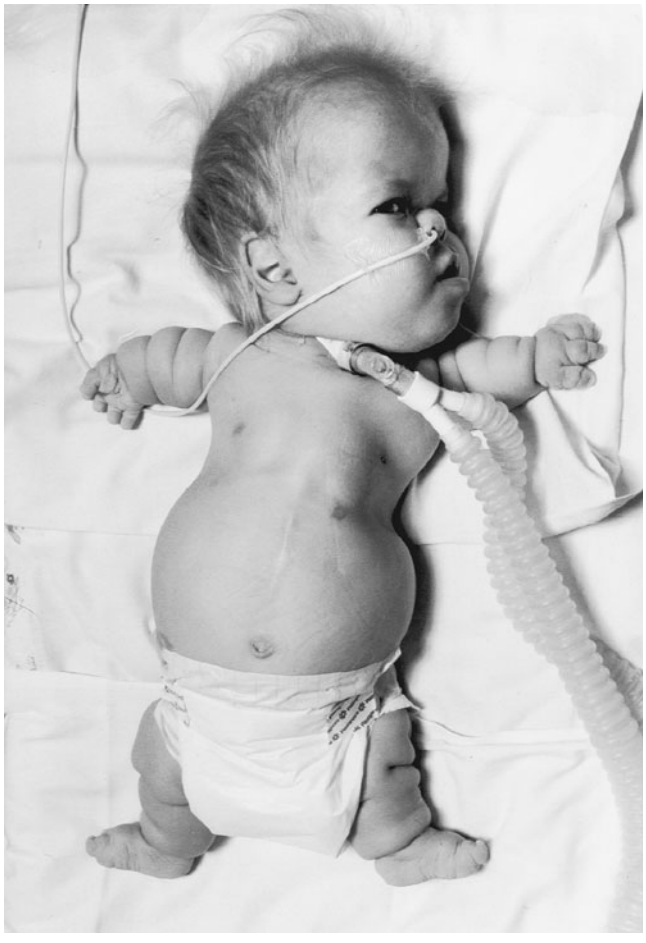

Figure 90-5 A long-term survivor with thanatophoric dysplasia. Note the placement of a tracheostomy tube. (*Reprinted, with permission, from MacDonald IM, Hunter AGW, MacLeod PM, MacMurray SB. Growth and development in thanatophoric dysplasia*. Am J Med Genet. *1989;33:508-512. Copyright 1989 Wiley-Liss. Reprinted, by permission, of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.*)

SURGICAL TREATMENT

Information exists on surgical treatment only for the extremely limited number of affected patients who survived past infancy. Affected infants eventually require tracheostomy for prolonged ventilatory support (see Figure 90-5), ventriculoperitoneal shunt for hydrocephalus, and foramen magnum decompression (MacDonald et al., 1989).

LONG-TERM OUTCOME

Several case reports discuss the longer survival of affected infants with TD due to modern neonatal care (Stensvold et al.,

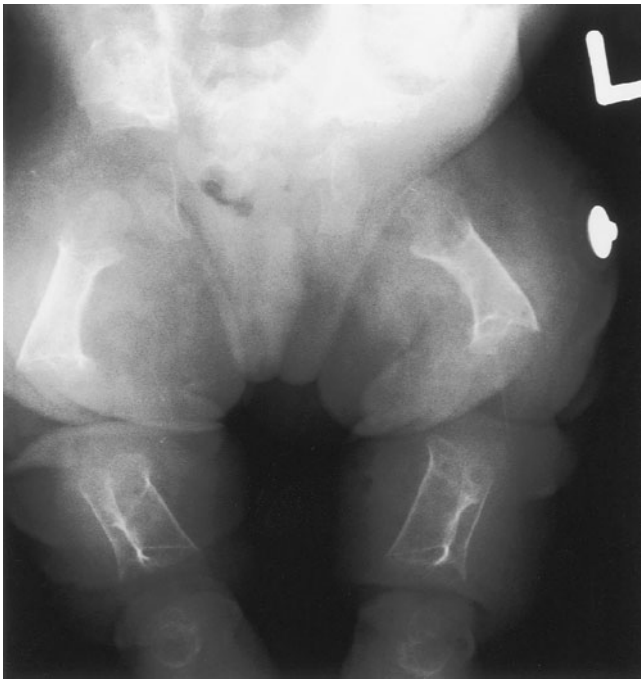

Figure 90-6 Postnatal radiograph of an affected infant demonstrating short tubular bones, metaphyseal widening, and spurs. (*Reprinted, with permission, from MacDonald IM, Hunter AGW, MacLeod PM, MacMurray SB. Growth and development in thanatophoric dysplasia.* Am J Med Genet. *1989;33:508-512. Copyright 1989 Wiley-Liss. Reprinted, by permission, of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.*)

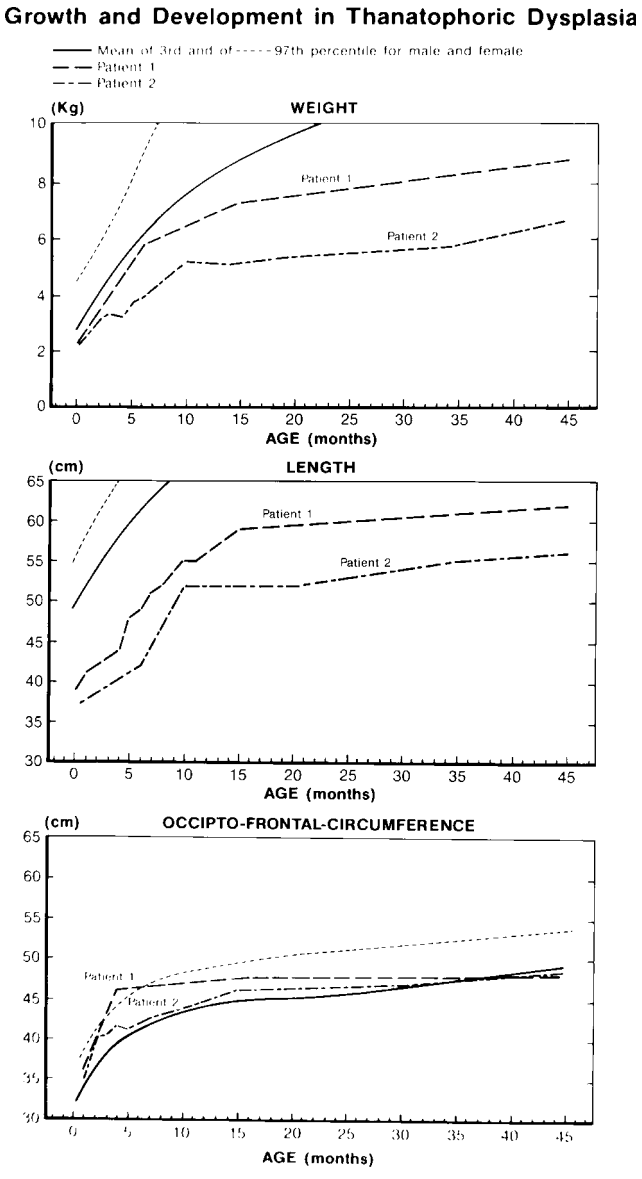

Figure 90-7 Growth curves of the two reported long-term survivors with thanatophoric dysplasia. (*Reprinted, with permission, from MacDonald IM, Hunter AGW, MacLeod PM, MacMurray SB. Growth and development in thanatophoric dysplasia.* Am J Med Genet. *1989;33:508-512. Copyright 1989 Wiley-Liss. Reprinted, by permission, of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.*)

1986; Tonoki, 1987; MacDonald et al., 1989). In one report, a female with TD who survived for 169 days was described. Her postnatal course was complicated by hypotonic muscles, absent reflexes, and increasing hydrocephalus. Eventually she required supplemental oxygen but died from respiratory failure (Stensvold et al., 1986). In another case report, a male was described who survived for 212 days. His delivery was by cesarean section and complicated by severe birth asphyxia. He required oxygen supplementation but was discharged from the hospital at 35 days of age. His neurologic development was normal until 4 months of age, when frequent apnea and cyanosis developed, which was questionably due to cord compression and a small foramen magnum. At 4 months of age, respiratory and cardiac failure developed and he required mechanical ventilation. He eventually died from respiratory failure secondary to pneumonia (Tonoki, 1987).

The most informative reports come from two cases of prolonged survival with TD. In both cases, ventilatory support was initiated due to respiratory distress of the newborn. Both patients eventually required ventriculoperitoneal shunts for hydrocephalus as well as decompression of the posterior fossa (MacDonald et al., 1989). The first patient survived to 5.2 years of age and was dependent on the ventilator. At age 4.75 years, development was estimated to be at the 2-week age level. At age 4.75 years, the patient weighed 8.82 kg (<3% for age), was 65 cm long (<3% for age), and had a head circumference of 47.5 cm (<3% for age) (Figure 90-7). By 10 months of age, growth of the long bones ceased. The femurs maintained their telephone-receiver appearance. An electroencephalogram in this patient initially revealed epileptiform activity, followed later by background disturbance. The computed tomographic scan revealed abnormal differentiation of gray and white matter in both hemispheres.

The second affected patient initially required 40% inspired oxygen and did not need mechanical ventilation. At 2 months of age, however, a respiratory infection developed and intubation and ventilation were required. There was a clinical question of brainstem compression, so a posterior

fossa decompression with laminectomy of the atlas and removal of the posterior third of bone around the foramen magnum occurred. At 4 months of age, the patient again required ventilatory support and a tracheostomy. Progressive hydrocephalus developed and a ventriculoperitoneal shunt was placed. After the placement of the ventriculoperitoneal shunt, the head circumference was <3% for age. At 3.7 years of age, the child could see and track objects, but had limited verbalization. This patient also manifested a prolonged period of nearly absent growth despite adequate nutrition.

On the basis of these two cases, these authors recommended that their long-term clinical experience with these two affected patients would "temper" their approach in the future (MacDonald et al., 1989).

GENETICS AND RECURRENCE RISK

TD is inherited as an autosomal dominant sporadic mutation with an extremely low risk of recurrence, most likely due to paternal gonadal mosaicism (Young et al., 1989). The chromosomes in affected patients have been normal, although one case has been described with a probably unrelated de novo 1:10 balanced translocation (Hersh et al., 1995). The disease is caused by missense mutations in the *FGFR3* gene, which maps to the short arm of chromosome 4 band 16.3 (McKusick et al., 1996). In addition to TD, five other diseases are due to mutations in *FGFR3* gene: achondroplasia (Chapter 89), hypochondroplasia, severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN), Muenke coronal craniosynostosis, and Crouzon syndrome with acanthosis nigricans (Bellus et al., 1999; Lemyre et al., 1999; Vajo et al., 2000) (see Chapter 10).

Several reports of TD have been described in monozygous twins (Young et al., 1989; Corsello et al., 1992). Monozygous twins have also been described who are discordant for the cloverleaf skull deformity (Horton et al., 1983; Corsello et al., 1992).

It is now known that there is a highly conserved genotype–phenotype correlation for the *FGFR3* mutations (Vajo et al., 2000). The subtype TD I consists of curved femurs with the variable presence of the skull deformity. To date all mutations identified in TD I result in a stop codon or missense mutation that creates a cysteine residue (Tavormina et al., 1995; Vajo et al., 2000). However, TD I is molecularly heterogenous. In contrast, in 95% of cases of TD II, there is a lysine-to-glutamine amino acid change at position 650 in the intracellular tyrosine kinase domain of *FGFR3* (Vajo et al., 2000). All individuals with this particular mutation have straight femurs and a severe cloverleaf skull deformity (Tavormina et al., 1995). Nested polymerase chain reaction primers have been designed for the rapid diagnosis of mutations. The mutations causing TD I and II are sporadic, as they were not seen in the parents who were tested (Tavormina et al., 1995). Of interest is that the manifestations of the disease are not simply due to heterozygous deletion of *FGFR3*, because a chromosomal abnormality syndrome, Wolf–Hirschhorn (4p-), does not result in a skeletal dysplasia. Thus, haploinsufficiency of the *FGFR3* gene is not the cause of TD.

Additional mutations have been documented in TD I. Rousseau et al. (1995) found three different base substitutions in the chain termination (stop codon) of the *FGFR3* gene in 5 of 15 TD I patients without a cloverleaf skull deformity. These mutations cause protein elongation, resulting in a highly hydrophobic domain with an α-helix structure at its C-terminal end. This possibly impairs signal transduction. In another report, 7 different sporadic mutations in three different protein domains have now been identified in 25 of 26 patients with TD I. No correlation exists between the position of the mutation and phenotypic or radiologic abnormalities. *FGFR3* mutations in the extracellular receptor create new unpaired cysteine residues (Bonaventure et al., 1996). Review of 91 cases from the International Skeletal Dysplasia registry at Cedars-Sinai Hospital in Los Angeles revealed that every case of TD had an identifiable *FGFR3* mutation (Wilcox et al., 1998). Although the recurrence risk is likely to be extremely small, prenatal diagnosis to reduce anxiety is characteristically performed by sonography with occasional supplementation by radiography. For families who have had a previously affected infant in which the *FGFR3* mutation was identified, definitive molecular prenatal diagnosis can be performed as early as 10 weeks by chorionic villus sampling.

Parents who have an affected fetus with TD may find comfort in an article written by a parent whose son was born with TD and survived for 3 months in a newborn intensive care unit (Stabosz, 1985).

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Osteogenesis Imperfecta

91 CHAPTER

Key Points

- Clinically and genetically heterogeneous disorder manifested by bone fragility and low bone mass.
- Seven distinct subtypes exist. Severity is as follows: type II > type III > types IV = V = VI = VII > type I.
- Most cases that present prenatally are types II or III. Only 10% of fetuses with type I have fractures in utero.
- Other findings include blue sclerae, abnormal teeth, joint hyperlaxity, adult-onset hearing loss, and normal intelligence.
- Prenatal sonographic findings include long bone fractures with callus formation, limb shortening, poor mineralization of the skull, and bent femurs.
- Differential diagnosis includes campomelic dysplasia, hypophosphatasia, and achondrogenesis.
- In 90% of cases there is a mutation in one of the genes that codes for type I procollagen, *COL1A1* or *COL1A2*.
- Most cases are dominantly inherited. If parents are asymptomatic there is a 7% recurrence risk due to the surprisingly high incidence of gonadal mosaicism.

CONDITION

Osteogenesis imperfecta is a clinically and genetically heterogeneous disorder of connective tissue, manifested by bone fragility and low bone mass. Affected patients have blue sclerae, hearing abnormalities, defective dentition, hyperlaxity of the joints, and normal intelligence (Brons et al., 1988). The majority of affected individuals are heterozygous for mutations of the *COL1A1* or *COL1A2* gene, which alters the structure of type I procollagen (Cole and Dalgleish, 1995).

Osteogenesis imperfecta was originally classified into four clinically distinct disorders that were first delineated by Sillence et al. (1979), and modified by Rauch and Glorieux (2004) (Table 91-1). Type I is the common mild form, type II is the perinatal lethal form, type III is the severe form, and type IV is the moderately clinically severe form (Cole and Dalgleish, 1995). More recently, an additional three types (V, VI, and VII) have been described (Rauch and Glorieux, 2004). The clinical severity of OI is type II > type III > types IV = V = VI = VII > type I.

Type I is a form of dominantly inherited osteoporosis that leads to fractures. Affected patients have distinctly blue sclerae and between 35% and 50% have presenile conductive hearing loss or deafness. The earliest age of onset of hearing loss is 10 years, and 40% of affected adults eventually require hearing aids. Approximately one fifth of patients with type I osteogenesis imperfecta (OI) have kyphosis and scoliosis, although severe spinal curves are rarely seen. These patients also bruise easily. All patients with type I OI are able to walk independently. Type I is further subdivided into type IA, patients with normal teeth and type IB, patients who have dentinogenesis imperfecta. Only 10% of patients with type I OI have fractures that are identifiable at birth (Sillence, 1981). Patients affected with type I OI have a progressive loss of height due to platyspondyly and kyphosis. Birth weight and length are generally normal and short stature is of postnatal onset. These patients are also notable for a head size that appears large for height.

Patients with type II OI comprise the majority of cases detected pre- and post-natally. Type II has been further subdivided into types IIA, IIB, and IIC. In type IIA broad, crumpled femurs and continuous beading of the ribs are present. In addition, the patients are small for gestational age and have severe osteoporosis of the skull and face. In type IIB, there are minimal or no rib fractures present. Because the ribs are less severely affected, the chest configuration is more normal and the resulting respiratory distress is less severe. Type IIB

Table 91-1

Expanded Sillence Classification of Osteogenesis Imperfecta

Type	Clincal Severity	Typical Features	Typically Associated Mutations
I	Mild nondeforming osteogenesis imperfecta	Normal height or mild short stature; blue sclerae; no dentinogenesis imperfecta	Premature stop codon in *COL1A1*
II	Perinatal lethal	Multiple rib and long bone fractures at birth; pronounced deformities; broad long bones; low density of skull bones on radiographs; dark sclerae	Glycine substitutions in *COL1A1* or *COL1A2*
III	Severely deforming	Very short; triangular face; severe scoliosis; greyish sclerae; dentinogenesis imperfecta	Glycine substitutions in *COL1A1* or *COL1A2*
IV	Moderately deforming	Moderately short; mild-to-moderate scoliosis; greyish or white sclerae; dentinogenesis imperfecta	Glycine substitutions in *COL1A1* or *COL1A2*
V	Moderately deforming	Mild-to-moderate short stature; dislocation of radial head; mineralized interosseous membrane; hyperplastic callus; white sclerae; no dentinogenesis imperfecta	Unknown
VI	Moderately to severely deforming	Moderately short; scoliosis; accumulation of osteoid in bone tissue; fish-scale pattern of bone lamellation; white sclerae; no dentinogenesis imperfecta	Unknown
VII	Moderately deforming	Mild short stature; short humeri and femora; coxa vara; white sclerae; no dentinogenesis imperfecta	Unknown

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is the only form with potential postnatal survival. In type IIC there are thin femurs and ribs with extensive fractures. In this form, the fetuses are very small for gestational age and severe osteopenia is present. However, many investigators state that distinction between the subgroups of type II is of limited value because all fetuses and infants with OI type II die during the perinatal period.

Type III is a rare form of OI, characterized by marked fragility and fractures of the long bones and skull, which are sometimes present at birth (Sillence et al., 1986). In utero, the defect in ossification of the skull is not as marked as it is in Type II. Posnatally, there are spine and long bone fractures, which result in progressive short stature and kyphoscoliosis. Although blue sclerae are present at birth, they fade with time. Hearing impairment is rare in type III OI. Affected patients have a triangle-shaped face with a wide bitemporal diameter. These patients are among the smallest of adults with OI. They have considerable difficulty walking. They suffer from multiple pulmonary complications.

Type IV is a dominantly inherited form of osteoporosis that leads to fractures. Variable deformity of the long bones exists, but affected patients have normal sclerae. There are no associated hearing abnormalites. Type IV has been further subdivided into IVA and IVB. In type IVA there is normal dentition and in IVB there is dentinogenesis imperfecta. To date, types V, VI and VII have not been associated with a specific prenatal presentation. All are associated with bone fragility, but none are known to be caused by mutations in *COL1A1* or *COL1A2*. Patients with Type V OI have hypertrophic callus formation at fracture sites, calcification of the interosseous membranes between bones of the forearm, and a radio-opaque metaphyseal band adjacent to the growth plates. The distinctive feature of type VI OI is the histologic appearance of bone lamellae that resemble fish scales. Patients with type VI OI also accumulate excessive osteoid. Type VII OI is inherited in an autosomal recessive pattern, and it is characterized by proximal shortening of the humerus and femur (Roughley et al., 2003).

INCIDENCE

The incidence of type I OI is 1 in 28,500 livebirths, while type II occurs in 1 in 62,000 livebirths and type III occurs in 1 in 68,800 livebirths (Sillence et al., 1979). In Sillence et al.'s original article, they did not quote an incidence for type IV OI (Sillence et al., 1979). Rasmussen et al. (1996) identifed 16 cases of OI among 126,316 deliveries that occurred over a 15-year period in a single teaching hospital. These authors estimated a prevalence (with exclusion of high-risk patients) of 0.24 in 10,000 deliveries of type II OI and 0.4 in 10,000 of types II and III OI combined. OI has been described in all ethnic groups (Sykes et al., 1986).

SONOGRAPHIC FINDINGS

The prenatal sonographic findings in OI are summarized in Table 91-2. The characteristic antenatal findings of OI include

Table 91-2

Prenatal Sonographic Findings in Osteogenesis Imperfecta (Listed in order of detection at earliest gestational age)

Type	Genetics	Clinical Findings	Ultrasound Findings	First Ultrasound Detection
OI II lethal perinatal	Autosomal dominant	Lethal perinatal type: Undermineralized skull, micromelic bones, "beaded" ribs on x-ray, bone deformity, platyspondyly	Undermineralization, broad crumpled and shortened limbs, thin beaded ribs, fractures, angulation or bowing of long bones, normal appearing hands, deformable calvarium	≥14 wks
OI III	Autosomal dominant	Progressively deforming type: Moderate deformity of limbs at birth, scleral hue varies, very short stature, dentinogenesis imperfecta (DI)	Thin ribs, short limbs, fractures, undermineralized skull, long bone length falls away from normal at 16–18 weeks	≥18 wks
OI IV	Autosomal dominant	Normal sclerae, mild/moderate limb deformity with fracture, variable short stature, DI, some hearing loss	Rarely, long bone bowing and/or fracture	After 20 wks but not common
OI I	Autosomal dominant	Fractures with little or no limb deformity, blue sclerae, normal stature, hearing loss, DI	Rarely, long bone bowing or fracture	>20 wks but not common
OI V	Autosomal dominant	Similar to OI IV plus calcification of interosseous membrane of forearm, radial head dislocation, hyperplastic callus formation	Unknown	Not described
OI VI	Unknown	More fractures than OI type IV, vertebral compression fractures, no DI	Unknown	Not described
OI VII	Autosomal recessive	Congenital fractures, blue sclerae, early deformity of legs, coxa vara, osteopenia	Unknown	Not described

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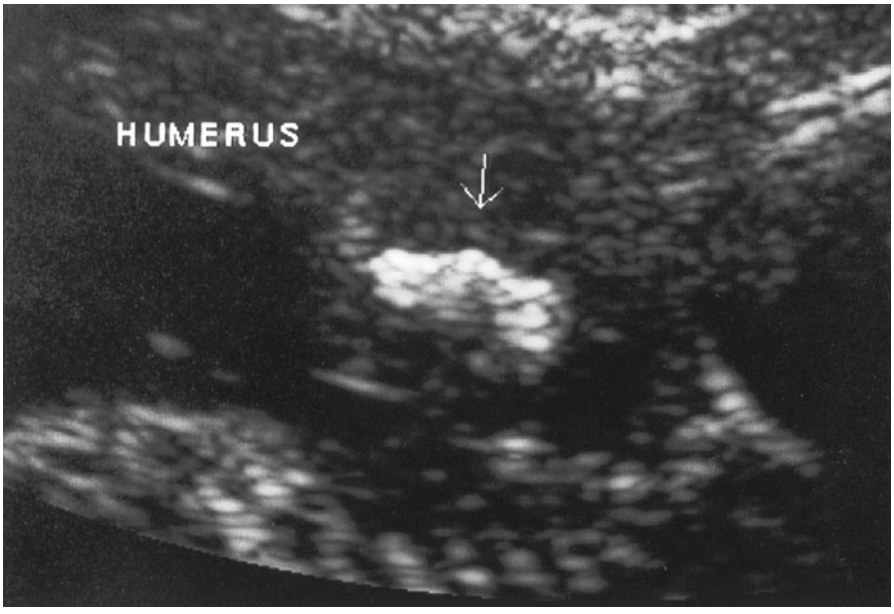

Figure 91-1 Sonographic image of an acutely angled humerus in a fetus with type II OI.

in utero fractures that occur with callus formation at the site of healing. These result in prenatally acquired long-bone deformities and significant limb shortening (Figure 91-1). Abnormalities of the fetal skull are the most striking findings in OI (Constantine et al., 1991). In addition, soft and fractured ribs contribute to a small thoracic circumference, which has been described as having a "champagne cork" appearance. The unusual clarity of intracranial structures is due to poor calvarial ossification (Figure 91-2). This has led to the term *supervisualization* (Andrews and Amparo, 1993). The compression of the fetal head by the ultrasound probe and the low echogenicity of the cranium should raise the suspicion of a skull dysplasia. However, this finding is not diagnostic for OI (Berge et al., 1995).

The following sonographic criteria have been proposed for type II OI: multiple fractures, demineralization of the calvarium, and a femoral length less than 3 SD below the mean for gestational age coupled with a wrinkled appearance of the long bones (Munoz et al., 1990). In a retrospective study of 459 fetuses and infants with bent femurs, 18.1% had OI (Alanay et al., 2007).

In the absence of a known family history of OI, most fetuses detected prenatally will have type II. The major diagnostic criteria for this type of OI include shortened deformed long bones, underossification of the cranial vault, which results in easily seen intracranial structures, an abnormal and varying skull shape, a small chest circumference with broad and irregular ribs (Figure 91-3), decreased fetal movements, and unusual fetal limb position (Constantine et al., 1991). In one case report, Morin et al. (1991) described a case of type IIA OI in one of dizygotic twins diagnosed at 27 weeks of gestation. In this report, the affected fetus was so translucent

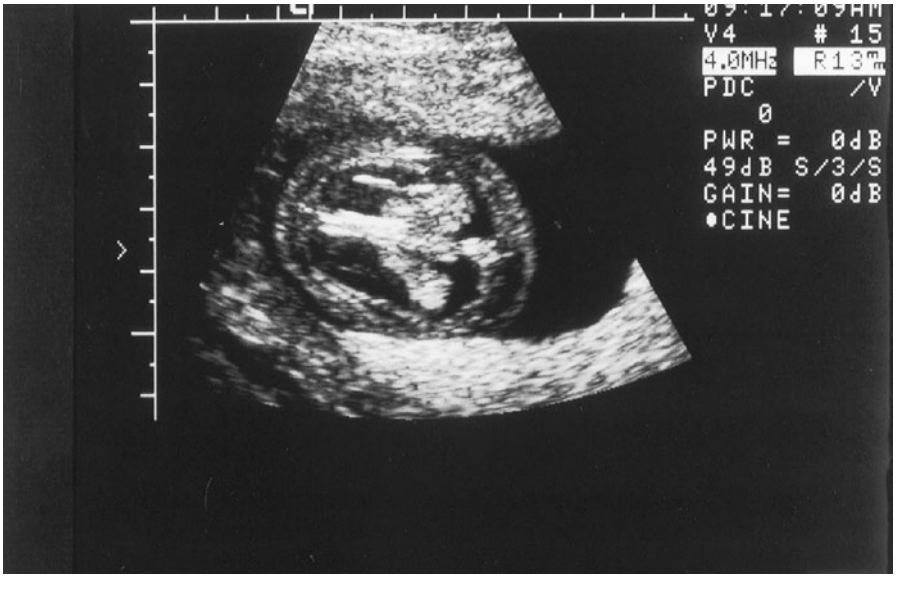

Figure 91-2 Cross-sectional view of a fetal head demonstrating significantly reduced skull ossification, resulting in unusually clear visualization of intracranial contents.

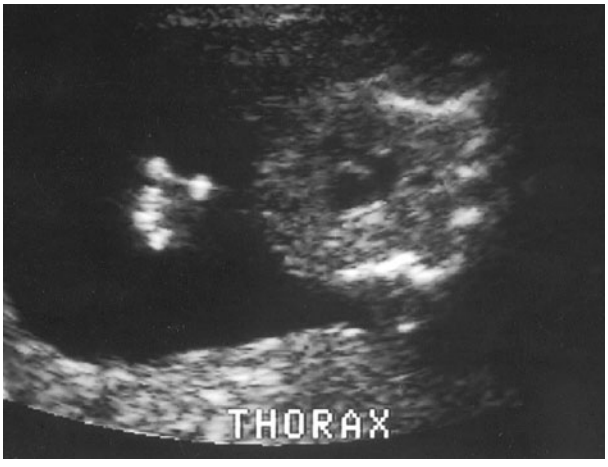

Figure 91-3 Cross-sectional view of fetal thorax, demonstrating small chest circumference with undermineralized, beaded, crumpled ribs.

that only one twin could be seen on a plain radiograph. In another case report, D'Ottavio et al. (1993) described a case of type II OI in the fetus of a woman at 14 weeks of gestation who underwent routine transvaginal ultrasonography. In this fetus, both femurs were short and severely angulated because of fractures. Even at this early point in gestation, the fetal skull was noted to be hypoechogenic, and an abnormal curvature of the right radius was present.

Prenatal diagnosis of OI types I and III is more difficult to make on a sonographic basis. Most of the cases described in the literature have been diagnosed in fetuses known to be at risk because of a positive family history. For example, Robinson et al. (1987) described a fetus at risk for type III OI that was followed with serial sonography. At 15 weeks of gestation, there was a low normal fetal femur length. By 20 and 22 weeks, however, shortening of the long bones and deformity of the femurs were noted. There was not an impressive decrease in ossification of the fetal skull. Several case reports of prenatal diagnosis of type I OI have appeared in families known to be at risk. Chervenak et al. (1982) described a fetus whose mother was affected with type I OI. This fetus had a normal sonographic examination at 20 weeks, but bowed femurs developed at 24 weeks. By 32 weeks of gestation, demineralization of the fetal skull was observed. No fractures were seen in utero, but a right femur fracture developed at 9 days of age, which was postulated to be due to the effect of intrauterine curvilinear stress on weakened bones.

Brons et al. (1988) reported on the sonographic diagnosis of OI in seven fetuses collected from the experience of three major teaching hospitals in the Netherlands. The gestational age at the time of scanning was between 15 and 34 weeks. The indications for sonography included large for gestational age (two fetuses), small for gestational age (two), previous child affected with OI (two), and routine anatomy scan (one). The biparietal diameter was normal in all seven. The abdominal circumference, however, was either normal or small for gestational age. In most cases, the chest circumference was narrow as compared with the abdominal circumference. The heart was noted to completely fill the chest. The limbs were the most severely shortened in type IIA OI. The prenatal diagnoses of types IIB, IIC, and III were made later in gestation than in type IIA (Brons et al., 1988).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes other causes of severe skeletal dysplasia and demineralization. Conditions that most resemble OI on prenatal sonographic examination include hypophosphatasia (see Chapter 98) due to demineralization of the skull, narrow chest circumference, and shortened extremities. Fetuses with hypophosphatasia generally do not have in utero fractures, but they can have bowing or angulation of the long bones (Pauli et al., 1999). The condition that seems to be most commonly confused prenatally with OI is campomelic dysplasia (see Chapter 92). Sanders et al. (1994) described three cases of OI that mimicked campomelic dyplasia and one case of campomelic dysplasia that was prenatally diagnosed as OI. The overlap between campomelic dysplasia and OI relates to the severe bowing of the limbs (Alanay et al., 2007) (see Figure 91-1). Tibial bowing is more pronounced in campomelic dysplasia, but some cases of severe nonlethal OI have tibial bowing without obvious fractures. Conversely, acute angulation of the femur seen in campomelic dysplasia can suggest a fracture. Cranial deformities, such as bossing, hypertelorism, and hydrocephalus can exist in both syndromes. The presence of arm fractures with callus formation, cranial compressibility with unusually clear visualization of the intracranial contents, and asymmetry in the length of the limbs favors a diagnosis of OI. The presence of clubfeet, micrognathia, and hydronephrosis favors the diagnosis of campomelic dysplasia (Sanders et al., 1994). Another condition that can closely resemble OI is achondrogenesis (see Chapter 97).

ANTENATAL NATURAL HISTORY

Two major biochemical phenotypes of OI exist: patients with normal stature and blue sclerae (type I) secrete half of the normal amount of a normal type I procollagen and do not have the presence of identifiable abnormal molecules. Patients with short stature and fractures (types II, III, and IV) produce and secrete both normal and abnormal type I procollagen molecules (Wenstrup et al., 1990) (Table 91-1).

The perinatal lethal form, type II OI, is the result of heterozygous mutations of the *COL1A1* and *COL1A2* genes that encode the α_1(I) and the α_2 (I) chains of type I collagen. These mutations act in a dominant negative manner because the mutant proα-chains are incorporated into type I procollagen molecules that also contain normal proα-chains. The

abnormal molecules that are poorly secreted are more susceptible to degradation and impair formation of the extracellular matrix. The collagen fibers are abnormally organized, and mineralization is impaired (Cole and Dalgleish, 1995).

Histologic and biochemical abnormalities in the dermis obtained from babies with type II OI demonstrate fibroblasts with a dilated rough endoplasmic reticulum due to impaired secretion of mutant type I procollagen molecules. The collagen fibrils are smaller than normal. There is a reduced amount of type I collagen and a mixture of normal and mutant type I collagen. The bone is severely porotic. The normal cortical and trabecular bone is replaced by woven bone. There is an abundance of plump osteoblast surrounded by small amounts of extracellular matrix. The osteoblast may contain dilated rough endoplasmic reticulum. The growth plate is normal but the cartilage cores persist in the trabeculae. The bone matrix is decreased in type I collagen and increased in types III and IV collagen.

These histologic findings suggest that the skeletal dyplasia in type II OI results from the action of muscular forces on a skeleton weakened by a complex disorder of endochondral and intramembraneous ossification. The paucity of primary metaphyseal trabeculae and subperiosteal cortical bone leads to pathologic fracture of the immature fiber bone and abnormal attempts at fracture repair (Marion et al., 1993).

MANAGEMENT OF PREGNANCY

The pregnant patient carrying a fetus in which OI is suspected should be referred to a tertiary care center capable of sophisticated anatomic diagnosis. The patient should meet with a medical geneticist or genetic counselor, who will obtain a detailed family history and a three generation pedigree. Specific questions should be asked regarding the height of first-degree family members, the presence of deafness, the color of the sclerae in family members, and whether there is a history of fractures. If previously affected infants have been born to the family, pathologic studies (if available) should be reviewed. However, most cases of affected fetuses will occur in the setting of a negative family history. Consideration should be given to obtaining a prenatal radiograph if the bones are not adequately visualized on a level II sonogram. For a presumed diagnosis of OI, there is no indication to obtain chromosomal analysis. Chorionic villi and amniotic fluid cells can serve as equally good sources of DNA for mutation analysis of the *COL1A1* and *COL1A2* genes. Amniocytes, however, synthesize inadequate amounts of type I procollagen, so they are not useful for prenatal biochemical diagnosis (Byers et al., 2006). In contrast, chorionic villi do synthesize adequate amounts of procollagen for biochemical analysis.

In the setting of a positive family history and a fetal presentation of skeletal dysplasia at earlier than 20 weeks of gestation, the presumed diagnosis is types II or III OI. In such cases, the poor prognosis should be discussed with the parents, who can be offered the opportunity to electively terminate the pregnancy.

In patients with a known family history of OI, prenatal sonographic and biochemical diagnoses are available. CVS should be offered for biochemical studies in types II, III, and IV. Prenatal diagnosis for type I OI is only accurate if the underlying familial DNA mutation is known. Note that prenatal sonography in fetuses at risk for type I OI can be normal, even when the fetus is affected.

Pregnant women who themselves are affected with type I OI are at risk for uterine rupture during a spontaneous vaginal delivery due to decreased amounts of collagen (Carlson and Harlass, 1993). Previous reports exist of dysfunctional platelet aggregation and prolonged bleeding times in women affected with type I OI. In addition, these patients can have a hypermetabolic state with hyperthermia due to abnormal oxidative metabolism. These women are at increased risk for developing malignant hyperthermia with general anesthesia for cesarean delivery. For affected mothers and fetuses with nonlethal types of OI, the goal is to provide a safe and atraumatic delivery for both mother and fetus.

In a review of 167 pregnancies affected by a fetal diagnosis of OI, Cubert et al. (2001) showed that cesarean section delivery did not decrease fracture rates at birth in infants with nonlethal forms, nor did it prolong survival in those with lethal types. Interestingly, there was an unusually high rate of breech presentation at term (37% of cases). Because of the maternal morbidity and mortality associated with cesarean section delivery, these authors suggested that operative delivery be reserved for standard obstetric indications such as breech presentation or fetal distress.

FETAL INTERVENTION

There has been at least one published report of a 32-week female fetus with OI that underwent transplantation with allogeneic HLA-mismatched male fetal mesenchymal stem cells (MSCs) (Le Blanc et al., 2005). In total, 6.5×10^6 fetal MSCs were injected into the umbilical vein and there were no post-procedural complications. Spontaneous rupture of the membranes occurred at 35 weeks. Delivery was by cesarean section. Postnatal radiography indicated multiple healed fractures and a new right femoral fracture, which was stabilized prior to discharge. Treatment with pamidronate was initiated at 4 months. At 9 months a bone biopsy showed regularly arranged bone trabeculae lined by a columnar layer of normal osteoblasts. FISH analysis was performed using centromeric X- and Y-chomosome specific probes. This showed that 0.3% of cells staining positive for osteopontin or osteocalcin were donor derived. At 2 years of age the patient was small, but had normal development. She had three fractures, but did not require any overnight hospitalization for treatment. This report was the first demonstration of donor MSC engraftment into an immunocompetent human fetus (Le Blanc et al., 2005).

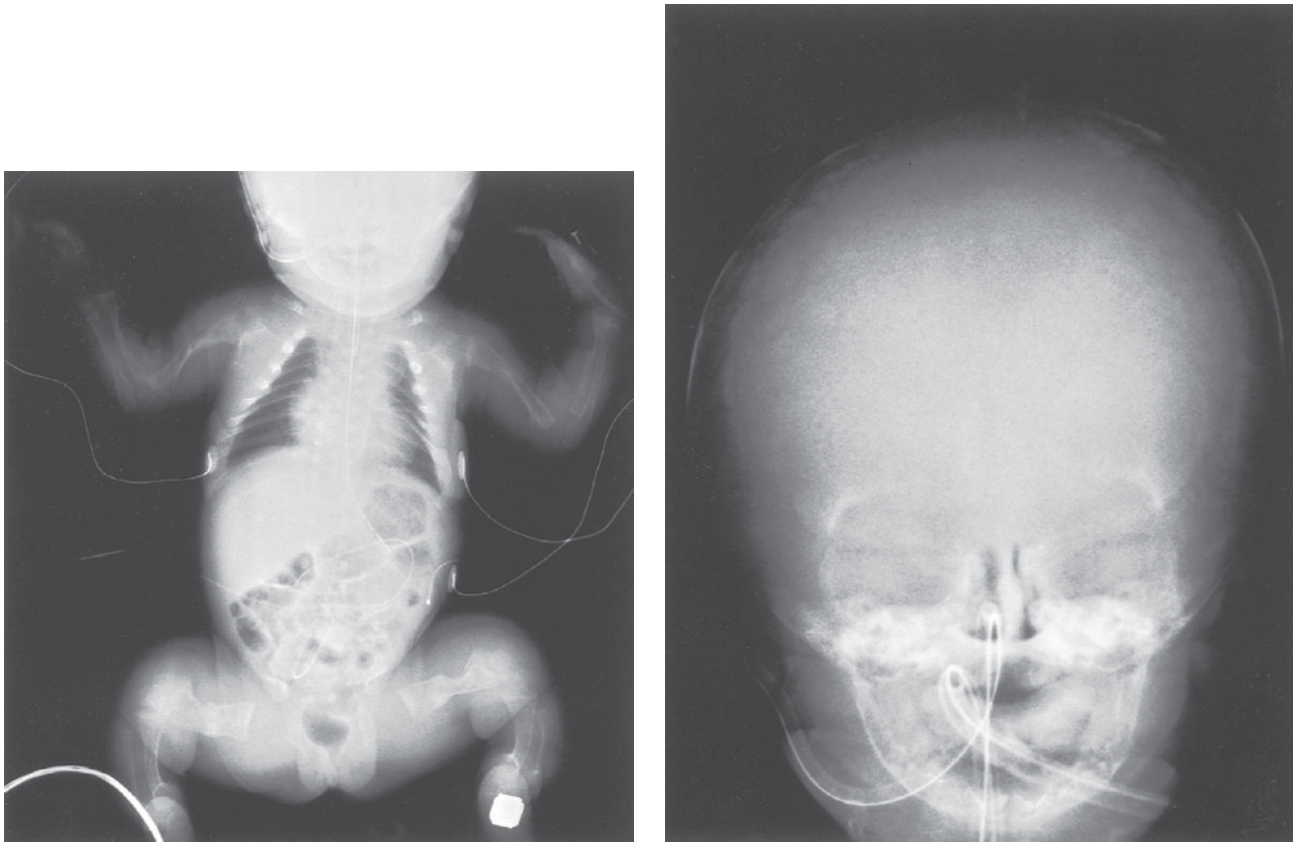

Figure 91-4 Postnatal radiographs of a newborn infant with type II OI. (*Left*) Multiple fractures are present in the long bones. The ribs are poorly mineralized. (*Right*) Close-up skull radiograph in same infant, demonstrating the lack of ossification that is characteristically observed in prenatal sonographic studies.

TREATMENT OF THE NEWBORN

The majority of newborns who present with fractures have type II OI. Postnatal radiography may aid in the determination of a definite diagnosis (Figure 91-4). The prognosis is poor for these infants, and the cause of death is usually secondary to respiratory difficulties associated with mechanical failure of the chest wall (Carlson and Harlass, 1993). Supportive care is indicated for infants likely to have type II OI. A skin biopsy should be obtained for definitive biochemical and/or DNA analysis. A fibroblast culture can be sent to a referral laboratory for analysis of quantity and quality of type I collagen chains.

For infants with nonlethal forms of OI, the mainstays of therapy are physical therapy, rehabilitation, and orthopedic surgery. These infants are likely to benefit from specific exercise, bracing, and ambulation training (Binder et al., 1993). Only routine hearing screening is recommended, as the hearing abnormalities characteristic of type I OI do not develop until later childhood or early adulthood. Parents of affected newborns should be counseled that blue sclerae represent a change in physical appearance and do not affect visual acuity.

Infants who survive the newborn period may benefit from bisphosphonate treatment (Glorieux, 2007). Bisphosphonates are pyrophosphate analogs that inhibit osteoclast-mediated bone resorption. In response to bisphosphonate therapy, bone mass increases due to a relative increase in osteoblastic activity. The first large scale clinical trial of children with severe OI who were treated with intravenous pamidronate (1 mg/kg/d) for 3 consecutive days every 4-6 months was published in 1998 (Glorieux et al., 1998). More than 50% of the study population showed improved mobility, fracture incidence was reduced to 1.7 per year, and the mean annual increment in spinal bone density was 42%. These results were quickly validated by others (Astrom and Soderhall, 1998). Many studies have now shown that treatment increases bone mineral density by increasing cortical bone width and the number of trabeculae present (Roughley et al., 2003). Most important to the affected individuals is the fact that chronic bone pain decreases with treatment. This permits increased mobility and improvement in muscle strenth. Several hundred patients have received bisphosphonate therapy for periods of up to 7 years and it is now considered to be standard care for children with moderate to severe OI (Glorieux, 2007). No benefits have been established for mild cases in which negative effects, such as

decrease in bone remodeling rate, reduction in growth plate cartilage resorption, and delay in osteotomy site healing may outweigh any positive effects. Bisphosphonates also stay in bone for many years following treatment. Although there is potential concern about teratogenic effects in fetuses of treated women with OI, at least one report describing two babies of two pregnant women with types I and IV OI did not show any skeletal modeling abnormalites consistent with in utero pamidronate exposure (Munns et al., 2004). Still unanswered questions regarding bisphosphonate treatment include criteria used to start treatment, optimal length of treatment, duration of treatment effect, dose and frequency of administration, and criteria for discontinuing treatment (Shaw and Bishop, 2005).

It is important to realize that bisphosphonate therapy does not cure OI. Alternative approaches include cellular therapy, such as bone marrow (Horwitz et al., 2002) or mesenchymal stem cell transplantation (Le Blanc et al., 2005), as well as ex vivo gene therapy (Chamberlain et al., 2004).

SURGICAL TREATMENT

The orthopedic manifestations of the nonlethal forms of OI consist of bone fragility, with resulting fractures, deformity, and scoliosis. When these fractures occcur, the bones heal with callus formation and a successive slight malalignment. Repetitive fractures of the same bone may lead to a significant deformity. Eventually, decreased range of motion of the joints and contractures can occur. Fractures are treated with immobilization or intramedullary rodding, which consists of a surgical insertion of a pin into the long bones to stabilize them. Scoliosis occurs in 30% to 70% of patients with OI. This requires body bracing with jackets that prevent progression of the curve.

Stabilization of the long bones in affected patients may help gross motor devlopment (Engelbert et al., 1995). In one study, the gross motor development of 10 children with type III OI was retrospectively studied. All patients were noted to have a severe delay in gross motor development. Interestingly, the sequence of achieving developmental milestones was different as compared with normal individuals. The static milestones, such as complete head control and sitting without support, developed earlier in patients with OI than the dynamic milestones, such as lifting the head in the prone position and rolling over from supine to prone. These authors hypothesize that affected infants protect themselves from developing fractures. They compared the gross motor development in their patients as a function of when they received intramedullary rodding. They found that the patients who underwent intramedullary rodding of the lower extremities before the age of 3.5 years had better neuromotor development. They recommended that before being considered for surgery, affected individuals should be able to sit unsupported. In this series, the median age of achievement of this milestone was 2.1 years. The recommendation, therefore, was that intramedullary rodding should be performed between 2 and 3.5 years of age to permit improved long-term ambulation (Engelbert et al., 1995).

LONG-TERM OUTCOME

Type I OI is the only type in which blue sclerae remain present throughout life. All types of OI put the patient at risk for fractures and scoliosis. The scoliosis may result in decreased cardiopulmonary reserve and predisposition to recurrent respiratory infections. Patients who have dentinogenesis imperfecta have abnormal dentin. The enamel is unable to adhere adequately and chips and erodes easily. Although the teeth are abnormal in appearance, the incidence of dental caries is not increased (Varni and Jaffe, 1984). Presenile hearing loss may develop in early adulthood in patients with type I OI. This is a conductive hearing loss due to the stapes being partially replaced by fibrous tissue.

Patients affected with OI also have an increased incidence of inguinal and umbilical hernias. Hypercalciuria is a common finding that correlates with the severity of the skull disease; renal function and postnatal renal sonographic studies are otherwise normal (Chines et al., 1995).

Paterson et al. (1996) reviewed the life expectancy for 743 patients with OI. Patients with type II, the perinatal lethal form, were excluded from the study. Their patient population included 383 patients with type IA, 77 with type IB, 123 with type III, 90 with type IVA, and 70 with type IVB. Patients with type IA OI had no difference in mortality from the general population. Types IB, IVA, and IVB had a modestly reduced life expectancy as compared with the normal population. Only patients with type III had significant impairment in their life expectancy. Of the 26 deaths reviewed in this study, 19 occurred before the age of 10 years. In a follow-up study, McAllion and Paterson (1996) reviewed 79 causes of deaths in patients affected with OI. Of the 79, 46 were due to respiratory causes and these occurred mainly in patients affected with type III. The respiratory deaths were primarily due to infection, and cardiac failure resulted from kyphoscoliosis. Other causes of death that were directly or indirectly due to OI included basilar invagination of the skull and lethal intracranial bleeding. These authors stress the importance of obtaining prompt care for respiratory infections and prevention of head trauma in affected patients.

GENETICS AND RECURRENCE RISK

In about 90% of cases of OI there is a mutation in either *COL1A1* or *COL1A2* (Byers et al., 2006). The loci *COL1A1* (α_1-chain) and *COL1A2* (α_2-chain) have been mapped to human chromosomes 17 and 7, respectively (Sykes et al., 1986).

The severity of the clinical phenotype is related to the type of mutation, its location on the α-chain, the surrounding amino acid sequences, and the level of expression of the

mutant allele (Cole and Dalgleish, 1995). Point mutations resulting in a substitution of Gly residues in Gly-X-Y amino acid triplets of the triple helical domain of the α_1(I) or α_2 (I) chains are the most frequent mutations. They interrupt the repetitive Gly-X-Y structure that is mandatory for formation of a stable triple helix.

Of affected individuals studied at the molecular level, it has been shown that most babies have their own private de novo mutation in type II OI. Few deletions have been identified. Exon skipping mutations are more common, which usually maintain the translational reading frame and the repetitive Gly-X-Y amino acid triplet structure. Deletions, skipping mutations, and insertions in triple helical domains produce abnormal alignment of the proα-chains. This interrupts the mandatory Gly-X-Y structure and may produce a bulge or a kink in the molecule (Cole and Dalgleish, 1995).

In type I OI, haploinsufficiency of *COL1A1* results in a 50% reduction of type I collagen. Most patients with type I have decreased mRNA levels of *COL1A1* (Willing et al., 1993). In types II, III, and IV there are dominant negative mutations that synthesize abnormal procollagen chains that bind to normal chains, thereby destroying their biologic activity. The dominant negative mutations are more harmful than the null mutations characteristic of type I OI. In fact, the goal of gene therapy is to degrade the mutant mRNA or disrupt the mutant gene to create essentially a null mutation. This would convert the more severe phenotypes seen in types II, III, and IV to a type I phenotype.

Most mutations associated with OI are dominantly inherited. Autosomal recessive phenotypes are rare, except in consanguinous families, and in type VII OI. Even with a negative family history, type II OI that results from an apparently new dominant mutation has an empiric recurrence risk of 7% (Byers et al., 1988). This risk increases significantly for unaffected parents after the diagnosis of a second affected fetus, because it identifies them as mosaic carriers of a mutant allele. Germline mosaicism for a mutation in one of the genes that encodes a chain of type I procollagen is surprisingly common. Both germline mosaicism and somatic mosaicism can occur (Sykes, 1990). In one report, a mutant allele was present in 80% of lymphocytes and 100% of skin fibroblasts of a parent of an affected child. Thus, the mutation must occur very early in embryonic development, before the somatic cell lines and germ cell lines segregate. In a prospective ascertainment of the recurrence risk for couples with one previous affected fetus for whom prenatal diagnostic studies were undertaken, only 1 in 50 pregnancies (2%) was affected (Pepin et al., 1997) (Table 91-3).

Prenatal diagnosis in subsequent pregnancies can be performed by sonography, biochemical, or molecular analysis. In type II OI, transvaginal sonography can readily detect abnormalities during the late first or early second trimester. If the molecular defect is unknown in a specific family, biochemical analysis of the collagen and procollagen molecules in fibroblasts obtained from chorionic villi sampling can provide first trimester prenatal diagnosis in types II, III, and IV OI (Pepin et al., 1997). Specific evidence can be sought of post-translational overmodification of the proα_1(I)-chains of type I procollagen. Cells from chorionic villi produce type I collagen chains with the same electrophoretic abnormalities as skin collagen (Grange et al., 1990). Chorionic villus sampling is the prenatal diagnosis method of choice for families with a positive history of types II, III, and IV OI. In pregnancies at risk for type I OI, identification of reduced amounts of type I collagen is inaccurate. Prenatal diagnosis of type I OI is best achieved by direct mutational analysis (Pepin et al., 1997).

The accuracy of prenatal diagnosis of OI is largely dependent on the prior study of an affected individual in a specific family (Pepin et al., 1997). Diagnostic information is usually available within 20 to 30 days of chorionic villus sampling using biochemical techniques and within 10 to 14 days when molecular analysis is utilized (Pepin et al., 1997).

Table 91-3

Prospectively Ascertained Recurrence Risk in 129 Prenatal Diagnoses of OI

	No. of Cases	Affected	Risk
Type I			
Affected parent	16	11	68%
Type II			
One prior affected fetus	50	1	2%
Two prior affected fetuses	7	2	28%
Type III or IV			
Affected parent	22	11	50%
One prior affected fetus	31	1	3%
Two prior affected fetuses	3	0	—

Source: Pepin M, Atkinson M, Starman BJ, Byers PH. Strategies and outcomes of prenatal diagnosis for osteogenesis imperfecta: a review of biochemical and molecular studies completed in 129 pregnancies. Prenat Diagn *1997;17:559-570.*

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Campomelic Dysplasia

92 CHAPTER

Key Points

- Distinct skeletal dysplasia characterized by bowing of the long bones of the lower extremity, phenotypic sex reversal, flat face, micrognathia, cleft palate, and renal and cardiac abnormalities.
- Incidence is 0.05 to 1.6 per 10,000 livebirths.
- Sonographic findings include acute femoral angulation, a small bell-shaped chest, and marked micrognathia.
- Differential diagnosis includes osteogenesis imperfecta type II, diastrophic dysplasia, Larsen syndrome, pelvis–shoulder dysplasia, and acampomelic campomelic dysplasia.
- Fetal karyotype is indicated to screen for chromosome 17 rearrangements, which have a better prognosis and to determine chromosomal gender.
- 72% of 46, XY fetuses have female genitalia.
- Delivery at a tertiary center is indicated.
- 95% of affected individuals die either in the perinatal period or during the first year of life.
- Long-term survivors have short stature, recurrent apnea and respiratory infections, progressive kyphoscoliosis, and developmental delay.
- Condition is caused by mutations in *SOX9*, an essential transcription factor in chondrogenesis.
- Campomelic dysplasia is inherited as an autosomal dominant. Rare reports of parent-to-child transmission exist.

CONDITION

Campomelic dysplasia is a distinct clinical and radiologic entity characterized by symmetric bowing of the long bones of the lower extremities, phenotypic sex reversal in some chromosomally male infants, and associated abnormalities including cleft palate, flat facies, micrognathia, hydrocephalus, and renal abnormalities. The term campomelia comes from the Greek *camptos*, meaning bent and *melos*, meaning limbs. Despite the name of the condition, campomelia is not obligatory for a diagnosis of campomelic dysplasia (Ninomiya et al., 1995). MacPherson et al. (1989) described two newborn infants with respiratory distress who demonstrated all of the clinical and radiologic manifestations of campomelic dysplasia except the bent lower extremities. This rare clinical variant is now known as acampomelic campomelia dysplasia (Thong et al., 2000). The various skeletal and extraskeletal manifestations of campomelic dysplasia, including sex reversal, are part of a contiguous gene syndrome that maps to chromosome 17 and is caused by mutations in the transcription factor, *SOX9*.

Classic campomelic dysplasia was first described by Maroteaux et al. (1971) and Bianchine et al. (1971) in independent reports. In a review of 43 affected patients, Hall and Spranger (1980) described four major radiologic features in patients with campomelic dysplasia: characteristic lower-limb bowing, absent or hypoplastic scapulas, nonmineralization of the thoracic pedicles, and narrow, vertical iliac bones (Figure 92-1A). They described other useful diagnostic features of the condition that included hypoplastic cervical vertebrae, widely spaced ischial bones, and absent ossification of the distal femoral and proximal tibial epiphyses. Khajavi et al. (1976) described campomelic dysplasia as a distinct entity consisting of short-limbed dwarfism with pretibial skin dimples, a peculiar facies, cleft palate, hypotonia, absent olfactory bulbs, and respiratory distress ending in neonatal death. These authors suggested that the condition could be classified into three varieties: a long-limbed type, a short-limbed type with craniosynostosis, and a short-limbed type with normocephaly. The long-limbed variety is considered to be the most common (Khajavi et al., 1976).

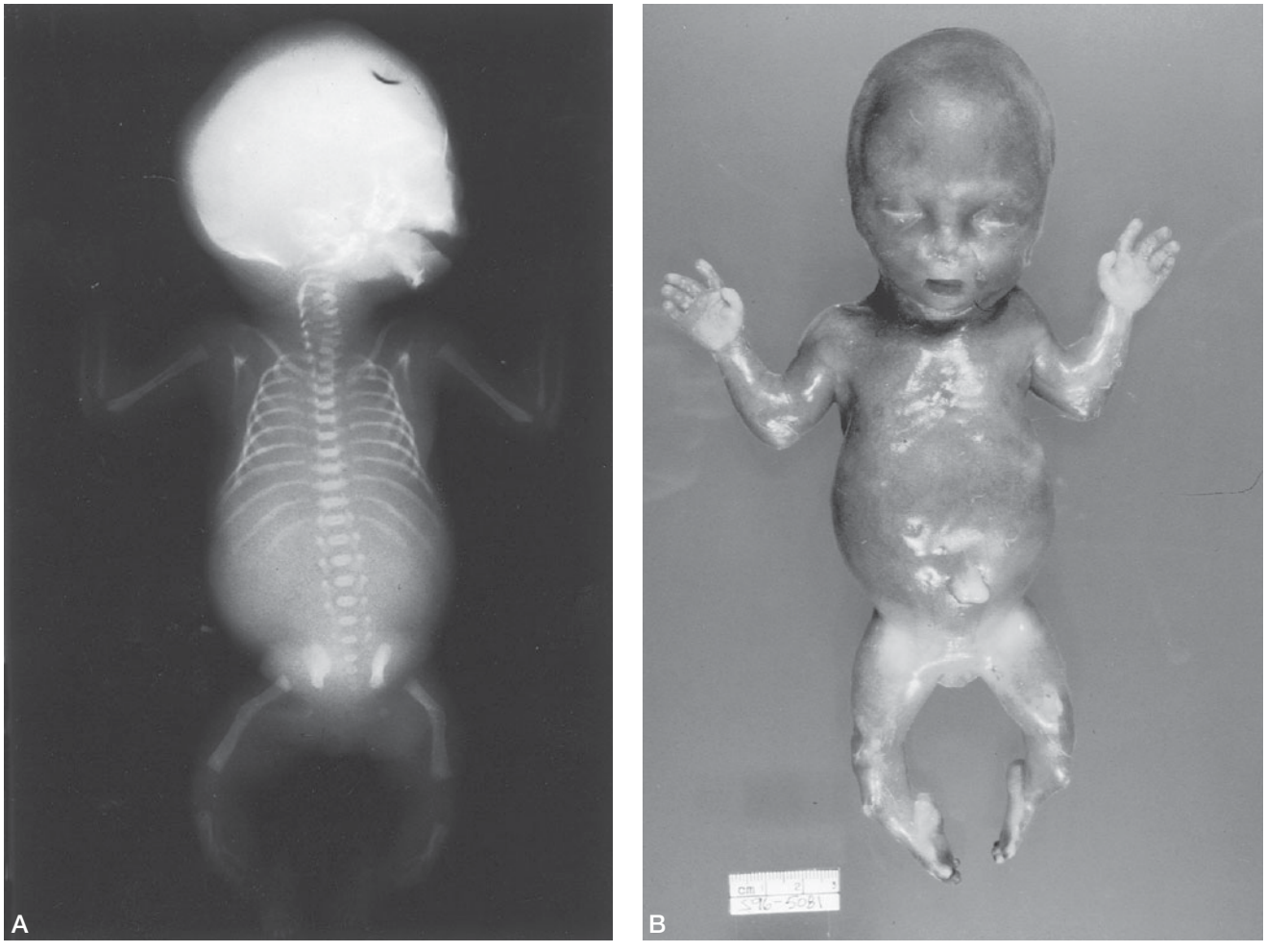

Figure 92-1 **A.** Postmortem radiograph obtained from a fetus with campomelic dysplasia at 18 to 19 weeks of gestation. Note the bilateral sharp angulation of the femurs, hypoplastic scapulas and narrow, vertical ischial bones. **B.** Postmortem appearance of the same fetus, showing characteristic hypoplastic midface, micrognathia, acute tibial angulation, and bilateral talipes equinovarus deformity.

A unique aspect of this condition is the phenotypic sex reversal. Over half of the apparently female infants have a male, XY, karyotype (Figure 92-2). In one study of 121 reported cases of campomelic dysplasia, 74 individuals had been karyotyped. Of these, 24 were 46, XX and phenotypically female. Of the remaining 50 who were 46, XY, 36 (72%) of them had normal female external genitalia, although a minority of them had some degree of ambiguity (Figure 92-3) (Foster et al., 1994).

Over the past few years, much progress has been made with regard to understanding the underlying molecular mechanisms in campomelic dysplasia. The chromosomal location of the gene has been mapped, the gene involved in the condition has been identified as *SOX9,* and the inheritance pattern has been clarified.

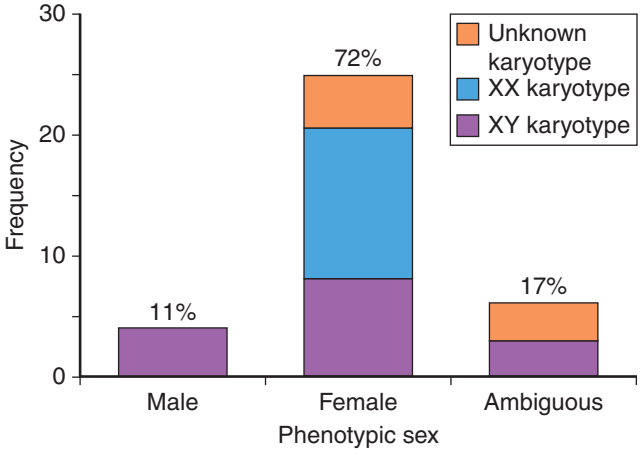

Figure 92-2 Association between phenotypic sex and karyotype in a population of individuals with campomelic dysplasia.

INCIDENCE

The incidence of campomelic dysplasia is 0.05 to 1.6 per 10,000 livebirths (Normann et al., 1993). There is no

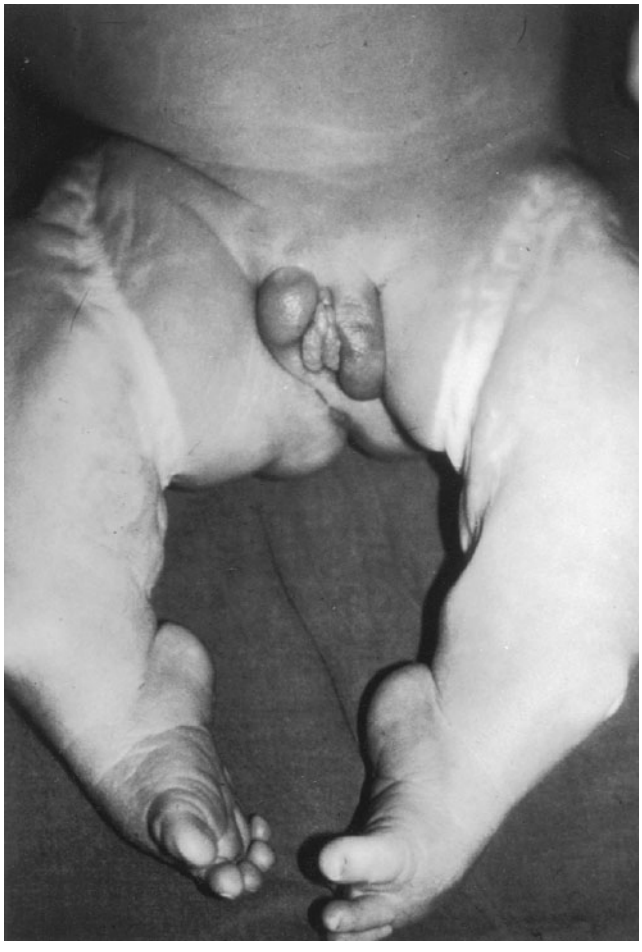

Figure 92-3 An affected infant with campomelic dysplasia, demonstrating skin dimpling over angulation of the femurs, prominent labia majora suggesting ambiguous genitalia, and bilateral clubfeet. *(Reprinted, with permission, from Mansour S, Hall CM, Pembrey ME, Young ID. A clinical and genetic study of campomelic dysplasia.* J Med Genet. *1995;32:415-420.)*

association between the incidence of campomelic dysplasia and advanced maternal or paternal age (Hall and Spranger, 1980; Mansour et al., 1995).

SONOGRAPHIC FINDINGS

Fetuses affected with campomelic dysplasia have a variety of anomalies. The most characteristic is the acute femoral angulation, which typically occurs at the junction of the upper third and lower third of both femora, with resulting symmetrical shortening (Figure 92-4). The femoral angulation is always anterior in the tibia and anterolateral in the femur (Pazzaglia and Beluffi, 1987). Other typical abnormalities include marked micrognathia, a small bell-shaped chest, mild bilateral hydronephrosis, hydrocephalus, cystic hygroma (Foster et al., 1994; Mansour et al., 1995), and clubfeet (Sanders et al., 1994) (Figure 92-1B). Polyhydramnios has been described in 25% to 48% of affected cases (Slater et al., 1985; Mansour et al., 1995). The associated hydrocephalus is thought to be due to atlanto-occipital occlusion (Deschamps et al., 1992). Approximately one fourth of patients may have associated cardiac malformations, which are always of the mild variety (Hall and Spranger, 1980; Mansour et al., 1995). The associated genitourinary anomalies may include hydronephrosis, hydroureter, renal hypoplasia, or renal cysts (Slater et al., 1985; Argaman et al., 1993). The association of hypoplastic scapulae, nonmineralized thoracic pedicles, and vertically narrow iliac bones is unique for this syndrome (Tongsong et al., 2000).

The first successful prenatal diagnoses for this condition occurred in families with a previously affected child. In 1981, Fryns et al. described such a family and successfully diagnosed recurrence of the campomelic dysplasia in a fetus with short, bowed limbs and hydrocephalus at 17 weeks of

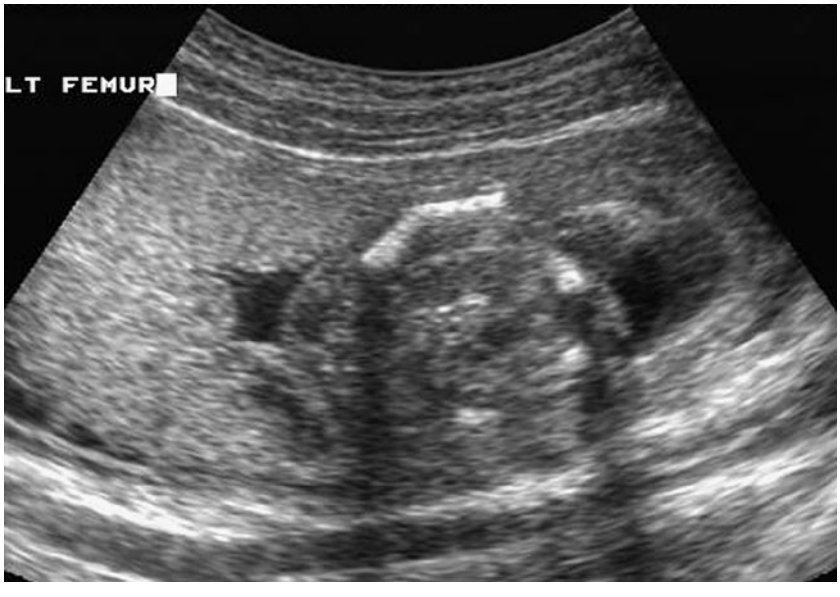

Figure 92-4 Sonographic image demonstrating typical femoral angulation seen in campomelic dysplasia. (*Image courtesy of Prenatal Diagnosis Center, Women and Infants' Hospital.*)

gestation. Sonographic examination revealed poorly ossified long tubular bones that were not bowed and massive hydrocephaly. At autopsy the infant was also shown to have a high forehead and micrognathia (Fryns et al., 1981). In families not at risk for campomelic dysplasia, affected infants have been identified by a discrepancy between upper- and lower-limb lengths (Gillerot et al., 1989). Cordone et al. (1989) described a fetus at 26 weeks of gestation with a normal amniotic fluid volume that demonstrated symmetrical anterior bowing of the lower extremities with hypoplasia of the fibulas and talipes equinovarus, hypoplastic scapulas, a bell-shaped chest, and facial abnormalities including a flat nasal bridge and micrognathia.

As in other skeletal dysplasias, an increased nuchal translucency measurement has been demonstrated at 13 weeks' gestation in a fetus that was subsequently shown to have campomelic dysplasia (Michel-Calemard et al., 2004). Three-dimensional ultrasound examination has aided in the diagnosis of campomelic dysplasia (Seow et al., 2004). Surface rendering 3-D studies demonstrate skin dimpling over a convex surface at the point of maximal deformity as well as the characteristic flat face and mid-facial hypoplasia.

DIFFERENTIAL DIAGNOSIS

A prenatal diagnostic overlap occurs between campomelic dysplasia and osteogenesis imperfecta type II (see Chapter 91). This is due to the presence of bowing in the lower limbs, which can be a manifestation of osteogenesis imperfecta. The tibial bowing, however, is more pronounced in campomelic dysplasia (Sanders et al., 1994). Campomelic dysplasia is also accompanied by mild bowing of the femurs. In one report, the authors described three cases of osteogenesis imperfecta in which tibial bowing was present without apparent fractures. They also described two cases of campomelic dysplasia misdiagnosed as osteogenesis imperfecta because the femurs showed an acute angulation that was suggestive of a fracture (Sanders et al., 1994). The presence of additional fetal anomalies – including clubfeet, micrognathia, and hydronephrosis – is more consistent with a diagnosis of campomelic dysplasia than osteogenesis imperfecta.

Other conditions that should be included in the differential diagnosis include diastrophic dysplasia (see Chapter 93). Both campomelic and diastrophic dysplasia share cervical vertebral anomalies, cleft palate, joint dislocations, bilateral talipes equinovarus, and laryngotracheal abnormalities, as well as abnormal ears, micrognathia, and brachydactyly (Hall and Spranger, 1980). Individuals with Larsen syndrome also manifest many of these abnormalities as well as a flat nasal bridge and apparent hypertelorism. Hall and Spranger (1980) recommended comparison of the scapulas, thoracic pedicles, and iliac bones to allow a specific diagnosis of campomelic dysplasia. The following major features of campomelic dysplasia occur with greater than 50% frequency in affected individuals: hypoplastic scapulas, nonmineralized thoracic pedicles, and vertically narrow iliac bones. These are rare findings when seen individually, but pathognomonic for campomelic dysplasia when found in combination (Hall and Spranger, 1980).

Other authors have indicated that in postnatal radiographs, scapular hypoplasia is the most consistent and unique feature. Potential overlap occurs between campomelic dysplasia and pelvis–shoulder dysplasia, which results in symmetric hypoplasia of the iliac wings and scapulas. In this condition, the iliac bones are small and square with flat acetabular roofs, which are different from the narrow iliac bones and steep acetabula of campomelic dysplasia. In pelvis–shoulder dysplasia, the lumbar vertebral bodies are rounded anteriorly, which gives them a bulletlike shape. Lordosis eventually develops in these patients. In campomelic dysplasia, however, the cervical and thoracic vertebral bodies are dysplastic, small, and flattened, and eventually result in development of a thoracic scoliosis. In the chest, the lack of ossification of the thoracic pedicles is the major feature of campomelic dysplasia (MacPherson et al., 1989).

ANTENATAL NATURAL HISTORY

Campomelic dysplasia is caused by mutations in *SOX9*, which is an essential transcription factor in chondrogenesis. It regulates expression of the type II collagen gene, *COL2A1*. In the absence of *SOX9,* there is a complete block in chondrocyte differentiation at the stage of mesenchymal condensation (Bi et al., 1999, 2001). Heterozygous *SOX9* mutant mice have many skeletal symptoms compared to that which are seen in human campomelic dysplasia, including bent bones (Bi et al., 2001). Premature mineralization occurs in many bones, including vertebrae and craniofacial bones. Two critical steps are sensitive to *SOX9* gene dosage: (1) early, at the stage of mesenchymal condensation of cartilage primordia, and (2) later at a step preceding the transition of chondrocytes into hypertrophic chondrocytes.

The various manifestations of campomelic dysplasia are associated with an increased incidence of stillbirth. It is thought that up to 50% of cases are lost during gestation (Slater et al., 1985).

Bone histology in infants affected with campomelic dysplasia suggests an ongoing repair process in the areas of angulation in the femur. New periosteal bone is laid down on the concave side, and remodeling of the mass of woven bone occurs. The process is similar to the healing of malaligned fractures. For most affected individuals, the growth plate cartilage and metaphyses appear normal (Pazzaglia and Beluffi, 1987). Other investigators have identified identical changes occurring in the bend at the diaphysis. Parallel masses of periosteal bone have been demonstrated to extend into the medullary cavity at right angles to the axis of the bone. A triangular wedge of woven bone extends from the cortex into the medulla of the diaphysis (Khajavi et al., 1976).

MANAGEMENT OF PREGNANCY

Fetuses in which campomelic dysplasia is suspected should be referred to a tertiary care center capable of anatomic sonographic diagnosis of the fetus. Fetal karyotyping is indicated for two reasons: to determine the chromosomal gender and prepare the parents for the possibility of phenotypic sex reversal, and to specifically screen for chromosome 17 rearrangements, which are associated with a milder phenotype and a better prognosis (Foster et al., 1994). Once a definitive sonographic diagnosis has been made, the parents should meet with a medical geneticist and/or genetic counselor to discuss the implications of the diagnosis. The overwhelming majority (95%) of cases are lethal during the newborn period or during the first year of life. The poor prognosis should be discussed with the prospective parents, and termination of pregnancy can be offered at less than 24 weeks of gestation.

Rare survivors with campomelic dysplasia have been reported. All affected infants manifest respiratory distress. Delivery at a tertiary care center is therefore indicated. The mean gestational age at delivery is 39.8 weeks (Mansour et al., 1995). There are no specific indications for delivery by cesarean section.

If the parents terminate the pregnancy or delivery results in a stillborn infant, placental material should be collected to establish a fibroblast culture, which can serve as a source of DNA for *SOX9* mutation analysis. Campomelic dysplasia is now considered to be inherited in an autosomal dominant manner. Although the majority of cases occur as a new mutation, occasional cases of parental mosaicism warrant prenatal diagnosis in subsequent pregnancies.

FETAL INTERVENTION

There are no fetal interventions for campomelic dysplasia.

TREATMENT OF THE NEWBORN

A complete physical examination should be performed on all infants in whom campomelic dysplasia is suspected. The physical examination will typically reveal a low-to-normal birth weigh; apparent macrocephaly (mean occipitofrontal circumference, 37 cm) (Argaman et al., 1993); extreme hypotonia; disproportionately short trunk and lower limbs; and flattened face, high forehead, and flattened nasal bridge. The palpebral fissures are narrow and give the appearance of hypertelorism. A cleft of the soft palate is present in two thirds of affected infants (Argaman et al., 1993). In the affected newborn the thighs are held in abduction (see Figure 92-3). The hips are frequently dislocated. There are characteristic subcutaneous dimples present over the bend of the tibia. These dimples result from the loss of subcutaneous tissue secondary to in utero stretching at the point of curvature (Gillerot et al., 1989; Argaman et al., 1993).

Table 92-1

Characteristic Clinical Findings in Campomelic Dysplasia

Bilateral bowing of the long bones of the legs, especially tibia	100%
Talipes equinovarus	100%
Skin dimpling overlying the tibial angulations	99%
Hypoplastic pelvis	97%
Hypoplastic scapulas	92%
Macrocephaly	90%
Cleft palate	50–80%
Scoliosis	70%
Cystic renal disease	33%
Hydrocephalus	23–25%
Polyhydramnios	25–48%

Source: Slater CP, Ross J, Nelson MM, Coetzee EJ. The campomelic syndrome: prenatal ultrasound investigations: a case report. S Afr Med J *1985;67:863-869.*

A complete set of radiographs should be obtained during the newborn period, which will demonstrate the bladeless scapulas, the small bell-shaped chest, the frequent occurrence of only 11 pairs of ribs, and a poorly mineralized sternum. Radiographs may also demonstrate a short first metacarpal (Mansour et al., 1995). The characteristic clinical findings for infants affected with campomelic dysplasia are summarized in Table 92-1.

All affected infants manifest respiratory distress syndrome and generally require mechanical ventilation. Respiratory distress is due to a small thoracic cage with consequent pulmonary hypoplasia, a narrow larynx, and underlying abnormalities of the tracheobronchial cartilage (MacPherson et al., 1989). The majority of patients die during the neonatal period from the respiratory abnormalities.

SURGICAL TREATMENT

Rare survivors with campomelic dysplasia have had severe orthopedic problems that can be treated surgically, including

kyphoscoliosis, hip dislocation, and clubfeet (Gillerot et al., 1989). In one report, a 6.5-year-old girl was described who survived initial respiratory problems and was subsequently treated with a Pavlik harness for subluxation of the hips. She underwent two cervical and two thoracic spinal fusions, a release of complex foot deformities, and had an osteostomy of her right tibia (Ray and Bowen, 1984). At 6.5 years of age, she had the height and weight of a 2.5-year-old child and the bone age of a 3.5-year-old child. She sat at 22 months of age. Despite the multiple orthopedic problems and apparent developmental delay, by age 6.5 years she was able to attend a normal first-grade class. In another report, an 18-year-old high school graduate with normal psychomotor development was described who required plastic surgery and orthodontic treatment to advance her hypoplastic midface (Mintz and Adibfar, 1994). In survivors, aggressive surgical treatment for kyphoscoliosis is now recommended, as this condition is always progressive and affects cardiopulmonary function at a young age (Khoshhal and Letts, 2002).

LONG-TERM OUTCOME

The outcome for most individuals with campomelic dysplasia is poor. Of 81 patients described with the more common long-limbed variety of campomelic dysplasia, 61 were stillborn or died during the first month of life. An additional 13 died between 35 days and 1 year of age. In this report, only 2 patients survived beyond the age of 2 years (Ray and Bowen, 1984). Other authors emphasize that most affected individuals who do not die during the perinatal period die within the first 10 months of life (Slater et al., 1985). Aspiration and severe feeding difficulties are common in affected infants, even while on mechanical ventilatory support. Infants who are on the respirator for prolonged periods tend to die of diffuse alveolar or massive tracheobronchial pulmonary hemorrhage (Argaman et al., 1993). Infants who come off the ventilator have complications of apnea, atelectasis, and pneumonia.

For the 5% of affected individuals who survive beyond the first year of life, the outlook improves somewhat. Infants can still have stridor, retractions, and chronic pulmonary disease, as well as bronchitis and frequent otitis media. In one report, a 5-year-old girl with campomelic dysplasia was described whose condition was extremely unstable during her first year of life, but she eventually experienced a progressive decrease in the number of respiratory infections. Her early childhood years were characterized by marked hypotonia and mental retardation, but surprisingly, at 4 years of age she experienced a dramatic improvement in her development so that she could eventually speak and play and walk. At 5 years of age, however, her size was extremely small for her age (weight, 10.5 kg; height, 89 cm; normal head size of 53.5 cm). The original patient of Maroteaux was again reported on at 17 years of age and was shown to have an IQ of 45, hearing loss, and severe kyphosis (Houston et al., 1983).

Mansour et al. (2002) described 5 long-term survivors with molecular or cytogenetic evidence of campomelic dysplasia. All had disproportionate short stature (<3% for age), recurrent apnea and upper respiratory infections, progressive kyphoscoliosis, mild-to-moderate learning difficulties, and hip dislocation. All 5 had very similar facial features. Other problems included global developmental delay and tracheomalacia that required tracheotomy.

All patients who survive beyond the age of 6 months have also been shown to have a profound hearing loss (Takahasi et al., 1992; Argaman et al., 1993). The deafness is now known to be due to histologic abnormalities in the temporal bone as well as deformities of the vestibular and semicircular canals. In this condition, the endochondral layer of the optic capsule contains no cartilage cells. In addition, the facial nerve follows an aberrant course. The size and position of the ossicles are abnormal (Tokita et al., 1979; Takahasi et al., 1992). Patients affected with campomelic dysplasia have a mixed type of hearing loss. Conductive hearing loss derives from anomalies of the ossicles and frequent otitis media. Sensorineural hearing loss derives from hypoplasia of the cochlea.

GENETICS AND RECURRENCE RISK

It is now known from molecular analyses that campomelic dysplasia is inherited as an autosomal dominant condition, with the majority of patients representing heterozygosity for a new mutation (Rimoin, 1996). Recurrence in families is now thought to be due to rare cases of parental gonadal mosaicism or mildly affected parents with unrecognized symptoms. One case report described a mildly affected mother with a more severely affected daughter who died during the newborn period from respiratory distress (Lynch et al., 1993). In another case, a man with normal intelligence and mild phenotypic and radiologic evidence of campomelic dysplasia had a 46, XY daughter with severe skeletal and neurologic manifestations of the syndrome. On retrospective analysis the father's early medical history was complicated by clubfeet, laryngobronchomalacia, and recurrent chest infections (Savarirayan et al., 2003). These cases demonstrate that there is variable expressivity within families. Therefore, both parents must be examined and questioned for specific mild symptoms of campomelic dysplasia. If a parent is shown to be affected, there is a 50% recurrence risk.

Cytogenetic studies performed in affected patients played a large role in gene mapping of this condition. In one patient with campomelic dysplasia, a de novo paracentric inversion of chromosome 17 was documented (Maraia et al., 1991). This report was followed by the description of a phenotypically female fetus with campomelic dysplasia whose karyotype was 46, XY, (2;17)(q35;q23-24). These authors suggested that the long arm of chromosome 17 was likely to be the site of the gene mutation in campomelic dysplasia (Young et al., 1992). A total of 5 different patients with chromosomal rearrangements in campomelic dysplasia enabled the *SOX9*

gene locus to be mapped to 17q 24.1-25.2 (Tommerup et al., 1993). Interestingly, patients who have the translocation survive longer (Foster et al., 1994). It is now known that the breakpoints involved in the chromosome 17 rearrangements are always 5' to the *SOX9* locus. Pop et al. (2004) used comparative genomic hybridization (CGH) arrays to show that there are cis-acting regulatory elements more than 380 kb upstream of *SOX9*.

The gene *SOX9* encodes a putative transcription factor that is strongly conserved throughout mammalian evolution. *SOX9* is structurally related to the testis-determining factor *SRY*, and is expressed in many adult tissues, fetal testes, and fetal skeletal tissue (Wagner et al., 1994). It is now known that haploinsufficiency for the *SOX9* gene is the cause of campomelic dysplasia and autosomal XY sex reversal. This was proven by demonstration of inactivating mutations of one *SOX9* allele. In one of the cases reported by Wagner et al. (1994), one parent of an affected child was shown to have a low-grade mosaic mutation and had DNA that contained both the normal and mutant *SOX9* genes. Simultaneously, Foster et al. (1994) demonstrated that both campomelic dysplasia and sex reversal were caused by mutations in the *SOX9* gene. They described mutations in a single allele of *SOX9* on chromosome 17 in 6 of 9 patients affected with campomelic dysplasia. These mutations destroyed gene function by causing premature chain termination and loss of one-third of the protein gene product. DNA analysis of parents of affected children demonstrated the absence of similar mutations. Therefore, this conclusively proves that most cases of campomelic dysplasia are new mutations that are inherited as autosomal dominant conditions (Foster et al., 1994).

Campomelic dysplasia arises by point mutations, truncations, and frameshift mutations that impede the ability of *SOX9* to activate target genes during organ development (McDowall et al., 1999). Although many different mutations are known, there is no correlation between genotype and phenotype (Meyer et al., 1997). Acampomelic campomelic dysplasia is also caused by mutations in *SOX9* (Thong et al., 2000).

Prenatal diagnosis is indicated for the rare survivors with mild manifestations of campomelic dysplasia, as their offspring will have a 50% likelihood of recurrence. Their offspring could be more severely affected, as demonstrated by the cases of Lynch et al. (1993) and Savarirayan et al. (2003). For completely normal parents who have previously had an affected fetus or infant with campomelic dysplasia, prenatal diagnosis by sonography is indicated in subsequent pregnancies, although the recurrence risk is extremely low. Parental DNA can be studied to detect rare cases of mosaicism for *SOX9* mutations (Cameron et al., 1996). DNA studies will detect a *SOX9* mutation in 90% to 95% of cases.

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93 CHAPTER Diastrophic Dysplasia

Key Points

- Distinct skeletal dysplasia characterized by disproportionate short stature, clubfoot, cleft palate, "hitch-hiker's thumb," and "cauliflower ear."
- Results from mutation in the diastrophic dysplasia sulfate transporter gene, *DTDST* (also known as *SLC26A2*).
- More common in individuals of Finnish ancestry due to a founder effect.
- Sonographic findings are short and curved limbs, micrognathia, clubfeet, abducted and proximally inserted thumbs and great toes, and normal ossification.
- Associated with normal intelligence and postnatal development.
- Autosomal recessive condition.
- Delivery should occur in a tertiary center due to the high incidence of associated airway problems.

CONDITION

Diastrophic dysplasia is a distinct clinical entity characterized by disproportionate short stature, cleft palate, clubfoot, progressive scoliosis, limited joint mobility, proximally placed first metacarpals ("hitch-hiker's thumb"), and cystic degeneration of the pinnae of the ear ("cauliflower deformity") (Figure 93-1) (Lachman et al., 1981). This condition was first described by Lamy and Maroteaux (1960), who used the Greek word *diastrophos*, meaning twisted, to describe the prominent involvement of the feet and spine in this type of dwarfism (Diab et al., 1994).

Diastrophic dysplasia exhibits distinctive histopathology, which consists of cytoplasmic accumulation of glycogen and fat in the chondrocytes, resulting in variability of chondrocyte size, shape, and viability (Diab et al., 1994). There is

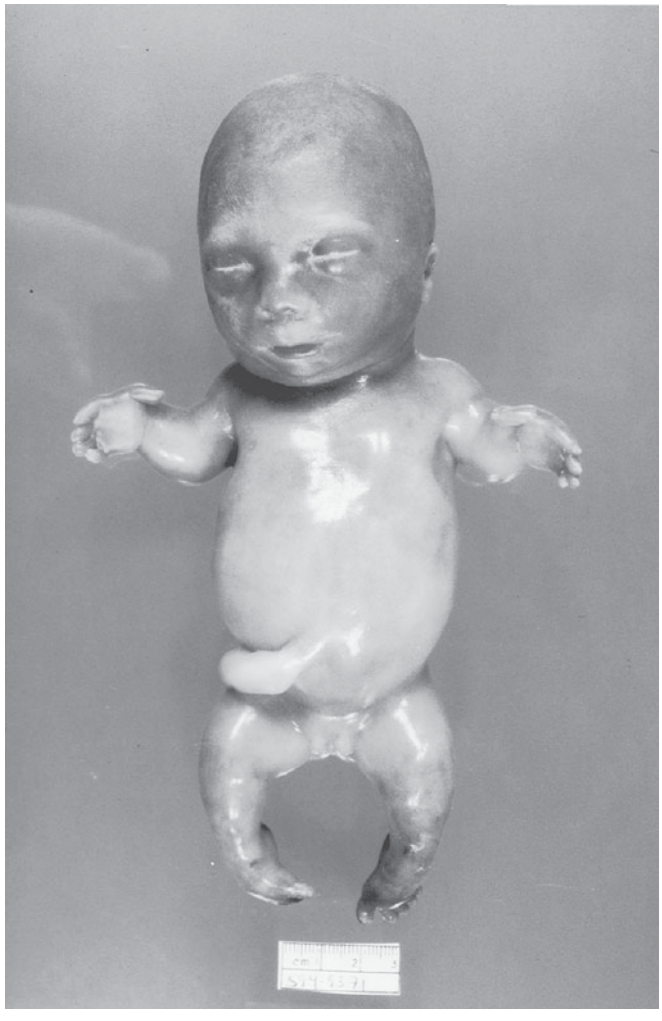

Figure 93-1 (*Left*) Postnatal photograph of a 19-week fetus with diastrophic dysplasia, illustrating severe micromelia, bilateral clubfeet, micrognathia, and bilateral hitch-hiker thumbs. (*Right*) Close-up of extreme lateral displacement of thumbs. (*Courtesy of Dr. Joseph Semple.*)

nonuniformity of the cartilage matrix with fibroblast and vascular ingrowth, resulting in fibrotic foci and areas of intracartilaginous calcification (Diab et al., 1994). The abnormalities of the cartilage matrix are considered pathognomonic and are visible with light microscopy. The underlying problem is an excessive amount of collagen deposition within the cartilage matrix rather than a lack of collagen. The excessive deposition of structurally abnormal collagen occurs predominantly in the growth cartilage rather than the resting cartilage (Shapiro, 1992). This cartilage abnormality affects the entire epiphyseal area, which leads not only to shortening of the long bones, but also to extreme malformation of the epiphyseal ends of the bones. This abnormality affects the articular surfaces, causing precocious osteoarthritis (Shapiro, 1992).

The underlying genetic basis of diastrophic dysplasia is the result of a mutation in a novel sulfate transporter gene, known as the diastrophic dysplasia sulfate transporter (*DTDST*) and also, more recently, as *SLC26A2* (Hästbacka et al., 1994, 1996). Impaired function of this gene product leads to undersulfation of proteoglycans in cartilage matrix, which leads to abnormal cartilage formation and results in the disease phenotype (Hästbacka et al., 1994).

INCIDENCE

Diastrophic dysplasia has been observed only in whites. To date, more than 300 patients with diastrophic dysplasia have been described, and interestingly, the majority of them are in Finland (Ryöppy et al., 1992), where the gene for diastrophic dysplasia is unusually common due to an apparent founder effect in this relatively genetically isolated population (Hästbacka et al., 1994). The incidence of diastrophic dysplasia is 1 in 32,600 livebirths in Finland, where it is the most common skeletal dysplasia (Poussa et al., 1991). The carrier frequency is 1 in 90 individuals there.

SONOGRAPHIC FINDINGS

Because of the rarity of this condition in the non-Finnish population, relatively few reports of the prenatal sonographic diagnosis of diastrophic dysplasia exist in the literature (Mantagos et al., 1981; Kaitila et al., 1983; Jung et al., 1998; Tongsong et al., 2002; Wax et al., 2003). The earliest prenatal diagnosis of this condition was made at 13 weeks using

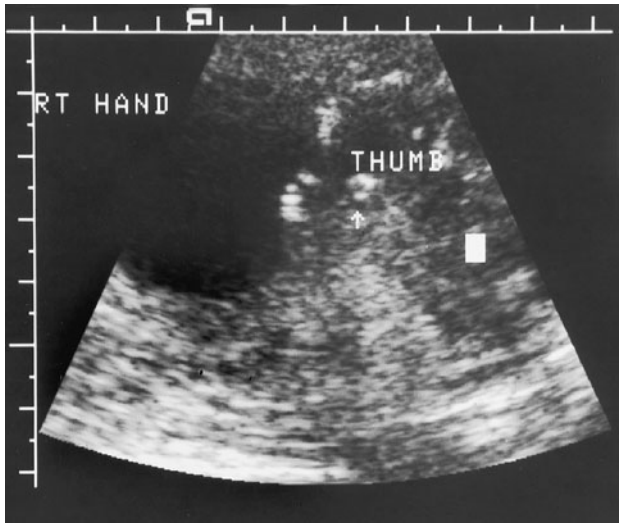

Figure 93-2 Prenatal sonogram of displaced ("hitch-hiker") thumb in a fetus with diastrophic dysplasia.

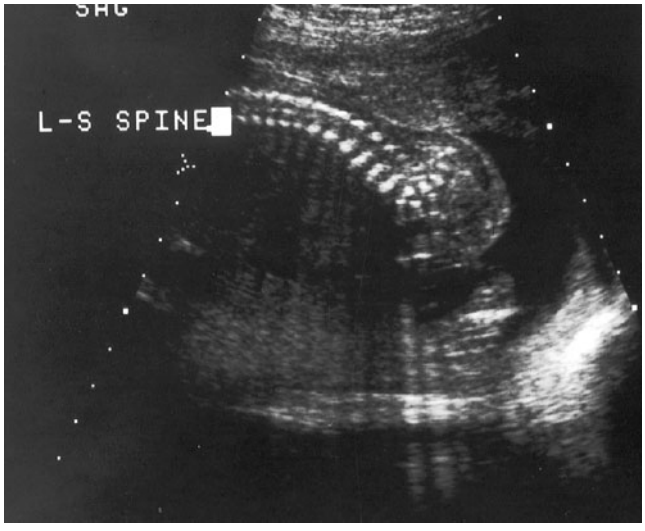

Figure 93-3 Prenatal sonogram demonstrating kyphosis in a fetus with diastrophic dysplasia.

transvaginal sonography (Severi et al., 2003). The prenatal diagnosis of diastrophic dysplasia was first described in 1980, when O'Brien et al. (1980) reported the diagnosis in a family with a previous affected child. Prenatal sonography was performed at 13 weeks 5 days of menstrual age, and revealed a crown-to-rump length of 43 mm, which corresponded to a gestational age of 11 weeks. The study was repeated at 16 weeks of gestation, when the femur length measured 13 mm (normal for gestational age: 19–26 mm). Thus, long bone shortening was retrospectively demonstrated in this condition during the early second trimester (13 weeks 5 days). In this report, fetoscopy demonstrated extremely short and curved limbs in the affected fetus. Examination of the face and oral cavity also showed micrognathia and cleft palate, other findings that are typically seen in diastrophic dysplasia. In another case, also complicated by a positive family history, prenatal sonography performed at 16 weeks of gestation demonstrated abnormally short limbs (less than 3 SD below the mean for gestational age) and lateral projection of the thumbs (Figure 93-2). These findings revealed an affected fetus. These authors recommended assessing fetuses at risk with serial examinations at 16, 20, 24, and 32 weeks of gestation because they were concerned that normal findings at 16 weeks might still be consistent with a diagnosis of an affected infant (Gollop and Eigier, 1987). In another affected case with no family history of diastrophic dysplasia, ultrasound examination performed at 31 weeks revealed severe micromelia (all long bones less than 2 SD below the mean for gestational age), normal amniotic fluid, ulnar deviation of the hands, abducted and proximally inserted thumbs and great toes, bilateral clubfeet, apparent elbow and knee joint contractures, cervical kyphosis (Figure 93-3), and micrognathia. The diagnosis of diastrophic dysplasia was confirmed postnatally (Gembruch et al., 1988).

Other sonographic findings in diastrophic dysplasia include normal skull and vertebral body ossification and occasional scoliosis. In a summary of 18 at-risk pregnancies in Finland, prenatal sonography performed during the second trimester was highly accurate in the diagnosis of this condition (Hästbacka et al., 1993). Of the 18 fetuses at risk, 5 were predicted to be affected and 13 were predicted to be unaffected by long bone measurements. All diagnoses were confirmed by postnatal or post-termination assessment.

More recently, three-dimensional ultrasound studies were compared to two-dimensional studies in a case of diastrophic dysplasia (Sepulveda et al., 2004). The three-dimensional study provided clearer views of the limb anomalies and the facial micrognathia.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes campomelic dysplasia, osteogenesis imperfecta, thanatophoric dysplasia, Kniest dysplasia, and chondrodysplasia punctata.

Other conditions to be considered within the differential diagnosis include pseudodiastrophic dysplasia and atelosteogenesis type II. In pseudodiastrophic dysplasia, patients exhibit a large cranium with midface hypoplasia, long clavicles, short limbs, and platyspondyly (Eteson et al., 1986), but the cauliflower ear characteristic of diastrophic dysplasia does not occur in this condition. The distinguishing features of pseudodiastrophic dysplasia include elbow and proximal interphalangeal joint dislocation and progressive scoliosis in infancy. Joint abnormalities seen in pseudodiastrophic dysplasia respond well to physical therapy. This is not true for diastrophic dysplasia. Pathologically, the two conditions are quite different. In pseudodiastrophic dysplasia the resting cartilage is normal, with no areas of fibrous degeneration in the cartilage matrix of these patients.

In atelosteogenesis type II, patients exhibit marked shortness of limbs with metaphyseal widening, a characteristic bifid humerus, cervical scoliosis, and abnormalities of the digits. Radiographs reveal more severe abnormalities of

the tubular bones of the hands and feet as compared with diastrophic dysplasia (Qureshi et al., 1995). On the other hand, the histologic abnormalities of the resting cartilage in atelosteogenesis type II are similar to those seen in diastrophic dysplasia. This is not surprising, as atelosteogenesis type II is caused by mutations in the same gene that causes diastrophic dysplasia, *DTDST* (Hästbacka et al., 1996).

ANTENATAL NATURAL HISTORY

In one report, Qureshi et al. (1995) described characteristic histopathologic abnormalities seen in three cases of diastrophic dysplasia diagnosed by prenatal sonography. In all three cases there was a negative family history, and routine second trimester sonography diagnosed a nonspecific skeletal dysplasia. All pregnancies were terminated electively and extensively studied, postmortem. Postmortem radiographs demonstrated moderately short long bones with a slight inward bowing. Broad metaphyses were demonstrated, especially in the femurs; mineralization of the bones was normal, and the vertebral bodies had normal widths. The ribs were normal, and there was no scoliosis demonstrated prenatally. On the postnatal radiographs, the characteristic hitch-hiker thumb deformity was easily demonstrated.

Histopathologic studies demonstrated morphologic abnormalities that were very similar to those reported in postnatally diagnosed cases. The predominant changes were demonstrated in the resting cartilage, where chondrocytes were surrounded by a halo of dense-appearing cartilage matrix. The chondrocytic nuclei were larger than normal and some lacunae contained two or more nuclei. Degenerative changes were also seen in the vertebral bodies and tracheal cartilage. Cystic degeneration was demonstrated in the pinnae of the ears, the larynx, and the costal cartilages. These findings clearly demonstrate that the morphologic consequences of the abnormal sulfate transporter gene occur relatively early in fetal life.

No evidence exists for increased in utero mortality due to diastrophic dysplasia.

MANAGEMENT OF PREGNANCY

Pregnancy management will depend on whether there is a family history of a pregnancy previously affected with diastrophic dysplasia. If there is, and if DNA was obtained from the previously affected fetus or infant, DNA analysis should be performed. If DNA is available from a previously affected individual, family studies should be performed prior to planned pregnancy to identify the specific mutation that occurs in the family. A limited number of mutations are present in individuals of Finnish ancestry. For non-Finnish individuals, however, mutations can occur in several places within the diastrophic dysplasia gene. Thus, it is important to identify the mutation that occurs within a specific family. If the family previously had an affected child and DNA was not obtained from the affected individual, prenatal diagnosis can be reliably performed by serial sonography, which is highly accurate in the detection of affected fetuses (Hästbacka et al., 1993).

The more likely scenario is a fetus that has no known family history of diastrophic dysplasia, but has a skeletal dysplasia demonstrated on a sonogram performed for uterine size less than gestational date. If findings characteristic of diastrophic dysplasia are demonstrated by sonography, the potential diagnosis can be discussed with the family. Discussion of the outcome in this condition should include the facts that intelligence is normal and that wide variation in the phenotype of diastrophic dysplasia exists. Reported adult heights include a range of 100 to 159 cm (3 feet 9 inches to 6 feet) (Gembruch et al., 1988), although the mean height in a series of 72 American patients with diastrophic dysplasia was 118 cm (3 feet 11 inches) (Horton et al., 1982). Termination of pregnancy can be offered if the diagnosis is made prior to 24 weeks of gestation. If the family elects pregnancy termination, a complete perinatal autopsy should be performed, because the cartilage abnormalities demonstrated by light and electron microscopy are pathognomonic for this condition. At termination of pregnancy, DNA should be obtained from the fetus or placenta to store for future DNA analysis. There is no indication for cesarean delivery other than for standard obstetrical reasons. Consideration should be given, however, to delivery at a tertiary care center for respiratory support of the newborn. In one report, 12% of patients with diastrophic dysplasia had respiratory difficulties at birth caused by glossoptosis (Rintala et al., 1986).

FETAL INTERVENTION

There are no fetal interventions for diastrophic dysplasia.

TREATMENT OF THE NEWBORN

The characteristic postnatal clinical findings seen in patients with diastrophic dysplasia are summarized in Table 93-1 and shown in Figures 93-4 and 93-5. Because of the high incidence of cleft palate and micrognathia, a neonatologist should be present at the delivery to manage the airway. The lungs are normal and not hypoplastic. Postnatal radiographs can be obtained to confirm the diagnosis (Figure 93-6). They may demonstrate calcification of the pinnae, precocious calcification of the larynx and costal cartilage, marked epiphyseal irregularities, delayed secondary ossification centers, and extreme shortening of the long bones (Diab et al., 1994). A clinical geneticist should be consulted for confirmation of the diagnosis and to provide genetic counseling for the family. The incidence of neonatal mortality is increased because of respiratory insufficiency related to tracheal cartilage weakness (Gustavson et al., 1985). After the newborn period, the lifespan is normal.

Table 93-1

Clinical Findings in Diastrophic Dysplasia

Cleft palate
Cystic changes in pinnae ("cauliflower" ear)
Lordosis, scoliosis
Joint limitation
Rhizomelic and/or mesomelic shortening
Ulnar deviation of hand
Shortened ovoid first metacarpal ("Hitch-hiker" thumb)
Clubfoot deformity
Symphalangy

Modified from Lachman et al. 1981

LONG-TERM OUTCOME

Patients with diastrophic dysplasia exhibit normal intelligence and development. Long-term medical problems include short stature, cleft palate, scoliosis (Remes et al., 2001), difficulty walking, and the need for osteotomies for hip, knee, and foot contractures (Shapiro, 1992). Specific growth curves for height are available for patients with diastrophic dysplasia (Horton et al., 1982).

In one report, 95 Finnish patients with diastrophic dysplasia were studied until 79 years of age. Of these, 41 (43%) had an open cleft palate and surgery was required in 37 of these patients. An additional 30 (32%) had submucous cleft palate or microforms of cleft palate. In these patients, no hypernasality of speech was noted. Only 16 (17%) of patients had a normal palate. Most patients had micrognathia (Rintala et al., 1986).

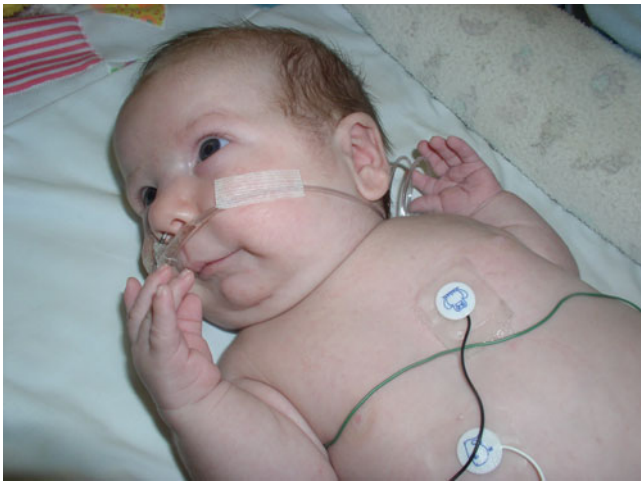

Figure 93-4 Postnatal photograph of the facial features seen in a newborn with diastrophic dysplasia. (*Photograph courtesy of Dr. Jodi Hoffman.*)

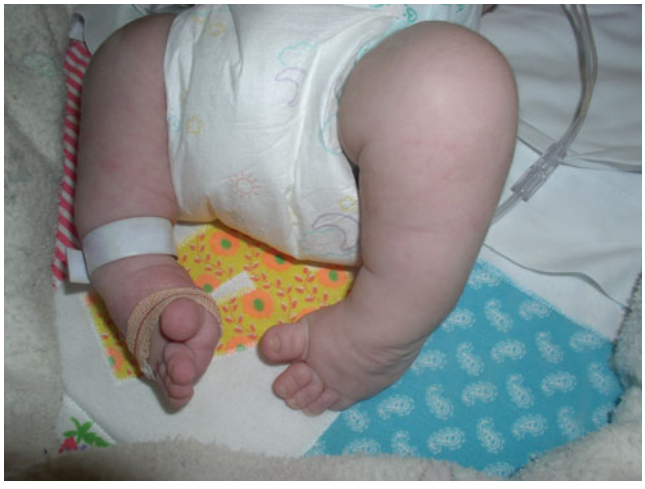

Figure 93-5 Postnatal photograph of the lower extremities of a newborn with diastrophic dysplasia, showing clubfeet and displaced great toe. (*Photograph courtesy of Dr. Jodi Hoffman.*)

In another study of a large cohort (101 patients) with diastrophic dysplasia, one-third were noted to have cervical kyphosis. Three of these cases resolved spontaneously before 5 years of age. Scoliosis was demonstrated in 49% of females and only 22% of males with diastrophic dysplasia. Only two of these patients required operation. In addition, spina bifida occulta was demonstrated in 73% of females and 59% of males (Poussa et al., 1991). Spinal involvement may be severe in affected patients, resulting in odontoid hypoplasia and C1–C2 subluxation. Atlanto-axial instability has also been reported (Richards, 1991; Diab et al., 1994). Spinal stenosis with cord compression can lead to neurologic complications (Gembruch et al., 1988; Diab et al., 1994). Joint changes are progressive in nature and painful osteoarthroses and joint contractures can develop at an early age (Hästbacka et al., 1994).

A wide spectrum of foot deformities exists in patients with diastrophic dysplasia. In one study of 102 patients, 43% were demonstrated to have a foot with a tarsal valgus deformity and metatarsus adductus. An additional 29% of patients had equinovarus adductus and 8% had equinus deformity. Sixty-three percent of feet studied were plantigrade (Ryöppy et al., 1992). These authors noted that the abnormality of cartilage in diastrophic dysplasia results in cartilage that is softer than normal. Thus, the cartilaginous parts of the skeleton tend to become progressively deformed with weight bearing. This particularly involves the feet, hips, and knees of affected patients. MRI studies have demonstrated degenerative changes in the articular cartilage of the knees from 6 years of age (Peltonen et al., 2003). After growth has been completed, total knee replacement may result in significant functional improvement. In a study of walking ability in adults with diastrophic dysplasia, 82% of affected individuals drove

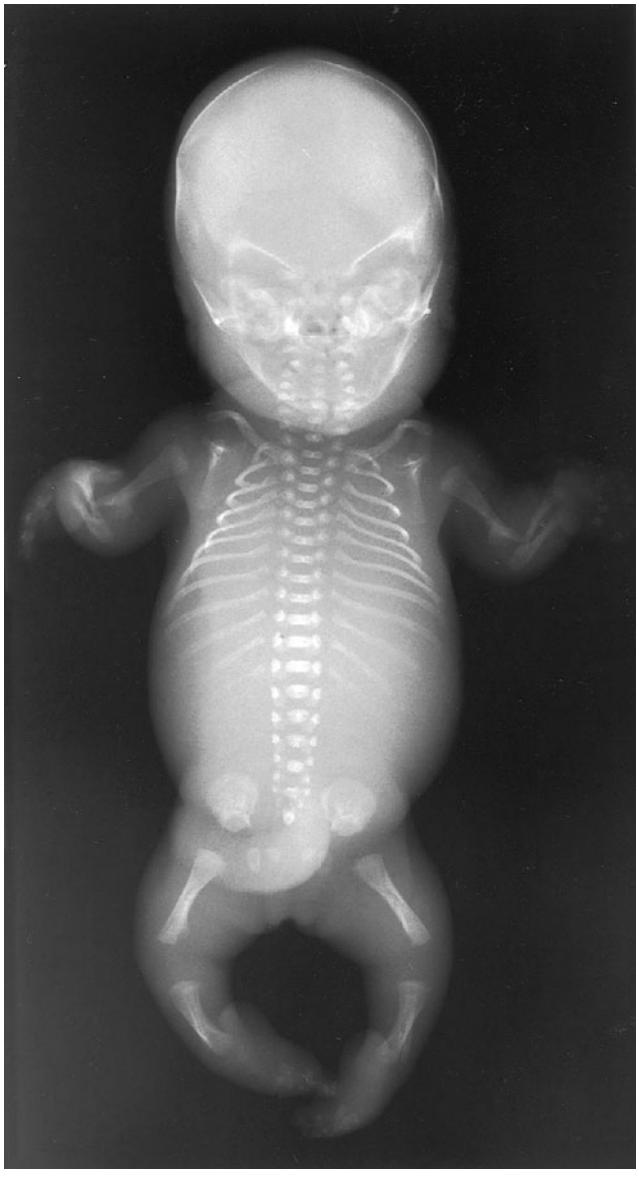

Figure 93-6 Postmortem radiograph of the fetus shown in Figure 93-1.

their own (adapted) car as their primary method of transportation (Remes et al., 2004)

Sexual development is normal in patients with diastrophic dysplasia and there is no indication that fertility is reduced.

GENETICS AND RECURRENCE RISK

Diastrophic dysplasia is inherited as an autosomal recessive trait with a wide variability of expression, even among siblings. The causative gene in diastrophic dysplasia, *SLC26A2* maps to chromosome 5q32-33. (Hästbacka et al., 1990, 1991). More than 30 different disease-associated mutations have been identified in the *SLC26A2* gene (Dawson and Markovich, 2005). Mutations in *SLC26A2*, also known as the diastrophic dysplasia sulfate-transporter gene (*DTDST*), lead to four different chondrodysplasias. Impaired function of this gene product leads to undersulfation of proteoglycans in the cartilage matrix. It has been demonstrated that the mRNA for this gene is minimally present in Finnish patients. Evidence of deficient sulfate transport has been shown in skin fibroblasts from an affected patient (Hästbacka et al., 1994). Population-based screening is possible in Finland because of the high carrier frequencies due to a founder effect.

The disorders atelosteogenesis type II, achondrogenesis type IB (see Chapter 97), and multiple epiphyseal dysplasia are also caused by mutations in the *DTDST* gene (Hästbacka et al., 1993; Superti-Furga, 1994; Superti-Furga et al., 1996). All four chondrodysplasias appear to demonstrate a correlation between genotype and phenotype. The most severe disorder, achondrogenesis type IB, always shows homozygosity for null mutations in the coding regions of both alleles (Karniski, 2001). Patients with atelosteogenesis type II have a null mutation on one allele and an intermediate or near-normal mutation on the opposite allele. Most individuals with diastrophic dysplasia or multiple epiphyseal dysplasia have 2 mutations with intermediate or near-normal sulfate transport activity (Karniski, 2001). This is presumably the reason that the phenotypes associated with diastrophic dysplasia and multiple epiphyseal dysplasia are milder.

First trimester prenatal diagnosis has been performed successfully by DNA-based diagnosis for five fetuses at risk because of a positive family history. In fetal DNA obtained by chorionic villus sampling at 10 weeks, three fetuses were predicted to be unaffected and two were predicted to be affected with >95% probability. These diagnoses were considered to be concordant with the sonographic findings and were ultimately confirmed by analysis of DNA obtained at termination or after the birth of the infant (Hästbacka et al., 1993).

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94 CHAPTER Ellis–van Creveld Syndrome

Key Points

- Autosomal recessive condition that results in short-limbed dwarfism, polydactyly, congenital heart disease, oral frenulae, defective teeth, and generally normal intelligence.
- Thirty percent of cases occur in consanguineous families.
- Differential diagnosis includes Jeune syndrome (asphyxiating thoracic dystrophy), short-rib polydactyly syndrome, achondroplasia, and Weyers acrodental dysostosis.
- Karyotype of affected individuals is usually normal.
- Caused by genetically heterogenous mutations in two genes, *EVC* and *EVC2*, that are next to each other on chromosome 4p16.
- Compatible with long-term survival.

CONDITION

Ellis–van Creveld syndrome is a recessively inherited single-gene disorder that results in short-limbed dwarfism, polydactyly, cardiac abnormalities in 50% to 60% of cases, fingernail dystrophy, oral frenulae, and defective teeth. It was first described in 1940 (Ellis and van Creveld, 1940). The other name for the condition, chondroectodermal dysplasia, does not adequately describe the extent of tissue involvement. Ellis–van Creveld syndrome is characterized by multisystem abnormalities, encompassing: (1) ectodermal dysplasia, affecting the teeth, nail, hair, gums, and lips but not the skin or sweat glands; (2) mesodermal involvement, affecting bone growth and shape, formation of the heart, and occasionally, the kidneys; and (3) endodermal involvement, affecting formation of the lungs and liver (Blackburn and Belliveau, 1971). At least three of the four following criteria are required for diagnosis: ectodermal dysplasia, chondrodysplasia, polydactyly, or the presence of congenital heart disease (Hill, 1977).

The chondrodystrophy in this condition is manifested by shortening of the extremities, with the distal segments more markedly affected than the proximal segments. In addition, there is metaphyseal thickening of the long bones, and curvature of the weight-bearing bones (Lynch et al., 1968). In Ellis–van Creveld syndrome, the fibula is usually 50% of its normal length (Feingold, 1966). Pathologic studies performed on long bones in affected patients reveal a decreased number of cartilage cells in the cartilage plate and a disorganized columnar arrangement of the chondrocytes (Blackburn and Belliveau, 1971).

Distinctive cardiac abnormalities are found in this syndrome, such as single atrium or large atrioseptal defect (Blackburn and Belliveau, 1971). Other cardiac abnormalities associated with this condition include aortic atresia, hypoplastic ascending aorta, and hypoplastic left ventricle (Blackburn and Belliveau, 1971).

Speculation exists as to whether King Richard III of England (1452–1485) had Ellis–van Creveld syndrome. He was the product of a consanguineous union, which makes an autosomal recessive condition more likely. In their writings, both Shakespeare and Sir Thomas Moore alluded to the presence of neonatal teeth, short stature, a skeletal dysplasia, and a crooked back when describing Richard III (Aird and McIntosh, 1978).

INCIDENCE

Ellis–van Creveld syndrome has been described in both sexes and all ethnic groups. The incidence of the syndrome is approximately 1 in 60,000 livebirths (Zangwill et al., 1988). It is notable that the syndrome is much more common in highly inbred genetic isolates. The birth frequency of Ellis–van Creveld syndrome is 5 in 1000 livebirths in the old-order Amish population of Pennsylvania (McKusick et al., 1964; Goldblatt et al., 1992). McKusick et al. described 52 cases of Ellis–van Creveld syndrome in 30 sibships in Lancaster County, Pennsylvania. They estimated that 13% of the Amish population was heterozygous for the gene mutation that resulted in Ellis–van Creveld syndrome (McKusick et al., 1964). All affected members can trace their lineage to one founding couple who emigrated to the United States during the 18th century from Southwestern Germany (McKusick, 2000). Other relatively isolated populations have also described an increased incidence of Ellis–van Creveld syndrome. For example, the incidence of Ellis–van Creveld syndrome in Western Australian aborigines is 1 in 6123 livebirths. This population has a calculated carrier frequency of the gene mutation of 1 in 39 individuals, making the Western Australian aborigines the second most common group worldwide to carry the mutation (Goldblatt et al., 1992). Also, a relatively high incidence of the disorder has been reported in an inbred rural Brazilian community (Oliveira da Silva et al., 1980).

SONOGRAPHIC FINDINGS

Sonographic findings that have been described in fetuses with Ellis–van Creveld syndrome include short long bones with normal density, a narrow thorax, appropriate weight for gestational age, and the presence of hand polydactyly, with the malformed finger usually occurring on the ulnar side (Guschmann et al., 1999; Tongsong and Chanprapaph, 2000) (Figure 94-1). Polydactyly of the feet only occurs in 10% of cases (Bui et al., 1984; Qureshi et al., 1993). Congenital heart disease, manifesting as an atrioseptal defect, ventriculoseptal defect, or a single atrium occurs in 50% to 60% of cases (Oliveira da Silva et al., 1980; Zangwill et al., 1988). Two

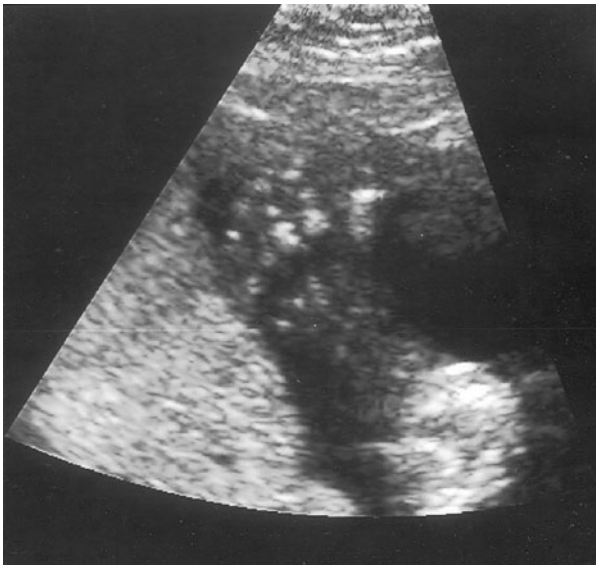

Figure 94-1 Prenatal sonographic image of a hand with polydactyly. The extra digit on the ulnar side is a characteristic finding in patients with Ellis–van Creveld syndrome.

patients have been described with Ellis–van Creveld syndrome and Dandy–Walker malformation (Zangwill et al., 1988), but, in general, central nervous system defects are not associated with the condition.

The earliest prenatal diagnosis of Ellis–van Creveld syndrome was made at 12 weeks in a family at risk for the condition (Dugoff et al., 2001). Both hands were noted to have polydactyly and there were no normal septal structures in the fetal heart. Increased nuchal translucency (NT) measurement has been reported in association with Ellis–van Creveld syndrome (Venkat-Raman et al., 2005).

The combined use of fetoscopy and ultrasound examination for prenatal diagnosis of Ellis–van Creveld syndrome was described in two families at risk for the condition due to previously affected offspring. In one case, sonography demonstrated a shortened femur and humerus. Fetoscopy permitted the visualization of the left hand, which had a well-formed sixth digit. On the basis of these findings, a presumed diagnosis of Ellis–van Creveld syndrome was made, and the condition was verified after termination (Mahoney and Hobbins, 1977).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes Jeune syndrome (asphyxiating thoracic dystrophy and short-rib polydactyly syndrome (see Chapter 95). Patients with Jeune syndrome may have similar radiologic and sonographic features, but do not have polydactyly, nail dystrophy, or the oral findings that are considered pathognomonic of Ellis–van Creveld syndrome. Also, the narrow chest seen in Jeune syndrome is less severe in Ellis–van Creveld syndrome. Jeune syndrome is also associated with cystic renal dysplasia. Another consideration in the prenatal diagnosis of Ellis–van Creveld syndrome is achondroplasia (see Chapter 89) but, in achondroplasia, there is more striking proximal shortening of the limbs. Ellis–van Creveld syndrome is characterized by mild micromelia and distal shortening of the limbs. In the postnatal differential diagnosis, ectodermal dysplasia might be considered for a patient with mild features of Ellis–van Creveld syndrome. However, patients affected with ectodermal dysplasia have completely normal bone growth and morphology and their defects are limited to the hair, teeth, nails, and sweat glands. Characteristically, patients with ectodermal dysplasia do not have polydactyly. Finally, Weyers acrodental dyostosis is in the differential diagnosis. It presents with polydactyly and similar heart defects to Ellis–van Creveld but is not associated with short stature.

ANTENATAL NATURAL HISTORY

Little is known about the antenatal natural history of Ellis–van Creveld syndrome. The histopathology of affected fetal cartliage shows disorganization of chondrocytes in the physeal growth plate (Qureshi et al., 1993).

MANAGEMENT OF PREGNANCY

For fetuses in which Ellis–van Creveld syndrome is suspected, a complete anatomic scan is indicated at a center capable of performing a detailed anatomic survey of the fetus. The chromosomes are normal in Ellis–van Creveld syndrome, so there is no indication to perform fetal karyotyping. Cesarean section should be performed only for the standard obstetric indications. This condition is compatible with postnatal survival outside the womb. Because of the narrowing of the chest seen in this condition, there is significant potential for respiratory distress in the newborn. Therefore, we recommend that the infant be delivered in a tertiary care center to permit resuscitation by a skilled neonatologist and evaluation for heart defects. An individual capable of mechanically ventilating the newborn should be present at the delivery.

FETAL INTERVENTION

There are no fetal interventions for Ellis–van Creveld syndrome.

TREATMENT OF THE NEWBORN

A newborn affected with Ellis–van Creveld syndrome can present in severe respiratory distress, so as stated above, a person trained in newborn resuscitation and endotracheal intubation should attend the delivery (Simon and Young, 1986).

A complete physical examination is indicated at birth. Typically, patients with Ellis–van Creveld syndrome have a normal birth weight, but a length that is less than the third percentile for gestational age (Reddy and Madenlioglu, 1967). Physical findings that may be present in the newborn include sparse hair, the suggestion of a cleft lip with a narrow upper lip, and characteristic oral findings. These include an abnormally short upper lip bound down by multiple frenulae, or "lip tie." The superior gingivolabial sulcus may be entirely missing or may be obliterated (Feingold, 1966). This finding is diagnostic for Ellis–van Creveld syndrome in an infant with a skeletal dysplasia. Other oral findings include a serrated or notched alveolar process and the presence of neonatal teeth (Mintz et al., 2005). Affected patients may have deep-set hypoplastic nails, cryptorchidism, epispadias, hypospadias, and clubfoot. Occasional patients have coloboma of the iris or strabismus.

Patients in whom Ellis–van Creveld syndrome is suspected should have a skeletal survey, which may demonstrate the presence of squat pelvic bones. The base of the iliac bones has a trident configuration in the acetabular region, similar to that seen in Jeune syndrome (Cremin and Beighton, 1974). The thoracic cage is less narrowed than in Jeune syndrome. In addition, patients have micromelia, and the metaphyses have a dumbbell appearance due to flaring of the lower ends. In the hand films, there is polymetacarpalia and polydactyly

(Cremin and Beighton, 1974; Taylor et al., 1984). The skull and spine are usually within normal limits.

Patients in whom Ellis–van Creveld syndrome is suspected should also have an echocardiogram and a cardiac consultation because of the high incidence of associated congenital heart disease. Ventriculoseptal defect is the most common abnormality, followed by atrioseptal defect, which may be large enough to effectively create a single atrium. Additional abnormalities seen in this condition include cleft mitral and tricuspid valves, an atrioventricular communis defect, and total anomalous pulmonary venous return (Lynch et al., 1968).

SURGICAL TREATMENT

Patients affected with Ellis–van Creveld syndrome may require hand surgery to remove the extra digits. These digits are usually associated with additional metacarpals, and the surgery may be complex (Feingold, 1966). Because of the high incidence of dental abnormalities, dental surgery may be required, and missing teeth may need to be replaced with dental prostheses. Patients who are affected with congenital heart disease may require cardiac surgery.

LONG-TERM OUTCOME

The overall prognosis for patients affected with Ellis–van Creveld syndrome is related to the presence or absence of cardiac abnormalities. Patients who do not have cardiac disease have a much better long-term prognosis. Pulmonary deaths associated with this condition are unusual, although they have been attributed to underlying abnormalities in the tracheobronchial tree (Lynch et al., 1968). Survivors are generally healthy except for limb bowing and joint pain (Simon and Young, 1986). Adults with this condition have moderately disproportionate short stature and achieve an adult height of between 107.5 and 150 cm (Simon and Young, 1986). Multiple case reports exist in the literature of functional adults with this condition. Mental retardation is the exception rather than the rule. Most adults described in the literature with this condition have average intelligence (Goor et al., 1965; Hill, 1977).

The long-term issues for affected patients include orthopedic problems, such as genu valgum (knock knees) and wrist problems. Affected adults are unable to make a tight fist due to the relatively long metacarpals (Reddy and Madenlioglu, 1967). In addition, an extracarpal bone is present in the wrists of all patients older than 5 years of age (Taylor et al., 1984). The carpal bones are deformed in this condition. Fusions occur between the capitate and hamate bones of the wrist. A medial supernumerary bone is present in the distal row of carpal bones. The fusions that occur between the supernumerary bones and the hamate and capitate bones may be a unique finding in Ellis–van Creveld syndrome (Taylor et al., 1984).

GENETICS AND RECURRENCE RISK

Ellis–van Creveld syndrome is caused by a single-gene mutation and is inherited in an autosomal recessive pattern. Thirty percent of cases occur in consanguineous families (Feingold, 1966). Results of chromosome analysis have been normal in patients affected with this condition (Goor et al., 1965). One case has been reported resulting from segmental uniparental disomy of chromosome 4 (Tompson et al., 2001).

Mutations in two genes have been identified in Ellis–van Creveld syndrome: *EVC* and *EVC2* (Ruiz-Perez et al., 2000, 2003). *EVC* and *EVC2* map to chromosome 4 band p16 (McKusick et al., 1996; Polymeropoulos et al., 1996). These two genes lie in a head-to-head configuration that is conserved in species from fish to humans. This gene is expressed in vertebrae and limb bones, but also in embryonic kidney. Affected individuals with mutations in *EVC* and *EVC2* are phenotypically indistinguishable from each other. There have been several case reports of unilateral postaxial polydactyly in parents and unaffected siblings of family members who have Ellis–van Creveld syndrome. It has been postulated that polydactyly may be a manifestation of the heterozygote in this condition (Fryns, 1991). Interestingly, another disorder, Weyers acrodental dysostosis, is also caused by mutations in *EVC*. Weyers acrodental dysostosis is milder than Ellis–van Creveld syndrome and is not associated with short stature. It is inherited as an autosomal dominant condition. Symptoms include heart defects and polydactyly (Ruiz-Perez et al., 2000).

For the family who has had a previously affected child with Ellis–van Creveld syndrome, the recurrence risk is 25%. At present, prenatal diagnosis in families at risk is most commonly performed by prenatal sonography, although the diagnosis has been made by embryoscopy or fetoscopy (Bui et al., 1984). Prior to the identification of the disease gene, linkage markers were used to diagnose a heterozygous (clinically unaffected) fetus with a 96% chance of accuracy (Torrente et al., 1998). Now that the disease genes are known, every attempt should be made to perform DNA testing to identify the specific familial mutation. Once that has been identified, prenatal DNA diagnosis can be performed in subsequent pregnancies by chorionic villus sampling or amniocentesis.

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95 CHAPTER

Short-Rib Polydactyly Syndrome

Key Points

- Refers to a group of rare, generally lethal skeletal dysplasias that have short limbs, short ribs, and polydactyly. Clinical overlap exists between the four subtypes.
- Extremely rare in the general population.
- Differential diagnosis includes Ellis–van Creveld syndrome, asphyxiating thoracic dystrophy (Jeune syndrome), Meckel–Gruber syndrome, and trisomy 13.
- All affected infants with short-rib polydactyly syndrome have severe pulmonary hypoplasia that prevents extrauterine survival.
- Chromosomes are usually normal. Genes responsible for these conditions have not yet been identified.

CONDITION

The short-rib polydactyly syndromes comprise a group of rare, generally lethal skeletal dysplasias. Much debate exists within the clinical genetics community as to the appropriate subclassifications, if any, for these conditions. Sonographic characteristics common to all the subtypes of the short-rib polydactyly syndromes include short horizontal ribs and long tubular bone changes that result in severe micromelia. Most of the conditions have associated polydactyly of the feet and hands. A variety of organ anomalies can also accompany this condition (de Sierra et al., 1992).

The short-rib polydactyly syndromes (SRPS) have been divided into four types. Type I SRPS (Saldino–Noonan syndrome) was first described in 1972 (Saldino and Noonan, 1972). It is characterized by extremely short bones with pointed and narrowed metaphyses. The ribs are also extremely short, causing compression of the developing lungs. This eventually results in severe pulmonary hypoplasia. Saldino–Noonan syndrome is also associated with more severe systemic abnormalities than exist in some of the other subtypes. These abnormalities include congenital heart disease, anorectal anomalies, and cysts in the kidneys. Polydactyly is present in more than 95% of cases of type I SRPS (Keating et al., 1989).

Type II SRPS (Majewski syndrome) was first described in 1971 (Majewski et al., 1971). These patients have very short ribs, severe pulmonary hypoplasia, micromelia, and polydactyly. A distinguishing feature of the syndrome is the presence of a median or midline cleft lip with or without cleft palate. These patients also have a very high frequency of central nervous system abnormalities (Lurie, 1994). The most common central nervous system abnormalities seen in Majewski syndrome include pachygyria, small cerebellar vermis, and absent olfactory bulbs (Martínez-Frías et al., 1993). Other central nervous system changes that have been demonstrated in type II SRPS include arachnoid cysts, agenesis of the corpus callosum, and arrhinencephaly (Prudlo et al., 1993). In addition to the midline cleft lip and cleft palate, patients with Majewski syndrome can have a cleft tongue, oral frenulae, natal teeth, and abnormalities of the epiglottis (Knapp et al., 1990).

Type III SRPS (Verma–Naumoff syndrome) was first described in 1977 (Verma et al., 1975; Naumoff et al., 1977). Patients with this subtype clinically resemble patients with type I because of the absence of cleft lip. These patients have the typical long narrow thorax with pronounced rib shortening, shortened long bones, and polydactyly. Their long bones can be distinguished from those in type I by the presence of the metaphyseal spurs (Figures 95-1 and 95-2). In addition to the presence of the spurs, there is a diagnostic shortening of the base of the skull. Patients with type III SRPS have small and poorly ossified vertebral bodies (Naumoff et al., 1977). The chondro-osseous histopathology is qualitatively similar in SRPS types I and III. The essential abnormality is a shortened or absent zone of proliferative chondrocytes with a loss of columnization (Sillence et al., 1987). In SRPS type II, shortening of the proliferative columns and irregularity in the columnization is not as marked as it is in types I and III.

Type IV SRPS (Beemer–Langer syndrome) was described in 1983 (Beemer et al., 1983). It clinically resembles type II SRPS, but the distinguishing feature is the general lack of polydactyly (Chen et al., 1994). Patients with type IV SRPS have the midline cleft lip, but the shape of the tibia differs significantly from that seen in the Majewski syndrome. Pathologic studies from patients with type IV SRPS reveal a disorganized physeal growth zone with a prominent zone

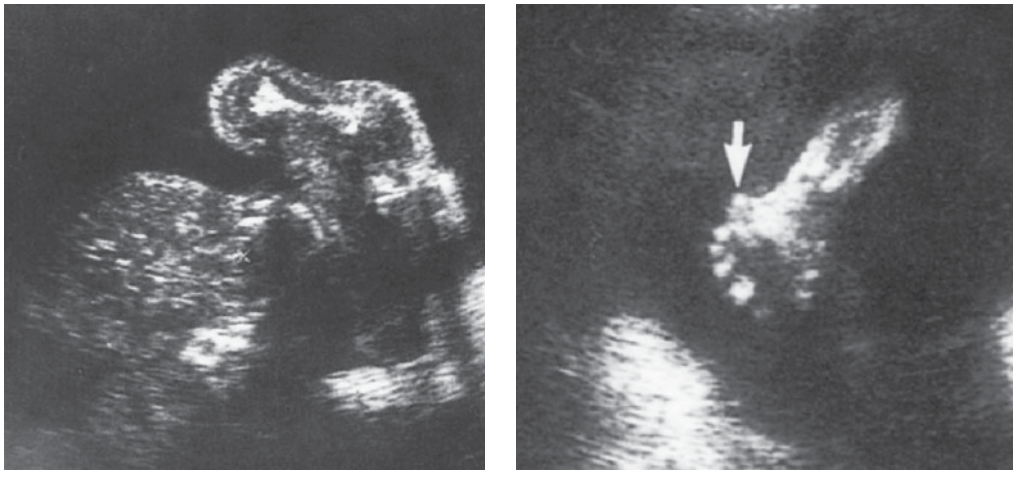

Figure 95-1 (*Left*) Prenatal sonographic image of a fetus at 20 weeks of gestation with SRPS type III, demonstrating widened metaphyses and marginal spurs. (*Right*) Prenatal sonographic image of a fetus at 20 weeks of gestation with SRPS type III, demonstrating postaxial polydactyly of the hand. (*Reprinted, with permission, from Meizner I, Barnhard Y. Short-rib polydactyly syndrome (SRPS) type III diagnosed during routine prenatal ultrasonographic screening: a case report.* Prenat Diagn. *1995;15:665-668. Copyright 1995 John Wiley & Sons. Reprinted, by permission, of John Wiley & Sons, Inc.*)

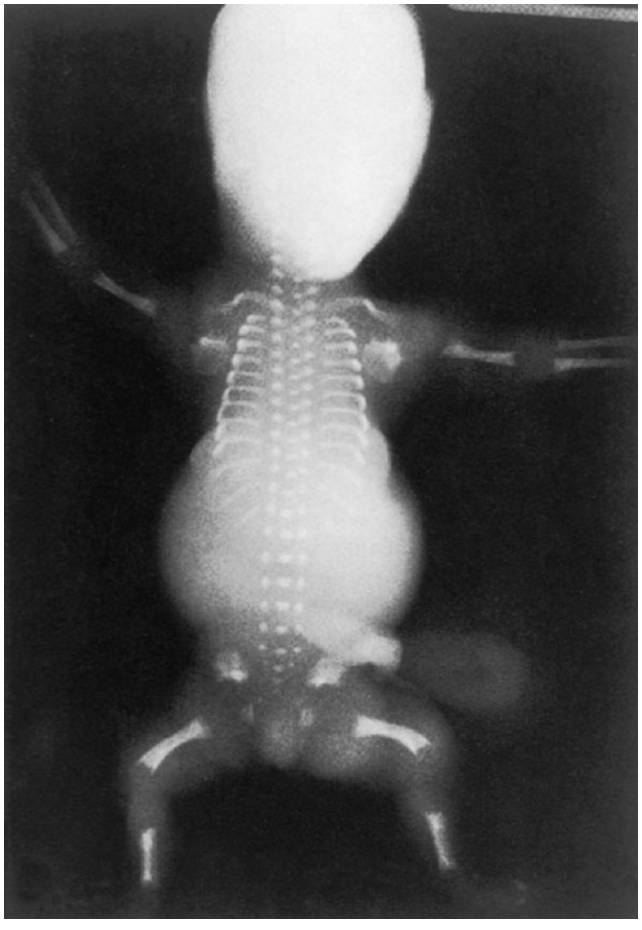

Figure 95-2 Postmortem radiograph of an affected fetus at 20 weeks of gestation demonstrating the marginal spurs on the femur characteristic of SRPS type III. The narrow ribs are especially well visualized. (*Reprinted, with permission, from Wu M-H, Kuo P-L, Lin S-J. Prenatal diagnosis of recurrence of short rib polydactyly syndrome.* Am J Med Genet. *1995;55:279-284. Copyright 1995 John Wiley & Sons. Reprinted, by permission, of John Wiley & Sons, Inc.*)

of hypertrophy that is composed of closely arranged large chrondrocytic lacunae (Chen et al., 1994).

Although each has distinguishing clinical symptoms, much overlap exists between the subtypes of SRPS (Figure 95-3) (Sarafoglou et al., 1999). There are multiple case reports in the literature describing patients with features of each subtype that defy definitive classification (Bernstein et al., 1985; Yang et al., 1991; Tsai et al., 1992; Wu et al., 1995). Debate in the literature persists as to whether or not this group of disorders represents one entity with a continuous spectrum of clinical manifestations (Sarafoglou et al., 1999). Controversy also exists about whether the different subtypes of SRPS are the result of point mutations occurring at different loci, different alleles at a single locus, or variability in the expression of the same mutant gene (Martínez-Frías et al., 1993). In one paper, Bernstein et al. (1985) argued that the SRPS subtypes represent a single entity with varying expressivity. It is hoped that when the mutant gene or genes responsible for this condition are identified, the controversy regarding classification will be settled by molecular analysis.

INCIDENCE

The SRPSs are extremely rare skeletal dysplasias. In the database of the Latin-American collaborative study of congenital malformations, representing 349,470 livebirths and stillbirths, no cases of short rib polydactyly were described (Orioli et al., 1986). In another report, evaluating the accuracy of prenatal diagnosis of skeletal dysplasias, there were eight cases of SRPS described in a study population of 226 stillbirths or fetuses with a prenatal diagnosis of skeletal dysplasia (Sharony et al., 1993). SRPS, therefore, is extremely rare in the general population but may represent 4% of fetuses evaluated in a perinatal center for a presumed skeletal dysplasia.

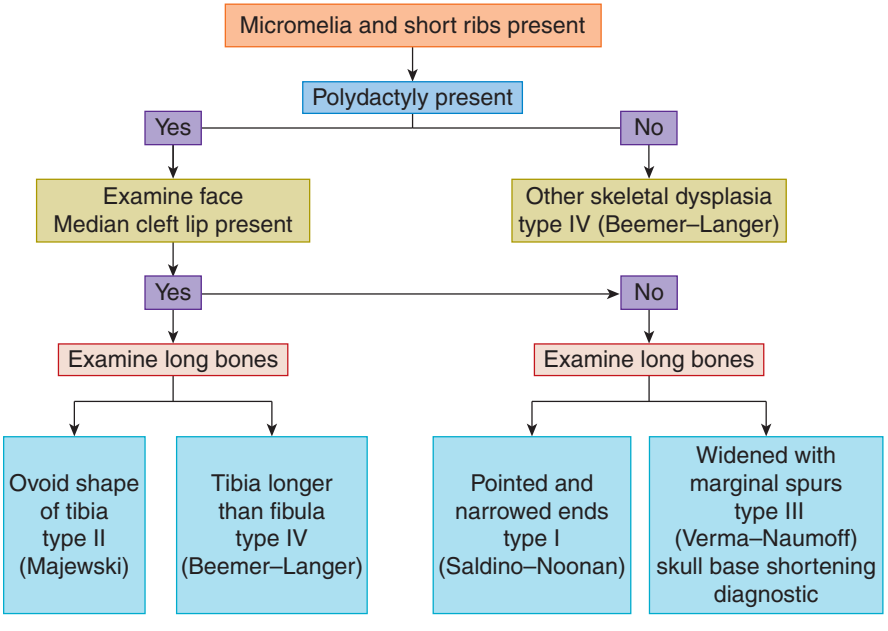

Figure 95-3 Approach to the sonographic diagnosis of the different short-rib polydactyly syndromes.

SONOGRAPHIC FINDINGS

Prenatal diagnosis by two-dimensional sonography has been reported for all of the subtypes of SRPS. Three-dimensional sonographic studies have been described in types II and III (Viora et al., 2002; Chen et al., 2005). Prenatal sonographic studies appear to be highly accurate in the setting of a family history that is positive because of a previously affected child. Prenatal diagnosis has also successfully been performed even in the setting of a negative family history (Meizner and Bar-Ziv, 1985; Benacerraf, 1993).

Prenatal diagnosis of type I SRPS has been described both in the first and early third trimesters (Hill and Leary, 1998; Meizner and Bar-Ziv, 1989). In the case ascertained at 13 weeks, a narrow chest, micromelia, polydactyly, and anasarca were seen on transvaginal sonography (Hill and Leary, 1998). In the case ascertained in the third trimester, a singleton fetus was reported with a markedly narrow thorax, severely shortened long bones with pointed metaphyses, polydactyly on both hands, a markedly bulging forehead, a large ventricular septal defect, a small penis, severe polyhydramnios, mild hydrops, and hypoplastic vertebral bodies (Meizner and Bar-Ziv, 1989). The prenatal diagnosis of type II SRPS is characterized by polyhydramnios, shortened long bones, and very short ribs extending less than halfway around the fetal thorax (Thomson et al., 1982; Gembruch et al., 1985; Benacerraf, 1993). This may give the heart a disproportionately large appearance within the thorax. In one report, the median cleft lip was visualized antenatally. In type II SRPS, the tibias have a diagnostic ovoid shape.

Prenatal diagnosis of type III SRPS consists of the typical findings of severe micromelia, narrowed thorax, short ribs, postaxial polydactyly, and severe polyhydramnios with mild edema (see Figure 95-1). The most useful diagnostic feature for discriminating type III from type I is that the ends of the long bones appear widened, with the presence of marginal spurs (see Figures 95-1 and 95-2). In addition, cases of type III SRPS demonstrate hypoplastic vertebral bodies with increased intervertebral spaces (Meizner and Bar-Ziv, 1985; Meizner and Barnhard, 1995). A fetus with type III SRPS has also been described with complete situs inversus and hypospadias (de Sierra et al., 1992). High airway obstruction due to epiglottal hypoplasia has been reported in type III SRPS (Golombeck et al., 2001; Chen et al., 2005).

Distinguishing type IV from type II SRPS is extremely difficult antenatally. In one case report, a fetus at 23.5 weeks of gestation was visualized with ascites, an extremely narrow thorax, short limbs, a flat midface with a median cleft lip, but no polydactyly. This patient was demonstrated on postmortem examination to have short intestines and pyloric stenosis (Balci et al., 1991). The differentiation between type II and type IV SRPS became even more confused with the report of Yang et al. (1991), who described a 30-week-old fetus with an antenatal diagnosis of SRPS but a postmortem diagnosis of Beemer–Langer syndrome with polydactyly. This fetus also had cerebral anomalies, a small heart, and ambiguous genitalia. Recently, transvaginal sonography has been used to diagnose two fetuses with type IV SRPS in the early second trimester (den Hollander et al., 1998).

Figure 95-3 illustrates a sonographic approach to the identification of the different SRPSs. Once the severe micromelia and short ribs have been demonstrated, the fetal hands and feet should be evaluated for the presence of polydactyly (Meizner and Barnhard, 1995). If polydactyly is absent, this could represent a different skeletal dysplasia, although type IV SRPS (Beemer–Langer syndrome) does not typically include polydactyly. A specific attempt should be made to examine the fetal face, because the presence or absence of a median cleft lip will help to separate types II and IV from types I and III SRPS. If a median cleft lip is present, then the diagnosis is either type II or IV SRPS. If the fetal face is completely normal, then the diagnosis is either type I or III. Examination of the long bones can help to further discriminate type II from type IV and type I from type III, because each of these subtypes has a characteristic long bone appearance on sonography (Cooper and Hall, 1982; Sillence et al., 1987; Yang et al., 1991; Meizner and Barnhard, 1995).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for a fetus with severe micromelia and short ribs with evidence of polydactyly includes chondroectodermal dysplasia (Ellis–van Creveld syndrome) (see Chapter 94), asphyxiating thoracic dystrophy (Jeune syndrome), Meckel–Gruber syndrome, and trisomy 13 (Meizner and Bar-Ziv, 1985) (see Chapter 129). Trisomy 13 can easily be differentiated from the other syndromes by chromosomal analysis. Fetuses with trisomy 13 generally do not manifest severe skeletal dysplasia. Polydactyly may be present, but the long bones are generally within the normal range or minimally shortened as compared with fetuses at the same gestational age. In Meckel–Gruber syndrome, the presence of the large polycystic kidneys and occipital encephalocele may help to distinguish this condition from the SRPSs.

It is important to demarcate the SRPSs from chondroectodermal dysplasia and asphyxiating thoracic dystrophy, because these latter two conditions are sometimes compatible with survival outside the womb. Chondroectodermal dysplasia is characterized by disproportionately short extremities, a small thorax, an atrial septal defect, cryptorchidism, clubfeet, unilateral renal agenesis, and variable pulmonary hypoplasia. In chondroectodermal dysplasia, polydactyly is always present in the hands, but the feet are affected only 10% of the time (Thomson et al., 1982). Asphyxiating thoracic dystrophy is characterized by a milder micromelia, less-shortened horizontal ribs, and the less frequent occurrence of polydactyly (Thomson et al., 1982). (See Table 95-1.)

ANTENATAL NATURAL HISTORY

Little is known about the antenatal natural history for these conditions, although there is an increased incidence of stillbirth, polyhydramnios, and hydrops fetalis in SRPS.

Table 95-1

Differential Diagnosis of Short-Rib Polydactyly Syndromes (SRPS)

	Type I (Saldino–Noonan)	Type II (Majewski)	Type III (Verma–Naumoff)	Type IV (Beemer–Langer)
Short ribs	+	+	+	+
Short long bones	+	+	+ (Spurs present)	+
Pulmonary hypoplasia	+	+	+	+
Polydactyly	+	+	+	–
Cleft lip/palate	–	+	–	+
CNS abnormalities	–	+	–	–
Congenital heart disease	+	–	–	–
Kidney cysts	+	–	–	–
Short skull base	–	–	+	–

MANAGEMENT OF PREGNANCY

Fetuses in which a skeletal dysplasia is suspected should have a targeted anatomic scan in a center with expertise in the diagnosis of fetal anomalies. The sonographic study should include a specific and detailed assessment of the bones (see Figure 95-3). In addition, attention should be paid to the documentation of associated anomalies that frequently occur in SRPS (see Table 95-1). Although the overwhelming majority of cases reported have had normal chromosomes, we recommend that an amniocentesis be performed to rule out trisomy 13 or to diagnose a chromosomal abnormality as the basis for the dysplasia. Many cases of SRPS in male fetuses are associated with absence of the penis or ambiguous genitalia. Therefore, obtaining a karyotype will help to diagnose the true fetal gender. Two case reports have documented chromosomal abnormalities in cases of SRPS. In one, a pericentric inversion of chromosome 4 was identified (Urioste et al., 1994). However, this abnormality was also present in the infant's clinically normal mother. In another case, a de novo pericentric inversion of the long arm of chromosome 17 was demonstrated in a case of Beemer–Langer syndrome. The abnormal karyotype [46, XY/46, XY, inv(17q21;q23)] was present in 8 of 60 cells (13%). This report raised the question of linkage of genes responsible for skeletal development to the long arm of chromosome 17 (Chen et al., 1994). In the past, fetoscopy was used to document the presence of the median cleft lip and polydactyly in families at risk for type II SRPS, Majewski syndrome (Toftager-Larsen and Benzie, 1984). At present, however, targeted sonography is considered to be the gold standard for prenatal diagnosis, but diagnostic fetoscopy may be contemplated when sonographic findings are unclear, and diagnosis will influence further management.

If the fetus is diagnosed as having one of the SRPS conditions, elective termination can be offered to the parents if the diagnosis is made at less than 24 weeks of gestation. The condition is uniformly lethal. To allow a definitive diagnosis, especially of the specific subtype of SRPS, we recommend delivery of an intact fetus to permit a full perinatal autopsy, radiographic studies, and collagen and DNA analysis (Figure 95-4).

FETAL INTERVENTION

There are no fetal interventions for SRPS.

TREATMENT OF THE NEWBORN

If a definitive diagnosis of SRPS has been made antenatally, newborn resuscitation is not indicated because these infants all have severe pulmonary hypoplasia that prevents survival outside the womb. The difficulty is that if the symptoms are due to asphyxiating thoracic dystrophy or chondroectodermal dysplasia, these latter conditions are compatible with survival. Therefore, a neonatologist should be present at the delivery to confirm the presumptive prenatal diagnosis. If the chest circumference is so narrow that severe pulmonary

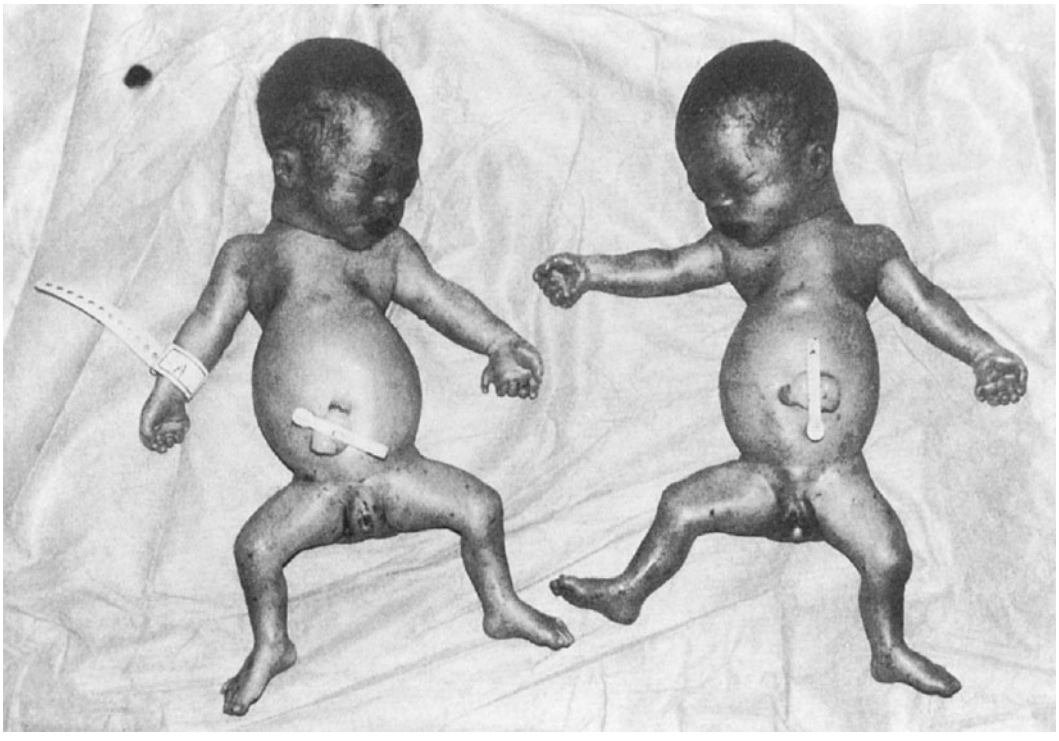

Figure 95-4 Postmortem appearance of monozygotic twins with SRPS delivered at 29 weeks of gestation each demonstrating polydactyly, short extremities, and an extremely narrow thorax. (*Reprinted, with permission, from Wu M-H, Kuo P-L, Lin S-J. Prenatal diagnosis of recurrence of short rib polydactyly syndrome.* Am J Med Genet. *1995;55:279-284. Copyright 1995 John Wiley & Sons. Reprinted, by permission, of John Wiley & Sons, Inc.*)

hypoplasia is present, the infant will not survive regardless of the underlying diagnosis. The cause of death in this condition is always respiratory insufficiency (Figure 95-5) (Prudlo et al., 1993).

As in the prenatal setting, we recommend that a complete autopsy be performed to permit definitive diagnosis. If the parents refuse an autopsy, postnatal radiographs should always be obtained. A complete radiologic assessment of the

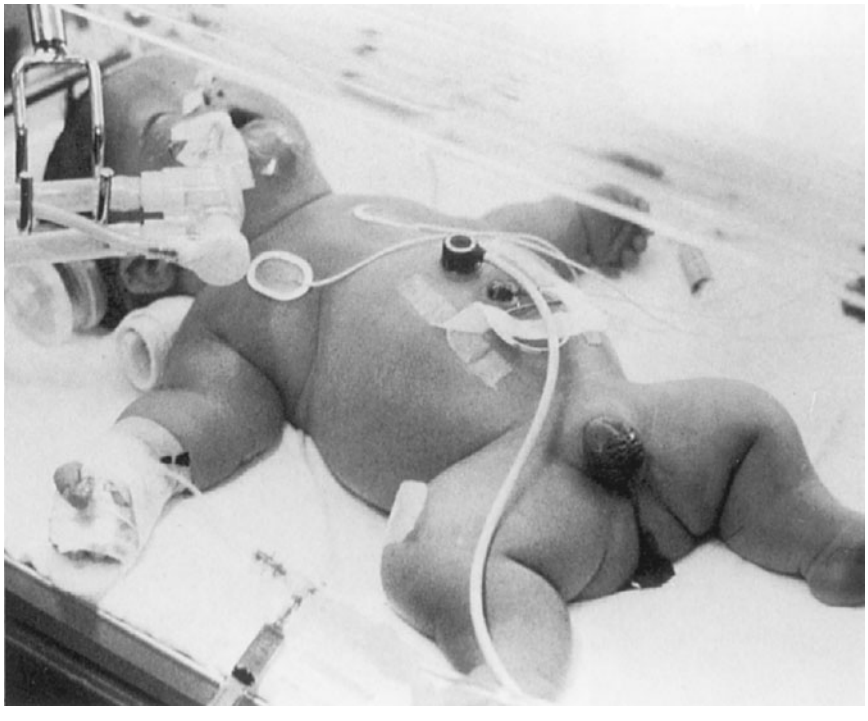

Figure 95-5 Postnatal appearance of an infant affected with SRPS of undetermined type, demonstrating shortened extremities, protuberant abdomen, and absent penis. (*Reprinted, with permission, from Wu M-H, Kuo P-L, Lin S-J. Prenatal diagnosis of recurrence of short rib polydactyly syndrome.* Am J Med Genet. *1995;55:279-284. Copyright 1995 John Wiley & Sons. Reprinted, by permission, of John Wiley & Sons, Inc.*)

fetus or infant should include anteroposterior and lateral views of the skull, spine, and chest; lateral view of one ankle; and anteroposterior views of the upper limb, lower limb, and pelvis. While radiographs may be helpful, there is no guarantee that they will contribute to a definitive diagnosis. In addition, a small sample of cartilage should be put into gluteraldehyde for subsequent electron microscopy. A generous amount of cartilage (from one complete long bone) should be frozen at −70°C for collagen and proteoglycan analysis. In addition, 1 cm^3 of tissue from the liver or spleen should be frozen and stored at −70°C for subsequent DNA analysis (Keating et al., 1989). This is important because the molecular bases for many of the skeletal dysplasias are currently being elucidated. Having tissue stored from the affected fetus or infant will permit eventual DNA analysis and definitive diagnosis. Once a DNA mutation is identified, prenatal diagnosis in a subsequent pregnancy is theoretically possible as early as 10 weeks of gestation by chorionic villus sampling.

Before the parents leave the hospital, an appointment should be made for approximately 6 weeks after delivery, when the results of these studies can be discussed.

SURGICAL TREATMENT

There are no surgical treatments for SRPS.

LONG-TERM OUTCOME

There is no long-term outcome for this condition, as it is invariably fatal during the neonatal period.

GENETICS AND RECURRENCE RISK

To date, all types of SRPS have been inherited as autosomal recessive disorders. In the majority of cases described, the chromosomes have been normal. The only two cases of chromosomal abnormalities found in cases of SRPS include a pericentric inversion of chromosome 4 (Urioste et al., 1994), and a de novo 17q pericentric inversion mosaicism (Chen et al., 1994). Thus far, the gene or genes responsible for SRPS have not been mapped. *EVC1*, the gene responsible for some cases of Ellis–van Creveld syndrome has been excluded as a cause of SRPS type III (Takamine et al., 2004). It is hoped that molecular analysis of the DNA obtained from affected fetuses and infants will help to clarify the confusing subclassification of this rare disorder.

Parents who have had a previously affected fetus or infant should be counseled regarding a 25% recurrence risk. Prenatal diagnosis by sonography appears to be highly accurate for diagnosis of recurrent cases within a family.

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Jarcho–Levin Syndrome

96 CHAPTER

Key Points

- "Jarcho–Levin" syndrome refers to a group of conditions characterized by short trunk dwarfism, rib and vertebral anomalies, and normal long bones.
- Inheritance may be autosomal recessive, autosomal dominant, or sporadic.
- Chromosomes are normal.
- Delivery should occur in a tertiary center due to increased likelihood of respiratory complications.
- No longer considered to be a lethal condition.
- All affected individuals are developmentally normal.

CONDITION

Jarcho–Levin syndrome is an eponym that refers to a group of conditions characterized by short trunk dwarfism, rib and vertebral anomalies, and normal long bones. The name Jarcho–Levin syndrome was attached to the condition because of an initial report in 1938 by Saul Jarcho and Paul Levin who described a brother and sister with severe malformations of their vertebral columns. In addition, the mother of these children had a minor cervical vertebral anomaly. The infants demonstrated a shortened thorax and a prominent abdomen. Both infants died from respiratory failure during the first year of life.

Subsequently, the classification of genetic syndromes that include rib and vertebral anomalies as their major symptoms has become progressively more confusing. Jarcho and Levin's original disorder was termed "hereditary malformation of the vertebral bodies." Related or identical conditions have also been called familial dwarfism due to hereditary multiple hemivertebrae, spondylothoracic dysostosis,

Table 96-1

Clinical and Genetic Features in the Jarcho–Levin Spectrum

	Spondylothoracic Dysplasia or Dysostosis (STD)	Spondylocostal Dysplasia or Dysostosis (SCD)
Sonographic Findings		
Ribs	Fused posteriorly creating "crablike" or "fan" appearance; no intrinsic malformations	Intrinsic malformations
Spine	Hemivertebrae	Hemivertebrae
	Fused vertebrae	Fused vertebrae
	Lordosis	Scoliosis
Long bones	Normal	Normal
Inheritance pattern	Autosomal recessive	Autosomal dominant or autosomal recessive
Causative gene	Unknown but linkage analysis maps gene to chromosome 2q32.1	Delta-like 3 (*DLL3*) on chromosome 19q13

Adapted from Wong G, Levine D. Jarcho–Levin syndrome: two consecutive pregnancies in a Puerto Rican couple. Ultrasound Obstet Gynecol. *1998;12:70-73.*

spondylocostal dysplasia, spondylocostal dysostosis, costovertebral dysplasia, and occipito-facial-cervical-thoracic-abdominal-digital dysplasia. The nosology of these various conditions is further complicated by the fact that some of them are inherited as autosomal dominant genes and some are associated with autosomal recessive inheritance (Table 96-1). The condition that most clinicians agree is the classical presentation of Jarcho–Levin syndrome is spondylothoracic dysplasia, and consists of multiple rib and vertebral anomalies associated with a "crab-claw" or "fanlike" configuration of the ribs on X-ray (Figures 96-1 and 96-2), with a resultant small thoracic volume and symptoms coincident with respiratory insufficiency. The majority of patients who manifest the classic Jarcho–Levin syndrome can trace their ancestry to Puerto Rico (Perez-Comas and Garcia-Castro, 1974).

INCIDENCE

The incidence of spondylothoracic dysplasia is unknown. It is rare. As previously stated, the disorder occurs most frequently in patients of Puerto Rican ancestry, although there have been multiple reports of familial Jarcho–Levin syndrome in Europeans and at least one report in an Arab family (Romeo et al., 1991; Eliyahu et al., 1997). The incidence of spondylocostal dysplasia is 0.25 per 10^5 livebirths (Martínez-Frias et al., 1994).

SONOGRAPHIC FINDINGS

Spondylothoracic dysostosis should be suspected in any fetus with multiple vertebral anomalies and spina bifida (Cornier et al., 2003). Jarcho–Levin syndrome has been diagnosed in the first trimester through a combination of increased nuchal translucency thickness and spine abnormalities visualized by two-dimensional or three-dimensional sonography (Hull et al., 2001; Kauffmann et al., 2003).

The fetal vertebral bodies can be visualized between 16 and 20 weeks of gestation on a longitudinal section that includes the entire spinal canal. At this point in the pregnancy, the normal parallel line configuration of the fetal spine should be obtainable no matter where the fetal spine is located within the uterus (Miskin et al., 1979). The first prenatal roentgenographic diagnosis of Jarcho–Levin syndrome was made in 1979 and the first prenatal sonographic diagnoses were made in the 1980s (Marks et al., 1989). In 1987, Tolmie et al. described a Scottish couple who had a previous child affected with Jarcho–Levin syndrome. In a subsequent pregnancy, at 20 weeks of gestation, a grossly deformed spine and incomplete rib cage were demonstrated on prenatal sonography. The pregnancy was electively terminated and postmortem study revealed associated anomalies, including an imperforate anus and ectopic adrenal glands. Simultaneously, another report at 22 weeks of gestation described the subtle spacing and

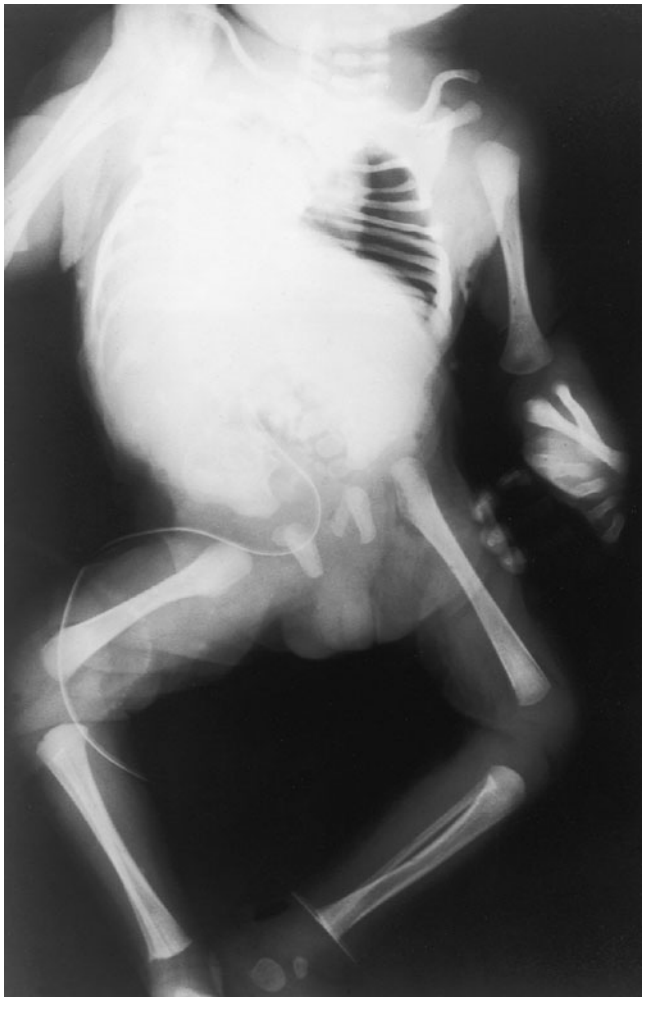


Figure 96-1 Anteroposterior radiograph of a newborn with Jarcho–Levin syndrome, demonstrating deformation of chest with characteristic "crab-claw" appearance.

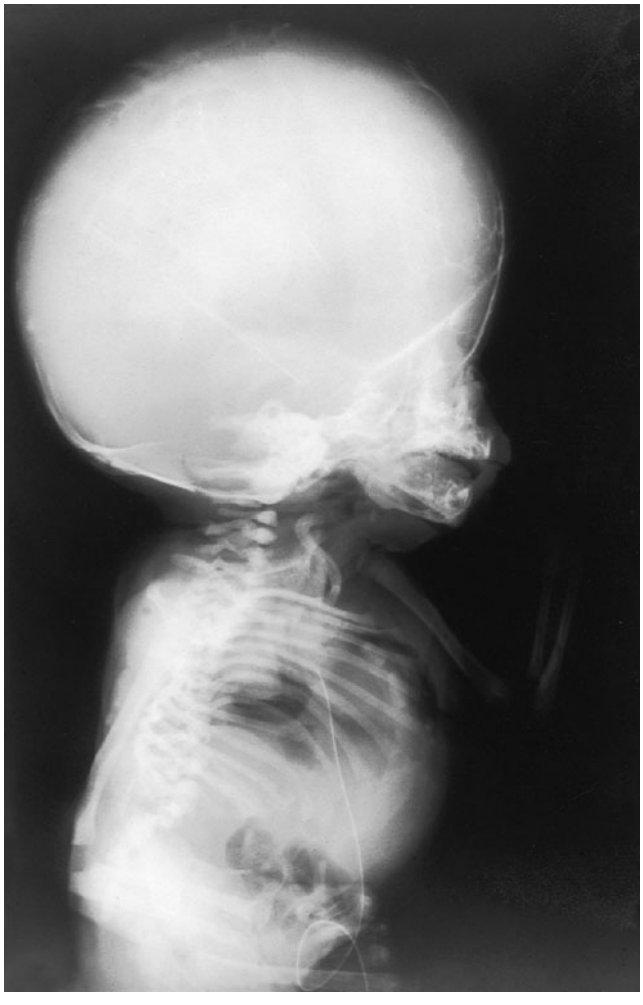


Figure 96-2 Lateral radiograph of the patient in Figure 96-1, showing the fanlike appearance of ribs.

widening of the fetal vertebrae seen in prenatal sonographic examination of a fetus with Jarcho–Levin syndrome. At 22 weeks of gestation, a slightly smaller than normal chest diameter was appreciated but the diagnosis was unclear. By 28 weeks of gestation, an abnormally shaped chest was appreciated that included slight flattening of the ribs and irregularly spaced vertebrae (Apuzzio et al., 1987). In the third report, a fetus at 23 weeks of gestation was described with a shortened spine, disorganization of the vertebral bodies, posterior fusion of the ribs, with a short thorax but normal thoracic diameter. In a coronal view, narrowing of the lateral laminae in the lower thoracic and upper lumbar region was described. In the sagittal and coronal planes, grossly malaligned vertebrae, disorganization of vertebral bodies, and posteriorly fused ribs were appreciated (Romero et al., 1988). In 1989, Marks et al. reported two fetuses with sonographic findings of Jarcho–Levin syndrome. They described the following sonographic criteria for diagnosis of this condition (Marks et al., 1989):

1. Unpaired and poorly formed vertebral centers resulting in a "pebblelike" appearance of the spine (Figure 96-3);
2. Multiple vertebral body fusion causing an irregular shortened spine;
3. Indistinct or joined ribs posteriorly;
4. A small or shortened thorax;
5. A protuberant abdomen resulting from the shortened thorax;
6. The presence of abdominal hernias;
7. Normal amniotic fluid volume;
8. Normal limb length and biparietal diameter measurements for gestational age.

Subsequent reports have described the utility of prenatal sonographic diagnosis in families known to be at risk because of the prior birth of an affected infant (Lawson et al., 1997; Wong and Levine, 1998). In one study, four affected fetuses were diagnosed as early as 12 weeks of gestation (Eliyahu et al., 1997).

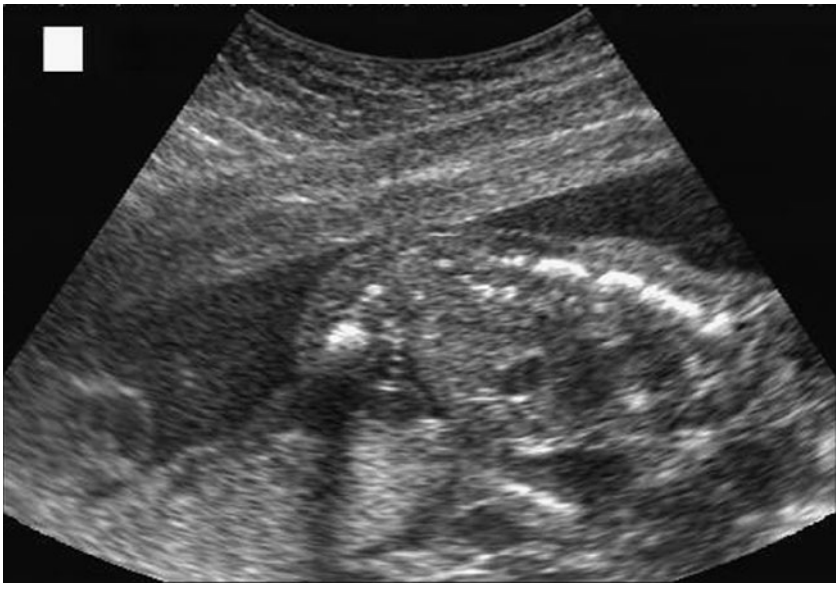


Figure 96-3 Sonographic image demonstrating unpaired and poorly formed vertebral centers resulting in an extremely abnormal appearance of the spine. (*Image courtesy of Prenatal Diagnosis Center, Women and Infants' Hospital.*)

DIFFERENTIAL DIAGNOSIS

The main consideration in the differential diagnosis is the determination of whether the findings are consistent with Jarcho–Levin syndrome or the related spondylocostal dysostoses, or whether the anomalies represent a more serious lethal skeletal dysplasia, such as Jeune syndrome, campomelic dysplasia, or thanatophoric dysplasia. These lethal conditions can be distinguished sonographically from Jarcho–Levin syndrome by the short long bones and narrow chest. In addition, in each of these three conditions there is no fusion of the ribs. Klippel–Feil syndrome can be distinguished from Jarcho–Levin syndrome because it affects the cervical rather than the thoracic ribs. Other conditions in the differential diagnosis include dyssegmental dysplasia and spondyloepiphyseal dysplasia congenita. In dyssegmental dysplasia the limbs are short with reduced mobility. In spondyloepiphyseal dysplasia congenita there is no rib fusion and platyspondyly is present. Any fetus that presents with thoracic vertebral anomalies should be further investigated to rule out the VACTERL association, which consists of vertebral, anal, cardiac, tracheal and esophageal, renal, and radial limb anomalies (Wong and Levine, 1998). The condition that is most similar to Jarcho–Levin syndrome is COVESDEM (costovertebral segmentation defects with mesomelia) syndrome (Wadia et al., 1978). In this condition, however, the thorax is not shortened and mesomelia of the limbs is present, affecting the upper extremities more severely than the lower.

ANTENATAL NATURAL HISTORY

Morphologic studies of affected fetuses have shown that the vertebral bodies are malformed and consist of asymmetrically distributed ossification centers that vary greatly in size and shape and rarely cross the midline (Solomon et al., 1978). Microscopic examination of fetuses with Jarcho–Levin syndrome that were terminated during the second trimester has demonstrated disorganized vertebral endochondral bone formation with a lack of orderly column formation of mature chondrocytes. Although the ribs are characteristically fused, the endochondral bone formation within the ribs is normal (Marks et al., 1989). These defects undoubtedly occur extremely early in gestation, as the paraxial mesoderm undergoes segmentation between 21 and 28 days of gestation (Tolmie et al., 1987). Because certain homeobox genes important in formation of body structure are expressed uniquely in spinal cord, the question has been raised as to whether Jarcho–Levin syndrome could represent a mutation in one of the master homeobox genes that control vertebral development, such as *Pax1* and *Pax9* (Tolmie et al., 1987). Bannykh et al. (2003) performed immunochemical analysis of the levels of Pax1 and Pax9 proteins in chondrocytes from two fetuses with Jarcho–Levin syndrome and found them to be significantly reduced compared to controls.

Approximately one-third of fetuses and infants with Jarcho–Levin syndrome have associated malformations that are outside of the thorax and vertebral bodies (Roberts et al., 1988). Some of the nonskeletal malformations that have been described in Jarcho–Levin syndrome include genitourinary anomalies such as uterus didelphys, bilobed bladder, hydronephrosis, undescended testes, urethral atresia, absent external genitalia, single umbilical artery, cerebral polymicrogyria, and congenital heart defects (Poor et al., 1983; Hatakeyama et al., 2003). Most reports do not emphasize central nervous system malformations, although spina bifida and diastematomelia were described in a patient with Jarcho–Levin syndrome. Spina bifida occulta is reported to occur in 40.6% of patients with Jarcho–Levin syndrome (Giacoia and Say, 1991).

MANAGEMENT OF PREGNANCY

The main consideration in management of pregnancy is an accurate sonographic diagnosis. Prenatal sonograms should be reviewed by an expert in diagnosis of skeletal dysplasias. Both decreased and elevated maternal serum α-fetoprotein levels have been reported in this condition (Apuzzio et al., 1987; Romero et al., 1988). All reports of fetuses and infants affected with this condition have had normal chromosomes (Cantu et al., 1971; Perez-Comas and Garcia-Castro, 1974; Tolmie et al., 1987; Romero et al., 1988; Karnes et al., 1991). Therefore, if the sonographic diagnosis is reasonably certain, there is no indication to obtain a fetal karyotype. The route of delivery should be vaginal unless otherwise indicated for obstetric reasons. It is important for fetuses with Jarcho–Levin syndrome to be delivered in tertiary care centers because most of these infants will require neonatal resuscitation, mechanical ventilation, and postnatal genetic assessment.

FETAL INTERVENTION

There are no fetal interventions for Jarcho–Levin syndrome.

TREATMENT OF THE NEWBORN

A complete and detailed physical examination is indicated. Typical findings of the infant with Jarcho–Levin syndrome include a short neck, prominent occiput, low hairline, and a dysmorphic facial appearance that consists of a broad forehead, wide nasal bridge, prominent philtrum, anteverted nares, and a triangle-shaped mouth (Figure 96-4A). Additional physical findings include a protuberant abdomen, poor muscle tone, abdominal hernias, long tapering fingers and toes, and soft tissue syndactyly.

Because of the abnormally shaped chest, infants with Jarcho–Levin syndrome are likely to have pulmonary hypoplasia and may require resuscitation in the delivery room. Optimal treatment of the newborn with Jarcho–Levin syndrome should include delivery in a tertiary care center with a neonatologist prepared to provide immediate respiratory support and mechanical ventilation.

Consultation with a clinical geneticist is indicated. In the newborn nursery, a complete postnatal skeletal survey should be performed. Radiographs should include the spine, which will demonstrate clefts, hemivertebrae, and abnormal vertebral body fusion and the chest, which may demonstrate hypoplasia and multiple rib fusion as well as a "scrambled" vertebral column (see Figures 96-1 and 96-2) (Herold et al., 1988). Additional bony anomalies that may be diagnosed postnatally include an absent coccyx and a hypoplastic sacrum. The typical posteroanterior chest radiograph will show the rib anomalies in a distribution that appears similar to a crab. The lateral chest radiograph should show the rib fusion anomalies in a manner that appears like a fan (see Figure 96-2). These findings are considered pathognomonic for this condition. In addition, long bone films will be helpful to rule out another skeletal dysplasia.

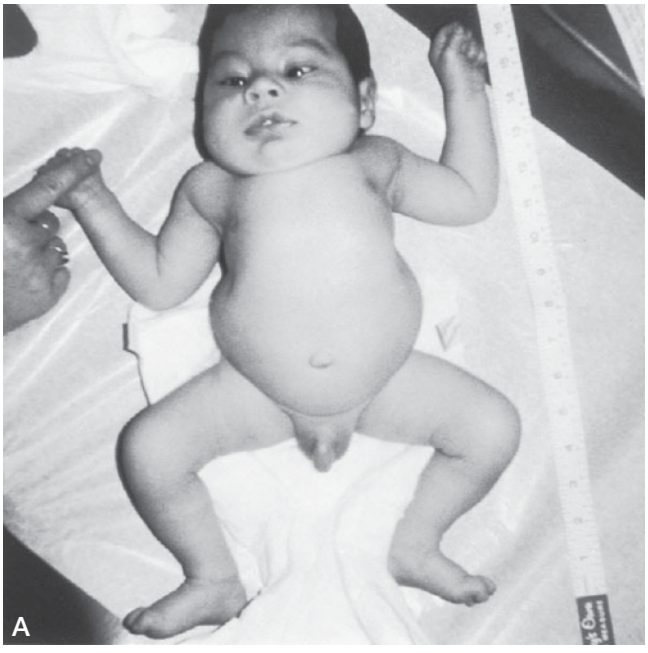
SURGICAL TREATMENT

The management of the orthopedic anomalies in Jarcho–Levin syndrome is difficult. The crablike rib deformity and consequent pulmonary hypoplasia often require mechanical ventilatory support. This can be compounded by flail segments of the chest wall. In order to optimize respiratory mechanics and improve the affected infant's ability to be weaned from mechanical support, chest wall reconstruction may be necessary. We successfully performed an extensive chest wall reconstruction in an infant with Jarcho–Levin syndrome. In addition to a flail anterolateral right chest wall, he had diaphragmatic insertion at the 6th rib, further compromising ventilation. A prosthetic patch and rib graft were used to stent the flail chest wall segment, and the diaphragm was repositioned at the 12th rib posteriorly. The infant subsequently died from infection. More recently, the use of vertical expandable titanium rib techniques has been advocated to stabilize the chest and prevent pulmonary complications from progressive scoliosis (Vázquez-López et al., 2005).

LONG-TERM OUTCOME

Jarcho–Levin syndrome was considered to be a lethal condition until Cornier et al. (2004) described a cohort of 27 prospectively evaluated patients with spondylothoracic dysplasia and a 56% long-term survival rate. The patients who died in the first 6 months did so due to respiratory insufficiency secondary to pneumonia and pulmonary restriction. Other complications include pulmonary hypertension (Rastogi et al., 2001). Affected infants generally require multiple hospital admissions during the first year of life due to upper respiratory infections, but after 2 years of age, this decreases significantly (Cornier et al., 2004). Approximately half of patients are diagnosed with reactive airway disease. Pulmonary function tests show a severe restrictive pattern. Patients have short stature, averaging at the 2nd percentile for age. They also have a prominent abdomen and recurrent inguinal hernias.

Importantly, mental retardation is not a component of this condition. In Cornier et al.'s (2004) report, all affected individuals were developmentally normal for their age, except for mild delays in their motor milestones during the first 18 months of life. Herold et al. (1988) described 10 cases of Jarcho–Levin syndrome, 8 of whom survived well into childhood and adolescence. One of the patients described in this report included a 14-year-old who had no respiratory problems and had good compensatory movement in the hip joints



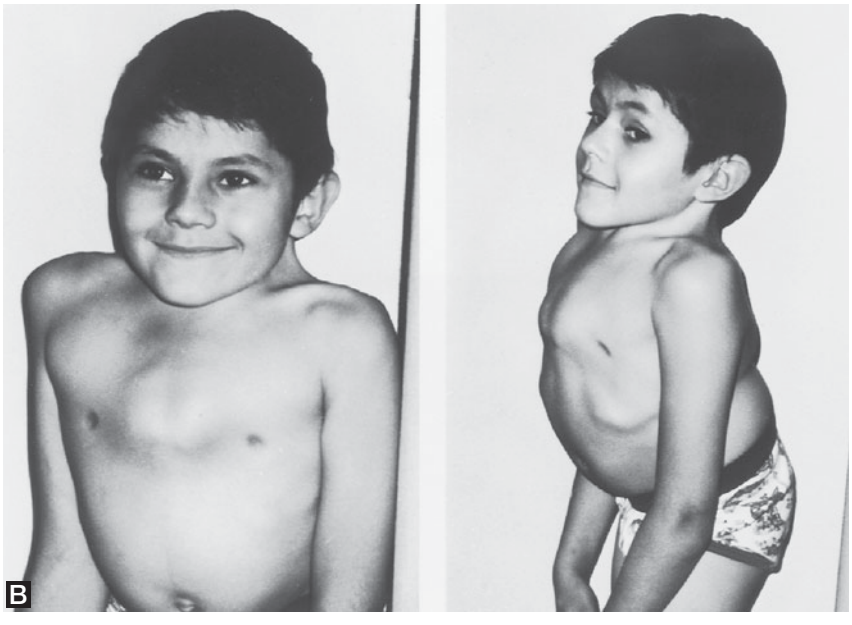


Figure 96-4 **A.** Infant with Jarcho–Levin syndrome who survived postnatally. **B.** Same patient as in (A), at age 7 years 8 months, demonstrating marked thoracic and neck shortness with severe pectus carinatum deformity. (*Reprinted, with permission, from McCall CP, Hudgins L, Cloutier M, et al. Jarcho–Levin syndrome: unusual survival in a classical case.* Am J Med Genet. *1994;49: 328-332.*)

despite marked restriction of the lumbar spine and rigidity of the cervical spine. This patient could bend and touch the floor without bending her knees. She was as active as other children with the exception of having back pain.

A long-term survivor, an 11-year-old Puerto Rican male was described in great detail in 1994 (McCall et al., 1994). This patient had the classic phenotype of Jarcho–Levin syndrome (Figure 96-4B). By 11 years of age, his height was more than 3 SD below the mean and equaled a height-age of 8 years. His weight was between the 5th and 25th percentile for age. His overall health was good, with the exception of recurrent otitis media in childhood and pneumonia at 5 months of age and then again at 3 years 6 months. This individual had normal development and hearing, and was attending a regular fifth-grade class. He was extremely active in sports and was limited only by pulmonary function. His physical examination at age 11 showed an extremely short neck with low hairline and limited neck movement. His arms were long in relation to his body. He had a pectus carinatum deformity and an increased anteroposterior diameter of his chest. He had a dorsal kyphoscoliosis and a lumbar lordosis with a prominent abdomen. His face was normal and he had no other anomalies. Pulmonary function testing at age 11 years revealed a moderately severe restrictive pulmonary disease, with a decreased forced vital capacity and decreased forced expiratory volume. Although his pulmonary function tests are slightly worsening with time, these authors felt that for an individual diagnosed with Jarcho–Levin syndrome, the prognosis was less pessimistic than previously thought (McCall et al., 1994).

GENETICS AND RECURRENCE RISK

The genetics of Jarcho–Levin syndrome are somewhat confused in the medical literature because of the different criteria used to establish the diagnosis. The clinical findings in 42 published patients were separated into three clusters based on their physical findings. The patients were grouped into the severely affected with recessively inherited Jarcho–Levin syndrome, the more mildly affected patients with autosomal recessive or autosomal dominant disorders, and the patients who appeared to have the segmentation defects (Ayme and Preus, 1986). In another study, 172 cases of spondylocostal dysostosis were reviewed for their patterns of inheritance. Of these, 78 appeared to be inherited as recessive disorders, 20 were dominantly inherited disorders, and 78 were new mutations in the family. The gene for autosomal recessive spondylocostal dystostosis is deltalike 3 (DLL3) on chromosome 19q13. More than 17 mutations have been described in DLL3, which is a somitogenesis gene that encodes a ligand for the Notch signaling pathway (Turnpenny et al., 2003).

There is good evidence for autosomal recessive inheritance of the classic phenotype of Jarcho–Levin syndrome. First of all, there is an increased incidence of consanguinity in affected cases (Herold et al., 1988). In a review of 21 patients with Jarcho–Levin syndrome of Puerto Rican or Hispanic ancestry, 43% had evidence of either consanguinity or more than one affected case in the family with normal parents. Linkage analysis in this group has mapped the as yet unknown causative gene to chromosome 2q32.1.

Parents of a fetus or infant identified with features that are likely to represent Jarcho–Levin syndrome should meet with a genetic counselor to have a complete three generation family history taken. Once a clinical diagnosis is established for the fetus or infant, genetic counseling is indicated to discuss recurrence risk. If autosomal recessive inheritance appears likely, the recurrence risk is 25%.

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97 CHAPTER Achondrogenesis

Key Points

- Second most common lethal short-limb dysplasia.
- Incidence is 1/40,000 to 1/50,000 livebirths.
- Characterized by severe micromelia, lack of vertebral ossification, and a large head with relatively normal ossification of the calvarium; also associated with polyhydramnios, cystic hygroma, and hydrops fetalis.
- Type I (20% of cases) is more severe and is inherited as an autosomal recessive. Type IB is caused by a mutation in the diastrophic dysplasia sulfate transporter (*DTDST*) gene.
- Type II (80% of cases) is caused by mutations in the *COL2A1* gene, which results in significantly decreased type II collagen. Type II is usually a de novo dominant mutation, with rare reports of recurrence due to germline mosaicism.
- Increased incidence of prematurity and stillbirth. Condition is lethal in perinatal period.

CONDITION

The term achondrogenesis refers to a diverse group of generally lethal chondrodysplasias characterized by a short trunk, severe micromelia, and a disproportionately large cranium. Achondrogenesis is the second most common lethal short-limb dysplasia. The term achondrogenesis is actually a misnomer, as it implies that cartilage is not made. In this condition, cartilage is made but it is profoundly abnormal. A more correct term would be chondrogenesis imperfecta (Eyre et al., 1986).

Subclassification of the different conditions included under the term achondrogenesis has been confusing. Historically, two types of achondrogenesis have been described: type I is referred to in the literature as Parenti–Fraccaro syndrome. This subtype accounts for 20% of cases and is the more severe of the two. Type II achondrogenesis—termed Langer–Saldino syndrome—accounts for 80% of cases. In 1983, Whitley and Gorlin reviewed 79 cases that presented with a lethal neonatal chondrodysplasia. Affected infants had a short trunk, extreme micromelia, and a disproportionately large cranium. Radiographically, they were demonstrated as having deficient spine ossification, short ribs with cupped and flared ends, and absent pubic and ischial ossification. On the basis of this study, they identified four subtypes. These included type I (Parenti–Fraccaro), which was characterized by multiple rib fractures and the most marked limb shortening. Within the type II category (Langer–Saldino), they identified three subtypes, characterized by differences in the severity of the micromelia and ossification of the vertebrae. Although type I achondrogenesis was traditionally called Parenti–Fraccaro syndrome, a review by Borochowitz et al. (1988) revealed that the original case described by Parenti had a well-ossified skull and ossification of the vertebral bodies. This original case, therefore, was more likely to represent a more mildly affected case of achondrogenesis type II.

Borochowitz et al. (1988) attempted to more accurately classify the subtypes of achondrogenesis (Figure 97-1). In this report, they divided achondrogenesis into three subtypes: the most severely affected is lethal achondrogenesis, type IA (Houston–Harris). This condition is characterized by a poorly ossified skull, multiple rib fractures, and a completely unossified spine (Figure 97-2). Type I also includes lethal achondrogenesis, type IB (Fraccaro), which follows the original case description of Fraccaro. These patients are characterized by a poorly ossified skull, absence of rib fractures, and some ossification of the posterior pedicles of the spine (Figure 97-3). The third subtype is known as lethal achondrogenesis, type II (Langer–Saldino), which is characterized by a normally ossified skull and some ossification of the vertebral bodies, which may make the spine appear flat and ovoid. All three types of achondrogenesis are lethal and they are distinguished from a rare nonlethal form, known as Grebe dysplasia that has been described in Brazilian patients.

Affected Bone	Type of Achondrogenesis by Eponym		
	Houston–Harris Achondrogenesis IA	Fraccaro Achondrogenesis IB	Langer–Saldino Achondrogenesis II/Hypochondrogenesis
Skull	Poorly ossified	Poorly ossified	Normally ossified
Ribs	Short & fractured	Short, no fractures Cupped ends	Short
Spine	Completely unossified	Posterior pedicles only	Flat & ovoid (when ossified)
Ilium	Arched	Crenated	Hypoplastic with medial spike
Ischium	*Ossified–hypoplastic	Unossified trapezoid	Ossified–hypoplastic
Femur	Wedged with metaphyseal spike	Crenated unossified	Short & broad with metaphyseal flare
Tibia	Short with metaphyseal flare		Short & broad
Fibula			Short & broad
	*Unossified 30 weeks' gestation		

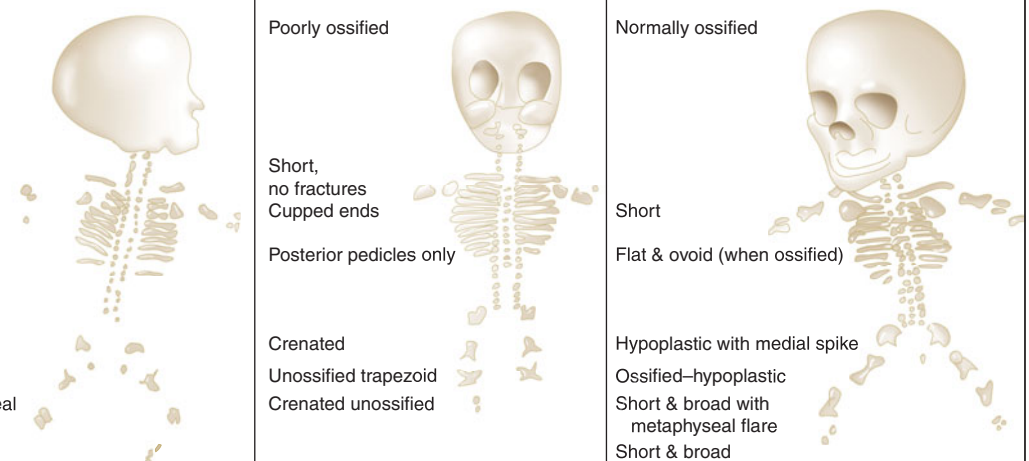

Figure 97-1 Diagrammatic representation of the major radiographic differences seen in the subtypes of achondrogenesis. (*Reprinted, with permission, from Borochowitz Z, Lachman R, Adomain GE, Spear G, Jones K, Rimoin DL. Achondrogenesis type 1: delineation of further heterogeneity and identification of two distinct subgroups.* J Pediatr. *1988;112:28.*)

The molecular basis of the achondrogenesis syndromes affirm the rationale behind the classification of Borochowitz et al. Achondrogenesis type IB is caused by an inborn error of cartilage metabolism and achondrogenesis type II is caused by a defect in type II collagen (Rimoin, 1996). The underlying basis for achondrogenesis type IA is currently unknown.

Achondrogenesis is part of the group of disorders known as osteochondrodysplasias, which highlights the fact that abnormalities of cartilage or bone growth and development are present (Rimoin, 1978). Autopsy studies performed on all patients with achondrogenesis reveal disorganization of the chondrocytes. In some cases, the cartilage matrix stains irregularly for mucopolysaccharides (Jimenez et al., 1973). For all cases of achondrogenesis, chondrocytes fail to align in columns and they are very irregularly distributed. In type IA, intracellular acid Schiff–positive inclusion bodies are seen with vacuolization of cytoplasm of chondrocytes of the growth plate (Jaeger et al., 1994). These intracytoplasmic inclusion bodies are pathognomonic of achondrogenesis type IA. Type IB is characterized by a decrease in type II collagen, with a peculiar arrangement of fibers in the cartilage matrix that form unique or multiple rings around the chondrocytes (Freisinger et al., 1994). In type II achondrogenesis, there are structural abnormalities present in the type II collagen. This results in an abnormal, poorly secreted type II collagen molecule. Ultrastructural studies have shown intracellular retention of type II collagen within vacuolar structures, probably existing within dilated rough endoplasmic reticulum observed in all chondrocytes by electron microscopy (Godfrey et al., 1988). Patients with type II achondrogenesis have increased amounts of type I and type III collagen (Feshchenko et al., 1989). Therefore, definitive diagnosis of the subtype of achondrogenesis is possible with histopathologic studies.

INCIDENCE

The incidence of achondrogenesis is 1 in 40,000 to 1 in 50,000 livebirths (Smith et al., 1981; Orioli et al., 1986; Lachman and Rappaport, 1990). Achondrogenesis accounts for 1 in 650 perinatal deaths (van der Harten et al., 1988).

SONOGRAPHIC FINDINGS

The major sonographic findings in achondrogenesis are that of a severe short-limb dwarfism with lack of vertebral ossification (Table 97-1). Typically, a large head is seen with either normal or decreased ossification of the calvarium. Additional findings include a small thorax, protuberant abdomen, and polyhydramnios or generalized edema (Figure 97-4) (Wenstrom et al., 1989). Large cystic hygromas have been described in association with types I (Özeren et al., 1999) and II (Won et al., 1999). To distinguish between types IA and IB and type II, a specific notation must be made of the degree of skull ossification. Type I is characterized by decreased or absent skull ossification. In addition, type IA is characterized by the presence of rib fractures, which can be visualized sonographically (see Figure 97-2) (Graham et al., 1983). In one report, the most specific finding for the diagnosis of achondrogenesis in a case of short-limb dysplasia was a transverse view

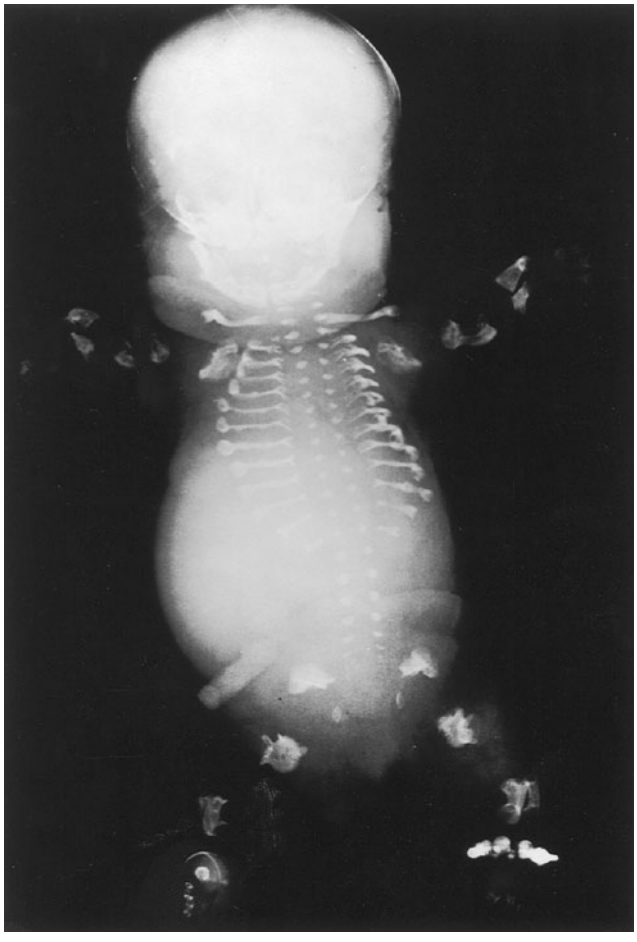

Figure 97-2 Postmortem radiograph of an infant with achondrogenesis, type IA, demonstrating the pathognomonic rib fractures, unossified spine, short long bones, arched ilium, and hypoplastic ischium. (*Reprinted, with permission, from Borochowitz Z, Lachman R, Adomain GE, Spear G, Jones K, Rimoin DL. Achondrogenesis type 1: delineation of further heterogeneity and identification of two distinct subgroups.* J Pediatr. *1988;112:24.*)

of the fetus demonstrating less than three ossification centers per spinal segment (Pretorius et al., 1986). Interestingly, approximately one-third of cases with achondrogenesis are associated with hydrops fetalis. It is postulated that this may be due to the primary collagen defect in type II, which may damage subcutaneous tissue as well as bone and cartilage (Soothill et al., 1993).

In one report of 15 cases of achondrogenesis, all fetuses were demonstrated to have severe micromelia. Of these 15 cases, 6 were detected early in the second trimester (between 15 and 19 weeks of gestation), 13 (87%) showed decreased or absent vertebral body ossification, 6 (40%) showed a narrow thorax, 5 (33%) showed deformed extremities, 7 (47%) had polyhydramnios, and 5 (33%) had hydrops fetalis (Figure 97-5) (Mahony et al., 1984). Multiple case reports exist in the literature in the setting of both positive and negative family histories, in which the diagnosis of achondrogenesis was made easily by sonography (Golbus et al., 1977; Graham et al., 1983; Benacerraf et al., 1984; Glenn and Teng, 1985; Tongsong et al., 1995). Transvaginal sonography has also been used to demonstrate that the pathologic abnormalities in achondrogenesis are present as early as 9 weeks of gestation (Fisk et al., 1991). In one case, a positive family history alerted the sonographer to the potential for achondrogenesis (Fisk et al., 1991). At 9 weeks of gestation, no movement was seen in the fetal limb buds. By 10 weeks of gestation, nuchal and dorsal edema were visualized. At 11 weeks of gestation, the edema was shown to be increased, with upper and lower extremities grossly shortened and held in abnormal and fixed position. Even at this early stage of gestation, the vertebral bodies and long bones were difficult to identify, although the crown-to-rump length was appropriate for gestational age. These early findings were thought to be consistent with a diagnosis of achondrogenesis type II. Of interest in this report was the discussion regarding the nuchal edema, in which cystic hygroma was ruled out because there was no endothelial lining surrounding the fluid-filled areas. These authors postulated that this finding was possibly due to lymphatic stasis, and they also stated that nuchal edema may be an important component in the first trimester sonographic diagnosis of achondrogenesis (Fisk et al., 1991). In an additional case (also in a pregnancy at risk because of a prior family history), a fetus at 12 weeks of gestation was diagnosed with achondrogenesis type II by transvaginal sonography. Even at this early point in gestation, severe hydrops and abnormal bone formation were noted (Soothill et al., 1993). Transvaginal prenatal diagnosis of achondrogenesis IB has also been described in the first trimester (Meizner and Barnhard, 1995). Pertinent findings included severely shortened extremities, thin ribs with fractures, deficient ossification of the vertebral bodies, and underossification of the calvarium. Three-dimensional imaging has also been used to diagnose a case of achondrogenesis type II (Krakow et al., 2003).

DIFFERENTIAL DIAGNOSIS

A multicenter study demonstrated that femur length was the best biometric parameter to distinguish amongst the five most common skeletal dysplasias (thanatophoric dysplasia, osteogenesis imperfecta type II, achondrogenesis, achondroplasia, and hypochondroplasia). Fifty-four percent of fetuses with a femur length measuring less than 30% of the mean for gestational age had achondrogenesis (Mahony et al., 1984). Furthermore, the combination of absent vertebral body ossification with normal skull ossification was shown to differentiate achondrogenesis from most other severe skeletal dysplasias.

The differential diagnosis for the fetus with a severe short-limb dysplasia and apparently absent vertebral bodies also includes hypophosphatasia. However, severe hypophosphatasia results in a diffuse underossification of all bones. The fetal skull in hypophosphatasia is not as well seen as it is in achondrogenesis type II. Other considerations in the setting of a severe short-limb dysplasia documented at less than 20 weeks of gestation include thanatophoric dysplasia, homozygous achondroplasia, and short-rib polydactyly

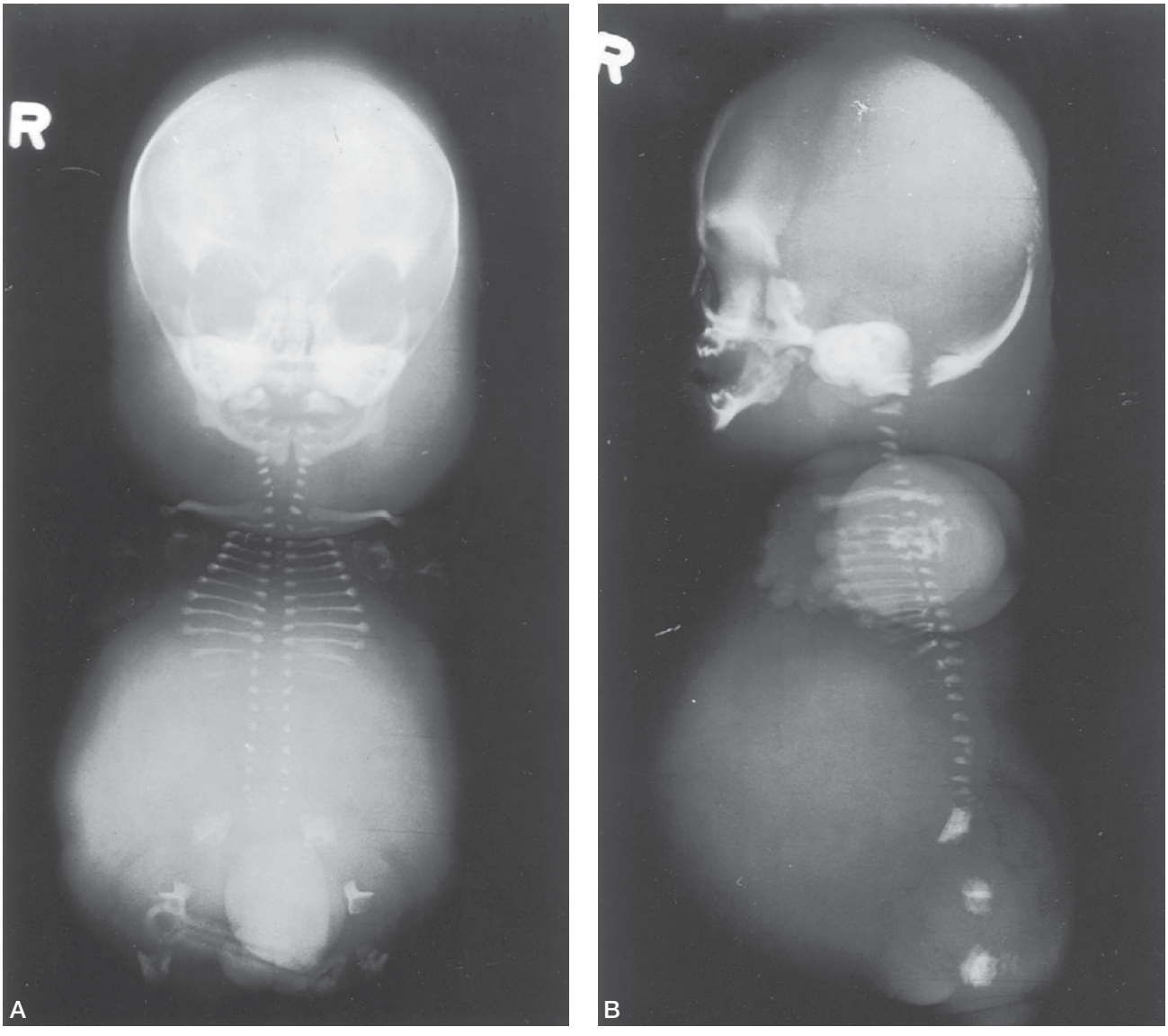

Figure 97-3 **A.** and **B.** Postmortem radiographs of an infant with achondrogenesis, type IB, demonstrating short ribs, ossified posterior spine pedicles, short long bones, crenated ilium, and unossified ischium. Note the absence of rib fractures, in contrast to type IA seen in Figure 97-2. (*Reprinted, with permission, from Borochowitz Z, Lachman R, Adomain GE, Spear G, Jones K, Rimoin DL. Achondrogenesis type 1: delineation of further heterogeneity and identification of two distinct subgroups.* J Pediatr. *1988;112:27.*)

syndrome. In all these conditions, underdevelopment of the vertebral bodies is seen, but there is normal calvarial ossification. In short-rib polydactyly syndrome, the presence of an extra digit can be demonstrated. Other considerations in the differential diagnosis include campomelic dysplasia, chondrodysplasia punctata with proximal limb shortening, Grebe syndrome, and osteogenesis imperfecta, type II (Pretorius et al., 1986).

ANTENATAL NATURAL HISTORY

For all types of achondrogenesis, there is an increased incidence of both prematurity and stillbirth. The condition is frequently complicated by polyhydramnios (Saldino, 1971; Borochowitz et al., 1988; Tongsong et al., 1995). In one study, the authors attempted to delineate the antenatal natural history for the different types of achondrogenesis. Type I was shown to have a 50% incidence of stillbirth. Type II was shown to have fewer stillbirths, a longer antenatal survival time, a longer gestational period, a larger birth weight, longer limbs, and characteristic craniofacial features (Chen et al., 1981).

MANAGEMENT OF PREGNANCY

A major consideration in management of pregnancy is the establishment of a definitive diagnosis. Because the sonographic

Table 97-1

Sonographic Findings in Achondrogenesis

Earliest age at diagnosis 9 weeks
First trimester findings Nuchal and dorsal edema Poor or absent ossification of spine and long bones Absent fetal movement
Second trimester findings Femur length >2 SD below normal Bent long bones Poor or absent ossification of spine, skull, and long bones Hydrops fetalis Polyhydramnios Rib fractures Small thorax

findings in achondrogenesis are so distinctive, a diagnosis of achondrogenesis should be possible on the basis of sonographic features alone. In all cases of achondrogenesis reported to date in which the chromosomes have been analyzed, the fetal karyotype has been normal. In the setting of a positive family history due to a prior affected child, once the definitive diagnosis has been made by sonography, the parents should be offered the opportunity to terminate the pregnancy, if before 24 weeks of gestation. With the possible exception of the mildest form of achondrogenesis, known as Grebe dysplasia, all affected fetuses with achondrogenesis will die during the perinatal period. This should be discussed with the family, as should importance of obtaining a perinatal autopsy to permit definitive histologic diagnosis. Cesarean delivery is indicated only for maternal health considerations.

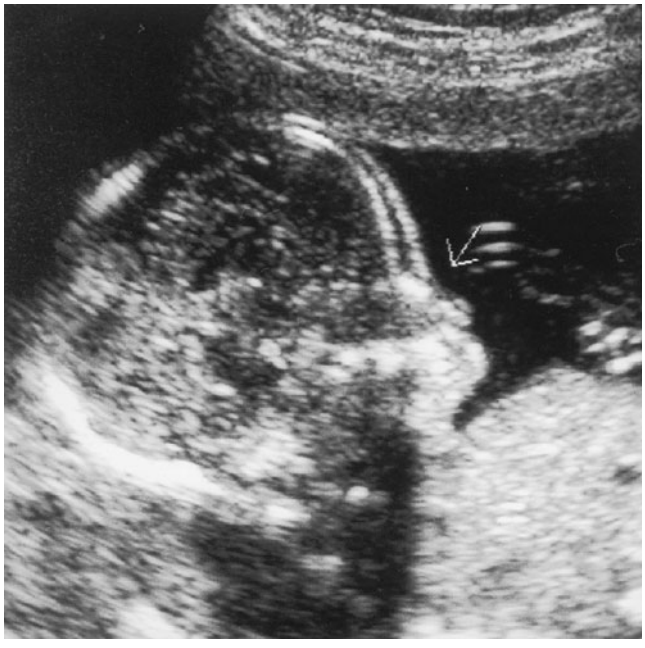

Figure 97-5 Facial profile of the same fetus shown in Figure 97-4, demonstrating flattened facies and subcutaneous edema.

FETAL INTERVENTION

There are no fetal interventions for achondrogenesis.

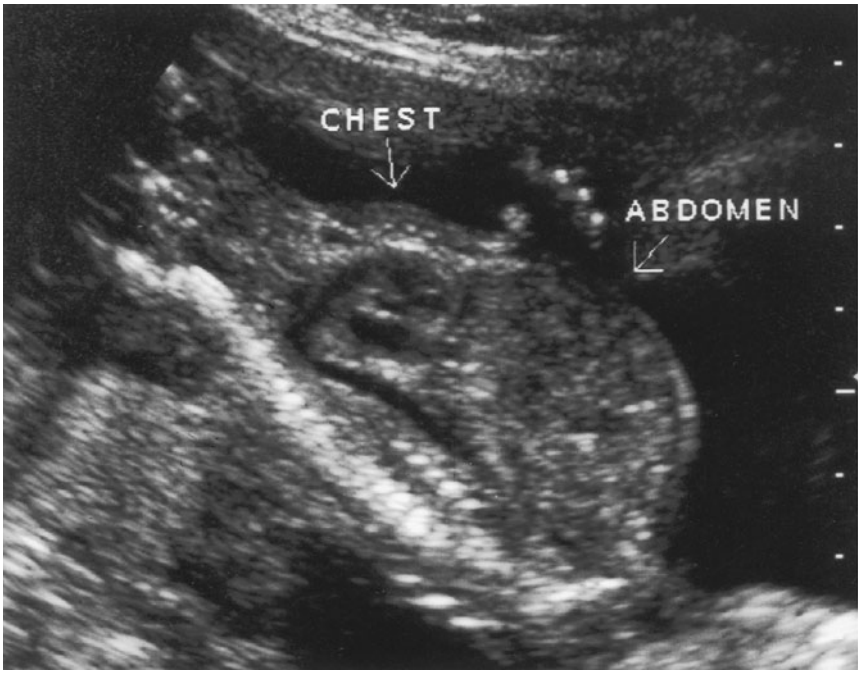

Figure 97-4 Prenatal sonographic image of a fetus with achondrogenesis demonstrating narrow thorax, protruberant abdomen, and absent rib ossification.

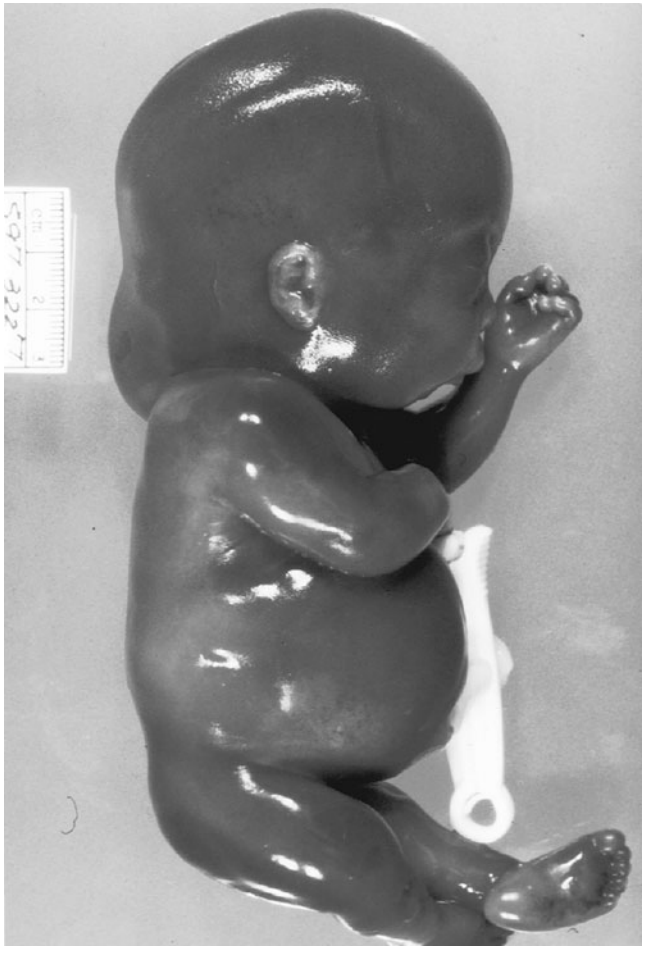

Figure 97-6 Post-termination photograph of the fetus shown in Figures 97-4 and 97-5, demonstrating nuchal edema, prominent abdomen, and clubfoot.

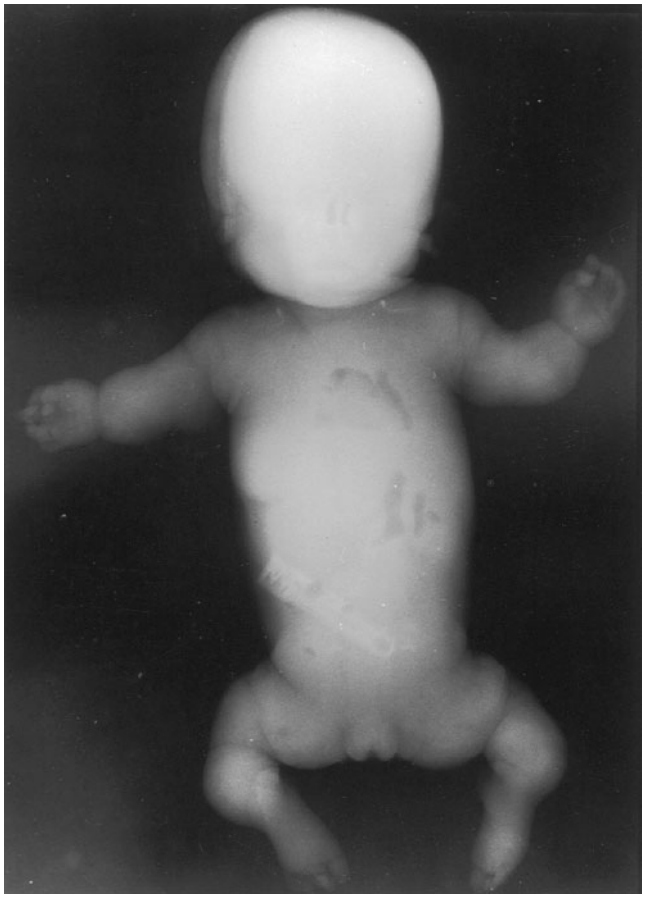

Figure 97-7 Postmortem radiograph of a newborn with achondrogenesis type I, demonstrating nearly total absence of ossification except for clavicles and ilia. (*Reprinted, with permission, from Jaeger HJ, Schmitz-Stolbrink A, Hulde J, Novak M, Roggenkamp K, Mathias K. The boneless neonate: a severe form of achondrogenesis type I.* Pediatr Radiol. *1994;24:320.*)

TREATMENT OF THE NEWBORN

If the diagnosis of suspected short-limb dysplasia is made during the third trimester, neonatal resuscitation is not indicated for an infant with achondrogenesis. At birth, physical examination findings consistent with a diagnosis of achondrogenesis include a large head, short neck, markedly shortened limbs, and a distended abdomen (Figure 97-6). In addition to the narrow thorax, these infants all have pulmonary hypoplasia, as documented by reduced weight of the lungs on autopsy. For achondrogenesis type II, it has been postulated that the pulmonary hypoplasia is due to the underlying abnormality in type II collagen (Pretorius et al., 1986). All of these infants die from respiratory complications.

If the diagnosis is unknown at birth, a series of radiographs should be obtained, which should include anteroposterior and lateral films of the skull, chest, lateral spine, pelvis, extremities, hands, and feet (see Figure 97-7) (Lachman and Rappaport, 1990). Typical findings will include a large calvarium with wormian bones, but normal suture diastases. The rib cage is bell-shaped and the spine is short and very poorly ossified. What is most striking on the radiographs is the almost complete absence of ossification of the vertebral bodies. The long bones are also shortened and widened and demonstrate a variety of abnormalities (Jimenez et al., 1973). Because the condition is lethal, only comfort measures should be offered for the infant.

LONG-TERM OUTCOME

There is no long-term outcome for this condition, as it is lethal during the perinatal period. The longest survivor with achondrogenesis documented in the literature lived for 10 to 12 days after birth (van der Harten et al., 1988).

GENETICS AND RECURRENCE RISK

Achondrogenesis types IA and IB are typically described as single-gene disorders inherited as autosomal recessive conditions. The possibility also exists that germline mosaicism is present in parents who have more than one affected child. Autosomal recessive inheritance is likely, given the documented

increased incidence of consanguinity in affected families (Ornoy et al., 1976). The underlying abnormality in type II achondrogenesis is decreased type II collagen, which is due to mutations in the *COL2A1* gene (Rimoin, 1996). Although formerly thought to be autosomal recessive, type II achondrogenesis is most commonly a de novo dominant mutation, although at least one case of recurrence within a family due to presumed germline mosaicism has been described (Faivre et al., 2004).

Under normal circumstances, type I collagen is not found in cartilage. However, in most cases of achondrogenesis type II, due to the mutations in the type II collagen gene, only type I collagen is seen in cartilage. Most defined mutations in achondrogenesis type II are single amino acid substitutions for a glycine residue in the type II collagen helix near the carboxyl terminal end of the molecule (Rimoin, 1996). In one study, genomic DNA was extracted from 12 patients with achondrogenesis type II to search for mutations in the *COL2A1* gene (Körkkö et al., 2000). The exons and flanking sequences of all 54 exons in the *COL2A1* gene were amplified by the polymerase chain reaction (PCR). PCR products were then scanned for the presence of a mutation using the relatively simple technique of conformation-sensitive gel electrophoresis. Abnormal products were then sequenced. Mutations in the *COL2A1* gene were found in all 12 affected patients (Körkkö et al., 2000).

Mutations in *SLC26A2*—also known as the diastrophic dysplasia sulfate transporter (*DTDST*) gene—cause abnormalities in the sulfation of chondroitin sulfate-containing proteoglycans, and are the basis for achondrogenesis type IB (Superti-Furga et al., 1996). Individuals with this condition have early stop codon mutations in the *DTDST* gene coding regions on both copies of chromosome 5, at bands q32-q33.1. Achondrogenesis type IB is now known to belong to a family of disorders caused by mutations in the *DTDST* gene. These include two lethal disorders, achondrogenesis type IB and atelosteogenesis II, and two nonlethal disorders, diastrophic dysplasia and multiple epiphyseal dysplasia (see Chapter 93) (Rimoin, 1996; Superti-Furga et al., 1996; Karniski, 2001; Rossi and Superti-Furga, 2001). Although *DTDST* is expressed in many tissues, the only tissue known to be affected by mutations in *DTDST* is cartilage (Haila et al., 2001). The gene product is a sulfate-chloride exchanger in the cell membrane. Inactivation of this exchanger leads to intracellular sulfate depletion and synthesis of undersulfated proteoglycans in chondrocytes and fibroblasts (Rossi and Superti-Furga, 2001). Genotype–phenotype correlations exist within this gene. Mutations that predict a truncated protein or a nonconserved amino acid substitution in a transmembrane domain result in the severe phenotypes, while nontransmembrane amino acid substitutions and splice site mutations result in the milder phenotypes (Rossi and Superti-Furga, 2001).

In one case report, a 17-week-old fetus was suspected of having achondrogenesis due to an abnormal prenatal sonographic examination. The family history was remarkable for two prior affected fetuses with achondrogenesis type IB. This fetus was electively terminated and genomic DNA was extracted from frozen femoral cartilage. Nucleotide sequencing of the *DTDST* gene demonstrated that the fetus was homozygous for both delVal340 and Thr689Ser mutations; the parents and a healthy brother were each heterozygous (Cai et al., 1998). This case demonstrates the importance of DNA analysis in affected fetuses with achondrogenesis type IB. Once the mutations in the *DTDST* gene are identified in a family, prenatal diagnosis by chorionic villus sampling then becomes an option in subsequent pregnancies.

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98 CHAPTER Hypophosphatasia

Key Points

- Rare hereditary metabolic bone disorder characterized by deficient activity of the tissue-nonspecific isoenzyme of alkaline phosphatase (TNSALP).
- Incidence is 1 in 100,000 births in most ethnic groups but 1 in 2500 in Canadian Mennonites.
- Two forms present perinatally: severe (lethal) and benign, which resolves spontaneously.
- In the severe form sonographic findings include increased nuchal translucency measurement, undermineralized skull, shortened, bent, fixed limbs with decreased echogenicity, and lack of ossification of vertebral bodies, neural arches, and hands. The benign perinatal form presents with symmetric bowing of long bones.
- Differential diagnosis includes anencephaly, osteogenesis imperfecta types II and III, thanatophoric dysplasia, campomelic dysplasia, achondrogenesis, and cleidocranial dysplasia.
- Amniocentesis should be offered to rule out anencephaly, confirm fetal karyotype, assay alkaline phosphatase activity, and check for DNA mutation(s).
- Causative gene is *TNSALP*.
- Severe form is recessively inherited with two mutations. Milder form is dominantly inherited with one mutation.
- Genetic consultation and counseling are indicated.

CONDITION

The term hypophosphatasia was first used by Rathbun in 1948 to describe an infant with severe rickets and very low alkaline phosphatase activity in serum and tissues (Henthorn and Whyte, 1992; Whyte et al., 1995). Hypophosphatasia is a rare inherited metabolic bone disorder characterized by deficient activity of the liver/bone/kidney isoenzyme of alkaline phosphatase. This isoenzyme is also known as the tissue-nonspecific form of alkaline phosphatase (TNSALP).

Alkaline phosphatase was first discovered in 1923, when Robert Robinson noted a large amount of phosphatase activity within ossifying bone and cartilage in rats and rabbits. He was the first to suggest that this catalytic action was important for mineralization of the skeleton due to hydrolysis of a phosphate ester, which would result in the local increase of inorganic (free) phosphate (Whyte, 1994). He subsequently showed that the enzyme functioned optimally at a distinctly alkaline pH, although he never specifically used the term *alkaline phosphatase*. Later, alkaline phosphatase was also demonstrated in tissues that normally do not mineralize, such as the liver, intestines, and placenta; thus, the role of alkaline phosphatase in skeletal mineralization was questioned. It is now known that at least four distinct genes encode four different human alkaline phosphatase isoenzymes. The TNSALP liver bone kidney form is especially rich in mineralizing bone. The location of this gene is on the short arm of chromosome 1, band p36.1-34 (Henthorn and Whyte, 1992; Whyte et al., 1995). The other three genes are found in a cluster on the end of the long arm of chromosome 2. These include placental, intestinal, and placental-like isoenzymes of alkaline phosphatase. Each of the alkaline phosphatase genes have now been sequenced, and the *TNSALP* gene is the largest of the four (Whyte, 1994).

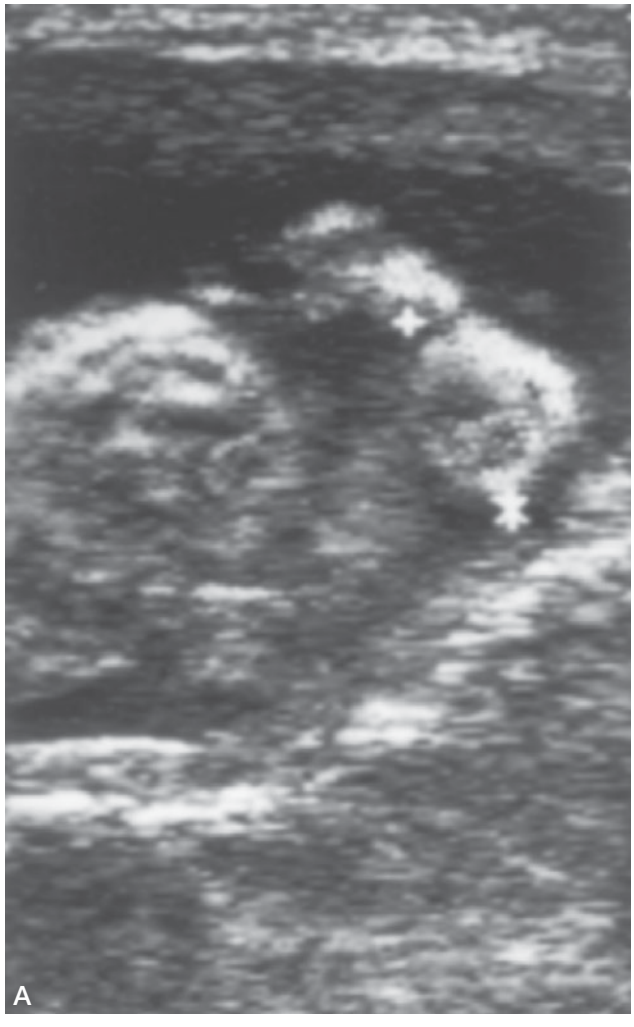
Hypophosphatasia is a clinically variable condition. Mutations in the *TNSALP* gene are responsible for perinatal hypophosphatasia, in which the severity of the disease usually correlates with the age of onset of symptoms. Fetuses detected in utero generally have the most severe form of hypophosphatasia, also known as the perinatal lethal form. Findings in this condition include profound undermineralization of the skeleton, lack of skull ossification resulting in a caput membraneceum, and shortened deformed limbs. Postnatal survival of affected infants is limited because of associated pulmonary hypoplasia and rachitic disease of the chest. Radiographic studies in the newborn are diagnostic. The infantile form of hypophosphatasia presents before the age of 6 months. The newborn can initially appear normal, but poor feeding subsequently develops, as do inadequate weight gain and symptoms of rickets. Additional problems include the development of craniosynostosis, increased intracranial pressure, hypercalcemia, renal failure, and seizures. Approximately 50% of affected infants die. The childhood form is variable in its clinical expression. It is characterized by premature loss of the deciduous teeth at an age of less than 5 years, resulting from abnormalities of the dental cementum, which is important for connection between the tooth roots and the periodontal ligament (Whyte, 1994). Affected children also have short stature, rickets, deformation of the legs, knees, ankles, and wrists, although some of these improve with age. Affected patients have characteristic abnormalities on radiographs, which include focal bony defects near the ends of the major long bones. These manifest as a tonguelike shape of radiolucency that projects from the growth plate into the metaphysis (Whyte, 1994). The adult form of hypophosphatasia generally presents during middle age. A childhood history of rickets or premature loss of deciduous teeth may or may not be present. In general, affected adults enjoy relatively good health as adolescents and young adults, but then develop recurrent metatarsal stress fractures and early loss of permanent teeth. The mildest form of hypophosphatasia is called "odontohypophosphatasia," which is reserved for patients whose only clinical manifestation is dental disease. Most recently, it has become appreciated that there is another mild form that presents in fetal life with severe symmetric long bone bowing that resolves spontaneously (Moore et al., 1999; Pauli et al., 1999; Comstock et al., 2005). No absolute diagnostic criteria exist for the separation of the various clinical presentations. A continuous spectrum of symptoms exists. This chapter will focus on the two forms that present in the antenatal period.

INCIDENCE

The incidence of hypophosphatasia, based on data from Toronto, is 1 in 100,000 livebirths (Mulivor et al., 1978; Greenberg et al., 1990). Cases of hypophosphatasia have been described throughout the world, occurring in all races (Whyte, 1994). During the years 1977 to 1986, six neonates affected with hypophosphatasia were born in southern Manitoba. After these infants were identified, it was appreciated that Mennonites in southern Canada have a 1 in 25 chance of being a carrier for at least one mutation in the *TNSALP* gene. The birth incidence of affected infants with hypophosphatasia in Mennonites is 1 in 2500 (Chodirker et al., 1990). This unusually high incidence is presumably due to a founder effect with inbreeding.

SONOGRAPHIC FINDINGS

The most striking abnormality described in cases of the severe form of perinatal hypophosphatasia is the absence of a normally formed fetal skull (Kousseff and Mulivor, 1981). The hallmarks for sonographic diagnosis of hypophosphatasia include a fetus that is small for gestational age with decreased echogenicity of the bones, a prominent falx cerebri due to undermineralization of the skull, various skeletal deformities,



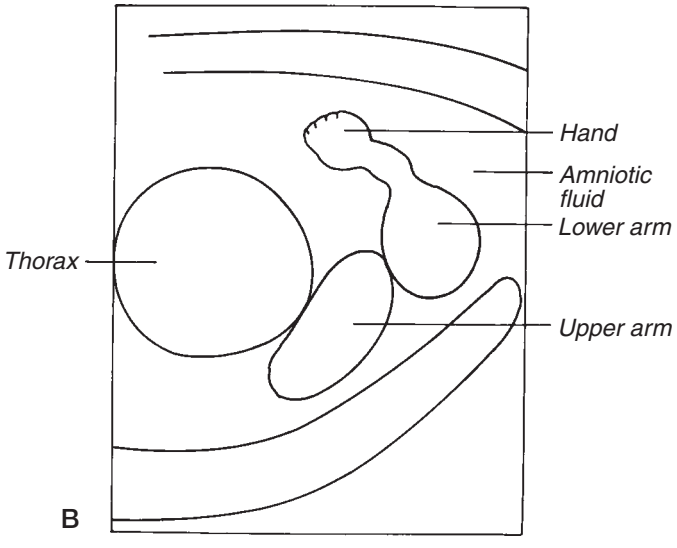
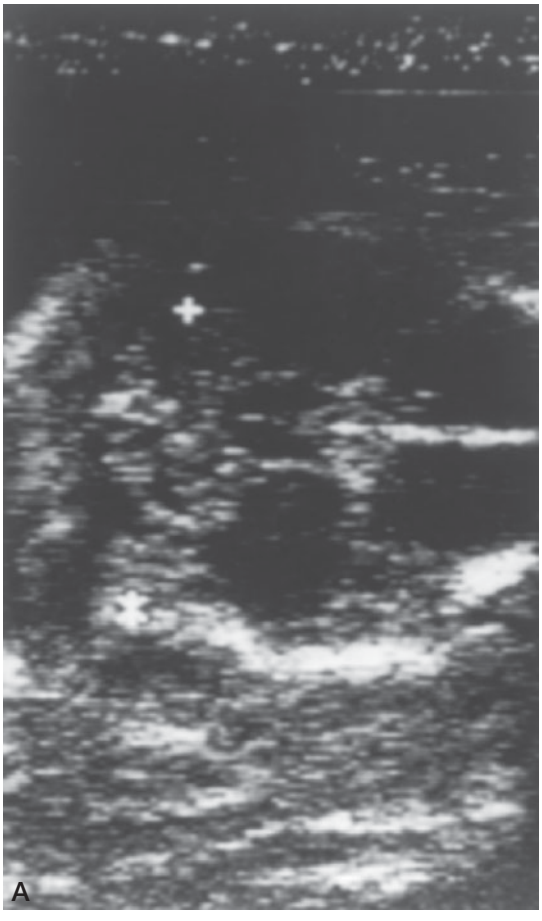


Figure 98-1 **A.** Sonographic image of a fetus at 24 weeks with hypophosphatasia, demonstrating severely shortened and bent forearm. **B.** Diagram of sonographic image in panel (A). (*Reprinted, with permission, from van Dongen PWJ, Hamel BCJ, Nijhuis JG, de Boer CN. Prenatal follow-up of hypophosphatasia by ultrasound: case report.* Eur J Obstet Gynecol Reprod Biol. *1990;34:283-288. Reprinted with the permission of Elsevier Science Ireland Ltd., Bay 15K, Shannon Industrial Estate, Co. Clare, Ireland.*)

and the presence of polyhydramnios occurring later in gestation (Wladimiroff et al., 1985). Also, pulmonary hypoplasia may be documented as a result of a severely reduced thoracic volume due to abnormal and short ribs. In one report, Van Dongen et al. (1990) described sonographic studies performed in a family with a previously affected child. Even as early as 8 weeks of gestation, the crown-to-rump length was suggestive of a fetus 1.5 weeks younger than the actual gestational age. The family was lost to follow-up until 24 weeks of gestation, when severe polyhydramnios was noted. Other findings included an active fetus with shortened, bent, fixed limbs with markedly decreased echogenicity, which prevented separate visualization of the fingers and toes (Figure 98-1A and 98-1B). The falx cerebri and other central nervous system structures could be distinguished unusually clearly due to the low echogenicity of the skull bones (Figure 98-2A and 98-2B). This was described as being similar to the fetal appearance in hydrocephalus. In another report of prenatal diagnosis in a family at risk for recurrence of hypophosphatasia, the failure to outline a fetal head was noted at 16 weeks of gestation (Rudd et al., 1976). The skull was described as a very thin, faint circular outline. In addition, skip defects were noted in the cervical spine vertebral bodies.

In another case, with a negative family history, but a conception marked by consanguinity, underossification of the skull, facial bones, ribs, and limbs was noted at 27 weeks of gestation (DeLange and Rouse, 1990). In addition, underossification of the metacarpals, neural arches of the spine, and vertebral bodies was present. This group made a presumptive prenatal diagnosis of hypophosphatasia based on (1) the generalized underossification of the fetal bones, (2) shortening of the limbs, and (3) lack of ossification of groups of vertebral bodies, the neural arches, and the hands.

Souka et al. (2002) demonstrated the presence of an increased nuchal translucency measurement in two fetuses with hypophosphatasia from the same family. In the first affected fetus, additional findings were seen at 14 weeks, including fixed flexed upper and lower limbs, hypomineralization of the skull and spine, narrowing of the chest with short ribs, shortening of all of the long bones, and bilateral talipes. In the second affected pregnancy, sonographic examination at 12 weeks showed hypomineralization of the skull



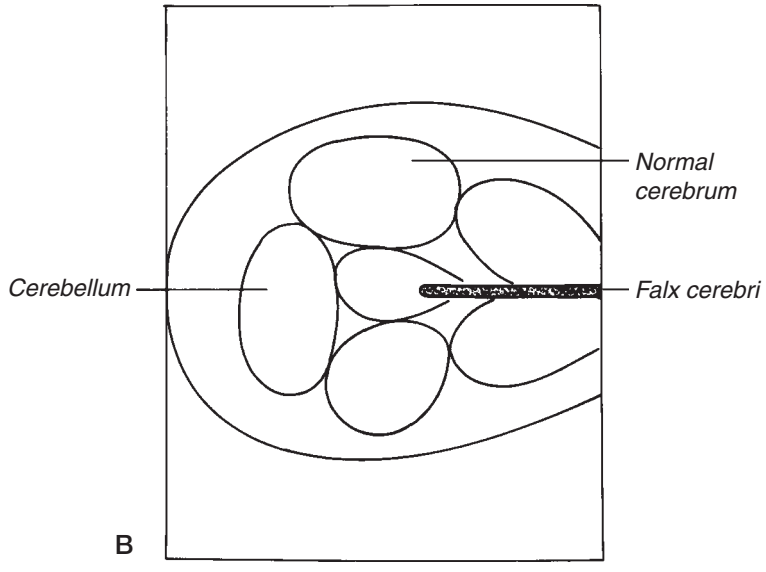


Figure 98-2 **A.** Sonographic image of the fetus seen in Figure 98-1A, demonstrating unusually clear visualization of the falx cerebri. **B.** Diagram of sonographic image in panel (A). (*Reprinted, with permission, from van Dongen PWJ, Hamel BCJ, Nijhuis JG, de Boer CN. Prenatal follow-up of hypophosphatasia by ultrasound: case report.* Eur J Obstet Gynecol Reprod Biol. *1990;34:283-288. Reprinted with the permission of Elsevier Science Ireland Ltd., Bay 15K, Shannon Industrial Estate, Co. Clare, Ireland.*)

and spine, narrowing of the chest, and shortening and bowing of the limbs. This report is the earliest prenatal sonographic diagnosis of specific findings associated with hypophosphatasia.

A dominantly inherited form of mild hypophosphatasia has also been described that presents in utero as severe bowing of the long bones (Moore et al., 1999; Pauli et al., 1999). Interestingly, in this condition, prenatal and postnatal improvement of the bone dysplasia occurs spontaneously although affected children remain short and have premature loss of teeth. Some authors suggest that the condition should be called the "benign prenatal" form of hypophosphatasia.

DIFFERENTIAL DIAGNOSIS

Failure to visualize the fetal skull may lead to an initial presumptive differential diagnosis of hypophosphatasia versus anencephaly. Other conditions that may result in malformation and undermineralization of the bones include osteogenesis imperfecta types II and III, thanatophoric dysplasia, campomelic dysplasia, and achondrogenesis. Achondrogenesis (see Chapter 97) can be distinguished from hypophosphatasia by an ossified calvarium, as well as better ossification of the neural arches with nonossification of the vertebral bodies. Cleidocranial dysplasia can be associated with decreased bone density and low alkaline phosphatase activity and may thus mimic hypophosphatasia (Morava et al., 2002).

ANTENATAL NATURAL HISTORY

Little is known about the antenatal natural history for fetuses affected with hypophosphatasia. There is an increased incidence of stillbirth for the severe perinatal form, although the cause for this is unknown.

MANAGEMENT OF PREGNANCY

The strategies for the definitive prenatal diagnosis of hypophosphatasia have included fetal radiography (in the early 1980s), prenatal sonography, assay of alkaline phosphatase activity in cultured amniocytes, fibroblasts, or chorionic villus samples, measurement of alkaline phosphatase activity in fetal

serum obtained by cordocentesis (Tongsong and Pongsatha, 2000), or analysis of DNA from fetal tissue (Henthorn and Whyte, 1995). Management of pregnancy differs in the setting of a positive family history of hypophosphatasia versus a negative family history. If the family history is positive, ideally DNA has been previously obtained from the affected proband before death. This material, along with parental blood samples, should be sent to a diagnostic reference laboratory with experience in the identification of mutations in the *TNSALP* gene. If the mutation(s) in the family is known, prenatal diagnosis is best performed by chorionic villus sampling (CVS) to identify the presence of parental mutation(s) in the fetus (Mornet et al., 1999).

If mutation analysis has not been performed on a previously affected child, other approaches to prenatal diagnosis may include the use of monoclonal antibody to the TNSALP isoenzyme on fetal material obtained by CVS. In one report of 16 pregnancies at risk for hypophosphatasia, a normal range for the TNSALP levels was established (50–150 μmol activity per minute per gram of tissue; median = 130). In 11 of the 16 at-risk cases, the fetus had greater than 50 μmol per minute per gram of tissue. These values were considered to fall within the normal range. All pregnancies continued to term and all infants were normal. In 5 of the 16 at-risk pregnancies, the TNSALP values were <25 μmol per minute per gram of tissue and all fetuses were terminated. Four of the 5 affected fetuses were confirmed as abnormal either by documenting sonographic abnormalities, autopsy diagnosis of abnormally foreshortened limbs, or by subsequent biochemical confirmation on fibroblast or liver tissue. One family was lost to follow-up (Brock and Barron, 1991). Muller et al. (1991) have cautioned that CVS material should be sampled at less than 12 weeks of gestation and that particular care should be taken to eliminate maternal decidual tissue from the sample. These authors have confirmed the very low activity of the TNSALP in early chorionic villus material in affected fetuses. Placental alkaline phosphatase was never detected by these authors before 9 weeks of gestation. Affected pregnancies have both low total alkaline phosphatase and 0% TNSALP (Muller et al., 1991). Thus, in families with a positive history of hypophosphatasia but with no knowledge of DNA mutation analysis, prenatal diagnosis may be performed in two different ways on chorionic villus material.

In the setting of a fetus with typical sonographic findings suggesting the presence of hypophosphatasia, but a negative or unknown family history, we suggest performing amniocentesis to measure amniotic fluid α-fetoprotein to rule out anencephaly and to confirm the fetal karyotype. The amniocytes may be placed into culture and used for both assay of alkaline phosphatase activity (Mulivor et al., 1978; Kousseff and Mulivor, 1981) and DNA analysis (Mornet et al., 1999). Alternatively, a cordocentesis can be performed to measure alkaline phosphatase levels (Tongsong and Pongsatha, 2000). Normal values are 51 ± 24 IU/L. Affected fetuses have undetectable or very low levels. Consultation with a clinical geneticist is indicated.

FETAL INTERVENTION

There are no fetal interventions for hypophosphatasia.

TREATMENT OF THE NEWBORN

No effective treatment is currently available for the perinatal form of hypophosphatasia. Vitamin D and mineral supplements normally used in the treatment of rickets should be avoided, since circulating levels of calcium, inorganic phosphorus, and the vitamin D metabolites are generally normal in affected patients with hypophosphatasia (Whyte, 1994). Unsuccessful attempts have been made to infuse several types of alkaline phosphatase intravenously (Whyte, 1994). Because perinatal hypophosphatasia is a lethal condition, treatment of the newborn should be directed toward confirming the diagnosis and ensuring that a mechanism is in place for follow-up genetic counseling.

Physical findings at birth include rhizomelic and asymmetric shortening of all four extremities, with very pliable skull bones and possible craniotabes (Kousseff and Mulivor, 1981). The infant's thorax is extremely compliant and a respirator may be required for ventilation. This should be considered only for the time needed to confirm the diagnosis, as the abnormalities in the thorax will not improve. Confirmatory postnatal radiographs may be obtained, which should reveal the extreme hypomineralization that is considered diagnostic of this condition (Figure 98-3). Serum may be obtained to demonstrate the decreased activity of TNSALP and increased urinary excretion of phosphoethanolamine. Serum calcium is typically normal except in infantile cases, in which hypercalcemia is a secondary effect of renal failure (Chodirker et al., 1990).

When the infant dies, an autopsy should be obtained to confirm the diagnosis. This will demonstrate that the cranium has been replaced by connective tissue. The absence of alkaline phosphatase activity in the bones, heart, and liver should be documented (Van Dongen et al., 1990).

SURGICAL TREATMENT

There is no surgical treatment for hypophosphatasia.

LONG-TERM OUTCOME

The long-term outcome is only an issue for infants with the benign perinatal and infantile forms of hypophosphatasia. These infants should be followed carefully for evidence of increased intracranial pressure due to functional or true premature craniosynostosis (Whyte, 1994). Affected infants also

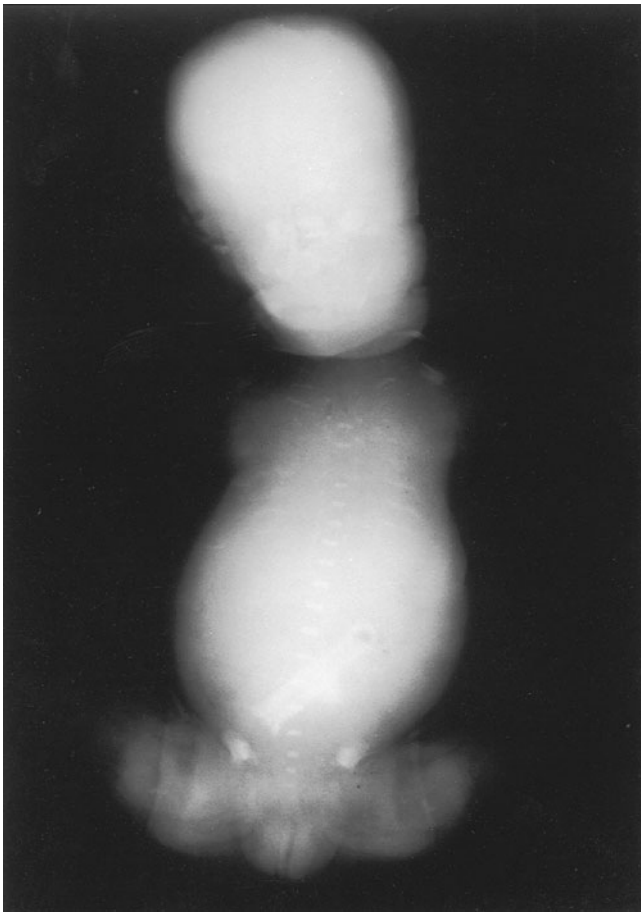


Figure 98-3 Postmortem radiograph of a newborn infant with hypophosphatasia. Note the severely hypomineralized bones. (*Reprinted, with permission, from van Dongen PWJ, Hamel BCJ, Nijhuis JG, de Boer CN. Prenatal follow-up of hypophosphatasia by ultrasound: case report.* Eur J Obstet Gynecol Reprod Biol. *1990;34:283-288. Reprinted with the permission of Elsevier Science Ireland Ltd., Bay 15K, Shannon Industrial Estate, Co. Clare, Ireland.*)

need close follow-up with an orthopedic surgeon and observation for the development and treatment of fractures. These infants need close follow-up with a dentist and careful attention to dental hygiene. Interestingly, adult survivors of infantile hypophosphatasia may have normal stature (Whyte, 1994). Bone marrow transplant has been suggested as a treatment for survivors that have poor growth, fractures, and respiratory problems (Whyte et al., 2003).

GENETICS AND RECURRENCE RISK

The *TNSALP* gene is the gene responsible for perinatal hypophosphatasia. This gene has been localized to chromosome 1p36.1-34 (Greenberg et al., 1990). The *TNSALP* gene is large, consisting of more than 50 kilobases of DNA. The gene contains 12 exons, 11 of which are translated. The nascent enzyme consists of 507 amino acid residues (Whyte, 1994). The tissue-specific (placental, intestinal, and placental-like) alkaline phosphatase genes are smaller and contain shorter exons. There is approximately 87% identity between the sequences of placental and intestinal alkaline phosphatase but only 52% to 56% identity between the tissue-specific isoenzymes and the tissue-nonspecific isoenzymes of alkaline phosphatase. In the placenta, expression of alkaline phosphatase is controlled through the fetal genome (Whyte, 1994).

Molecular studies have determined that the primary genetic defects in hypophosphatasia are missense mutations in the *TNSALP* gene (Henthorn and Whyte, 1992; Henthorn et al., 1992). Hypophosphatasia is molecularly heterogeneous, with a correlation between genotype and phenotype (Zurutuza et al., 1999). More than 128 mutations have been described to date (Gehring et al., 1999; Witters et al., 2004). Individuals with the recessive form of hypophosphatasia have two mutant *TNSALP* alleles. Individuals with the milder, dominant form of hypophosphatasia have only one mutant *TNSALP* allele. Normal biomineralization occurs if a single normal copy of *TNSALP* is present (Hu et al., 2000).

Following the birth of an affected infant, the carrier status of parents can be confirmed by both biochemical and DNA studies. In obligate carriers, the TNSALP isoenzyme is lower than normal and urinary phosphoethanolamine is significantly higher. Carriers also have a relative hyperphosphatemia with normal serum inorganic phosphate (Chodirker et al., 1990). Families that have an affected infant with the perinatal form of hypophosphatasia should have DNA mutation analyses coordinated by a genetic counseling center and sent to a referral laboratory. Genetic counseling is definitely indicated for this condition, and prenatal diagnosis is available for subsequent pregnancies (see "Management of Pregnancy").

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Chondrodysplasia Punctata

99 CHAPTER

Key Points

- Chondrodysplasia punctata comprises a group of genetically heterogenous skeletal dysplasias characterized by small calcified densities in the epiphyses of the long bones.
- The rhizomelic form (RCDP) is more severe and inherited as an autosomal recessive condition. Rhizomelic chondrodysplasia punctata is a disorder of the peroxisomes.
- The nonrhizomelic form, also known as Conradi–Hünermann syndrome, can be inherited as an autosomal dominant, X-linked recessive or dominant condition. It is generally milder.
- Sonographic findings include profound humeral and femoral shortening in rhizomelic chondrodysplasia punctata. Multiple hyperechoic foci (puncta), nasal hypoplasia, midface depression, vertebral anomalies, and congenital heart defects are associated with both RCDP and Conradi–Hünermann syndrome.
- Differential diagnosis includes skeletal dysplasias, autosomal trisomies, Zellweger syndrome, disorders of vitamin K metabolism, warfarin exposure, Smith–Lemli–Opitz syndrome, and GM_1 gangliosidosis.

Key Points (cont.)

- Pregnant women carrying fetuses with punctate calcifications should be referred to a tertiary center and to a medical geneticist. Chromosome analysis is indicated to rule out trisomy and deletions of Xp22.3.
- There are three types of RCDP; type 1 is most common, caused by mutations in *PEX7*. Molecular diagnosis is possible for all three types.
- Prognosis is poor for RCDP. Only 50% of affected infants survive past the age of 6 years. All affected infants have severe failure to thrive, mental retardation, joint contractures, and cataracts.
- Infants affected with Conradi–Hünermann syndrome have milder symptoms, generally normal intelligence and, with the exception of the X-linked dominant form in males, a fairly normal lifespan.

CONDITION

Chondrodysplasia punctata denotes a group of skeletal dysplasias characterized by locally disordered bone mineralization that results in bone stippling observed on radiographs obtained during the newborn period (Pryde et al., 1993). The areas of punctate calcification were first described by Conradi in 1914. In 1931, Hünermann designated the disorder "chondrodystrophia calcificans congenita." This term was defined as the X-ray finding of small calcified densities in the epiphyses (Hyndman et al., 1976). The disorder recognized by Hünermann also included micromelia, a saddle nose deformity, flexion contractures, cataracts, and a dermopathy. As used today, the term chondrodysplasia punctata comprises a group of genetically heterogeneous disorders (Spranger et al., 1971). Some of these are associated with rhizomelia (proximal limb shortness) and some are not. The rhizomelic form is generally more severe. It has been subdivided into three types, each of which is associated with a mutation in a different gene (see Figure 99-1). All three types are inherited as autosomal recessive conditions. The nonrhizomelic form of chondrodysplasia punctata, also known as Conradi–Hünermann syndrome, is milder and can be inherited as an autosomal dominant, X-linked recessive, or X-linked dominant condition. A rarer form of mild chondrodysplasia punctata, known as the tibia-metacarpal type, is inherited as an autosomal dominant condition.

Rhizomelic chondrodysplasia punctata is a disorder of the peroxisomes. Peroxisomes are intracellular organelles that catalyze a number of metabolic functions (Wanders and Waterham, 2004). These include β-oxidative chain shortening of fatty acids and their derivatives, synthesis of ether phospholipids, and detoxification of glyoxalate (Hoefler et al., 1988; Schutgens et al., 1989; Wanders et al., 1993). Human peroxisomal disorders are subdivided into two categories: those in which the organelle is not normally formed (peroxisome biogenesis disorders) and those that involve a single peroxisomal enzyme (Moser, 1999).

In patients with rhizomelic chondrodysplasia punctata, the peroxisomes are present, but they have lost many of their normal functions. Four distinct abnormalities have been found in patients with rhizomelic chondrodysplasia. These involve deficiency of enzymes important in phospholipid synthesis and phytanic acid oxidation (Hoefler et al., 1988; Schutgens et al., 1989; Wanders et al., 1993). A severe deficiency in plasmalogen synthesis is associated with deficient activities of the peroxisomal enzymes acyl coenzyme A (acyl CoA, dihydroxyacetone phosphate [DHAP] acyltransferase) and alkyl-dihydroxyacteone phosphate synthase. In addition,

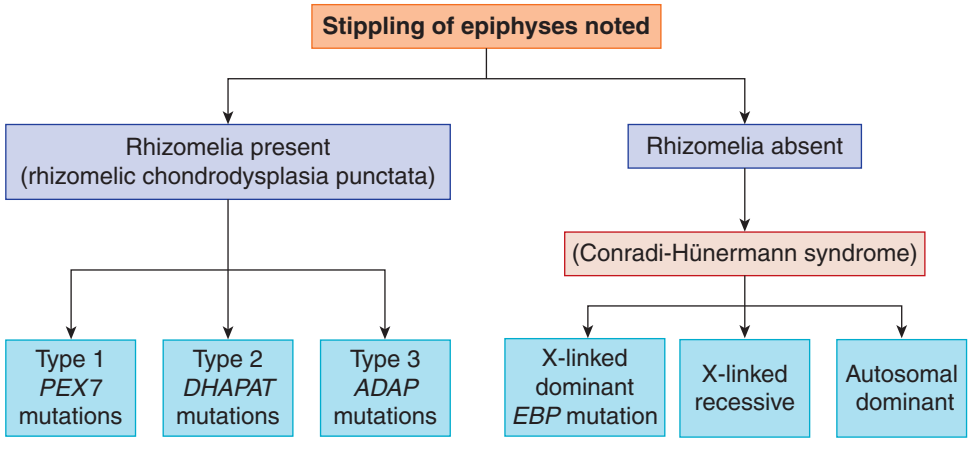

Figure 99-1 Approach to the diagnosis of the conditions characterized by small calcified densities in the epiphyses of the long bones.

there is deficient activity of phytanic acid oxidase, and the enzyme peroxisomal 3-oxo-acyl-CoA thiolase is present in an abnormal unprocessed form (Gendall et al., 1994; Suzuki et al., 1994). Because of these enzyme abnormalities, the characteristic biochemical abnormality in rhizomelic chondrodysplasia punctata is increased phytanic acid levels and decreased plasmalogens (Singh et al., 1988). In rhizomelic chondrodysplasia punctata, unlike in other peroxisomal conditions, the amount of very long-chain fatty acids is normal. In the absence of a known familial DNA mutation, one way to identify rhizomelic chondrodysplasia punctata prenatally is to analyze the plasmalogen levels in chorionic villi and erythrocytes (Wanders et al., 1993).

To date, 32 peroxisomal (peroxins, or *PEX*) genes have been identified (Wanders and Waterham, 2004). Most of them are also found in yeast, indicating their essential importance for cellular metabolism. Thus far, 16 *PEX* genes have been identified in humans (Subramani, 1997; Wanders and Waterham, 2004). Of these, twelve have been implicated in human disorders. Patients with rhizomelic chondrodysplasia punctata are deficient in a subset of peroxisomal enzymes.

INCIDENCE

The incidence of rhizomelic chondrodysplasia punctata is approximately 1 in 100,000 livebirths (Connor et al., 1985; Stoll et al., 1989). Parental consanguinity has been noted in 8% to 10% of recessively inherited cases (Stoll et al., 1989). The incidence of dominantly inherited Conradi–Hünermann syndrome is presumably higher, as clinically the condition appears to be at least twice as common (Stoll et al., 1989). Precise incidence figures are unavailable because many mildly affected patients go unrecognized. The incidence of Zellweger syndrome, another peroxisomal disorder that can be associated with punctate calcifications around the extremities, is 1 in 50,000, with an estimated gene frequency of 1 in 110 individuals in the United States (Zellweger et al., 1988).

SONOGRAPHIC FINDINGS

The major sonographic criterion for a diagnosis of rhizomelic chondrodysplasia punctata includes profound humeral shortening that is less marked than the femoral shortening, without shortening of other bones. In addition, expanded epiphyses are present, which contain multiple hyperechoic foci (the so-called puncta) (Figure 99-2). In normal fetuses, the distal femoral epiphyseal ossification center is never identified before 28 weeks and is more commonly appreciated after 34 weeks (Pradhan et al., 2002). In addition, nasal hypoplasia or midface depression with frontal bossing may be observed in the fetal profile. Approximately 10% of cases have associated congenital heart disease, predominantly pulmonic stenosis, and pulmonary artery and aortic calcifications (Fourie, 1995). In nonrhizomelic chondrodysplasia punctata (Conradi–Hünermann syndrome), the major finding is the long bone epiphyseal calcifications. Similar facial abnormalities to those seen in the rhizomelic form may also be present.

The first prenatal diagnosis of Conradi–Hünermann syndrome was made incidentally, when radiography was performed to assess fetal maturity in a woman who was post-term (Hyndman et al., 1976). The radiograph demonstrated stippling of the epiphyses at the fetal ankles, knees, pubic and ischial bones, and femur. At birth, the infant was noted to have a saddle nose deformity as well as coronal cleft vertebrae in the lumbar spine.

Cases of sonographic prenatal diagnosis of Conradi–Hünermann syndrome have also been described in the

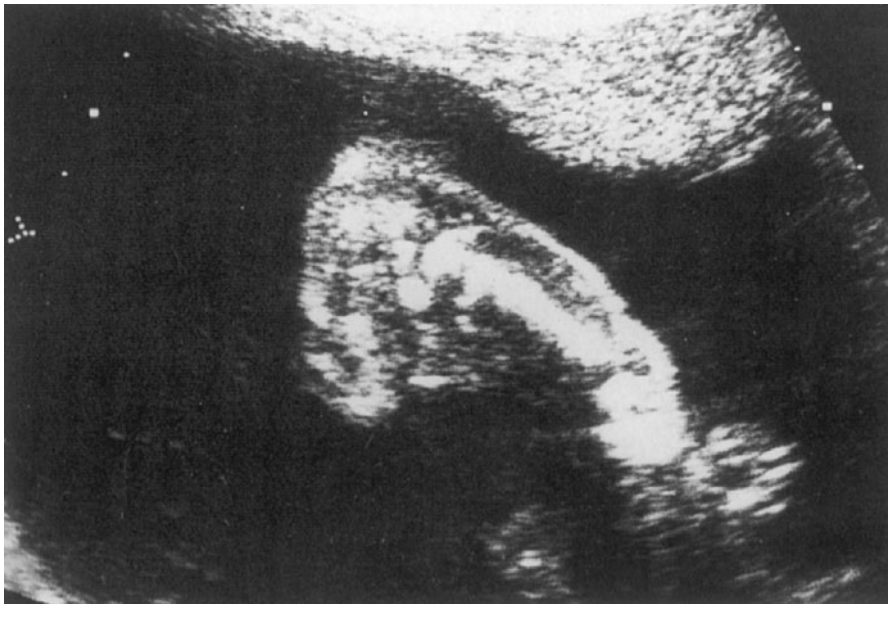

Figure 99-2 Prenatal sonographic image of a fetal femur at 22 weeks of gestation demonstrating proximal shortening and increased echogenicity due to punctate epiphyseal calcification. *(Reprinted, with permission, from Sastrowijoto SH, Vandenberghe K, Moerman P, Lauweryns JM, Fryns JP. Prenatal ultrasound diagnosis of rhizomelic chondrodysplasia punctata in a primigravida. Prenat Diagn. 1994;14:770-776. Copyright 1994 John Wiley & Sons. Reprinted, by permission, of John Wiley & Sons, Ltd.)*

literature. In one report, Tuck et al. (1990) described a 21-year-old primigravida with a known diagnosis of Conradi–Hünermann syndrome. She had ichthyosis; sparse, dry hair; and asymmetrical limb shortening. She had surgery performed on her right hip at 6 years of age and subsequently had operations to lengthen her right femur at the age of 9 years. As an adult, she had short stature (144 cm) and a pronounced limp. When she became pregnant, sonographic survey of fetal anatomy was performed at 17 weeks of gestation and revealed a 3 mm asymmetry between the lengths of the right and left fetal femora and humeri. This asymmetry persisted on prenatal sonograms performed at 21, 24, 32, and 35 weeks of gestation. At birth, radiographs of her infant demonstrated epiphyseal stippling that was missed on prenatal sonogram. Physical examination also revealed a low nasal bridge, malar hypoplasia, and ichthyotic skin (Tuck et al., 1990).

As shown in the case above, the diagnosis of Conradi–Hünermann syndrome is more straightforward when it is known that one of the parents is affected. In one report, Pryde et al. (1993) described a pregnant woman, who herself had been diagnosed with Conradi–Hünermann syndrome at birth, who presented with scoliosis, punctate calcifications of the spine and femoral epiphyses, asymmetric limb shortening, postaxial polydactyly, cataracts, and irregular macular skin hyperpigmentation. In her first pregnancy, her fetus was noted to have asymmetrical short limbs, scoliosis, and mild ventriculomegaly. In her second pregnancy, at 16 weeks of gestation a 5 mm difference was noted between the right and left femoral lengths. At 32 weeks, severe polyhydramnios developed. At birth, the diagnosis was confirmed by the presence of a saddle nose, ichthyotic skin, and epiphyseal stipplings seen on radiographs. In this report, an affected fetus with a negative family history was also described. Prenatal sonograms were characterized by severe disorganization of the fetal spine observed at 18 weeks of gestation, represented by malsegmentation of the vertebrae along the entire length of the spine. No definitive scoliosis or short long bones was observed. At 21 weeks, the fetal profile demonstrated a flat nasal bridge. In addition, hyperechoic regions were observed at the femoral epiphyses that suggested premature calcification. In the same fetus, polyhydramnios was observed at 30 weeks (Pryde et al., 1993).

The diagnosis of rhizomelic chondrodysplasia punctata is easier to make than Conradi–Hünermann syndrome because of the severe shortening of the extremities in combination with premature ossification and stippling of the ephiphyses (Hertzberg et al., 1999). Since the condition is inherited in an autosomal recessive manner, there will be a negative family history for most cases. The prenatal sonographic findings reveal bilateral symmetric proximal shortening of the humeri and femora (less than the 3rd percentile for gestational age), along with marked epiphyseal echogenicity that suggests the presence of the punctate epiphyseal calcifications (Sastrowijoto et al., 1994). Additional fetal findings may include brachycephaly, hydrocephalus, scalp edema, hypertelorism, hypoplastic nose, and coronal clefts of the vertebral bodies. Bilateral cataracts have been detected by sonogram in a fetus with rhizomelic chondrodysplasia, type 1, at 30 weeks of gestation (Başbuğ et al., 2005). Congenital heart disease has also been reported in the rhizomelic form of chondrodysplasia punctata (Sastrowijoto et al., 1994).

Duff et al. (1990) described the sonographic diagnosis of rhizomelic chondrodysplasia punctata at 28 weeks of gestation in a woman with a previous affected infant. These investigators demonstrated stippling at the proximal end of the right humerus and both femurs over an 8-week period. The tibia consistently measured at the 20th percentile for gestational age, but both the femur and humerus were consistently at less than the 5th percentile. Over the period observed, a progressively more mottled appearance of the proximal end of the right humerus was demonstrated. The bone became more and more attenuated, irregular, and stippled in appearance, making it difficult to precisely define the end of it (Duff et al., 1990). In another report, a set of dichorionic twins was described, in which one was noted to have rhizomelic limb shortening at 25 weeks of gestation. In this fetus, the humeri were shaped like dumbbells and multiple hyperechoic foci were noted in the humeral epiphyses and the proximal femoral epiphyses. A 15-week sonogram was reanalyzed retrospectively; it revealed that the profound humeral shortening had previously been missed. Even at 15 weeks of gestation, flared humeral metaphyses and widened hyperechoic proximal ends of the humeri were visible (Gendall et al., 1994). After postmortem examination, the diagnosis of rhizomelic chondrodysplasia punctata was confirmed in this twin by demonstration of absent alkyl-dihydroxyacetone phosphate synthase activity in cultured skin fibroblasts.

Although two-dimensional ultrasound is adequate for diagnosis, at least one report exists that demonstrated enhanced resolution of pathologic findings in rhizomelic chondrodysplasia punctata using three-dimensional sonography and three-dimensional helical computer tomography (Ruano et al., 2004).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of conditions that result in limb shortening with punctate epiphyses is given in Table 99-1. The conditions include skeletal dysplasias, other genetic or metabolic disorders, disorders of vitamin K metabolism, and teratogens. To distinguish among the conditions grouped under the term chondrodysplasia punctata, fetal limb length must be measured. The humeri are the shortest in the rhizomelic form of chondrodysplasia punctata. The presence of polydactyly may suggest the more mildly X-linked dominant form of Conradi–Hünermann syndrome (Poznanski, 1994). The major consideration in the differential diagnosis is to distinguish between the rhizomelic form of chondrodysplasia punctata and the milder, Conradi–Hünermann type.

The other major condition that can present with punctate epiphyses is Zellweger (cerebrohepatorenal) syndrome,

Table 99-1

Differential Diagnosis of Punctate Epiphyses

Skeletal dysplasias
Chondrodysplasia punctata
Conradi–Hünermann type
Rhizomelic type
Brachytelephalangic type
Mesomelic metacarpal type
Sheffield type
Other genetic disorders
Zellweger syndrome
Trisomy 21
Trisomy 18
Smith–Lemli–Opitz syndrome
DeLange syndrome
GM_1 gangliosidosis
Child syndrome
Vitamin K disorders
Warfarin embryopathy
Vitamin K epoxide reductase deficiency
Teratogens
Fetal alcohol effects
Hydantoin exposure
Phenacetin intoxication
Maternal febrile illness

Source: Poznanski AK. Punctate epiphyses: a radiological sign, not a disease. Pediatr Radiol *1994;24:418-424.*

which is also characterized by lack of peroxisomes. In this condition, fetal limb length should be appropriate for gestational age, but additional antenatal findings may include hepatomegaly, hypotonia, and cystic changes in the liver and kidney. The calcifications in Zellweger syndrome tend to be centered around the patella. A number of other metabolic conditions, such as Smith–Lemli–Opitz syndrome and GM_1 gangliosidosis, can also present with punctate epiphyses (see Table 99-1).

Fetal exposure to warfarin, an anticoagulant, or the presence of a vitamin K epoxide reductase deficiency can result in stippled epiphyses. Warfarin exerts its effect on the developing fetus by inhibiting vitamin K–dependent posttranslational carboxylation of certain bone proteins. Vitamin K is normally converted to vitamin K epoxide. The enzyme vitamin K epoxide reductase then converts this metabolite back to vitamin K. Warfarin inhibits this reductase, so vitamin K–dependent carboxylases do not have their cofactor. The vitamin K disorders can result in fetal findings that are very similar to chondrodysplasia punctata, including nasal hypoplasia, calcification of the trachea, and brachytelephalangic changes of the digits (Poznanski, 1994; Tongsong et al., 1999). The effects of warfarin and other coumarin derivatives are most significant when the fetus is exposed during the sixth to ninth week of gestation (Poznanski, 1994). In both fetal alcohol exposure and the autosomal trisomies, the puncta are characteristically seen in the tarsal bones.

ANTENATAL NATURAL HISTORY

The underlying bone abnormalities that result in the chondrodysplasia punctata phenotype are present in the early second trimester. In studies of fetuses from pregnancies that have been terminated, extensive characteristic calcifications have been noted in the sites of endochondral bone formation in the limbs and trunk. The calcifications are distinct from endochondral bone. Ossification appears delayed in areas where calcifications are most prominent (Silengo et al., 1980). In rhizomelic chondrodysplasia punctata, histopathologic studies reveal that the abnormal areas of calcification are characterized by irregular distribution of cartilage cells, mucoid degeneration, presence of cystic spaces, increased vascularity, and proliferation of fibroblasts (Duff et al., 1990). The growth plates of the long bones are normal and the chondrocytes are arranged in normal columns (Sastrowijoto et al., 1994).

In fetuses with Zellweger syndrome, stippled calcifications of the patella, femur, and humerus are all observed by 20 weeks of gestation. In addition, the renal microcysts and macrocysts are also present. This condition is also characterized by neuronal migrational abnormalities. Cortical plate defects and heterotopias that are apparent at the light microscope level are associated with lipid inclusions at the ultrastructural level (Powers, 1995). These abnormalities are all because of the absence of peroxisomes.

MANAGEMENT OF PREGNANCY

Fetuses that are suspected of having punctate calcifications or rhizomelic limb shortening should be referred to a center capable of detailed anatomic scanning. Once the suspected diagnosis of chondrodysplasia punctata has been confirmed, it is prudent to refer the parents to a medical geneticist, who could then examine both of them for mild signs of Conradi–Hünermann syndrome. This is extremely important, as the prognosis for the infant will differ depending on the cause of the puncta. If one of the parents is affected, as opposed to neither parent being affected, the prognosis will be considerably improved. It is critical that the person who examines the parents looks for nonskeletal manifestations of Conradi–Hünermann syndrome. As an example, Silengo et al. (1980) reported that a 27-year-old woman presented for genetic counseling because her 32-month-old daughter had Conradi–Hünermann syndrome. Despite the fact that the mother walked with a limp, was short, had patches of alopecia, and had follicular atrophoderma, she herself had not been

diagnosed as having Conradi–Hünermann syndrome. A slit-lamp examination revealed the presence of early lenticular cataracts in the mother. This woman had no abnormalities in her long bones or spine, but because of her hip dysplasia and eye and skin abnormalities, she was retrospectively diagnosed as affected. Therefore, for any fetus in which chondrodysplasia punctata is suspected, parents and close relatives should be specifically examined for the presence of a hypoplastic nose, cataracts, optic atrophy, alopecia, or pigmentary skin changes.

In addition, a chromosome analysis should be performed on the fetus to evaluate for the X-linked recessive form of chondrodysplasia punctata, which may be due to a deletion of chromosome X at band p22.3 (Bick et al., 1992). Several investigators have described the existence of a contiguous gene syndrome at Xp22.3 that consists of chondrodysplasia punctata, steroid sulfatase deficiency, and X-linked Kallman syndrome, which includes hypogonadism due to hypothalamic gonadotropin-releasing hormone deficiency and anosmia secondary to absence of the olfactory bulbs and tracts (Bick et al., 1992).

For families who have had previously affected children with the rhizomelic form of chondrodysplasia punctata, prenatal diagnosis can be performed by biochemical analysis of either chorionic villi or amniocytes, although the recent identification of DNA mutations in the *PEX7, DHAPAT*, and *ADAPS* genes (see "Genetics and Recurrence Risk") should facilitate prenatal DNA diagnosis.

No specific indication exists for cesarean delivery. Fetuses in which chondrodysplasia punctata is suspected should be delivered at a tertiary care center because of the risk of respiratory distress.

FETAL INTERVENTION

There are no fetal interventions for chondrodysplasia punctata.

TREATMENT OF THE NEWBORN

Treatment of the newborn begins with an extensive and detailed physical examination. A list of the comparative clinical findings associated with nonrhizomelic chondrodysplasia punctata is given in Table 99-2. For many of the conditions associated with chondrodysplasia punctata, nasal hypoplasia is commonly seen (Seguin et al., 1993). This finding may be associated with a small and/or calcified airway. In one study, 29% of affected infants had respiratory distress syndrome during the newborn period that was attributed to the small airway (Seguin et al., 1993). The airway obstruction improves with age, as it is not typically found in older children (see Figure 99-3).

Many of the typical radiographic findings that aid in obtaining the diagnosis are best observed during the newborn period, as they tend to disappear with age. These include the punctate epiphyses and vertebral clefts. A diagnosis of Conradi–Hünermann syndrome may be presumptively made by the characteristic facial appearance that consists of a flattened face due to malar hypoplasia, a small nose with a flat nasal bridge, a prominent forehead, wide-set eyes, and upslanting palpebral fissures. Cataracts are seen in 18% of affected infants (Poznanski, 1994). Infants affected with Conradi–Hünermann syndrome may have ichthyosiform erythroderma or systemic atrophoderma. They may also have patches of alopecia and contractures of the extremities. The limb shortening is usually mild but it can be asymmetric. Polydactyly may be observed in the X-linked dominant form.

Infants affected with rhizomelic chondrodysplasia punctata have much more marked shortening of the upper limbs. The metaphyses are generally flared. Radiographs demonstrate the puncta less commonly than in Conradi–Hünermann syndrome (see Figure 99-4). The physical examination reveals the presence of full cheeks, giving the infant the appearance of a chipmunk (see Figure 99-3). The skin changes are much less commonly observed in rhizomelic chondrodysplasia punctata. Cataracts are present in 75% of infants affected with this disorder (Poznanski, 1994). Developmental abnormalities are typical of the rhizomelic form of chondrodysplasia punctata. Magnetic resonance imaging (MRI) may reveal the presence of migrational disturbances in the brain. An additional helpful radiographic finding is the presence of coronal clefts that can be seen on lateral films of the lumbar and thoracic vertebrae.

There are several milder forms of chondrodysplasia punctata, characterized by abnormalities of the extremities. In the tibia-metacarpal type of chondrodysplasia punctata, short third and fourth metacarpals are observed. These children also have a hypoplastic midface and a flattened nasal bridge. In later life, they have a height that is 2 to 4 SD below normal. The brachytelephalangic type of chondrodysplasia punctata is characterized by an extremely small, anteverted, grooved nose that resembles the one in infants affected with Binder syndrome. On radiographs, the distal phalanges have a characteristic triangular appearance. This condition may be associated with a terminal deletion of the short arm of the X chromosome.

Another important consideration during the newborn period is the diagnosis of Zellweger syndrome, characterized by calcification of the patella. These infants are much more severely hypotonic than other infants. Renal sonography may also indicate the presence of cortical cystic changes. These infants also have progressive hepatic failure.

SURGICAL TREATMENT

For more mildly affected patients with Conradi–Hünermann syndrome, orthopedic surgery may eventually be needed to correct limb length asymmetry.

Table 99-2

Comparative Manifestations of Nonrhizomelic Chondrodysplasia Punctata Subtypes by Inheritance Patterns

Inheritance	Synonyms	Punctate Calcifications	Limb Shortness	Saddle Nose Deformity	Skin Changes (Ichthyosiform Erythroderma)	Cataracts	Mental Retardation	Other	Overall Prognosis
Autosomal dominant	Chondrodystrophia calcificans congenita	Variable severity asymmetric	Mild or none	Present	Present in 28% of cases	Symmetric, present in 17% of cases	None or minimal	Skeletal dysplasia	Good
X-linked recessive without chromosome deletion	Brachytelephalangic chondrodysplasia punctata	Mild severity, symmetric	Mild overall growth lag	Variable severity	No changes	None	None or mild	Uniform distal phalangeal hypoplasia	Good
X-linked recessive with Xp deletion	CPXR	Extensive bilateral symmetric	Shortness of stature	Typically severe with nasal hypoplasia	Marked skin changes	Occasional	IQ range, 50–70	Steroid sulfatase deficiency, and frequent distal phalangeal hypoplasia	Survival good, but neurodevelopmentally impaired
X-linked dominant	CPXD	Variable asymmetric	Proximal variable, asymmetric	Present	Marked cicatrical "patchy" changes	Asymmetric	Normal	Occasional scoliosis	Lethal in hemizygous males
Teratogenic phenocopy	Vitamin K–dependent coagulation defect, warfarin embryopathy	Irregular asymmetric pattern, variable severity	Moderate to severe	Moderate to severe with frequent nasal hypoplasia	None	None	Mild or none	Common mild distal phalangeal hypoplasia	Good

Source: Pryde PG, Bawle E, Brandt F, Romero R, Treadwell MC, Evans MI. Prenatal diagnosis of nonrhizomelic chondrodysplasia punctata. Am J Med Genet. *1993;47:426-431.*

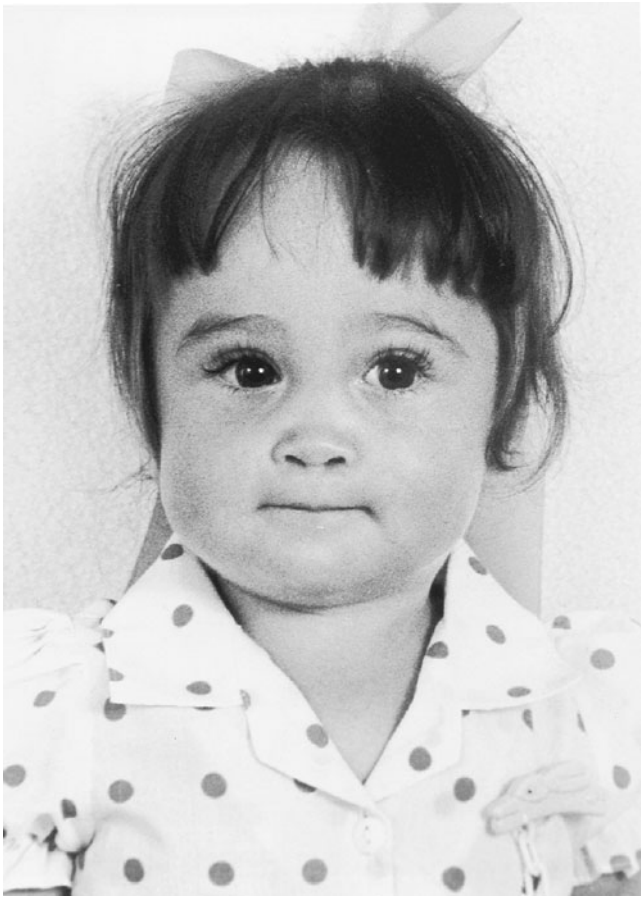

Figure 99-3 A child with chondrodysplasia punctata demonstrating severe nasal hypoplasia. *(Reprinted, with permission, from Fourie DT. Chondrodysplasia punctata: case report and literature review of patients with heart lesions. Pediatr Cardiol. 1995;16:247-250.)*

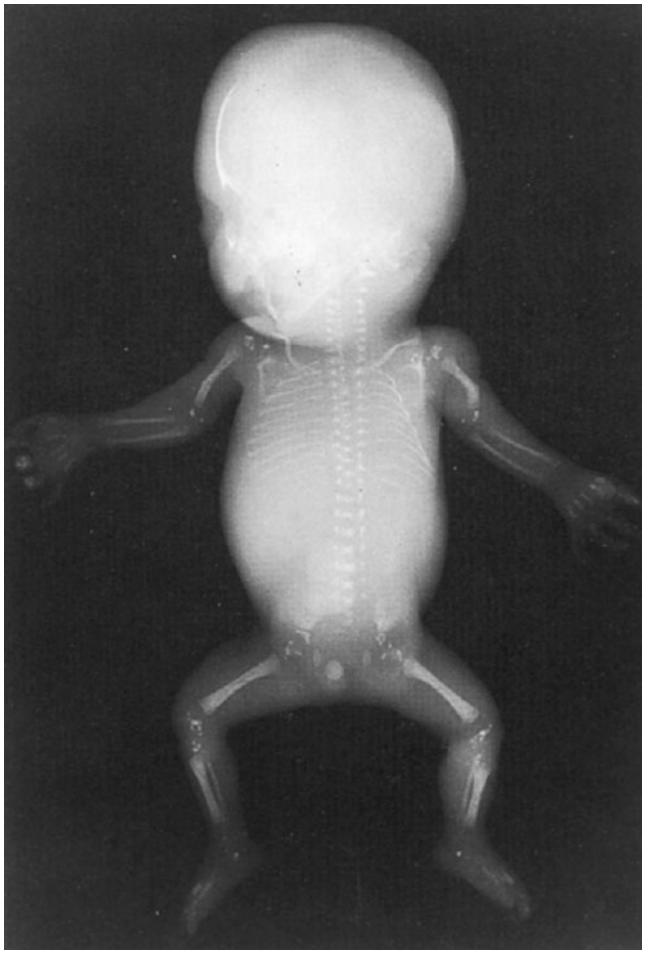

Figure 99-4 Postmortem radiograph demonstrating presence of epiphyseal calcifications in an infant with rhizomelic chondrodysplasia punctata. This is from the same individual shown in Figure 99-2. *(Reprinted, with permission, from Sastrowijoto SH, Vandenberghe K, Moerman P, Lauweryns JM, Fryns JP. Prenatal ultrasound diagnosis of rhizomelic chondrodysplasia punctata in a primigravida. Prenat Diagn. 1994;14:770-776. Copyright 1994 John Wiley & Sons. Reprinted, by permission, of John Wiley & Sons, Ltd.*

LONG-TERM OUTCOME

The long-term outcome is related to the underlying condition. The rhizomelic form of chondrodysplasia punctata is the most severe, with a poor prognosis. A recent review of 97 affected cases reported that survival is better than previously reported, with 90% of infants surviving up to 1 year and 50% surviving up to 6 years (White et al., 2003). All infants with rhizomelic chondrodysplasia have severe failure to thrive, profound mental retardation, joint contractures, and bilateral cataracts. Surgical removal of cataracts is recommended to increase visual stimulation and environmental interaction. Seizures are common. Death is usually due to respiratory complications.

Patients affected with Conradi–Hünermann syndrome are shorter than normal at birth and remain so throughout life. The typical calcific stippling disappears by 3 to 4 years of age (Poznanski, 1994). During infancy and early childhood, these infants may have cataracts, growth failure, or feeding problems. Affected infants are very susceptible to respiratory infections, generally because of the airway abnormalities. The laryngeal and tracheal calcifications usually resolve within the first 3 years of life (Seguin et al., 1993). Laryngoscopy and bronchoscopy can be considered electively during the first year of life to identify any lower airway abnormalities (Seguin et al., 1993).

For infants who survive the first year of life, the skeletal deformities eventually become less pronounced and the contractures may disappear. The clinically unrecognized adults with Conradi–Hünermann syndrome described in the literature have had normal intelligence.

GENETICS AND RECURRENCE RISK

To adequately calculate the recurrence risk, the definitive diagnosis must be known. For infants affected with rhizomelic chondrodysplasia punctata, the condition is inherited in an autosomal recessive fashion and parents should be counseled

that there is a 25% recurrence risk. Prenatal diagnosis is available as early as 10 weeks of gestation by demonstration of decreased plasmalogen synthesis and decreased phytanic oxidation in chorionic villi. In addition, immunoblot studies of the peroxisomal 3-oxo-acyl-CoA thiolase can also definitively diagnose the presence of an affected fetus with rhizomelic chondrodysplasia punctata (Hoefler et al., 1988). If the biochemical studies of the chorionic villi or cultured amniocytes are normal, prenatal sonography can be used as additional confirmation of fetal status (Schutgens et al., 1989; Gray et al., 1990).

Mutations in the human *PEX7* gene are the molecular basis for rhizomelic chondrodysplasia punctata type 1 (Braverman et al., 1997; Motley et al., 1997; Purdue et al., 1997; Braverman et al., 2002; Motley et al., 2002). The *PEX7* gene maps to human chromosome 6q22–24 and consists of eight exons spanning more than 40 kb of DNA. In one study, 26 of 36 patients with rhizomelic chrondrodysplasia punctata had a single inactivating mutation known as L292X. This mutation was seen exclusively in patients of northern European descent because of a founder effect (Braverman et al., 1997) Type 1 rhizomelic chondrodysplasia punctata is the most common of the rhizomelic forms (Motley et al., 2002). In type 2, there is an isolated deficiency of DHAP acyltransferase because of mutations in the acyl CoA: dihydroxyacetone phosphate acyltansferase (*DHAPAT*) gene. Type 3 is caused by mutations in the alkyl-dihydroxyacetone phosphate synthase (*ADHAPS*) gene.

Once a mutation is identified in a particular family, DNA diagnosis by molecular studies of chorionic villi in subsequent pregnancies is definitive. Therefore, arrangements should be made to establish fibroblast cell cultures from affected fetuses or infants who are electively terminated or die during the perinatal period in order to identify the familial mutation.

Similarly, Zellweger syndrome is inherited as an autosomal recessive condition. This condition can be diagnosed definitively during the newborn period by measurement of plasma very long-chain fatty acids. Prenatal diagnosis in subsequent pregnancies can demonstrate the very long-chain fatty acid abnormalities and the absence of peroxisomes in cultured chorionic villus cells.

The diagnosis of Conradi–Hünermann syndrome depends on a complete examination of both parents as well as taking a complete family history to rule out the autosomal dominant, X-linked dominant, and X-linked recessive forms. Parents who are retrospectively diagnosed as being affected with Conradi–Hünermann syndrome, such as in the case of Silengo et al. (1980), will be counseled that their fetuses have a 50% risk of recurrence. If possible, DNA diagnosis should be performed on an affected parent to permit prenatal diagnosis. In one case, a pregnant woman with a mild form of X-linked dominant chondrodysplasia punctata (Conradi–Hünermann syndrome) was shown to have a mutation in the emopamil binding pathway (*EBP)* gene (Whittock et al., 2003). This allowed molecular prenatal testing on her male fetus, who was shown to be unaffected.

Gene mapping studies have suggested that another form of chondrodysplasia maps to chromosome 4p16 (Dimmick et al., 1991) and that the X-linked dominant form maps to Xq28. The X-linked recessive and brachytelephalangic forms map to Xp22.3.

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Amniotic Band Syndrome

100
CHAPTER

Key Points

- Amniotic band syndrome is a group of congenital anomalies involving limbs, craniofacial region, or trunk.
- Amniotic band syndrome can range from constrictive bands involving a digit to thoracoabdominoschisis, encephalocele, or the limb–body wall complex.
- The incidence ranges widely from 1 in 1200 to 1 in 15,000 livebirths depending on how it is defined.
- Ultrasound examination is the mainstay of diagnosis.
- Amniotic bands can occur spontaneously or as a result of instrumentation of the pregnancy.
- Fetoscopic release of amniotic bands may prevent limb amputation when it involves an extremity or may be lifesaving if they involve the umbilical cord.
- Almost all cases of amniotic band syndrome deliver prematurely.

CONDITION

The amniotic band syndrome (ABS) is a group of sporadic congenital anomalies that involve the limbs, craniofacial regions, and trunk, ranging from constrictive bands, pseudosyndactyly to amputation, as well as multiple craniofacial, visceral, and body wall defects (Torpin, 1965; Jones et al., 1974; Higginbottom and Jones, 1979; Seeds et al., 1982; Ray et al., 1988; Lockwood et al., 1989; Seidman et al., 1989; Kulkarni and Gopal, 1990). The term *amniotic band syndrome* encompasses many congenital anomalies, including amniotic band disruption complex (Higginbottom and Jones, 1979), amniochorionic mesoblastic fibrous strings (Torpin, 1965), aberrant tissue bands (Jones et al., 1974), amniotic deformity, adhesion and mutilation (ADAM) complex (Keller et al., 1978; Orioli et al., 2003), amniotic adhesion malformation syndrome (Herva and Karkinen-Jaaskelainen, 1984), and the limb and/or body wall defect (Bamforth, 1992).

Several theories have been advanced to explain the occurrence of these anomalies but two are most commonly held. In 1930, Streeter proposed that a disruption in embryogenesis at the time of formation of the germ disk and the amniotic cavity initiated a chain of events leading to the multiple defects. He suggested that amniotic bands were the result, not the cause, of the pathologic process. In 1992, Bamforth reviewed this theory in a series of 54 cases of ABS and concluded that it may be caused by a localized disturbance in establishment of basic embryonic organization. The most widely accepted theory was proposed by Torpin in 1965. He examined the placenta and fetal membranes in a number of affected individuals and concluded that the disorder was caused by primary rupture of the amnion early in gestation (Keller et al., 1978; Higginbottom and Jones, 1979; Seeds et al., 1982; Herva and Karkinen-Jaaskelainen, 1984).

More recently, Moerman et al. (1992) proposed that the ABS is a collection of three distinct entities that can reconcile

both Streeter's and Torpin's hypotheses. They suggested that ABS consists of three distinct lesions: (1) constrictive tissue bands; (2) amniotic adhesions; and (3) the more complex pattern of anomalies designated the limb–body wall complex (LBWC) (see Chapter 60). In this report of the fetopathologic evaluation of 18 cases of ABS, 4 had clearly constrictive bands, which formed as a result of the amnion rupture sequence. The bands that resulted from amnion rupture encircled the limbs, resulting in annular constrictions, secondary syndactyly, and intrauterine amputations. In addition, constriction of the umbilical cord is a recognized cause of fetal death (Hong and Simon, 1963; Torpin, 1965). These authors distinguish cases caused by constrictive bands from those caused by broad amniotic adhesions. Moerman et al. (1992) suggested that adhesive amniotic bands were morphologically and pathogenetically different from constrictive bands. Adhesive amniotic bands are usually associated with severe defects such as encephalocele and facial clefts. This group demonstrated pathologically that cranioplacental adhesions are broad adhesions, with the fetal skin fused to the amnion at the margins of the cranial defect. They speculated that the amnion covering the placenta or membranes seals the cranial defect separating the protruding brain from the chorion. Van Allen et al. (1987) proposed that the amnion becomes adherent to the embryo in areas of ischemic necrosis following vascular disruption. In short, the amniotic adhesions are secondary to fetal defects.

Moerman et al. (1992) considered the LBWC to be due to both band-related and non–band-related defects. The band-related defects include limb defects such as clubfoot. Non–band-related defects occur as a result of vascular disruptions or from compression (Miller et al., 1981). The thoracoabdominoschisis of LBWC is characterized by an anterolateral body wall defect with evisceration of abdominal and/or thoracic organs. The eviscerated organs are in an extra-amniotic sac bounded by the chorionic plate, a persistent extraembryonic coelom. The amnion is continuous with the skin. The umbilical cord is extremely short, with umbilical vessels running in the amniotic sac, often with an absent umbilical artery. The severe scoliosis is a postural deformity caused by abnormal fixation of the fetus to the placenta. They also cite the high incidence of internal structural defects such as cardiac anomalies, unilateral absence of a kidney, or intestinal atresia, which do not fit with simple amnion rupture.

The fetal malformations that can occur as a result of ABS can be categorized into neural tubelike defects, craniofacial anomalies, limb anomalies, and constrictive bands (Seeds et al., 1982; Lubinsky et al., 1983; Ho and Liu, 1987; Seidman et al., 1989). The neural tubelike defects include cases of anencephaly and encephalocele, which may be asymmetric or multiple. The craniofacial anomalies include facial clefts, nasal deformity, asymmetric microphthalmia, and abnormal cranial calcification. Limb anomalies may be multiple and asymmetric, including limb or digital amputation, pseudosyndactyly, abnormal dermatoglyphics, and some cases of clubbed feet. Abdominal wall and thoracic wall defects can occur, and some cases are mistaken for gastroschisis or omphalocele with rupture.

The most puzzling component of the ABS is its association with visceral anomalies, including bladder exstrophy, vertebral hypoplasia, and other renal, gonadal, cardiac, and pulmonary defects (Bamforth, 1992). Constrictive bands involving the extremities are the most common defect associated with the ABS (Huang et al., 1995).

The variation in manifestations of the ABS are thought to be due to differences in timing of amniotic rupture and the degree to which the fetus becomes entangled by strands of amnion (Higginbottom and Jones, 1979; Seeds et al., 1982). The effects the amniotic bands have on the developing fetus have been classified into malformation, disruption, and deformation (Higginbottom and Jones, 1979). Amniotic bands that interrupt the normal sequence of embryologic development lead to malformations such as cleft lip and palate, and abdominal wall defects. In contrast, bands may tear normally developed structures, leading to disruption such as central nervous system or calvarial defects, acrosyndactyly, amputations, and nonanatomical facial clefts (Lockwood et al., 1989). The effects of fetal compression and tethering may lead to deformations such as clubbing of the feet and angulation of the spine.

The timing of amnion rupture has been suggested to occur between 28 days after conception to 18 weeks of gestation. If amnion rupture occurs prior to 45 days of gestation, the results are likely to be devastating, including severe skull defects and major visceral defects (Huang et al., 1995). Rupture occurring after 45 days of gestation is likely to result in more limited defects.

The cause of amnion rupture and band formation is not well understood, but it has been observed following amniocentesis (Rehder, 1978). Late gestation bands, even in the absence of an amniocentesis, can also occur. Lage et al. (1988) reported ABS presenting at birth with multiple abnormalities of the extremities despite a normal sonographic appearance at 21 weeks of gestation. There have also been cases of ABS associated with underlying disease. Young et al. (1985) reported two cases in fetuses with Ehlers–Danlos syndrome type IV and one with osteogenesis imperfecta. They speculated that the premature amnion rupture may have been due to reduced or abnormal collagen in the amnion. There have been rare familial cases of ABS, and some teratogens, such as lysergic acid diethylamide and methadone, have been reported in association with the syndrome (Chemke et al., 1973; Lubinsky et al., 1983; Daly et al., 1996). Other significant exposures include misoprostol and maternal fever (Orioli et al., 2003; Ribeiro et al., 2004).

Chorioamniotic separation, occurring spontaneously or as a consequence of invasive procedures, is a potential cause of the ABS. The incidence of chorioamniotic separation diagnosed by ultrasound is reported to range from 1 in 187 to 1 in 4333 births (Kaufman et al., 1985; Borlum, 1989). The natural history of chorioamniotic separation occurring in normal pregnancies was initially thought to be benign. However, Graf et al. (1997) reported a case of chorioamniotic

separation that resulted in the formation of amniotic bands involving the umbilical cord, resulting in fetal death. The incidence of chorioamniotic separation may be even higher in cases of fetal surgery. In the same report, Graf and colleagues described 5 cases of chorioamniotic separation occurring in a series of 40 patients undergoing open fetal surgery. Three of the five fetuses had amniotic bands involving the umbilical cord, leading to fetal death in one. This report speculated that because the amnion is adherent and fixed to the umbilical cord, once formed amniotic bands may retract to the cord, causing strangulation. Heifetz (1984), in a review of ABS, reported that as many as 10% of cases had umbilical cord strangulation.

ABS is often misdiagnosed, especially in cases of early amniotic band rupture. Infants affected by early amniotic rupture present with anencephaly, encephalocele, abdominal or thoracic wall defects, and severe limb abnormalities. The severity of the anomalies obscures the cause, especially if the amniotic bands are not evident at birth. It has been estimated that a correct neonatal diagnosis of ABS is made in only 24% to 50% of patients without specialized genetic consultation (Seeds et al., 1982).

INCIDENCE

Because of difficulties in accurately diagnosing ABS, the estimates of its incidence vary widely. The reported incidence ranges from 1 in 1200 to 1 in 15,000 livebirths (Chemke et al., 1973; Seeds et al., 1982; Ho and Liu, 1987; Ray et al., 1988). More recent estimates place the incidence of ABS at 1 in 1200 because of the more frequent recognition of an amniogenic cause for congenital anomalies (Ossipoff and Hall, 1977; Seeds et al., 1982; Moerman et al., 1992). In a retrospective analysis of 3173 autopsies performed during a 14-year period, Czichos et al. (2005) found 744 cases of malformations of which 14 had anomalies thought to be a consequence of amnion rupture. This series yielding an incidence of 1:226 among fetuses and newborns undergoing autopsy suggested that it may be a more common cause of anomalies than generally appreciated.

Hands are more frequently affected than feet, with the largest fingers (third, fourth, and second) more commonly afflicted (Ribeiro et al., 2004).

SONOGRAPHIC FINDINGS

ABS is associated with numerous antenatal sonographic features, as there are numerous forms of the syndrome and these features may occur as isolated problems or in combination. The earliest that amniotic bands have been seen is at 12 weeks of gestation, by endovaginal probe. The bands can be extremely difficult to detect sonographically and ABS is more often diagnosed by the effect that they have on fetal anatomy

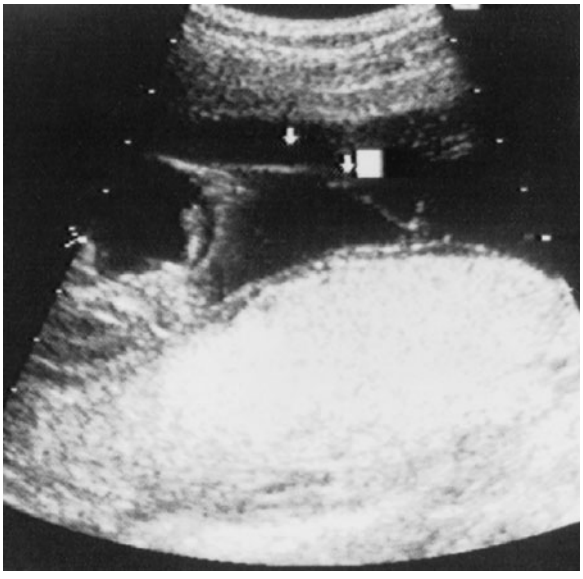

Figure 100-1 Sonographic image demonstrating an amniotic band attached to the fetus and floating in the amniotic fluid.

(Figure 100-1). The effect of amniotic bands on the extremities may be manifested by absent digits or portions of limbs, or a swollen distal arm or leg resulting from constrictive amniotic bands (Paladini et al., 2004) (Figure 100-2). ABS may affect the face with cleft lip or palate, asymmetric microphthalmia, or severe nasal deformity. Encephalocele may be a manifestation of ABS, especially when eccentrically placed (Figure 100-3). Abdominal wall defects can be the result of ABS, typically with large defects with free-floating intestine herniated outside the abdomen. The characteristic appearance of an aberrant sheet or band of amnion attached to the fetus with resultant deformity and restriction of motion allows a diagnosis of ABS to be made (Figure 100-3). However, prenatal diagnosis is the exception rather than the rule.

The findings in ABS may be limited to isolated defects, including isolated facial cleft, digital amputation, or mild elephantiasis of an extremity beyond a constrictive band (Sentilhes et al., 2004; Dyson et al., 2000). These isolated features may be difficult to diagnose sonographically because the detailed fetal visualization required is beyond the scope of routine obstetrical ultrasound examinations. At the worst end of the spectrum, the fetus may be so severely deformed by the amniotic bands that the spine is contracted and organs are formed in perplexing and bizarre proportions. The head may be completely misshapen or absent. The bands responsible for these deformities are rarely seen and a presumptive diagnosis of ABS is made based on the commonly associated deformities.

The spinal deformities in ABS can be severe, manifesting as kyphotic lordosis or scoliosis as well as severe rotational abnormalities and even spinal amputation (Chen, 2001). While spinal deformity can be seen in other syndromes, severe spinal deformity should suggest ABS.

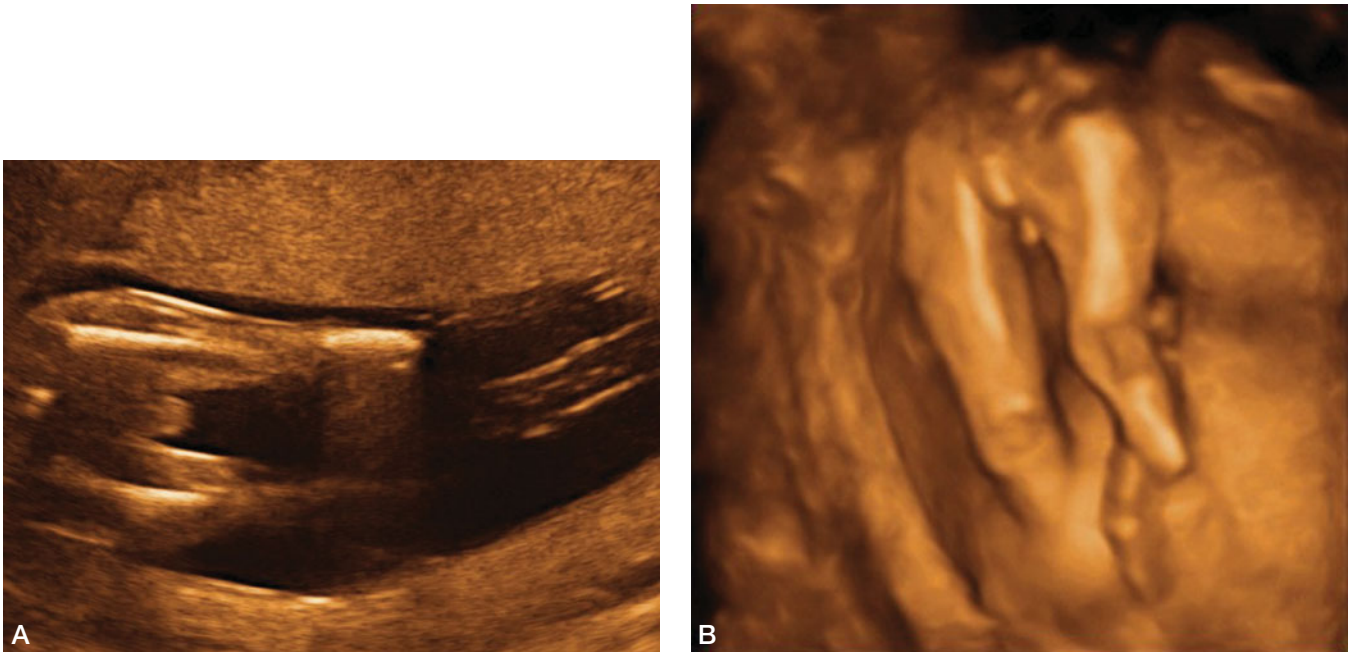

Figure 100-2 Sonographic image of a fetus with a constricting amniotic band of an extremity. **A.** 2-D image depicting amputation of the distal portion of both lower extremities as a result of amniotic bands. **B.** 2-D image of the same fetus showing bilateral limb reduction defects.

Spinal deformity associated with an abdominal wall defect is particularly suggestive of ABS. While the typical appearance of an omphalocele is possible, the more common defect is a large slashlike defect of both the thoracic and abdominal cavities with evisceration. These defects are associated with exteriorized bowel, liver, and sometimes heart without an enveloping membrane. When associated with limb abnormalities, this is characteristic of the LBWC form of ABS (Figure 100-4).

Deformation of the calvarium is another group of anomalies characteristic of ABS. If complete, the fetus may appear anencephalic or to have acrania (Chen et al., 2004). If partial, the fetus may appear to have an encephalocele. The distinguishing features that characterize these defects as

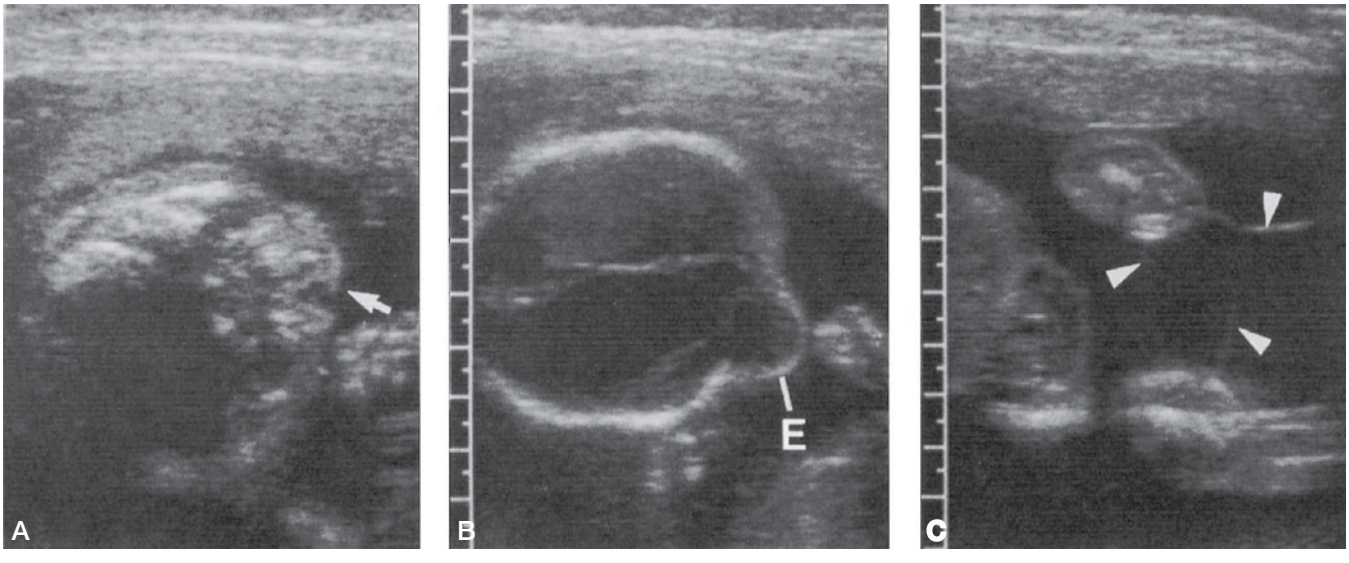

Figure 100-3 Sonographic image of a fetus with amniotic band syndrome manifesting as **A.** a "slash" defect in the maxillary region, and **B.** an eccentric encephalocele. **C.** Amniotic bands were also noted to be attached to the extremities (*arrowheads*). *(Reprinted, with permission, from Filly RA, Golbus MS. The fetus with amniotic band syndrome. In: Harrison MR, Golbus MS, Filly RA, eds. The Unborn Patient. 2nd ed. Philadelphia, PA: WB Saunders; 1991:440-447.)*

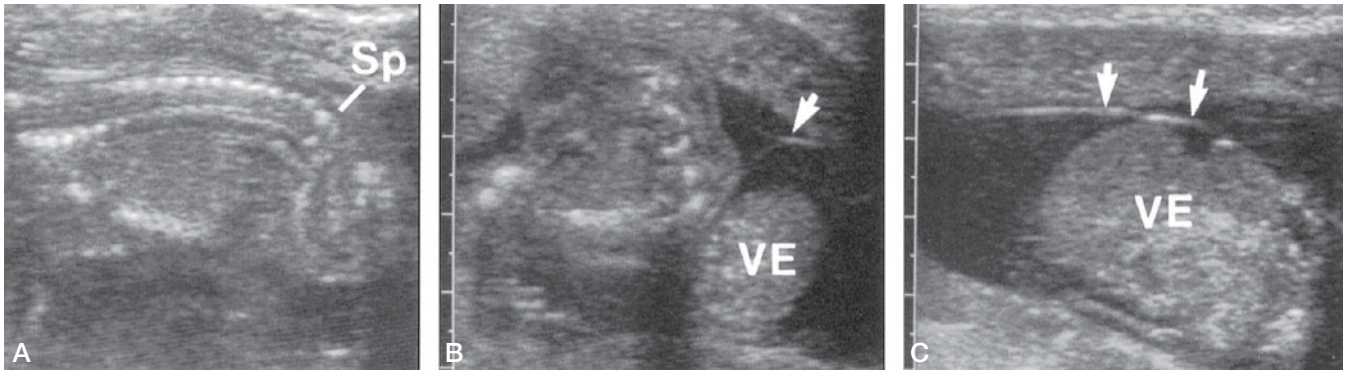

Figure 100-4 Sonographic image of a fetus with limb–body wall complex showing severe twisting deformity of the spine associated with gastropleuroschisis and amniotic bands attached to the extremities. **A.** The fetal spine (Sp) has a severe twisting deformity. **B.** The twisting deformity is so severe that the viscera (VE) herniated through the gastropleuroschisis are found posterior to the fetus. **C.** The amnion (*arrows*) encircles the exteriorized viscera. *(Reprinted, with permission, from Filly RA, Golbus MS. The fetus with amniotic band syndrome. In: Harrison MR, Golbus MS, Filly RA, eds. The Unborn Patient. 2nd ed. Philadelphia, PA: WB Saunders; 1991:440-447.)*

ABS are their asymmetric nature and associated spinal deformity or abdominal wall defects. In classic anencephaly, the calvarial bones are symmetrically absent (see Chapter 7). In anencephaly caused by ABS there is some portion of calvarium present, usually near the base of the skull or near one other orbit. Similarly, classic encephaloceles occur near the midline, while ABS causes encephaloceles off the midline.

The presence of bands is unnecessary for the diagnosis of ABS in the presence of characteristic fetal anomalies. The sonographic detection of bands is helpful in confirming the diagnosis of ABS as the cause of fetal deformity. However, observation of these bands without fetal abnormality is not ABS. It is important for the sonographer to distinguish amniotic bands from other membranes and separations within the amnion. Separation of amnion and chorion is normal in early pregnancy until fusion occurs at approximately 16 weeks of gestation (Sauerbrei et al., 1980; Burrows et al., 1982; Patten et al., 1986).

Chorioamniotic separation may occur as a result of amniocentesis or fetal surgery, and extrachorionic hemorrhage may separate the chorioamniotic membrane from the uterine wall (Spirit et al., 1979; Burrows et al., 1982; Graf et al., 1997). In both of these instances, a membrane may be observed sonographically. Other causes of membranes in the developing fetus include septate uterus, blighted twin, and circumvallate placenta (Fillyand Golbus, 1991).

Adhesions that form in the uterus as a result of curettage, cesarean section, or myomectomy may cause sheets of amnion that protrude into the lumen of the amniotic cavity (Asherman, 1948; Comninos and Zourlas, 1969; Mahony et al., 1985; Randal et al., 1988; Filly and Golbus, 1991). Randal et al. (1988) found that 76% of patients with amniotic sheets had undergone prior instrumentation. This results in an adhesion that becomes covered by chorion and amnion and has a thickness similar to the intertwin membrane of dichorionic diamniotic twins. These amniotic sheets do not adhere to the fetus because the amnion is intact (Tan et al., 2005). The uterine adhesion may rupture with growth of the fetus. Filly and Golbus (1991) have described the sonographic appearance of these synechiae as having a thickened base and a fine edge that undulates. There may be a bulbous edge, presumably due to the synechiae. There are no associated fetal abnormalities and there is free fetal movement around the sheet. The synechiae may not be seen in the third trimester, because of rupture or compression by the growing fetus.

In the LBWC there is a constellation of abnormalities, including myelomeningocele or caudal regression, thoracoabdominoschisis, or abdominoschisis and limb defects (see Figure 100-4). At least two of the three abnormalities listed above are necessary to make a diagnosis of LBWC. The umbilical cord is usually short or absent, with the placenta attached to the fetus. If present, there may be only a two-vessel cord. The limbs may be missing or the feet clubbed. The spine is often short and curved and sacral regression is common. There may be Arnold–Chiari malformation and hydrocephalus associated with the meningomyelocele. There may be ectopia cordis as part of the thoracoabdominoschisis. Facial clefts may also be seen in LBWC.

ABS involving the umbilical cord can be recognized by abnormal clustering of loops of umbilical cord, which may be adherent to a bend fixed to a limb. These findings may be subtle and should be sought in any case of ABS as umbilical cord involvement may result in fetal demise (Figure 100-5).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis in ABS depends on the sonographic findings. In isolated constrictive amniotic bands associated with distal limb edema, possible lymphatic or vascular malformations should be considered. However, color Doppler studies should closely show the flow characteristics of a vascular malformation. Constrictive bands involving the upper extremity should suggest the possibility of the VACTERL association if the radius is affected, and Fanconi anemia if radial

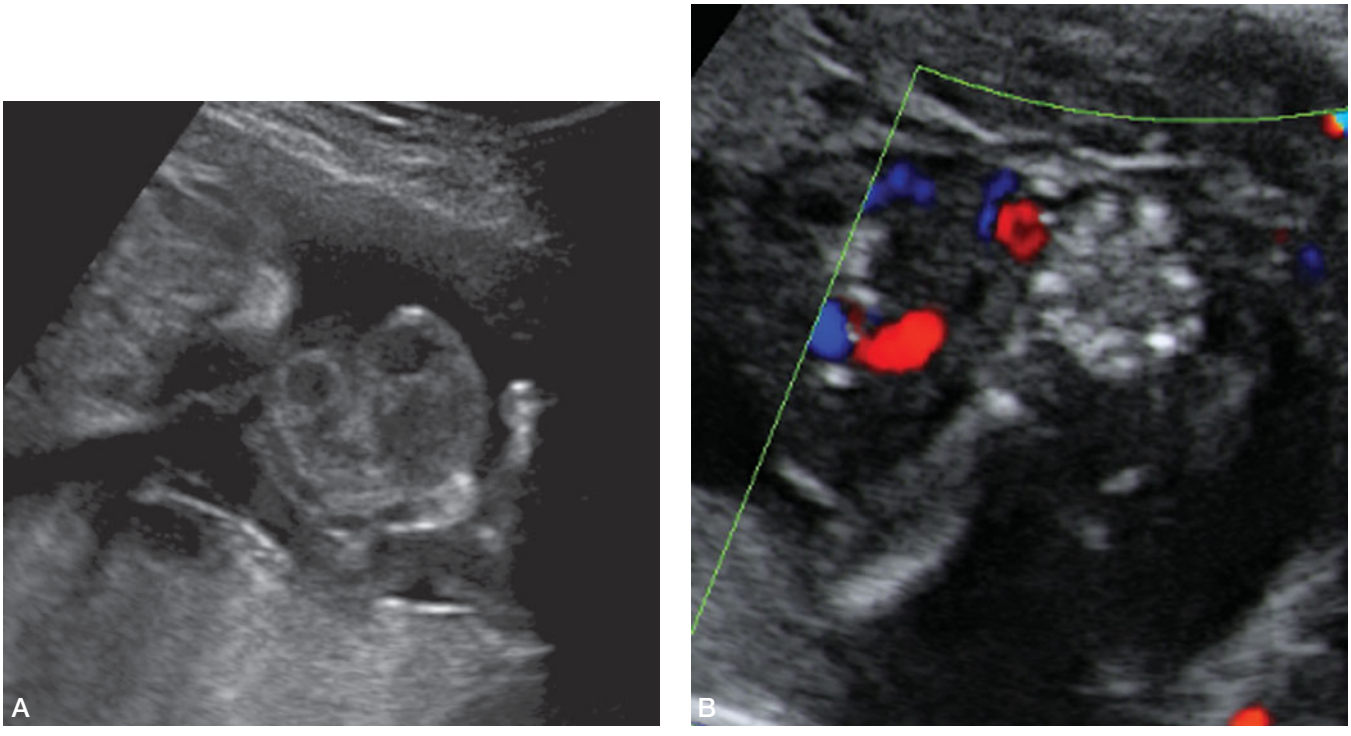

Figure 100-5 **A.** Sonographic image of amniotic bands involving the umbilical cord and the right upper extremity. **B.** Color doppler of the same patient.

hypoplasia or absent thumbs are observed. Amniotic membranes within the amniotic cavity without associated fetal anomalies may be amniotic sheets secondary to intrauterine synechiae or remnant of a blighted twin, or secondary to amniocentesis or chorionic villus sampling.

A diagnosis of LBWC requires two of three of the following abnormalities: (1) myelomeningocele or caudal regression, (2) abdominal or thoracoabdominal wall defect, or (3) limb defects. The main differential diagnoses are cases of isolated neural tube defects or ruptured omphalocele, which do not meet the criteria for LBWC. The body stalk anomaly has a similar constellation of anomalies but the placenta is attached to the trunk of the fetus.

ANTENATAL NATURAL HISTORY

There is great controversy about the pathogenesis of the various forms of ABS. Part of this controversy involves the timing in gestation of the development of amniotic bands. However, in constrictive amniotic bands of the extremities, the progression of constriction combined with fetal growth has resulted in extremity amputation (Figures 100-2, 100-6, and 100-7) (Hill et al., 1988). ABS can be associated with either polyhydramnios or oligohydramnios. Despite the severity of some forms of ABS, there are no adverse maternal consequences for this diagnosis. The incidence of intrauterine fetal death from ABS involving the umbilical cord is not known but numerous cases have been reported (Torpin, 1965; Kanayama

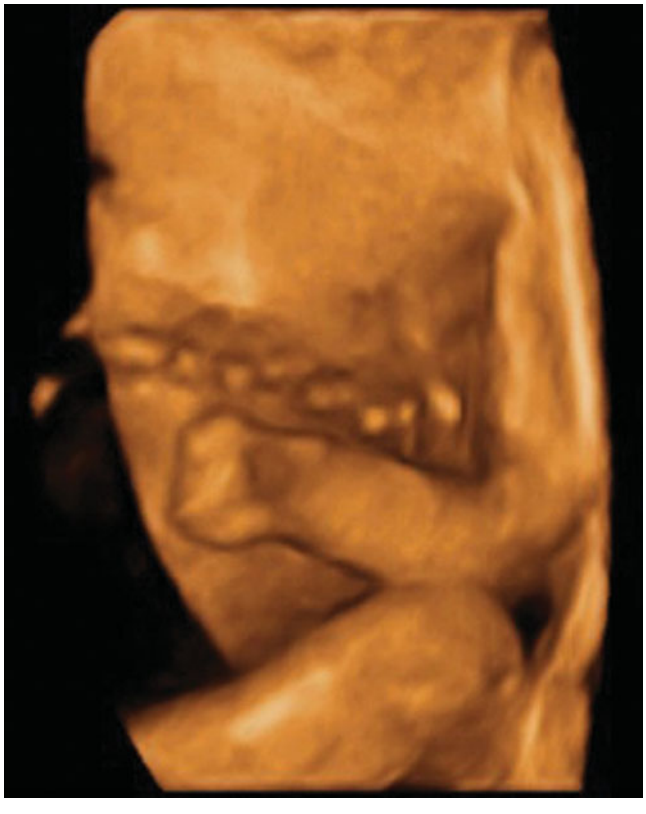

Figure 100-6 3D image demonstrating absence of the left fetal hand in a pregnancy complicated by amniotic bands.

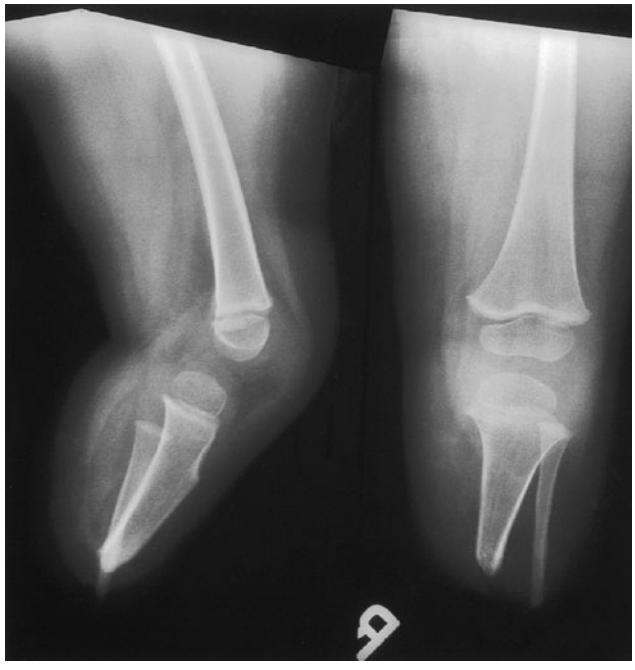

Figure 100-7 Plain radiograph of the right leg of a newborn who sustained amputation in utero of the right leg and foot from amniotic bands. *(Courtesy of Benjamin Alman, MD)*

et al., 1995; Graf et al., 1997). However, the poorly characterized pathogenesis of this syndrome and limited sonographic surveillance, limit our understanding of its prenatal natural history.

ABS is a relatively common, if underappreciated, cause of fetal and neonatal morbidity and mortality. The fetal lamb model of ABS will be useful to better define the pathophysiology of ABS and to provide a tool to understand the unique fetal response to tissue injury, repair, and regeneration. Sonographic identification of ABS affecting the umbilical cord may be an indication for fetoscopic surgical intervention. In the future, intervention for nonlethal limb deformation may also be considered if maternal risk is sufficiently lowered. ABS is another in a growing list of conditions for which fetal surgery may be considered in the future.

Constrictive bands most commonly affect the extremities, but can also involve the umbilical cord, with resulting fetal death. Kanayama et al. (1995) described the reversal of diastolic flow observed in a fetus with umbilical cord constriction due to amniotic bands. Graf et al. (1997) similarly reported a case of amniotic bands involving the umbilical cord following the development of chorioamniotic separation. Despite initially normal umbilical artery Doppler waveforms, this fetus died within 2 weeks from a constrictive amniotic band of the umbilical cord. Reports have described constrictive amniotic bands as a cause of fetal death (Torpin, 1965; Moerman et al., 1992). However, until the reports by Kanayama and Graf and their colleagues, this was a diagnosis made pathologically after the fact. It is in cases like these that fetoscopic lysis of amniotic bands could be lifesaving (see "Fetal Intervention").

Cases of ABS, by definition, have ruptured membranes and typically deliver prematurely with an average gestational age of 32 weeks.

MANAGEMENT OF PREGNANCY

In managing a pregnancy with suspected ABS, it is essential to have a detailed sonographic fetal survey to accurately assess any anomalies present. Fetal echocardiography is indicated in cases of abdominal wall or abdominothoracic wall defects because of the increased incidence of associated cardiac defects. Amniocentesis is not necessary in clear-cut cases of ABS, as these are sporadic deformations with no association with chromosomal abnormalities. However, in instances in which the diagnosis is uncertain, genetic amniocentesis should be considered. For example, in cases of abdominal wall defects in which a ruptured covered omphalocele cannot be excluded, genetic amniocentesis is indicated.

A fetus with ABS should pose no increased risk for the mother in the management of the pregnancy. There is no indication for cesarean section, except for obstetrical indications. In severe cases of ABS, such as LBWC, in which survival is not anticipated, conventional labor and vaginal delivery without intervention for fetal distress should be considered.

FETAL INTERVENTION

The indications for fetal surgery are, with few exceptions, only for life-threatening conditions such as congenital pulmonary airway malformation (CPAM) with hydrops, diaphragmatic hernia with a low lung-to-heart ratio, bladder outlet obstruction with oligohydramnios, or sacrococcygeal teratoma with placentomegaly (see Chapters 35, 37, 38, 82, and 115). However, as experience with the techniques of fetal surgery has grown and the natural histories of certain non–life-threatening conditions have been better defined, the indications for fetal surgery have been extended. Two examples of this are in utero repair of meningomyelocele to prevent the devastating neurologic injury to the spinal cord (Adzick et al., 1998) and fetoscopic cord ligation in monochorionic twins with imminent death of one twin to prevent neurologic injury in the surviving twin (Crombleholme et al., 1996). The indications for fetal surgery in the ABS may be either for a life-threatening condition if it involves constriction of the umbilical cord or, more commonly, threatened limb amputation due to amniotic band constriction (Torpin, 1965; Ashkenazy et al., 1982; Kanayama et al., 1995; Quintero et al., 1997; Tadmor et al., 1997; Crombleholme, 2001; Keswani et al., 2003).

Torpin (1965) reported 36 cases of fetal death due to cord constriction from amniotic bands. In each case, the diagnosis was made retrospectively. Recognition of amniotic bands constricting the umbilical cord has been reported by Kanayama et al. (1995), who were able to document fetal compromise by reversal of diastolic flow in the umbilical

artery by color Doppler. It is in cases like the one reported by Kanayama et al. that fetoscopic lysis of amniotic bands could be lifesaving.

On the basis of their experience with fetoscopy for cord ligation in TRAP sequence and the experimental work by Crombleholme et al. demonstrating the potential for functional recovery of banded extremities once released, Quintero et al. performed the first fetoscopic lysis of amniotic bands in human fetuses (Crombleholme et al., 1995; Quintero et al., 1997). Their first case was a fetus at 21 weeks of gestation with bilateral cleft lip and bands attached to the face and left upper extremity with distal limb edema. In order to avert limb amputation, fetoscopic lysis of bands was attempted at 22 weeks of gestation using a two-port technique. However, because of bleeding encountered on insertion of the second operating port, it was removed. The endoscissors were passed through the port used for the fetoscope, and the lysis was performed under ultrasound guidance. There was resolution of the distal edema within 6 days of the procedure. At 32 weeks, microphthalmia and anophthalmia of the right orbit were first noted at the site of the previously attached amniotic band. The infant was delivered at 39 weeks and was found to have a type IV Tessier craniofacial cleft and right microphthalmia. The extremity showed minimal residual scarring where the band had been attached and lysed. The infant's hand had radial paresis and mild hypoplasia.

The second case was a fetus at 23 weeks of gestation with a thick amniotic band constricting the left ankle of the fetus. There was marked edema distal to the band and minimal blood flow to the foot was observed by color and pulsed Doppler. Fetoscopy was performed using a 2.7-mm 5-degree endoscope and confirmed the sonographic findings. Again, bleeding was encountered on insertion of the operating port, necessitating its removal. Attempts at ultrasound-guided lysis using endoscissors were unsuccessful. A 2.4-mm 0-degree operating scope with a 400-μm contact YAG laser fiber was used to lyse approximately 85% of the band. Complete lysis of the band was not achieved for fear of injury to "important elements in the ankle." Postoperatively, the edema markedly improved, as did distal arterial blood flow, and there was return of flexion and extension on follow-up sonographic examination. The mother was hospitalized 8 weeks postoperatively at 31 weeks of gestation with premature rupture of membranes and delivered at 34.5 weeks of gestation. The infant underwent Z-plasties for residual effects of the amniotic band, and full functional recovery was anticipated.

The rationale for performing fetoscopic lysis of constricting extremity amniotic bands is based on the hypothesis that progressive compromise of fetal growth leads to amputation. However, this assumes that the procedure can be accomplished with no maternal morbidity and minimal fetal morbidity. This procedure would be hard to justify in the face of a serious maternal complication or a fetal death due to severely premature delivery at 21 or 23 weeks of gestation, even in the face of certain fetal limb amputation.

The experience reported by Keswani et al. (2003) similarly supports the use of fetoscopic release of amniotic bands for limb salvage. However, the sequelae of the ABS may not completely remove or may result in secondary lymphedema. It is worth noting that the cases reported that all had additional amniotic bands encircling limbs not appreciated by ultrasound examination that were also lysed. Crombleholme has experience with fetoscopic release of amniotic bands involving the umbilical cords in five fetuses (Crombleholme TM, unpublished observation, 2009). All were successfully lysed with all three fetuses surviving the procedure.

While extremity ABS may have devastating morphologic and functional effects on a limb, possibly resulting in amputation, it is not lethal. Extremity ABS is not an indication for fetoscopic surgery unless maternal risks and incidence of preterm labor are fully appreciated by the mother. However, there are forms of ABS that are lethal or have devastating neurologic sequelae that may justify the current risks of intervention. Torpin (1965) has reported 36 cases of constrictive amniotic bands of the umbilical cord, which were uniformly fatal. Although rarer than other forms of ABS, umbilical cord constriction, once diagnosed sonographically, may be amenable to fetoscopic release to avert fetal death as shown by Crombleholme (unpublished observation, 2008).

TREATMENT OF THE NEWBORN

A fetus known to have ABS should be delivered in a tertiary care center with neonatologists, pediatric surgeons, and pediatric plastic and orthopedic surgeons available. Treatment depends on the nature of the ABS and the severity of the deformation. In cases of umbilical cord involvement, early or even emergency delivery may be indicated if there are signs of fetal compromise (Kanayama et al., 1995). After delivery, a careful physical examination should assess the severity of the ABS. Often there will be no evidence of the amniotic band at the time of delivery. In the case of extremity amniotic bands, treatment is dictated by the severity of the deformation. The severity of deformity can range from a mildly constrictive band, requiring release, to near amputation, requiring debridement. More often there is a bandlike deformation that requires Z-plasties to surgically correct it (Dyer and Chamlin, 2005; Findik et al., 2006) (Figure 100-8).

In cases of amniotic bands involving the face and head, there may be severe facial clefts, anophthalmia, and encephalocele. These deformities may require many extensive reconstructive procedures to achieve an acceptable cosmetic result. Cases of the LBWC form of ABS are always fatal, and no reconstructive procedures are indicated.

LONG-TERM OUTCOME

The outcome in ABS depends on the severity of the deformation. Cases of extremity ABS usually have an excellent long-term outcome. Even in cases of limb amputation, ambulation

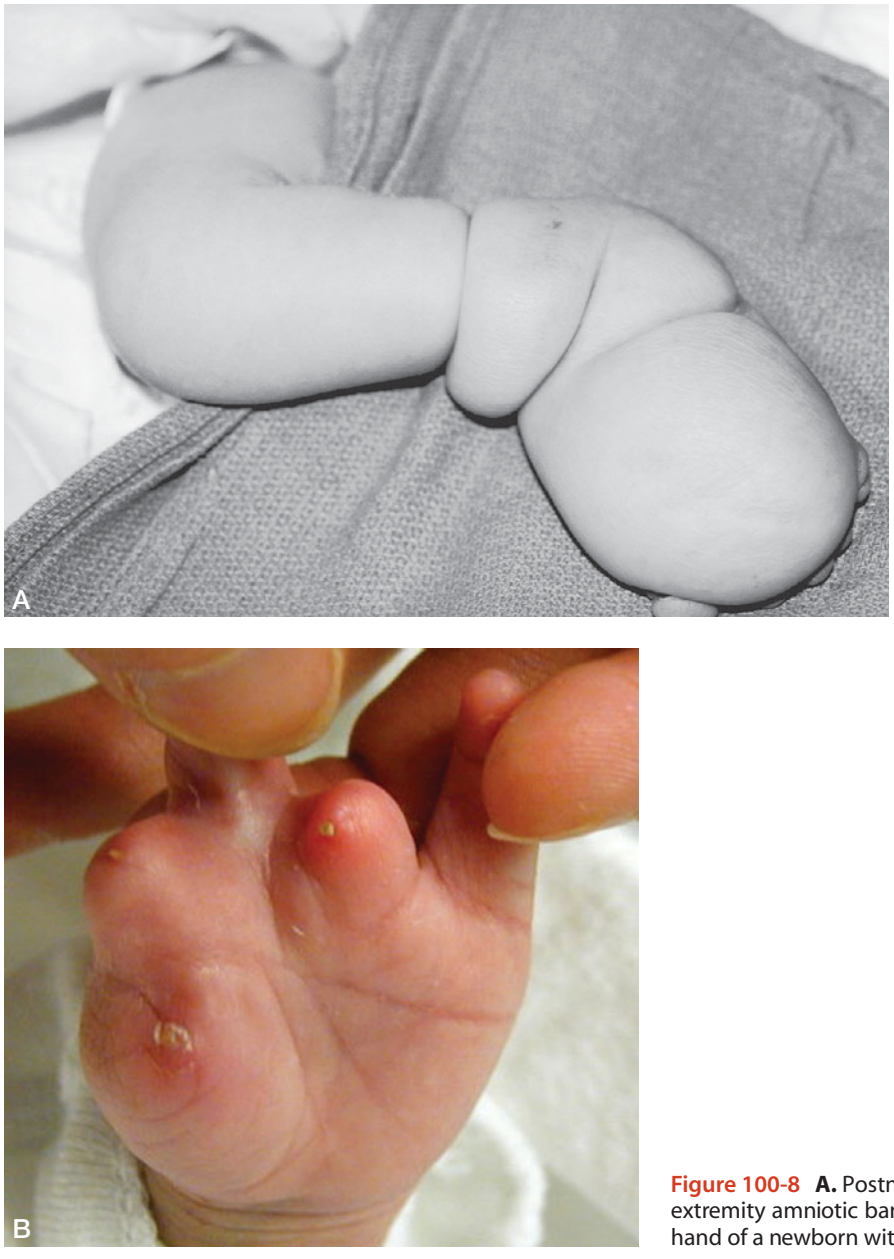

Figure 100-8 **A.** Postnatal appearance of the leg of a newborn with extremity amniotic band syndrome. **B.** Postnatal appearance of the hand of a newborn with extremity amniotic band syndrome.

is possible with the aid of a prosthesis. The cosmetic results following extensive craniofacial reconstructive surgery are often acceptable, but the severity of these defects may leave these children permanently disfigured. ABS in which fetoscopic release was performed may show evidence of secondary lymphedema, which may require multiple surgical procedures to provide an acceptable functional result (Marler et al., 2002).

GENETICS AND RECURRENCE RISK

Most cases of ABS are sporadic and there is no risk of recurrence in subsequent pregnancies. There have been cases of ABS associated with underlying disease, such as Ehlers–Danlos syndrome type III or osteogenesis imperfecta. Similarly, ABS has been reported in association with teratogens such as methadone and lysergic acid diethylamide (Chemke et al., 1973; Daly et al., 1996). While associated maternal disease or teratogenic exposure may predispose to recurrence, these are rare causes of the ABS.

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101 CHAPTER

Arthrogryposis

Key Points

- Descriptive term that refers to the presence of congenital contractures in two or more joints. Does not necessarily represent a syndrome but is a compensatory connective tissue response.
- Causes include abnormal muscle tissue, abnormal nerve function, abnormal connective tissue, and mechanical limitation of fetal movement.
- Incidence is 1 in 3000 livebirths.
- Sonographic findings include malpositioned limbs, limited fetal movements, hypoechogenicity of long bones. May be associated with increased nuchal translucency, polyhydramnios, and cystic hygroma.
- Differential diagnosis includes more than 150 conditions. Amyoplasia is the most common. Chromosome abnormalities are unlikely, but should consider trisomy 18 and mosaic trisomy 8.
- Examine both prospective parents for signs of distal arthrogryposis, which is dominantly inherited and associated with 10 conditions.
- Treatment of newborn focuses on whether only limbs are affected or if there are abnormalities of nervous or muscular systems.
- Treatment for isolated joint abnormalities begins with plaster casts in newborn period. Surgery, if performed, occurs at 3 to 12 months.

CONDITION

The term arthrogryposis, a mixture of Latin and Greek words, means curved or crooked joint (Hageman et al., 1988). This term was first used in 1923 by Stern. The first medical description of arthrogryposis occurred in 1841, when Otto described an infant with multiple congenital contractures and referred to the condition as "congenital myodystrophy" (Swinyard and Bleck, 1985).

Arthrogryposis refers to a symptom complex characterized by multiple joint contractures that are present at birth. The muscles in the affected area or areas are replaced by fat and fibrous tissue (Shapiro and Specht, 1993). Although the term arthrogryposis is in wide use, the preferred descriptive term is multiple congenital contractures. These contractures do not represent a syndrome but a compensatory connective tissue response (Swinyard and Bleck, 1985).

Clinical features of arthrogryposis include rigidity of several joints, resulting from short, tight muscles and capsular contractures, dislocation of joints, "featureless" extremities (normal skin creases are absent and there is an increase in the amount of subcutaneous fat), presence of deep skin dimples in the vicinity of affected joints, absence or fibrosis of muscles, and normal intellectual development (Williams, 1978).

According to Hall (1981), the term arthrogryposis multiplex congenita was coined to describe infants with multiple congenital contractures. Confusion has arisen because the term was used as a diagnosis. The term is descriptive, and the

presence of congenital contractures only indicates a clinical sign with multiple underlying causes. In general, anything that decreases intrauterine movement may lead to limitation of joint movement and the subsequent formation of contractures. The earlier in development it occurs and the longer the duration of limitation of movement, it will result in more severe contractures at birth.

There are four major causes of congenital contractures (Hall, 1981):

1. *Abnormal muscle tissue:* Examples of this are muscular dystrophy, congenital myopathies, and congenital absence of muscle (amyoplasia).
2. *Abnormal nerve function:* This includes central nervous system malformations, congenital neuropathy, failure of the nerves to form or myelinate, or exposure to toxins that affect nerve function.
3. *Abnormal connective tissue:* This interferes with the normal development of tendons, bone, cartilage, or joint tissue.
4. *Mechanical limitation to movement in utero:* This includes uterine fibroids, oligohydramnios, amniotic bands, or the presence of a multiple gestation.

INCIDENCE

The incidence of multiple congenital contractures is approximately 1 in 3000 livebirths (Hall, 1985). In one study of 66 cases of arthrogryposis multiplex congenita, the mothers were significantly older than average (Wynne-Davies and Lloyd-Roberts, 1976). Davis and Kalousek (1988) identified 16 cases of fetal akinesia deformation sequence in 948 not yet viable fetuses at 9 to 20 weeks of gestation. The fetal akinesia deformation sequence was defined as joint contractures with or without formation of webs, with intrauterine growth restriction, pulmonary hypoplasia, micrognathia, short umbilical cord, and a short gut (Davis and Kalousek, 1988). In addition, arthrogryposis multiplex congenita has been described in association with cases of failed termination of pregnancy (Hall, 1996). These authors hypothesized that the contractures were due to vascular compromise during attempted termination with a secondary loss of functional neurons leading to fetal akinesia and subsequent contractures. A rupture of membranes with continuous leakage of amniotic fluid after attempted termination may have worsened the existing contractures.

SONOGRAPHIC FINDINGS

Detailed examination of the fetal extremities is not listed in the most recent American College of Obstetricians and Gynecologists or American Institute of Ultrasound and Medicine (AIUM) guidelines, but it is a critical adjunct to fetal imaging and is needed to diagnose conditions such as arthrogryposis

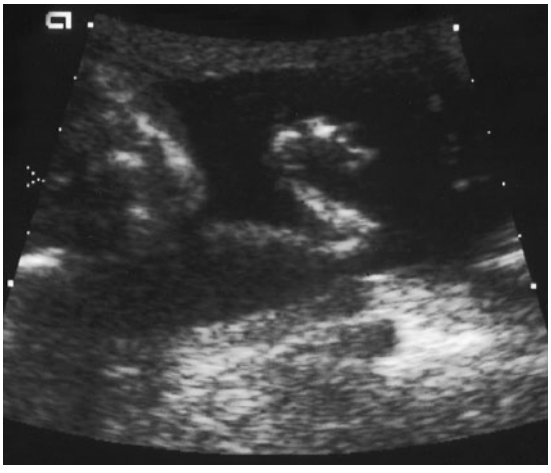

Figure 101-1 Sagittal sonographic image of a fetal lower extremity with contractures at the knee and ankle.

(Bromley and Benacerraf, 1995; ACOG, 2008). The sonographic diagnosis of arthrogryposis is made by observation of the malposition of the limbs (Figure 101-1). The morphologic aspects of the bones are normal but the range of movements is limited (Deschamps et al., 1992). Increased nuchal translucency, polyhydramnios, and cystic hygroma are often observed in association with arthrogryposis (Goldberg et al., 1986; Bui et al., 1992; Hyett et al., 1997; Scott et al., 1999).

Murphy et al. (2002) described three cases of fetal arthrogryposis with severe hypoechogenicity of the long bones that was noted after 30 weeks' gestation. They speculated that fetal osteoporosis developed as a consequence of absent fetal movement.

Baty et al. (1988) reported the prenatal diagnosis of distal arthrogryposis by sonographic examination at 18 weeks of gestation in a family with two other affected members. Real-time sonographic evaluation demonstrated a flexed position of the fingers and extension of the right wrist, which did not change despite active motion of the shoulders and elbows. The fetal hands were in a fist and the fingers did not extend (Figure 101-2). These authors described the following important variables in the sonographic diagnosis of fetal joint contractures (Baty et al., 1988):

1. The gestational age of the fetus.
2. The timing of the development of the joint contractures.
3. The severity of the joint contractures.
4. The index of suspicion of the ultrasonographer.
5. The skill, patience, and previous experience of the sonographer.
6. The divergence of the affected joints from the neutral position.
7. The amount of joint movement.
8. The presence of other sonographically detectable anomalies.
9. The persistence of findings over time.

Amyoplasia is the most common cause of joint contractures. Sepulveda et al. (1995) diagnosed a case of fetal

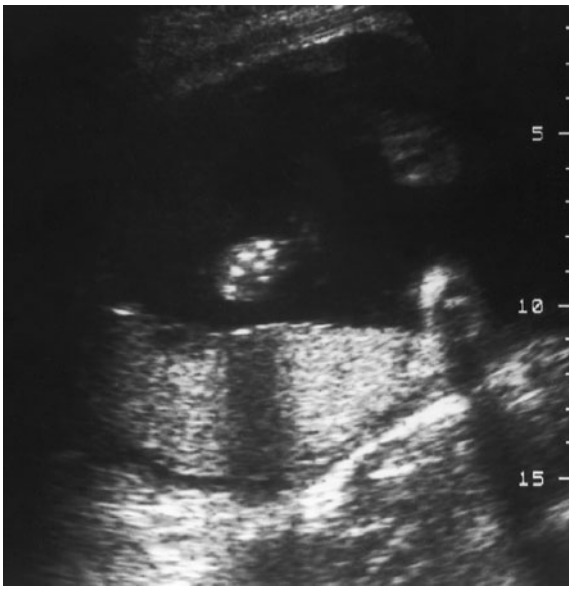

Figure 101-2 Sonographic image of a fetal hand demonstrating fixed flexion of all digits.

amyoplasia at 19 weeks of gestation with absent fetal movements, severe multiple congenital contractures, hydrops fetalis, and polyhydramnios. No spontaneous fetal movements were seen over a 40-minute period of observation. Autopsy of this affected fetus revealed small groups of poorly developed muscle fibers within areas of fat. These authors noted that fetal movements were absent during intrahepatic venous sampling in the fetus with amyoplasia. This was in contrast to their previous observations that second trimester fetuses normally react with vigorous movements during fetal blood sampling.

Stoll et al. (1991) studied two children born to a mother with myasthenia gravis. Her first pregnancy was a 33-week-old fetus with multiple flexion contractures, which died 1 hour after birth from respiratory insufficiency. Her second pregnancy was remarkable for an abnormal ultrasound examination at 20 weeks, which showed decreased fetal movements and multiple flexion contractures. In myasthenia gravis, a maternal factor is transferred to the fetus, which affects the fetal joints. This has been confirmed in an animal model by injecting pregnant mice with plasma from women who have antibodies to the acetylcholine receptor (Jacobson et al., 1999). Many pups were stillborn and showed fixed joints.

Goldberg et al. (1986) described a case of fetal arthrogryposis at 30 weeks of gestation in a fetus with scalp edema but no ascites. Moderate polyhydramnios was present. In this fetus, the lower extremities were tightly flexed and crossed in a squatting position. No normal limb activity was noted. These authors stated that late identification of arthrogryposis was valuable in minimizing the birth trauma associated with the vaginal delivery of an infant with fixed joints.

More recently, three-dimensional (3D) surface-rendering images were used to show the fixed postural abnormalites of the fetal extremities (Ruano et al., 2003). When viewed in real time, the authors were able to show that there was absence of fetal movement, leading to a diagnosis of fetal akinesia deformation sequence.

DIFFERENTIAL DIAGNOSIS

More than 150 conditions are known in which multiple congenital contractures are a predominant sign (Hall, 1985). In a review of 155 patients with arthrogryposis, Sarwark et al. (1990) noted that 43% of patients had amyoplasia, 35% had other contracture syndromes, 7% had the dominantly inherited form of distal arthrogryposis, 6% had multiple congenital anomalies, and 2% had chromosomal abnormalities.

Amyoplasia is the single most common cause of multiple congenital contractures. A very specific limb positioning exists in this condition. There is a marked decrease in muscle mass. Contractures are symmetric, with all four limbs affected. Affected patients have a round face with a mild micrognathia and a midline hemangioma. Intelligence is normal in this condition.

Distal arthrogryposis refers to syndromes in which there are congenital distal contractures but the proximal joints are largely spared (Beals, 2005). There is a lesser degree of involvement of the extremities and preservation of good muscle tone and bulk. Affected patients have a clenched-fist deformity of the hand, occasional congenital dislocation of the hip, mild to severe positional deformities of the foot, and normal intelligence (Baty et al., 1988). In most distal arthrogryposis conditions, the function of the hands improves with time, use, and physical therapy.

Currently, there are 10 different syndromes described that have a common pattern of distal congenital contractures, minimal proximal contractures, and other findings (Bamshad et al., 1996; Beals, 2005). All are inherited as autosomal dominant conditions with variable expression. This group of conditions includes Freeman–Sheldon syndrome, (also known as distal arthrogryposis type 2A), which presents with a distintive facies, flexion, and ulnar deviation of the fingers and vertical talus. Congenital contractural arachnodactyly (Beals syndrome), also known as distal arthrogryposis type 9, presents with ear deformities and finger contractures. This condition is in the differential diagnosis for Marfan syndrome.

Another consideration in the differential diagnosis is Pena–Shokeir syndrome, which manifests as severe intrauterine growth restriction, a short umbilical cord, pulmonary hypoplasia, micrognathia, and facial anomalies. The overall appearance, however, is somewhat nonspecific.

Only a small percentage of patients with arthrogryposis will have a chromosomal abnormality. The most common abnormalities associated with this condition are trisomy 18 and mosaic trisomy 8. In one study, approximately a fourth of the cases of trisomy 18 (23/89) were associated with arthrogryposis (Chen, 2005).

In Scandinavia, a lethal congenital contracture syndrome is inherited as an autosomal recessive condition. This

condition is lethal in utero at a mean gestational age of 29 weeks. Affected fetuses present with hydrops fetalis and malpositioning of the hips and knees with webbing of the neck and elbows. The muscles are hypoplastic, and there is severe thinning of the ventral half of the spinal cord (Kirkinen et al., 1987; Herva et al., 1988).

Maternal myasthenia gravis is in the differential diagnosis, as neonatal myasthenia develops in 12% of babies born to mothers with this condition. In the subgroup of patients with contractures due to neurogenic abnormalities, spinal muscular atrophy is a consideration. DNA analysis of 12 unrelated patients with congenital contractures, generalized muscle weakness, evidence of denervation on electromyographic studies, and muscle biopsy evidence of denervation, revealed that 50% of affected patients lacked the survival motor neuron gene (Börglen et al., 1996). The survival motor neuron (*SMN*) gene is absent or interrupted in 90% to 100% of patients with spinal muscular atrophy.

ANTENATAL NATURAL HISTORY

Joint development starts at 5.5 weeks of gestation, and by the 8th week, the first movement of the limbs can be observed (Ajayi et al., 1995). Absence of motion leads to stiff joints, pterygium formation, pulmonary hypoplasia, and a short umbilical cord. The primary underlying problem in arthrogryposis is due to degeneration of the anterior horn cells, occurring during the early months of gestation (Williams, 1978). Early destruction of muscle fibers in utero will result in certain muscles being affected earlier or more severely. Affected muscles tend to lose tone and fail to counterbalance the tone of the normally developed antagonist muscles. This further restricts the normal movements of the muscles and joints during periods of rapid fetal growth (Williams, 1978). According to Hall (1996), an ischemic event occurring during a critical period of anterior horn development may result in contractures. Handling of the pregnant uterus disturbs uterine blood flow, which may result in temporary hypoxia and bradycardia of the embryo. Disruption or decreased flow in the anterior spinal arteries or decreased uterine vessel blood flow will lead to damage or loss of neurons or muscles. The anterior horn cells are particularly susceptible to hypoxic damage or loss at 8 to 14 weeks of gestation (Hall, 1996). The subsequent lack of normal anterior horn cell function leads to fetal akinesia and secondarily to multiple joint contractures.

Moessinger (1983) developed an animal model of fetal akinesia deformation sequence by paralyzing rat fetuses with injections of curare. The anomalies noted at the time of delivery included multiple joint contractures, pulmonary hypoplasia, micrognathia, intrauterine growth restriction, short umbilical cord, and polyhydramnios. The polyhydramnios in association with fetal akinesia is mediated by lack of swallowing activity.

Clarren and Hall (1983) studied the neuropathologic findings in the spinal cords of 10 infants with neurogenic arthrogryposis and compared them to 8 infants with spinal muscular atrophy type I and II age matched controls. The numbers of α-motor neurons were reduced in affected patients with arthrogryposis and spinal muscular atrophy. Abnormal histology was seen in patients with arthrogryposis. In five patients, the pathologic pattern was consistent throughout the entire spinal cord. In five patients there was an unequal distribution across the spinal cord and this correlated with the muscle groups involved clinically.

MANAGEMENT OF PREGNANCY

The pregnant patient should be asked whether there is a history of decreased fetal movement. This may be difficult to ascertain in a first pregnancy. She should also be asked whether there is a history of infection, fever or hypothermia, or exposure to teratogens. Additional considerations include the exclusion of uterine masses, the presence of a twin gestation, placental abnormalities, or oligohydramnios. The diagnoses of myotonic dystrophy or myasthenia gravis should be ruled out in the pregnant patient. The pregnant woman should be specifically asked whether she has any history of use of phenytoin, insulin, ethanol, or phencyclidine (PCP or angel dust) (Thompson and Bilenker, 1985). A prenatal karyotype should be obtained to rule out an associated chromosomal abnormality. Prenatal factors that potentially predict severe respiratory insufficiency at birth include decreased fetal movements, presence of polyhydramnios, micrognathia, and thin ribs (Bianchi and Van Marter, 1994). If the fetus appears to have arthrogryposis and has a strong likelihood of respiratory insufficiency at birth, the prospective parents can be offered termination of pregnancy. If the diagnosis is made later than 24 weeks of gestation, or if the parents do not desire termination, the fetal position should be checked close to term. There is an increased incidence of breech positioning associated with arthrogryposis. Delivery can be complicated by abnormal fetal position and lack of flexibility of the limbs (see Figure 101-1) (Hall, 1981). Therefore, an elective cesarean section may be necessary for safe delivery. We recommend delivery in a tertiary care center because of the potential for respiratory difficulties at birth and the potential need for mechanical ventilation. The pregnant patient and her partner should be examined for any signs of distal contractures that might suggest a dominantly inherited condition.

FETAL INTERVENTION

There are no fetal interventions for arthrogryposis.

TREATMENT OF THE NEWBORN

The primary consideration in the treatment of the newborn is to determine if only the limbs are affected, if there is

evidence of central nervous system dysfunction, or if there is evidence of additional organs being affected (Hall, 1981). A complete and detailed physical examination should be performed, including specific notation of the appearance and position of the joints and the passive range of motion of the joints. The physical examination should specifically rule out the presence of a "whistling face," micrognathia, cleft palate (including the submucous isoform type), scoliosis, muscular imbalance, hemivertebrae, or a covered neural tube defect. Common skin defects associated with arthrogryposis include scalp defects, amniotic bands, and dimples over the joints with limitation of movement. Midline hemangiomas are particularly common in amyoplasia.

Laboratory tests that are recommended for diagnosis include cranial imaging by computed tomographic or magnetic resonance imaging scan (Hageman et al., 1988), chromosome analysis if not performed antenatally, electroencephalography, electromyography with nerve conduction velocity studies (Thompson and Bilenker, 1985), and radiography. Thin ribs are associated with congenital muscular disease (Chassevent et al., 1978). Creatine kinase levels are nonspecifically elevated and are not useful in confirming a diagnosis (Bianchi and Van Marter, 1994). A muscle biopsy can be performed as early as days 6 to 15 of postnatal life (Bianchi and Van Marter, 1994).

Physical examination findings consistent with a diagnosis of amyoplasia include a round face with a midline hemangioma (Figure 101-3), the presence of bilateral clubfeet, hands that are always flexed at the wrists, and shoulders that are internally rotated. The elbows are usually straight and the hand is rotated posteriorly in what is known as the "waiter's tip" position. Affected children with amyoplasia have decreased muscle mass. It is important to mobilize the joints as soon as possible after birth. Physical therapy for children with amyoplasia should be initiated during the newborn period. Treatment includes a mixture of application of plaster casts with periods of vigorous therapy (Figure 101-4).

A neuromuscular work-up may be warranted in cases of arthrogryposis. Patients should be closely examined for the occurrence of perinatal fractures. This can be suspected if a localized deformity, soft tissue swelling, or irritability occurs. Rigid joints and hypotonia contribute to the occurrence of fractures at delivery (Shapiro and Specht, 1993).

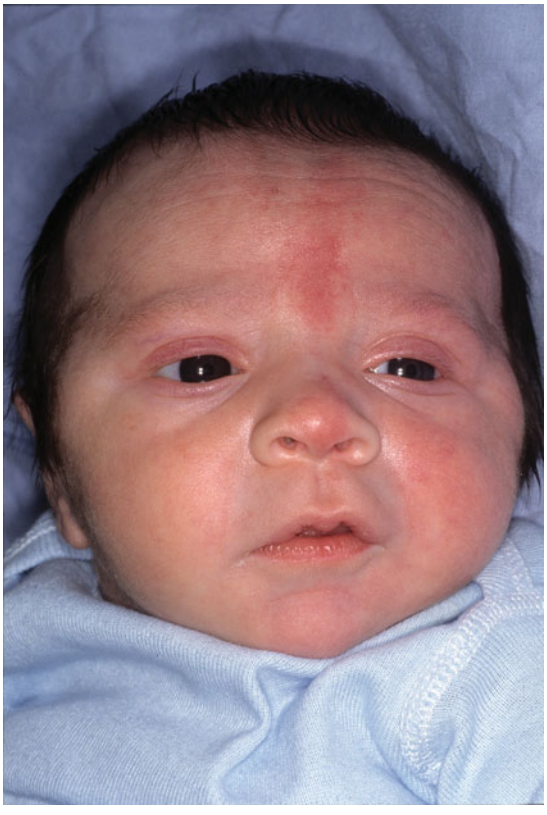

Figure 101-3 Postnatal photograph of a newborn infant with amyoplasia, demonstrating typical round face and a midline hemangioma on forehead and tip of nose.

SURGICAL TREATMENT

The goal of surgical treatment is to achieve the maximum function possible for each involved joint. Major surgery is generally performed between 3 and 12 months of age (Mennen et al., 2005).

Clubfoot is the most common abnormality in arthrogryposis. Ninety percent of children with arthrogryposis have severe bilateral clubfeet (Solund et al., 1991). Treatment of the foot is the dominant orthopedic problem throughout the first year of life. Solund et al. (1991) treated 10 children with 17 affected feet for a mean follow-up period of 13 years. Fourteen of the 17 feet were satisfactorily treated, defined as painless and plantigrade at the time of examination. These authors recommended performing a talectomy (removal of the talus) before the expected age of walking.

Knee contractures are generally treated with physical therapy to extend the range of motion. If operative correction is necessary, this is performed with lengthening of the hamstrings with a posterior capsulotomy. Thomas et al. (1985) reported on 104 patients treated between 1952 and 1982. Seventy-four of the 104 had significant knee contractures, and they were followed for a period of 2 to 20 years. Of the 74, 43 had nonoperative treatment, which included physical therapy, bracing, or serial casting. Thirty-one patients had operative procedures, and these authors stated that the most useful procedure in the growing child was a posterior capsule release with hamstring tenotomy.

Affected patients can also have hip dislocation. The characteristic deformity is flexion abduction–external rotation contractures, accompanied by unilateral or bilateral hip dislocation (Shapiro and Specht, 1993).

Scoliosis often occurs in patients with arthrogryposis due to contractures of the muscles of the trunk. This almost invariably responds to stretching and orthopedic management. Most patients have a history of uterine malposition.

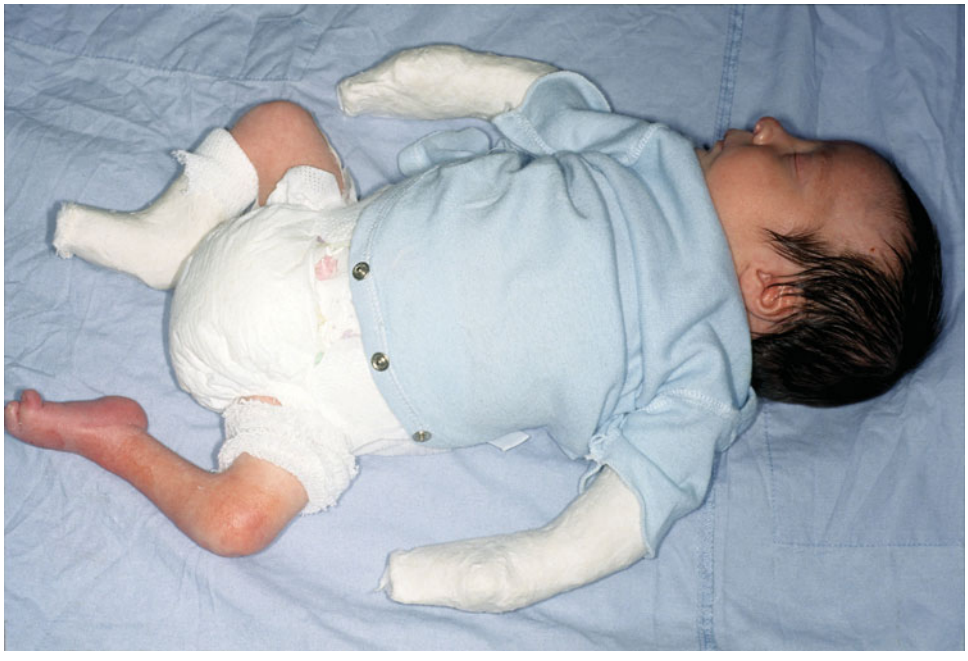

Figure 101-4 Postnatal appearance of same infant in Figure 101-3, demonstrating early treatment with plaster casts. At the time the photograph was taken, the left clubfoot was receiving a new cast. Symmetric contractures of all four extremities are found in amyoplasia.

Surgical correction is recommended for curves of greater than 15 degrees (Sarwark et al., 1990).

Treatment options for contractures that involve the upper extremity include passive joint stretching, serial casting, and surgical intervention. In one study of 17 infant patients with both distal and classical arthrogryposis, outcome was analyzed with an average follow-up of 6 years (Smith and Drennan, 2002). For both groups, the maximal gain in wrist motion occurred after the first casting session. Infants with distal arthrogryposis had the largest improvement in passive wrist motion, had no recurrence, and were more functionally independent at final follow-up. Infants with classic arthrogryposis had more rigid contractures that were more likely to recur after casting and interfere with daily living. These authors suggested that repeat serial casting is unlikely to improve wrist extension and that surgical options should be considered in the absence of improvement (Smith and Drennan, 2002).

LONG-TERM OUTCOME

Bianchi and Van Marter (1994) performed a retrospective medical review and identified 15 newborns over a 10-year period that had arthrogryposis multiplex congenita and required ventilatory support at birth. Fourteen of the 15 patients died; 13 were electively extubated after a variable time course (2 hours to 64 days). All were totally apneic without respiratory support. Autopsies were performed on all 14 nonsurvivors and revealed an approximately equal distribution of central nervous system malformations, peripheral neuropathies, and peripheral myopathies. The single patient who survived had a different clinical course from the other infants. She was weaned spontaneously from the ventilator at age 7 days and was ultimately diagnosed with myasthenia gravis. These authors recommended performing an edrophonium challenge test prior to elective extubation of any infant with arthrogryposis multiplex congenita and inability to breathe. However, most infants with arthrogryposis do not have respiratory problems, and their prognoses are considerably better.

Amyoplasia is an example of a severe birth defect that can improve with appropriate intervention. Sarwark et al. (1990) described a better than expected prognosis in amyoplasia. The size of the limbs at birth and presence or absence of pterygia (webs) can be used to predict response to therapy. Sells et al. (1996) reviewed the outcome of 38 children with amyoplasia, diagnosed by a medical geneticist. Eighty-four percent of the 38 had symmetrical four-limb involvement. Affected patients had an average of 5.7 orthopedic procedures performed. By age 5 years, 85% of affected children were ambulatory, although mobility aids were used by a large proportion of them. Most of the children were relatively or completely independent in their activities of daily living. Most were in regular classrooms at the appropriate grade level. Although infants with amyoplasia have pronounced musculoskeletal involvement at birth and require orthopedic and rehabilitative interventions during childhood, the authors concluded that functional outcome in physical and education areas is excellent (Sells et al., 1996). Of note, 11.6% of the children with amyoplasia had anomalies suggesting a vascular

compromise in utero, including gastroschisis, bowel atresia, or abdominal wall defects.

Carlson et al. (1985) identified a different population of 52 patients who were at least 16 years old with arthrogryposis. The mean age was 27.3 years (range, 17–42 years). Although these patients had limitation in shoulder motion they had no significant functional handicaps despite the presence of elbow deformities. Fifty-two percent had wrist deformities, and approximately half of them were not treated. Fifteen of the 27 patients with wrist deformities had serial casts and splints and 7 required subsequent surgical correction. Following carpectomy or wrist fusions patients had no pain and had satisfactory wrist function. Seventy-one percent of the 52 patients had knee involvement and 85% had foot involvement, mainly clubfoot. Twenty-six patients required surgery and an average of 4.9 procedures on each foot. Fifty-six percent of patients had hip problems but functioned well as adults. The majority of patients had normal intelligence and 50% of adults were married. In this mixed population of patients with arthrogryposis, half walked independently, nine walked with crutches or other mobility aids, and only eight were nonambulatory. Most of the patients had no limitations in their activities of daily living.

GENETICS AND RECURRENCE RISK

The recurrence risk for arthrogryposis depends on the underlying cause for the condition. Amyoplasia is sporadic with little or no recurrence risk. Distal arthrogryposis types 1 to 10 are autosomal dominant conditions with a 50% risk of recurrence. The gene for one of the subtypes of distal arthrogryposis type 1 maps to the pericentromeric region of chromosome 9 (Bamshad et al., 1994). The Scandinavian form of lethal congenital contracture syndrome is an autosomal recessive condition with a 25% risk of recurrence (Vuopala and Herva, 1994).

There is an increased incidence of clubfeet, dislocated hips, and hyperextensibility in children with multiple contractures (Hall, 1981). Hall (1985) personally studied a group of more than 350 children with congenital contractures. Twenty-eight percent of these cases had a known recognizable genetic disorder caused by a single gene, chromosomal, or multifactorial condition. Six percent were the result of an environmental insult or exposure to a teratogen. Forty-six percent of cases had known diagnoses (such as amyoplasia) with no risk of recurrence. In only 20% of cases there was no diagnosis made. In situations where there was no diagnosis or cause for the arthrogryposis, Hall stratified the recurrence risk. If the limbs are primarily affected, there is a recurrence risk of 4.7%. If the limbs are affected in addition to other malformations, there is a recurrence risk of 1.4%. If the limbs and the central nervous system are both affected, there is a recurrence risk of 7%. However, Hall cautioned that these numbers should be used only if a specific diagnosis has not been made for the index case with arthrogryposis.

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102 CHAPTER Clinodactyly

Key Points

- Medial deviation of finger at distal interphalangeal joint. Fifth finger most commonly affected.
- Not an anomaly. Usually due to developmental delay or arrest.
- Present in 1% of normal individuals, but also found in 60% of newborns with Down syndrome.
- Associated with many genetic syndromes.
- A detailed fetal ultrasound evaluation should be performed. If clinodactyly is isolated, karyotype is not indicated. If an additional anomaly is found on a detailed scan, obtain a fetal karyotype.
- Isolated clinodactyly can be inherited as an autosomal dominant trait.

CONDITION

The term clinodactyly derives from the two Greek words—*kleinin*, meaning "to bend," and *dactylos*, which means "finger." Clinodactyly is a descriptive term that refers to incurving or medial deviation of the finger at the distal interphalangeal joint (Figure 102-1). The fifth finger is most frequently affected. Usually, this is due to wedging of the middle phalanx so that the planes of the proximal and distal ends are not parallel but converge toward the radial side (Birkbeck, 1975). Clinodactyly is frequently accompanied by brachymesophalangy, which means that the middle phalanx of the fifth finger is short and has increased breadth. There have been several attempts to provide an objective definition of clinodactyly. In one approach, clinodactyly is defined as the relationship between the length of the fifth middle phalanx to the length of the fourth middle phalanx (Birkbeck, 1975). Other authors have used an angle of greater than 8 degrees between the long axis of the distal phalanx and the middle phalanx (Birkbeck,

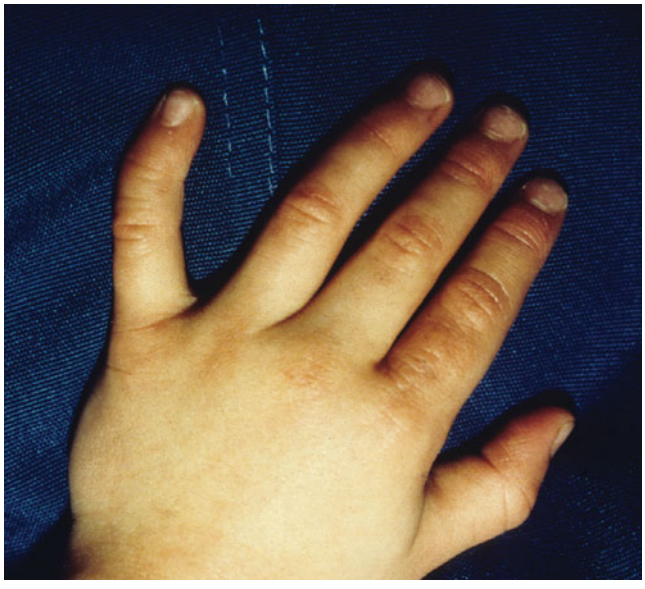

Figure 102-1 Photograph of a child's hand demonstrating medial incurving of the fifth finger consistent with a clinical diagnosis of clinodactyly.

1975). Yet other groups use a more stringent definition of a distal phalanx deviation of at least 15 degrees (Skvarilova and Smahel, 1984).

Clinodactyly may be isolated or part of a syndrome. It may be a sporadic developmental event or it may be familial (Poznanski et al., 1969). Approximately 60% of newborns with Down syndrome have bilateral fifth finger clinodactyly (Hall, 1970). The association between clinodactyly and Down syndrome has been known for more than 100 years (see Chapter 131). In 1896, Smith published the first X-ray illustrating fifth finger clinodactyly in a patient with Down syndrome (Smith, 1896).

INCIDENCE

Several large population studies have addressed the incidence of clinodactyly in healthy infants and children. In Czechoslovakia, Skvarilova and Smahel (1984) studied 911 healthy children from Prague, age 6 to 18 years. They defined clinodactyly as the presence of any distal phalanx axis deviation of greater than 15 degrees on clinical examination. Affected children underwent radiography and the hands of their immediate family members were examined. Clinodactyly of the fifth finger was seen in 10 individuals (1.1%). Of these, 6 individuals also had brachymesophalangy. In 9 of the 10 affected cases at least one parent was confirmed as being similarly affected. In the remaining case, the father was unavailable for examination. Affected children had considerable bilateral symmetry. The ratio of boys to girls affected was 3:2. An incidence of clinodactyly of approximately 1% in the normal population was confirmed in a study of healthy white newborns, in which clinodactyly of the fifth finger was seen in 0.99% of cases (Marden et al., 1964). Poznanski et al. (1969) have noted significant racial and ethnic differences in fifth finger clinodactyly. For example, they cite an incidence of 3.4% in a Guatemalan population and an incidence of 5% in a population from Hong Kong. Clinodactyly is not an anomaly, per se, but rather a developmental delay or arrest. Mehes et al. (1973) reported that 0.5% of normal full-term Hungarian newborns had clinodactyly, but that this percentage increased to 0.9% in full-term small for gestational age infants. This study also noted an increased incidence of clinodactyly in preterm infants at less than 25 weeks of gestation, in which the incidence was 2.56%. Clinodactyly is seen in 12% of newborns with other major congenital anomalies (Marden et al., 1964).

SONOGRAPHIC FINDINGS

Although ossification of the middle phalanx of the fifth finger occurs normally early during the second trimester of pregnancy, the major concern when fifth finger clinodactyly is detected on a prenatal sonogram is its potential association with trisomy 21 (Deren et al., 1998). In one study of ultrasound markers of chromosomal disease, 3 of 21 cases of Down syndrome had postmortem or postnatal findings of fifth finger clinodactyly (Twining and Zuccollo, 1993).

In 1988, Benacerraf et al. demonstrated hypoplasia of the middle phalanx of the fifth digit in four of five fetuses with Down syndrome examined at 17 to 20 weeks of gestation. They described a radial curve to the fifth digit. One of the five affected fetuses had no visible ossification of the middle phalanx of the fifth digit (Figure 102-2). These authors suggested that fifth finger clinodactyly could be used in addition to other sonographic signs in screening for trisomy 21. This observation was followed by a prospective study examining the middle phalanx of the fourth and fifth digits in

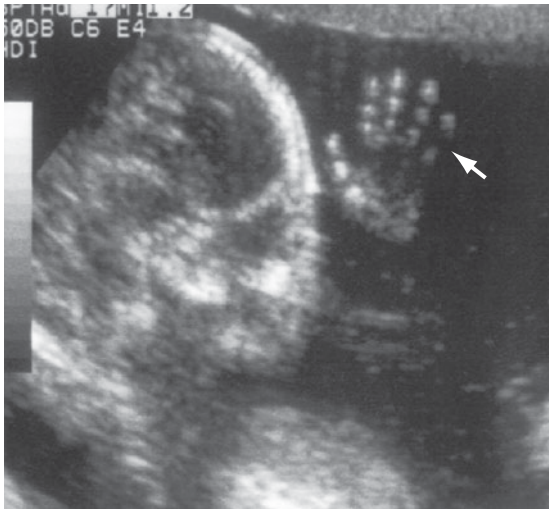

Figure 102-2 Prenatal sonographic image demonstrating absent ossification of the middle phalanx of the fifth finger (*arrow*) with radial incurving, suggesting a diagnosis of clinodactyly.

1032 fetuses between 15 and 20 weeks of gestation prior to routine genetic amniocentesis (Benacerraf et al., 1990). These authors constructed a ratio of the middle phalanx of the fifth digit divided by the middle phalanx of the fourth digit and obtained a median value for normal fetuses of 0.85. In eight fetuses with trisomy 21, the median ratio was 0.59. These authors suggested a cutoff value of 0.70, which would identify 75% of the Down syndrome fetuses and 18% of normal fetuses at the same gestational age. This gave a positive predictive value of this finding of 3.2%. These authors noted that the ratio appeared to rise slightly between 15 and 16 weeks of gestation and at greater than 17.5 weeks of gestation in normal fetuses, implying that the ratios would be affected by normal developmental maturation of this bone. Ossification of the middle phalanx was completely absent in 65 (6.3%) of normal fetuses, although 50% of these fetuses were between 15 and 16 weeks of gestation. Thus, ossification of the middle phalanx of the fifth finger is a gradual process that is not normally complete at 15 weeks of gestation. This has also been confirmed by other investigators (Birkbeck, 1975). The conclusion of this report was that measurement of the middle phalanx of the fourth and fifth digits may be useful as an adjunct to sonographic screening for Down syndrome (Benacerraf et al., 1990).

Deren et al. (1998) examined whether the detection of subtle sonographic abnormalities, including clinodactyly, improved screening efficiency for fetal trisomy 21. Clinodactyly alone had a 28.6% detection rate. Clinodactyly, when seen in association with increased nuchal thickness or short humerus, increased the detection rate of trisomy 21 from 53.3% to 63.2%.

Bahado-Singh et al. (2002) compared the performance of different sonographic markers for fetal Down syndrome detection at 14 to 16 weeks versus 16 to 24 weeks of gestation. As an individual sonographic marker, clinodactyly had a 59.1% sensitivity for detection of Down syndrome with a false-positive rate of 6.2% at <16 weeks' gestation. After 16 weeks the sensitivity decreased to 28.2% and false-positive rate was 2.9%.

DIFFERENTIAL DIAGNOSIS

Clinodactyly has been observed in 1% of normal individuals. Therefore, the most likely diagnosis is a normal fetus. However, the finding should elicit some concern, as clinodactyly is a component of many genetic syndromes, including Down syndrome (clinodactyly observed in 60% of cases), Russell–Silver dwarfism (76% of cases), Cornelia de Lange syndrome (88% of cases), Klinefelter syndrome (84% of cases), oto-palatal-digital syndrome, oro-facial-digital syndrome, oculo-dento-digital syndrome, Holt–Oram syndrome, Prader–Willi syndrome, Alagille syndrome, and Turner syndrome (Poznanski et al., 1969). Many of these syndromes will be characterized by the presence of additional anomalies or a chromosomal abnormality.

ANTENATAL NATURAL HISTORY

Birkbeck (1975) examined radiographs of the silver-stained hand bones of 210 human fetuses obtained between 8 and 20 weeks of gestation. In 179 (85%) of fetuses studied, clinodactyly of the fifth finger was demonstrated. He suggested that clinodactyly and brachymesophalangy of the fifth finger were both normal developmental stages that diminished with advancing age and bone development. He demonstrated that a normal transition occurs from the characteristic wedge shape of the middle phalanx of the fifth finger to the more typical postnatal form with a series of radiographs taken at different gestational age intervals.

Thus, demonstration of clinodactyly and brachymesophalangy in the fetus after 16 weeks of gestation should be considered examples of subtle developmental delays and not malformations.

MANAGEMENT OF PREGNANCY

The documentation of fifth finger clinodactyly mandates that a targeted fetal sonographic scan should be performed to screen for additional anomalies typical of Down syndrome, including increased nuchal fold measurement, cystic hygroma, atrioventricular canal defect of the heart, duodenal atresia, polyhydramnios, and an increased gap between the first and second toes (see Chapters 2, 3, and 131). We do not advocate karyotyping for isolated fifth finger clinodactyly, especially if both parents have been examined and at least one has fifth finger clinodactyly. In the setting of both fifth finger clinodactyly and an additional fetal anomaly, we would recommend obtaining a prenatal chromosome analysis, as there are many reports in the literature of abnormal karyotypes associated with this combination of findings.

FETAL INTERVENTION

There are no fetal interventions for clinodactyly.

TREATMENT OF THE NEWBORN

No treatment is required for isolated fifth finger clinodactyly. However, a thorough physical examination of the newborn is indicated to elicit subtle anomalies that may have been missed on the prenatal sonographic examination. If not examined prior to their infant's birth, an attempt should be made to examine the hands of both parents. If a hand of one of the parents demonstrates clinodactyly on physical examination, radiographic studies are not necessary. Parental hand films might be helpful to detect subtle abnormalities of the phalanges.

SURGICAL TREATMENT

For most cases of fifth finger clinodactyly, there is no indication for surgical treatment. However, rare case reports exist in which the clinodactyly has been treated surgically (Godunova, 1982). In most of these case reports, additional hand anomalies, such as the absence of the fifth metacarpal, have also been present, creating a more serious hand deformity.

LONG-TERM OUTCOME

For isolated clinodactyly, the long-term outcome is expected to be excellent. The presence of the clinodactyly seldom impairs manual dexterity.

GENETICS AND RECURRENCE RISK

For a discussion of the genetics of trisomy 21, see Chapter 131. Most cases of clinodactyly are isolated or are due to an autosomal dominant trait with variable expressivity (Skvarilova and Smahel, 1984; Leung and Kao, 2003). There are multiple reports of three and four generation pedigrees in which clinodactyly is inherited as an asymptomatic autosomal dominant trait, as summarized in Leung and Kao (2003). Clinodactyly may be one feature of the syndromes listed under "Differential Diagnosis." In addition, it can be one component of rarer syndromes, such as the dominantly inherited syndrome of characteristic facial appearance, preauricular pits, fifth finger clinodactyly, and tetralogy of Fallot (Jones and Waldman, 1985). When clinodactyly occurs as part of a genetic syndrome, or if it is due to a chromosome abnormality, the recurrence risk is that of the specific syndrome or chromosome abnormality.

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103 CHAPTER Ectrodactyly

Key Points

- Developmental malformation that consists of missing digits, a deep median cleft, and fusion of remaining digits.
- Occurs as either a nonsyndromic split hand/foot malformation or as a syndromic condition with associated anomalies.
- Most syndromic ectrodactylies are inherited as autosomal dominant conditions and are due to mutations in the *p*63 gene.
- Incidence is 1/18,000 in newborns.
- Fetuses with ectrodactyly should be referred for detailed fetal sonographic anatomic evaluation due to the high incidence of associated anomalies.
- Parents should be examined by a medical geneticist to specifically rule out subtle malformations such as missing teeth.
- Fetal karyotype is indicated.
- Intelligence is generally normal and functional outcome of the hands is good following surgical repair.

CONDITION

The term ectrodactyly derives from the Greek *ektroma*, meaning "abortion," and *daktylos*, meaning "finger." Ectrodactyly is a human developmental malformation that consists of missing digits, a deep median cleft, and fusion of remaining digits, all of which result in clawlike extremities (Scherer et al., 1994). A central ray defect is the hallmark of the split hand and split foot malformation. This deformity was first reported in the medical literature in 1575, when Ambroise Paré described a 9-year-old boy with a right split hand and an absence deformity of the long bones of the legs (cited in Temtamy and McKusick, 1978) (Figure 103-1).

Although the common usage of the term ectrodactyly is as a descriptive term for the split hand or foot malformation, the term was actually first used in 1832 by St. Hilaire to denote "absence of fingers." According to Temtamy and McKusick (1978), ectrodactyly refers to a specific hand deformity with a partial or total absence of the distal segments of the hand and normal proximal segments. In this broader definition, ectrodactyly may involve certain phalanges (aphalangia), only the digits (adactylia), or the full hand (acheiria). More recently, it has become clear that ectrodactyly occurs in two clinical settings—the split nonsyndromic hand/foot malformation, a single-gene defect that is transmitted as an autosomal dominant disorder in families; and the syndromic ectrodactylies that include split hand and split foot as one component of a group of anomalies, which occur in approximately 40% of cases (Czeizel et al., 1993; Evans et al., 1994).

The syndromic ectrodactylies encompass many different conditions, such as ectrodactyly ectodermal dysplasia cleft syndrome (EEC syndrome). Many of these syndromic ectrodactylies are due to mutations in the *p*63 gene (Brunner et al., 2002). *P*63 is specifically expressed in embryonic ectoderm. The *p*63 knockout mouse dies at birth and has absent epidermis, prostate, breast, and urothelial tissues as well as limb anomalies.

INCIDENCE

The incidence of split hand malformation is 1 in 18,000 newborns (Czeizel et al., 1993; Evans et al., 1994)

SONOGRAPHIC FINDINGS

The characteristic sonographic findings in ectrodactyly are the absence of the central digits of the hand with normal or enlarged digits at the lateral aspects (Figure 103-2) (Leung et al., 1995). Prenatal diagnosis of ectrodactyly was first reported

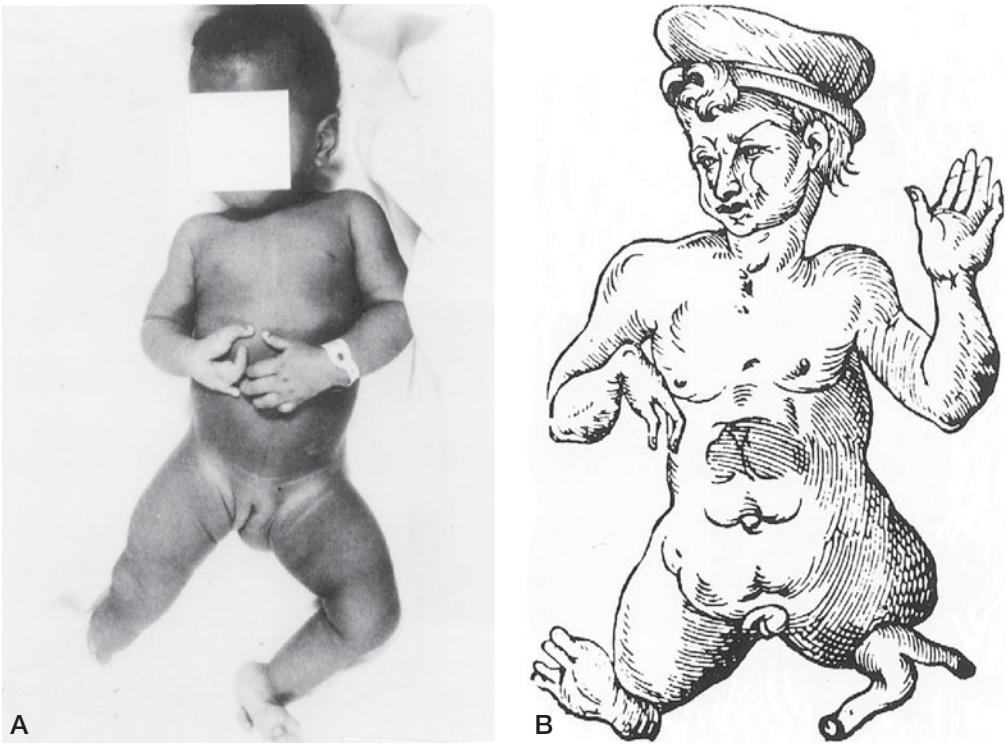

Figure 103-1 Similarities occurring between two cases of split hand/split foot malformation in cases separated by four centuries. **A.** Affected infant with ectrodactyly of the right hand. **B.** Nine-year-old affected boy described by Ambroise Paré in 1575. (*Reprinted, with permission, from Temtamy S, McKusick V.* The Genetics of Hand Malformations. *New York : Liss, 1978. Copyright 1978 Alan R. Liss. Reprinted, by permission, of John Wiley and Sons, Inc.*)

in 1980, when a fetus studied at 16 and 19 weeks of gestation was noted to have one hand with syndactyly and both feet with lobster-claw deformities. This diagnosis occurred in the setting of a father known to be affected with ectrodactyly. These parents elected to terminate the pregnancy. Examination following termination confirmed bilateral syndactyly of the third and fourth fingers and bilateral lobster-claw deformities of the feet (Henrion et al., 1980). Kohler et al. (1989) described the detection of a 30-week appropriate-for-gestational-age male fetus with cleft palate, syndactyly, and lobster-claw deformity and no family history of ectrodactyly.

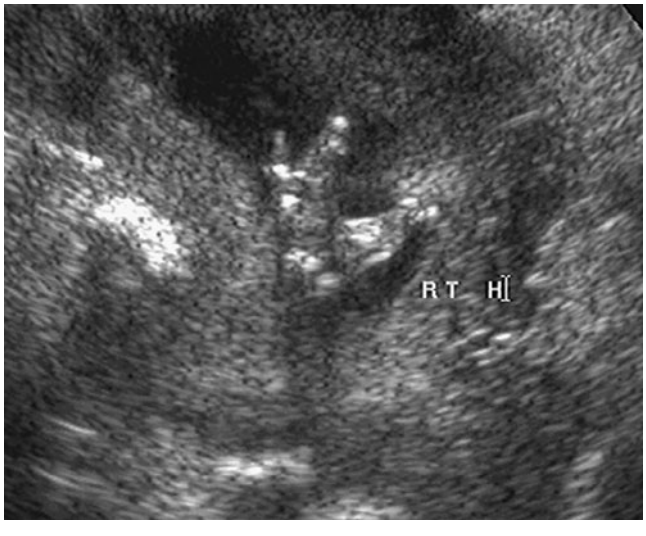

Figure 103-2 Prenatal sonographic image of a fetal hand with ectrodactyly. Note the absence of central digits.

Transvaginal sonography has also been used to diagnose bilateral cleft lip with lobster-claw deformities of the hands and feet in a fetus with an apparently negative family history at 14 weeks of gestation (Figure 103-3). Post-termination studies confirmed the diagnosis of EEC syndrome. The mother was a healthy 24-year-old woman who had sonography performed as an anatomic screen without a specific clinical indication. After diagnosis of EEC syndrome in this fetus, the mother was more closely examined and was found to have microdontia of two lateral upper incisors. This was not apparent initially because cosmetic dental work had been performed. The authors suggested that the dental anomalies could represent an extremely mild form of EEC syndrome in the mother. She was advised to have transvaginal sonography after the 10th week of gestation in a subsequent pregnancy, when fetal fingers and toes can be visualized (Bronshtein and Gershoni-Baruch, 1993). Approximately 8% of patients with EEC syndrome also have urologic anomalies. Chuangsuwanich et al. (2005) described a fetus with EEC and a large nephrogenic cyst that resulted in bladder and pulmonary hypoplasia.

We described a case of ectrodactyly in all four fetal extremities observed on a sonogram performed for assessment of pre-eclampsia at 33 4/7 weeks (O'Brien et al., 2002). The father of the fetus had bilateral foot and right hand

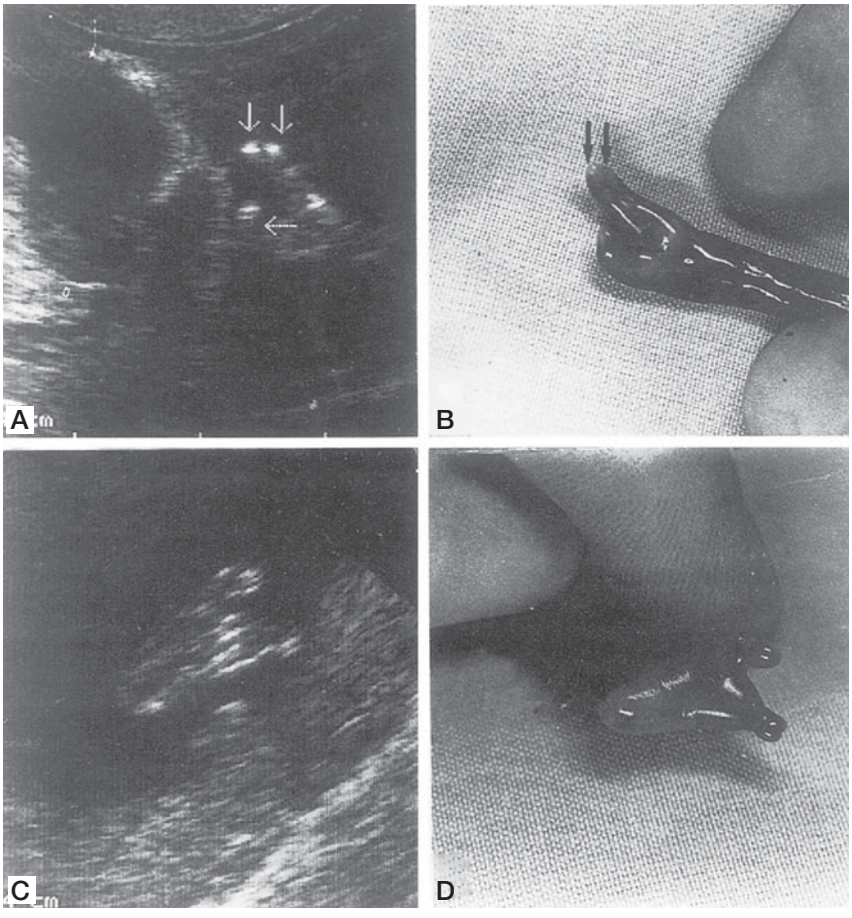

Figure 103-3 Corresponding transvaginal sonographic and pathologic views at 14 weeks of gestation of the fetal hand, demonstrating absent digits and symphalangism (panels **A** and **B**) and the fetal foot, showing absent digits and split foot malformation (panels **C** and **D**). (*Reprinted, with permission, from Bronshtein M, Gershoni-Baruch R. Prenatal transvaginal diagnosis of the ectrodactyly, ectodermal dysplasia, cleft palate (EEC) syndrome.* Prenat Diagn. *1993;13:519-522. Copyright 1993 John Wiley and Sons. Reprinted, by permission, of John Wiley and Sons, Inc.*)

ectrodactyly, small peg-shaped teeth, microretrognathia, nail dysplasia, and a history of lacrimal duct blockage requiring surgery during his infancy. This prompted a diagnosis of acro-dermato-ungual-lacrimal-tooth (ADULT) syndrome, a dominantly inherited condition. Remarkably, the father had never been seen by a geneticist, and was told by his primary care physician that his condition would not affect his offspring. Following publication of the sonographic findings (O'Brien et al., 2002) the father and son were shown to have mutations in the *p*63 gene.

Ectrodactyly has also been described in association with autosomal recessively inherited disorders, such as Smith–Lemli–Opitz syndrome (de Jong et al., 1998), bilateral tibial agenesis with ectrodactyly (Witters et al., 2001), and acro-cardio-facial syndrome (Guion-Almeida et al., 2000).

DIFFERENTIAL DIAGNOSIS

The main consideration in the prenatal diagnosis of ectrodactyly is the distinction between the nonsyndromic split hand and foot malformation, inherited as a single-gene autosomal dominant disorder, versus the syndromic ectrodactylies. Some of the clinical features of the various ectrodactyly syndromes are described in Table 103-1. The most well known of the syndromic ectrodactylies is the EEC syndrome (ectrodactyly, ectodermal dysplasia, cleft lip and palate). In the EEC syndrome, the ectodermal dysplasia is manifested by lightly pigmented, sparse and wiry hair, a decreased number of hairs in the eyelashes and eyebrows, hypopigmented skin with numerous pigmented nevi in the head and neck region, abnormalities of the primary and permanent teeth, including hypoplasia of the enamel, severe caries, brittle or dystrophic nails, atretic lacrimal puncta, a decrease or absence of the orifices of the meibomian glands, and corneal vascularization and scarring, which results in limitation of visual acuity or functional blindness (Bystrom et al., 1975). A conductive sensorineural hearing loss may be a complication of the cleft palate seen in EEC syndrome (Anneren et al., 1991). In one large study of 123 affected patients, 100% had ectodermal dysplasia, 84% had tear duct anomalies, 83.7% had ectrodactyly, 72.4% had cleft lip and/or palate, 33.3% had genitourinary anomalies, and 14% had deafness (Rodini and Richieri-Costa, 1990). EEC syndrome is characterized by variability in clinical expression. A variety of other disorders overlap the EEC syndrome.

The EE syndrome (Wallis, 1988) is a distinct autosomal dominant disorder that manifests as ectrodactyly and ectodermal dysplasia. Wallis (1988) described six members of a four-generation Mauritian family with ectrodactyly and ectodermal dysplasia but with no evidence of cleft lip and/or palate, no abnormalities in the nasolacrimal ducts or sac, and no abnormalities of the scalp. Similarly, families have

Table 103-1

Clinical Features of the Ectrodactyly Syndromes

Condition	Mode of Inheritance	Ectrodactyly	Ecto-dermal Dysplasia	Cleft Lip/ Palate	Tear Duct Abnormality	Genito-urinary Abnormality	Hearing Loss	Dysmor-phic Facies
EEC	Autosomal dominant	+	+	+	+	+	+	+
EE	Autosomal dominant	+	+		+			
ECP	Autosomal dominant	+		+				
E-HL	Autosomal dominant	+					+	
LADD	Autosomal dominant	+	+		+			
ADULT	Autosomal dominant	+	+		+			
Goltz–Gorlin	X-linked dominant			+	+	+	+	

For definitions of abbreviations, see text.
Source: Scherer SW, Poorkaj P, Massa H, et al. Physical mapping of the split hand/split foot locus on chromosome 7 and implication in syndromic ectrodactyly. Hum Mol Genet. *1994;3:1345-1354.*

been described with ectrodactyly and cleft lip (ECP syndrome) but no evidence of ectodermal dysplasia. To further confuse matters, there is another autosomal dominant disorder that presents as ectrodactyly and absent or hypoplastic long bones of the extremities (Hoyme et al., 1987; Genuardi et al., 1990). In this latter condition, approximately 68% of patients have hand malformations and 64% have foot malformations. The associated defects observed in affected kindreds include craniosynostosis, a bifid xiphoid process, and kidney stones. The other abnormalities characteristic of EEC syndrome are not observed in this unique disorder. Patients have also been described with ectrodactyly and hearing loss (E-HL syndrome). The lacrimo-auriculo-dental-digital (LADD) syndrome is characterized by tear duct abnormalities, nasolacrimal duct obstruction, ear anomalies, deafness, small and peg-shaped teeth with hypoplastic enamel, and renal anomalies. These patients are distinguished from patients with EEC by the lack of characteristic lobster-claw deformities (Rodini and Richieri-Costa, 1990). The ADULT syndrome is another dominantly inherited disorder characterized by hypodontia, early loss of permanent teeth due to weak fixation, ectrodactyly, obstruction of the tear ducts, onychodysplasia, and excessive freckling (Propping and Zerres, 1993). In this unique disorder, intelligence is normal and skin pigmentation with sun exposure is normal. Patients have some overlap with EEC syndrome. In Goltz–Gorlin syndrome, affected patients are female. This disorder is inherited as an X-linked dominant condition with lethality in males. Affected patients have ectodermal dysplasia, facial clefts, limb abnormalities, (but not typically ectrodactyly), tear duct and genitourinary abnormalities, and hearing loss. These patients also typically exhibit growth and neuropsychomotor delay, which is not a characteristic of EEC syndrome or the split hand and foot malformation. In patients with Goltz–Gorlin syndrome, the presence of characteristic focal dermal hypoplasia facilitates the diagnosis (Rodini et al., 1992). A relatively recently appreciated genetic disorder, limb–mammary syndrome, consists of mammary gland abnormalities and nipple hypolasia, ectrodactyly, and cleft palate but not cleft lip (van Bokhoven et al., 1999).

ANTENATAL NATURAL HISTORY

Little is known about the antenatal natural history of the ectrodactyly syndromes. Pregnancy loss is not a characteristic feature of these syndromes.

MANAGEMENT OF PREGNANCY

Fetuses ascertained to have ectrodactyly on a prenatal sonographic examination should be referred to a perinatal center capable of performing a complete anatomic study, due to the high incidence of associated anomalies. Particular attention should be paid to the diagnosis of cleft lip and/or palate (see Chapter 23), genitourinary abnormalities, and other anatomic defects. Once ectrodactyly has been diagnosed, it is important to examine both parents and to obtain a complete family history. The ectrodactyly syndromes are characterized by extreme variation in clinical expression. Thus, it is important to be aware of extremely mild manifestations of these disorders such as missing teeth in the parents. A number of ectrodactyly conditions have been associated with chromosomal abnormalities, particularly involving chromosome 7q22 (Naritomi et al., 1993; Scherer et al., 1994; McElveen et al., 1995). Therefore, prenatal karyotyping is recommended when ectrodactyly is observed in the fetus. Furthermore, consideration should be given to obtaining amniocytes for DNA analysis of mutations in the *p*63 gene (South et al., 2002).

Patients with EEC syndrome have been described with low birth weight and a slightly increased incidence of prematurity (Anneren et al., 1991).

There is no indication for delivery by cesarean section solely for the diagnosis of ectrodactyly. Decisions regarding route of delivery should proceed according to standard obstetrical management. There is no indication for delivery in a tertiary care center, as many of the malformations characteristic of the ectrodactyly syndromes generally present with symptoms later in life. However, arrangements should be made for postnatal referral to a clinical genetics unit and a plastic surgeon. Infants with severe cleft lip and cleft palate may need to have a feeding team evaluation.

FETAL INTERVENTION

There are no fetal interventions for ectrodactyly.

TREATMENT OF THE NEWBORN

Infants affected with split hand/foot malformation or one of the ectrodactyly syndromes generally do not have difficulty with their cardiopulmonary systems and do not require neonatal resuscitation. A thorough postnatal physical examination is mandatory. Infants diagnosed prenatally with ectrodactyly should have a complete examination of the palate, including the soft palate and the uvula. Given that these infants are at a reasonably high risk for underlying genitourinary abnormalities, we recommend administration of prophylactic antibiotics until renal anatomy can be studied postnatally. In addition, an early audiologic investigation should be performed, as there is also a significant risk of associated hearing loss. For further management of cleft lip and cleft palate, see Chapter 23. If evidence of decreased lacrimal secretion is present, consideration can be given to administration of artificial tears.

SURGICAL TREATMENT

Surgical treatment for affected patients with EEC syndrome includes functional improvement of the hands, repair of cleft lip and/or cleft palate, and removal of lacrimal duct blockage. None of these surgical procedures are performed during the newborn period. Although the hands will never appear normal, the main surgical consideration is the successful establishment of opposition between two digits.

LONG-TERM OUTCOME

Functional impairment of the hands of affected patients with ectrodactyly is not usually very significant, provided that opposition of two digits can be obtained (Buss et al., 1995). Surgical procedures are directed mainly toward closing an exceptionally wide cleft of the hands and separating syndactylous digits. Patients with ectrodactyly also have difficulty finding proper-fitting shoes. For patients with split hand/foot malformation or EEC syndrome, there is little evidence that intelligence is affected. In one study of 24 cases of patients with EEC syndrome, there was no evidence of mental retardation or developmental delay (Buss et al., 1995). In this study, every affected patient attended a normal school and each patient had normal language milestones despite some of them having problems with hearing loss.

The major difficulties associated with EEC syndrome with regard to long-term outcome include visual difficulties resulting from corneal scarring due to meibomian gland dysfunction and recurrent blepharitis. This latter condition has been ameliorated by operations that improve lacrimal drainage. Orofacial clefting, seen in 14 of 24 patients described with EEC syndrome, may also affect hearing (Buss et al., 1995).

Since the major complications of EEC syndrome are related to repeated infections of the eyes, upper respiratory tract, teeth, and urogenital system, the question has been raised as to whether these patients have an underlying immunodeficiency. In one report, four patients with EEC syndrome were studied and shown to have normal immunoglobulin production, complement activity, and lymphocyte and granulocyte function. These authors concluded that the recurrent infections in EEC syndrome were due to the predisposing anatomic abnormalities and recommended surgical repair of the nasolacrimal duct and extraction of hypoplastic teeth to reduce the frequency of infections (Obel et al., 1993). They also recommended prophylactic use of antibiotics to prevent deafness and ophthalmic sequelae.

GENETICS AND RECURRENCE RISK

The split hand/foot malformation and the ectrodactyly syndromes are characterized by wide variability of clinical expression. Autosomal dominant inheritance of ectrodactyly was first suggested in 1908 (Temtamy and McKusick, 1978). Families with pedigree evidence of autosomal dominant inheritance have a 50% risk of recurrence.

The autosomal dominant form of nonsyndromic split hand/foot malformation was mapped to chromosome 7q21.3-q22.1 by studying multiple patients with cytogenetic rearrangements (Naritomi et al., 1993; Scherer et al., 1994; McElveen et al., 1995) Ectrodactyly is present in 41% of patients who have a deletion of 7q21.2-7q22.1. Based on cytogenetic information, molecular mapping has identified a critical region of DNA for a locus designated as *SHFM1* (split hand/foot malformation number 1). There are at least two other separate genetic loci for isolated split hand/foot malformation. There is an X-linked gene that maps to Xq26.1, known as *SHFM2*, and an additional locus, *SHFM3*, that maps to chromosome 10q24, (Nunes et al., 1995; Roscioli et al., 2004).

Mutations in the *p63* gene have been found in four syndromes associated with ectrodactyly to date (Brunner et al., 2002; Duijf et al., 2002). In nine unrelated families affected with EEC, mutations were demonstrated in the *p63* gene (Celli et al., 1999). In a larger study, 40/43 individuals with EEC syndrome, 2/3 individuals with limb-mammary syndrome, and 4/35 individuals with isolated split hand/foot malformation were shown to have *p63* mutations (van Bokhoven et al., 2001). There is a genotype–phenotype correlation for the *p63* mutations. EEC syndrome is characterized by missense mutations whereas limb–mammary syndrome is associated with frameshift mutations. Functional data suggest that these mutations are consistent with a partial loss of function in combination with dominant gain or change of function defects (Celli et al., 1999; Brunner et al., 2002). *P63* mutations have also been demonstrated in ADULT syndrome (Amiel et al., 2001; O'Brien et al., 2002).

Families with clear-cut evidence of a dominantly inherited form of ectrodactyly should be encouraged to submit blood samples to one of the laboratories investigating the various ectrodactyly genes. If linkage is documented within an individual family, prenatal DNA diagnosis is possible (South et al., 2002). When the case is isolated or there is no evidence of DNA mutation in one of the previously identified *SHFM* or *p63* loci, prenatal diagnosis of ectrodactyly can be performed by sonography starting at 10 weeks using a transvaginal probe.

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104 CHAPTER Polydactyly

Key Points

- Defined as the presence of a hand or foot with more than 5 digits.
- May be "radial/tibial" (formerly preaxial), "ulnar/fibular" (formerly postaxial), or "central".
- Incidence is 1/100 to 1/698 depending on ethnic origin of population studied.
- Major consideration is to determine if isolated or associated with other anomalies. Isolated polydactyly is frequently inherited as an autosomal dominant condition.
- Polydactyly is a component of at least 119 recognized conditions.
- Differential diagnosis includes trisomy 13, Meckel–Gruber syndrome, Bardet–Biedl syndrome, Ellis–van Creveld syndrome, short-rib polydactyly syndrome, and Smith–Lemli–Opitz syndrome.
- Refer for detailed fetal sonographic anatomic evaluation, consider karyotype.
- Surgical outcome and prognosis are good if isolated.
- If associated with other anomalies, consider genetics consultation and DNA mutation testing.
- Recurrence risk depends on underlying diagnosis.

CONDITION

Polydactyly is the presence of a hand or a foot with more than five fingers or toes. Although the medical term polydactyly was first ascribed to the 17th century Amsterdam physician Theodor Kerckring (Blauth and Olason, 1988), the presence of polydactyly was mentioned in the Bible (Nicolai and Schoch, 1986) and is even evident on the left leg of St. Joseph in Raphael's famous 16th century painting of "The Marriage of the Virgin" (Mimouni et al., 2000). Polydactyly is the most frequent congenital anomaly of the human hand (Tsukurov et al., 1994). Polydactyly affecting the thumb or great toe is now classified as "radial/tibial" (formerly preaxial), which refers to a duplication of digits on the radial side of the hand and the tibial side of the foot, or "ulnar/fibular" (formerly postaxial), in which the extra digits occur on the

ulnar and fibular sides of the hand and foot, respectively (Talamillo et al., 2005). Cases in which the three central digits are affected are referred to as "central polydactyly" and are the least common of the three types. In general, radial/tibial polydactyly is more common than ulnar/fibular polydactyly (Temtamy and McKusick, 1978). Polydactyly has been further subclassified on a descriptive basis. In ulnar/fibular polydactyly, type A denotes fully developed extra digits. Type B describes rudimentary extra digits or a pedunculated skin tag that is usually found on the hands and only rarely on the feet. This type is very common among blacks. In radial/tibial polydactyly, when the thumb is polydactylous it is known as type I, when a triphalangeal thumb is present it is known as type II, when the index finger is polydactylous it is type III, and when polysyndactyly occurs it is known as type IV.

Morphogenetically, the hand and foot malformations can be considered as a process of bifurcation of one or several finger or toe rays in the longitudinal axis progressing from peripheral to central. Segment polarity genes initially identified in *Drosophila*, such as sonic hedgehog (*SHH*), play a critical role in this process.

INCIDENCE

Notable differences exist in the incidence of polydactyly according to race and gender. In a 1963 study performed in New York City, the incidence of ulnar/fibular polydactyly in blacks was 10.7 in 1000 livebirths, whereas in a comparable white population, the incidence was 1.6 in 1000 livebirths. In this study, polydactyly was noted to be twice as common in males as in females (Mellin, 1963). In general, there is a 1% incidence of ulnar/fibular polydactyly of the hand in black individuals. This is inherited as an autosomal dominant trait. There is also a high frequency of ulnar/fibular polydactyly in some Latino populations (Orioli, 1995). In one Japanese study, radial/fibular polydactyly was demonstrated in the hand and ulnar/fibular polydactyly in the foot (Masada et al., 1986). Affected females predominated when the foot was involved and males predominated when the hand was involved. In this study of 523 cases, associated anomalies were seen in 5% of patients (Masada et al., 1986). In another Japanese study of 330 feet in 265 patients affected with foot polydactyly, a 10% incidence of a positive family history was noted (Watanabe et al., 1992). More recently, in a sonographic study of 17,760 consecutive Israeli women, Zimmer and Bronshtein (2000) detected 26 fetuses with polydactyly. This equated to an incidence of 1 in 698 women. Most of the examinations in this study were performed at 14–16 weeks of gestation.

Maternal smoking increases the chance of fetal limb defects (Hampton, 2006; Man and Chang, 2006).

SONOGRAPHIC FINDINGS

The phalanges are identifiable as early as the 13th week of gestation by transabdominal sonographic examination (Figures 104-1 and 104-2) (Deschamps et al., 1992), and by 11 weeks of gestation by transvaginal scan (Hobbins et al., 1994). The major consideration in the prenatal sonographic examination is to determine whether the polydactyly is isolated. As polydactyly is a component of many genetic syndromes, it is especially important to perform a thorough anatomic survey to look for associated anomalies. Specific associations that should be ruled out include skeletal dysplasia, polycystic kidneys, and encephalocele. Once polydactyly is identified it is especially important to note the length of the long bones (Bromley and Benacerraf, 1995). Polydactyly of the hand is easier to diagnose than that of the foot (Figures 104-3 and 104-4). An ulnar/fibular skin tag can be easily overlooked, whereas a normally formed extra digit will be more easily visualized. Triphalangeal thumbs are also considered within the diagnostic spectrum of polydactyly. Three dimensional (3D) sonography may provide improved resolution of

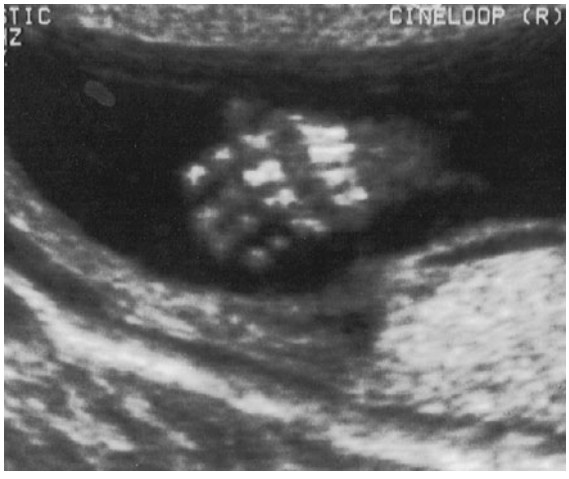


Figure 104-1 Prenatal sonographic image of a fetus with five normal digits. In this image two phalangeal bones are demonstrated in the thumb, whereas the other digits each have three clearly visualized phalangeal bones.

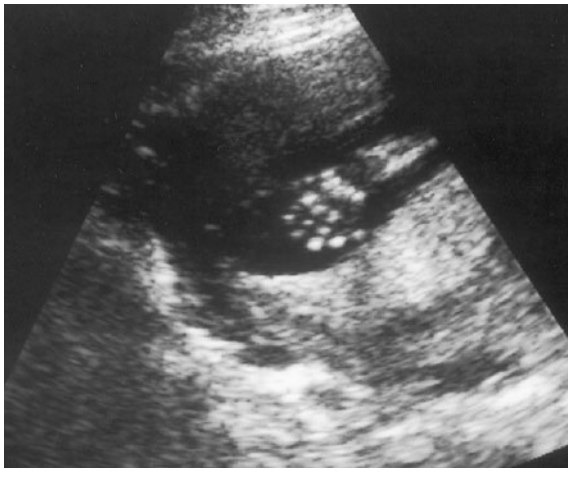


Figure 104-2 Prenatal sonographic image of a fetus with ulnar/fibular polydactyly. Note the presence of a single phalanx that appears to be on the ulnar side of the fifth digit.

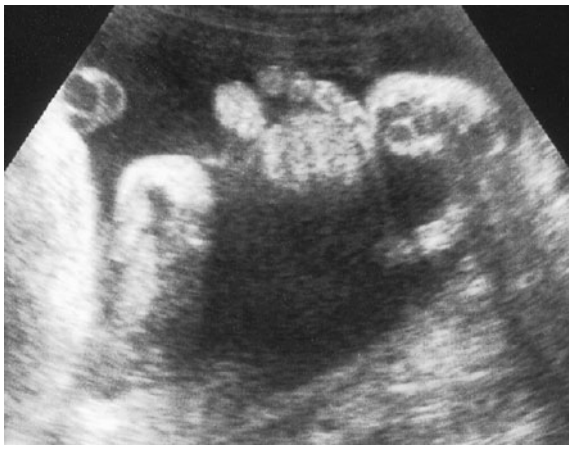


Figure 104-3 Sonographic image of the base of a normal fetal foot indicating the great toe and four additional smaller toes.

the fingers and toes, especially when using transparent mode reconstruction (Kos et al., 2002).

DIFFERENTIAL DIAGNOSIS

The majority of antenatally diagnosed cases of polydactyly will be isolated and associated with a normal prognosis (Bromley et al., 2000). The major consideration in the differential diagnosis is to determine whether the condition is isolated and familial or due to a syndrome. Isolated polydactyly is also considered to be a manifestation of the heterozygote (carrier) state for Ellis–van Creveld and Meckel–Gruber syndromes (Goldblatt et al., 1992; Nelson et al., 1994; Wright et al., 1994). Trisomy 13, which manifests as polydactyly in 75% of affected patients (Tsukurov et al., 1994) should be ruled out by prenatal karyotyping if additional sonographic abnormalities are present (see Chapter 129). Fetuses with trisomy 13 have polydactyly, cardiac defects, central nervous system defects including holoprosencephaly, and other major organ abnormalities. If the chromosomes are normal but the fetus is noted to have polydactyly and holoprosencephaly, a possible diagnosis is pseudotrisomy 13, which is inherited as an autosomal recessive condition (Verloes et al., 1991). For patients to receive this diagnosis, the karyotype must be normal and holoprosencephaly must be present with polydactyly or other anomalies.

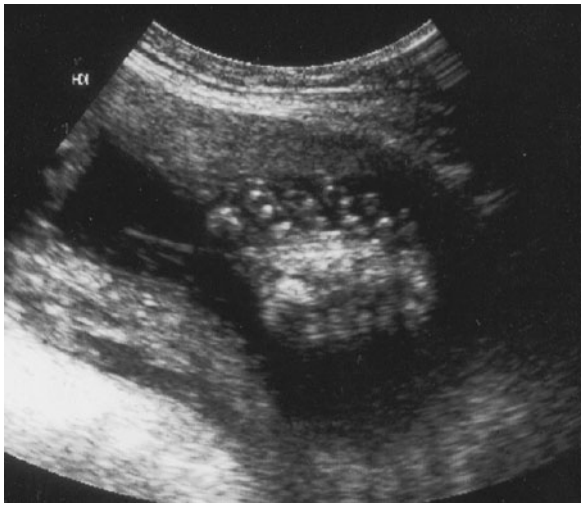


Figure 104-4 Sonographic view of a fetus with polydactyly of the foot, indicating the presence of six well-formed toes.

Alternatively, polydactyly with other serious central nervous system defects can be present (Lurie and Wulfsberg, 1993). The constellation of brain abnormalities in the setting of polydactyly suggests Meckel–Gruber syndrome, which is also inherited as an autosomal recessive trait (Gershoni-Baruch et al., 1992). Fetuses with Meckel–Gruber syndrome characteristically have an occipital encephalocele, polycystic kidneys, and polydactyly. This condition was first described in 1822 (Ueda et al., 1987). Isolated polydactyly has been questioned in carriers of the Meckel–Gruber syndrome. Nelson et al. (1994) described a family in which three boys were affected. Their father and paternal first cousin had bilateral ulnar/fibular polydactyly, which raised the question of whether they were manifesting heterozygotes. One hundred percent of patients affected with Meckel–Gruber syndrome have cystic renal dysplasia and 55% of these patients have polydactyly.

The constellation of ulnar/fibular polydactyly, obesity, progressive retinal dystrophy, hypogonadism, renal dysfunction, and learning difficulty suggests the diagnosis of Bardet–Biedl syndrome, which is also inherited as a recessive trait. Bardet–Biedl syndrome is genetically heterogenous, and eight genes have been identified to date (*BBS1-BBS8*) (Karmons-Benailly et al., 2005). In cases of Bardet–Biedl syndrome, prenatal sonographic findings such as polydactyly and cystic kidneys may initially suggest a diagnosis of Meckel–Gruber syndrome. In one study, 13 fetuses that presented with these findings and did not have encephalocele, but were diagnosed as having Meckel–Gruber syndrome, underwent DNA sequencing for *BBS1–8* mutations (Karmons-Benailly et al., 2005). In six of the 13 cases, recessive mutations in *BBS* genes were identified. Thus, the antenatal presentation of Bardet–Biedl syndrome mimics Meckel–Gruber syndrome.

The combination of short-limb dysplasia, thoracic hypoplasia, multiple visceral abnormalities, and polydactyly suggest a diagnosis of short-rib polydactyly syndrome (see Chapter 95). Ellis–van Creveld syndrome (see Chapter 94) presents with polydactyly and a skeletal dysplasia, along with cardiac malformations. If a midline abdominal cyst is seen in association with the polydactyly, the underlying diagnosis could be McKusick–Kaufman syndrome (Chitayat et al., 1987). Smith–Lemli–Opitz syndrome, a recessive condition that is due to deficiency of 7-dehydrocholesterol reductase, presents antenatally as growth restriction with polydactyly and ambiguous genitalia in males (Goldenberg et al., 2004). The findings of radial/tibial polydactyly and club hands with hypoplastic first metacarpal have been described in DiGeorge syndrome and 22q11.2 deletion (see Chapter 139) (Cormier-Daire et al., 1995; Fryer, 1996). Additional considerations in the differential diagnosis are given in Table 104-1.

Table 104-1

Differential Diagnosis of Polydactyly

Condition	Major Associated Prenatal Findings
Bardet–Biedl syndrome	Cystic kidneys, micropenis
Cephalopolysyndactyly (Greig syndrome)	Craniosynostosis, syndactyly
Chondrodysplasia punctata (X-linked)	Skeletal, midface anomalies
DiGeorge syndrome	Cardiac, renal anomalies
Ellis–van Creveld syndrome	Skeletal dysplasias, cardiac anomalies
Holt–Oram syndrome	Cardiac anomalies
Isolated (familial)	None
McKusick–Kaufman syndrome	Cystic abdominal mass (hydrometrocolpos)
Meckel–Gruber syndrome	Encephalocele, renal dysplasia, liver cysts
Pallister–Hall syndrome	Midline central nervous system anomalies
Pseudotrisomy 13	Holoprosencephaly
Short-rib polydactyly syndromes	Skeletal dysplasia
Smith–Lemli–Opitz syndrome	Intrauterine growth retardation, holoprosencephaly, ambiguous genitalia
Trisomy 13	Central nervous system, cardiac, renal anomalies

ANTENATAL NATURAL HISTORY

The antenatal natural history depends entirely on the underlying associated diagnosis. Isolated polydactyly has no apparent effect on the antenatal natural history. Conditions such as trisomy 13 have a profound effect on the antenatal natural history and may result in miscarriage. Autoamputation of extra digits has been observed in utero (Zimmer and Bronshtein, 2000).

MANAGEMENT OF PREGNANCY

Fetuses in which polydactyly is suspected should be referred to a tertiary care center capable of detailed fetal anatomic diagnosis. A complete family history should be obtained regarding the occurrence of polydactyly in other family members. Occasionally, parents are unaware of the fact that they themselves had small digits removed during infancy. Both parents should be examined for the presence of scars on the ulnar sides of their hands. For fetuses with isolated polydactyly, there is no indication for delivery at a tertiary care center, especially in light of a positive family history. However, if the fetus is shown to have associated abnormalities, consideration should be given to delivery in a tertiary care center, where clinical geneticists are available for syndromic diagnosis. Consideration should be given to performing antenatal karyotyping to specifically rule out trisomy 13. As stated earlier, sonographic attention should be paid to the length of the long bones, the central nervous system, the heart, and the kidneys as these are the organs that are abnormal in major conditions that are associated with polydactyly. For families known to be at risk for a single-gene disorder associated with polydactyly, embryofetoscopy has been performed successfully to diagnose polydactyly (Quintero et al., 1993). In one report, in a family at risk for recurrence for Meckel–Gruber syndrome, ulnar/fibular polydactyly was observed on both the hands and feet of a fetus at 10 menstrual weeks (Dumez et al., 1994). In addition, bilateral cystic lesions in the mesonephros and metanephros were visualized. The fingers and toes can be observed as early as 9 weeks of gestation by embryoscopy in fetuses at high risk for an inherited abnormality (Dumez et al., 1994). Given the advances in high frequency transvaginal ultrasound transducers, it is unlikely that embyrofetoscopy offers any advantages for diagnosis in contemporary practice.

FETAL INTERVENTION

There is no fetal intervention for polydactyly.

TREATMENT OF THE NEWBORN

Newborns who are delivered with polydactyly should have a thorough physical examination by a clinical geneticist to rule out associated findings (Figures 104-5 and 104-6A). If karyotyping has not been performed prenatally, it should be considered at the time of birth to rule out trisomy 13. A case of 22q11 deletion has been associated with polydactyly (Fryer, 1996). If evidence of polysyndactyly is present, radiographs may be obtained to document the underlying bony anatomy (see Figure 104-6B). A pediatric orthopedic surgeon should be consulted.

In cases of ulnar/fibular polydactyly that consist of a small skin tag, consideration can be given to their removal. Pediatricians are commonly taught to ligate the base of these lesions with suture material as a simple, inexpensive form of

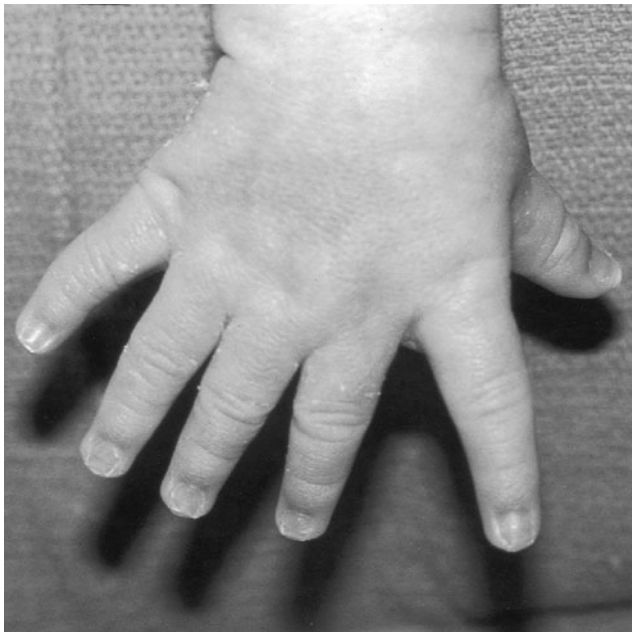
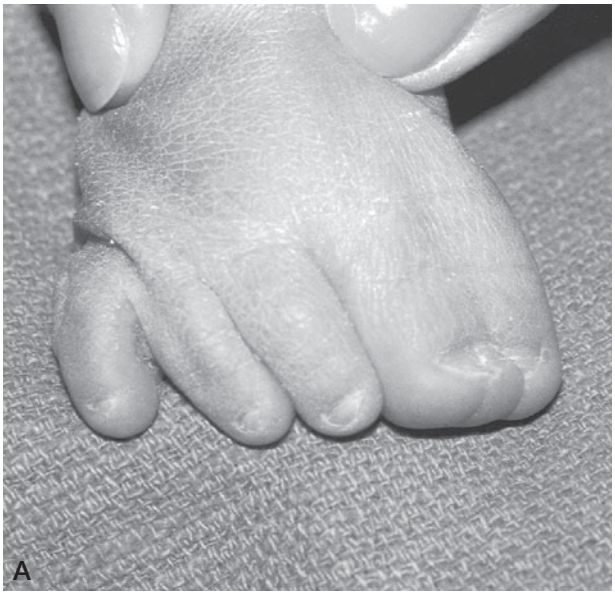


Figure 104-5 Postnatal photograph of a newborn infant at term with six well-formed fingers. This patient has radial/tibial polydactyly of the index finger (type III). At 3 months of age this infant was diagnosed with Pallister–Hall syndrome.

removal (Frieden, 1995). However, because these supernumerary digits may vary in size and internal contents, consultation with a pediatric orthopedic surgeon may be advisable. Extra digits with a wide pedicle at the base are at increased risk for infection, scarring, or incomplete removal. Frieden, (1995) suggest infiltrating the base of the extra digit with a local anthestic and removing the lesion with sterile iris scissors. They suggest that hemostasis will occur with firm, direct pressure for several minutes, or with 20% ammonium chloride or ferric subsulfate solution or a silver nitrate stick.

SURGICAL TREATMENT

For well-formed digits that interfere with hand function, consultation with a hand surgeon is advisable. The goal of surgical treatment is to achieve optimal function and as normal an appearance as possible. In one report, Ganley and Lubahn (1995) performed a follow-up study of 21 patients with radial/tibial polydactyly who were treated between 1979 and 1994. There were 26 thumbs affected. Of their patients, 9 were boys and 12 were girls. Of the 26 thumbs, 6 were treated with ablation alone, 10 were treated with ablation and radial collateral ligament reconstruction and shaving of the metacarpal, 5 thumbs were treated with the Bilhaut–Cloquet procedure (see below), and 5 thumbs were treated conservatively with only observation. Of the 6 thumbs treated with ablation alone, 5 required subsequent radial collateral ligament reconstruction. Patients who underwent ablation with ligament



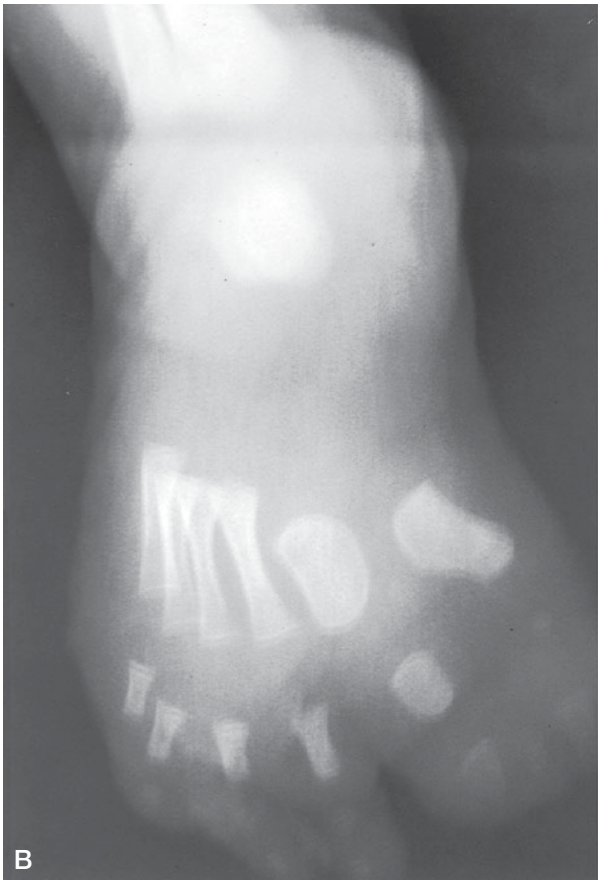


Figure 104-6 **A.** Postnatal photograph of the same infant in Figure 104-5 with polysyndactyly of the toes. **B.** Radiograph of this foot.

reconstruction showed improvement in clinical alignment and stability of the thumbs, but they did not have normal joint motion. The Bilhaut–Cloquet procedure involves removing the middle portions of the two adjoining thumbs; the remaining thumbs are sewn together, resulting in a narrower single digit. Patients who underwent this procedure had improved cosmetic appearance and function, however, they did not have normal joint motion. These authors recommended that ablation be performed only in the context of reconstruction of the radial collateral ligament. They also cautioned that no surgical techniques guarantee ultimately normal joint motion. However, all of their patients were satisfied that the postoperative thumb was significantly improved as compared with their preoperative condition (Ganley and Lubahn, 1995).

LONG-TERM OUTCOME

See under "Surgical Treatment."

GENETICS AND RECURRENCE RISK

There are at least 119 human disorders associated with polydactyly (Biesecker, 2002). Of these, 97 are syndromic and 22 are nonsyndromic. Mutations in at least 26 genes have been identified. The major genes involved are *GLI3* (Greig cephalopolysyndactyly, Pallister–Hall syndrome), *MKS* (McKusick–Kaufman syndrome), *EVC* (Ellis-van–Creveld syndrome), and *DHCR7* (Smith–Lemli–Opitz syndrome). The genes that have been identified to date in association with polydactyly are all critical for normal mammalian development (Biesecker, 2002). They consist of transcription factors, DNA repair genes, signal transduction molecules, chaperonins, and growth factors.

Several of the genes responsible for polysyndactyly have been mapped to chromosome 7q36 (Roberts and Tabin, 1994; Zguricas et al., 1999). Hing et al. (1995) described a six-generation North American white kindred with radial/tibial polydactyly; they showed linkage to chromosome 7q36. In addition, genes responsible for polysyndactyly and radial/tibial polydactyly types II and III have also been mapped to the same region (Tsukurov et al., 1994; Zguricas et al., 1999). Interestingly, both *EN2,* the human homologue of the engrailed gene of Drosophila, which is important for axial patterning, and *SHH,* sonic hedgehog, map to the same region of the human genome.

Greig cephalopolysyndactyly syndrome is a rare autosomal dominant disorder characterized by craniofacial abnormalities, polydactyly, as well as syndactyly of the hands and feet. Point mutations in the human *GLI3* gene, as well as cytogenetic rearrangements of chromosome 7p13 that disrupt the *GLI3* gene, are the underlying basis of this condition (Wild et al., 1997).

Patients with isolated polydactyly generally inherit this trait as an autosomal dominant condition. In one report, Radhakrishna et al. (1993) described a five generational pedigree of 71 affected members of an Indian family in Gujarat. All affected family members had radial/tibial polydactyly manifesting as a well formed, articulated digit of the hand or foot. An additional 20 family members had triphalangeal thumbs or duplication of the great toe. The digital anomalies were isolated. Patients had no other abnormalities, and the polydactyly did not interfere with their work as agricultural laborers. There was no effect of this gene on reproductive fitness. This autosomal dominant gene was manifested by three different phenotypes: radial/tibial polydactyly, duplication of the thumbs or great toes, or the presence of triphalangeal thumbs.

The recurrence risk for isolated familial polysyndactyly is 50%. The recurrence risk for many of the associated conditions depends on the specific condition. Many of these conditions are inherited as autosomal recessive genes, which carry a 25% recurrence risk. Trisomy 13 has a 1% recurrence that is independent of maternal age. Prenatal diagnosis is possible as early as 11 weeks of gestation by transvaginal sonography, or possibly earlier by fetoscopy. If a specific condition has been identified in a prior affected fetus DNA mutation information may be available. If this is the case, prenatal diagnosis will be most accurate if a CVS is performed to obtain fetal DNA.

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105 CHAPTER Syndactyly

Key Points

- Syndactyly refers to apparent fusion of digits, either osseous or cutaneous.
- Prenatal ultrasound examination reveals an inability to distinguish separate digits of fingers or toes or to demonstrate independent movement of fingers.
- May be isolated or syndromic.
- Many syndromes are associated with craniosynostosis.
- Fetuses with syndactyly should undergo detailed fetal sonographic examination to look for associated anomalies.
- Review results of estriol levels in maternal serum screen, as low levels are present in triploidy and Smith–Lemli–Opitz syndrome.
- Consider karyotype to rule out triploidy. Obtain complete family history. Review results of estriol levels in maternal serum screen.
- A complete physical examination of infant at birth is essential.

CONDITION

The term syndactyly comes from the Greek *syn,* meaning together and *daktylos,* meaning finger. It describes an apparent fusion of the digits. Syndactyly can be osseous, which refers to fusion of the bones, or cutaneous, defined as webbing of the skin between two digits. In fetal life, the limb buds may be recognized sonographically as early as 8 weeks of gestation, but the digits become visible only at 11 to 12 weeks (Bromley and Benacerraf, 1995). After the 12th week, the hand is fully formed, but separate movements of the digits are not easily observed until 15 weeks of gestation (Deschamps, et al., 1992). Absence of digital dissociation implies a diagnosis of syndactyly.

Although mild cutaneous syndactyly, or webbing, of the toes is a common familial trait, it is generally too subtle to be appreciated on a prenatal sonogram. Syndactyly severe enough to interfere with digital movement suggests a more serious pathology, such as one of the acrocephalosyndactyly syndromes. These syndromes are generally associated with abnormalities of the skull shape due to craniosynostosis (Chapter 10).

INCIDENCE

Mild syndactyly is relatively common. It has an incidence of 1 in 1650 to 1 in 3000 livebirths (Temtamy and McKusick, 1978). Syndactyly severe enough to interfere with fetal digital movement is rare. Triploidy, which is associated with syndactyly, has an incidence of 1 in 10,000 livebirths. The incidence of Apert syndrome, which includes syndactyly as one component, is 1 in 160,000 livebirths. There is an associated high neonatal mortality rate in this condition, which results in a 1 in 2 million incidence in the general population (Hill et al., 1987; Filkins et al., 1997; Boog et al., 1999).

SONOGRAPHIC FINDINGS

Syndactyly is suggested by the inability to distinguish separate digits of the fingers and toes or to demonstrate independent movement of the fingers. Syndactyly is excluded if the fetus splays or interdigitates the fingers (Ginsberg et al., 1994).

Syndactyly may be one component of a syndrome. To make a syndromic diagnosis, the sonographer needs to decide if all four limbs are involved and what associated anomalies are present. Many of the syndromes associated with syndactyly also have synostosis of the cranial sutures. This may appear as acrocephaly, a tall, peaked skull shape with a high forehead, frontal bossing, and a prominent metopic suture.

One of the better known acrocephalosyndactyly syndromes is Apert syndrome. In Apert syndrome, complete syndactyly of the second through fourth digits is present, which leads to the characteristic "mitten-like" hands and feet (Figures 105-1 and 105-2). This condition also frequently involves the fifth finger. Multiple case reports have appeared in the literature regarding the prenatal sonographic diagnosis of Apert syndrome (Kim et al., 1986; Hill et al., 1987; Narayan and Scott, 1991; Parent et al., 1994; Filkins et al., 1997; Boog et al., 1999). The hallmark of the sonographic diagnosis of this condition is that despite prolonged observation, the fetus is never noted to have distinct or separate finger movements. The hands are never seen to open in this condition (Figure 105-1A). In addition, the toes appear fused (Figure 105-2A). Additional abnormalities characteristic of Apert syndrome include polyhydramnios and an acrocephalic calvarium (Hill et al., 1987), ventriculomegaly, partial agenesis of the corpus callosum (Parent et al., 1994), hydrocephalus (Kim et al., 1986), and dysmorphic features, including a high forehead, hypertelorism, and a depressed nasal bridge (Parent et al., 1994). Prenatal sonographic diagnosis of Apert syndrome has been made in both the setting of an affected mother with a fetus at 50% risk for inheriting the condition (Narayan and Scott, 1991), as well as in the setting of a negative family history with the disorder presumably due to a spontaneous mutation (Filkins et al., 1997; Hill and Grzybek, 1994; Parent et al., 1994). Three dimensional sonography improves visualization of both cranial and extremity anatomy (Esser et al., 2005).

Prenatal sonographic diagnosis of Carpenter syndrome has been reported in a twin gestation first studied at 17 weeks (Ashby et al., 1994). In this case report, one twin was noted to have clublike fetal hands, with the fingers maintained permanently in a flexed position. At 20 weeks of gestation, an abnormal, diamond-shaped head was noted in the axial plane along with preaxial polydactyly of the feet and duplication of the great toe. The fingers were described as being "pulled together," and they never spread normally, which was noticed easily because the other twin had normal digital movements (Ashby et al., 1994).

Synpolydactyly is a rare dominantly inherited malformation of the distal limbs (Goodman, 2002). Its severity can range from partial cutaneous syndactyly to complete duplication of the digits.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of syndactyly is listed in Table 105-1. Syndactyly can be isolated or syndromic. Fetuses with triploidy (see Chapter 132) have characteristic, pathognomonic cutaneous syndactyly of the third and fourth digits. Fetuses with triploidy also have second trimester growth restriction, cystic and/or small placentae, ventriculomegaly, and congenital heart defects (Mittal et al., 1998). The differential diagnosis also includes Apert syndrome (acrocephalosyndactyly type I). Patients with acrocephalosyndactyly type II (Carpenter syndrome) have acrocephaly, with variable synostoses of the sagittal lambdoid, and coronal sutures

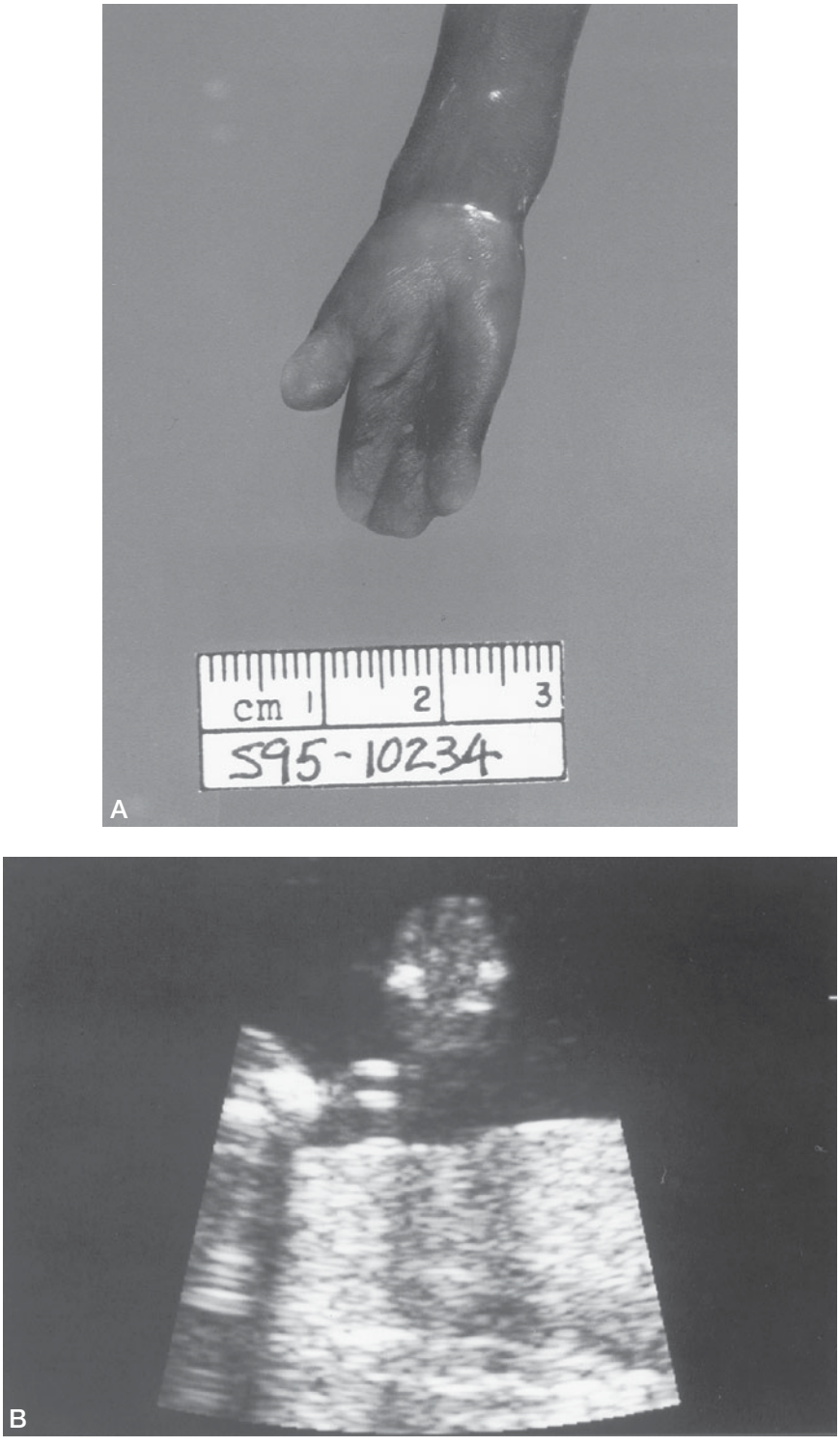
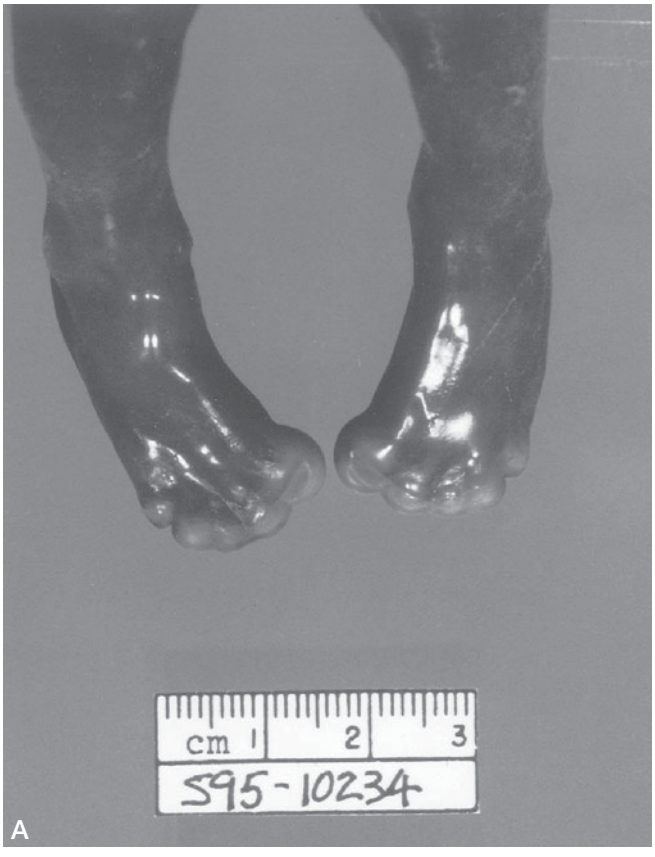


Figure 105-1 **A.** Postmortem photograph of a hand from a fetus at 21 weeks of gestation demonstrating the "mitten-like" appearance due to syndactyly of the second, third, and fourth digits. **B.** Corresponding prenatal sonographic image obtained from the fetus shown in (A), showing syndactyly. *(Courtesy of Dr. Joseph Semple.)*

(see Chapter 10). They also have syndactyly, preaxial polydactyly of the toes, and brachydactyly of the hands and feet with short or absent middle phalanges. One of the difficulties in the prenatal diagnosis of Carpenter syndrome is that marked variability exists even within a family. Pfeiffer syndrome, another acrocephalosyndactyly syndrome, is characterized by craniosynostosis, hydrocephalus, large thumb, and partial cutaneous soft-tissue syndactyly of the hands and feet (Hill and Grzybek, 1994). Magnetic resonance imaging may be helpful in demonstrating both the syndactyly and the broad thumbs that are characteristic of this condition (Itoh et al., 2006). Syndactyly that occurs between the second and third digits is a major manifestation of Smith–Lemli–Opitz syndrome, a recessively inherited disorder of cholesterol metabolism. Fraser syndrome (see Chapter 29) is characterized by cryptophthalmos and syndactyly (Fryns et al., 1997). Patients with Fraser syndrome also have renal agenesis, laryngeal stenosis or atresia, abnormalities of the ears and external genitalia, and other minor anomalies (Rousseau et al., 2002). Syndactyly is a major feature of Fraser syndrome.



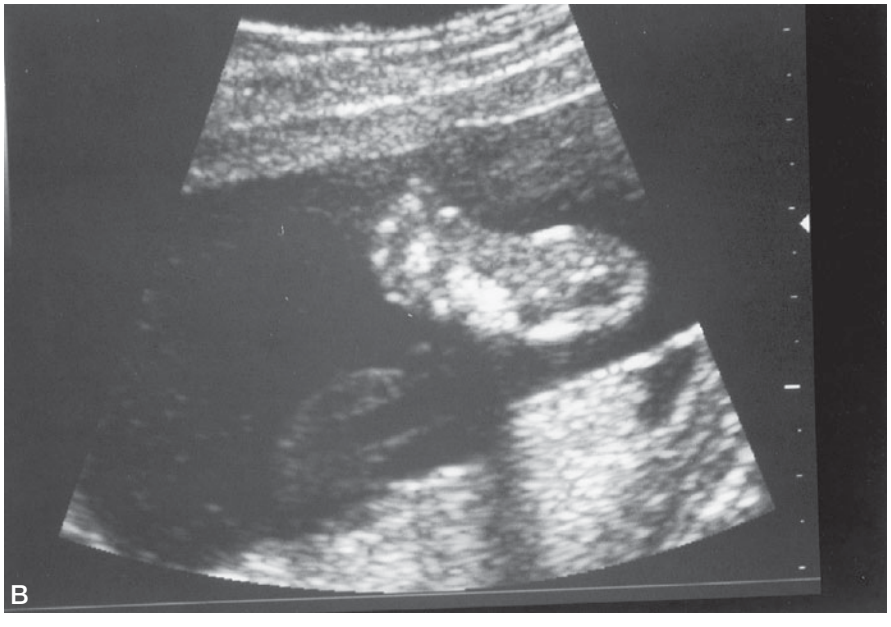


Figure 105-2 **A.** Postmortem photograph of the fetus in Figure 105-1 demonstrating syndactyly of all of the toes. The pregnancy was terminated due to a diagnosis of Apert syndrome. *(Courtesy of Dr. Joseph Semple.)* **B.** Corresponding prenatal sonographic image obtained from the same fetus shown in (A), showing fusion of the toes.

It occurs in 77% of patients with this condition (Ramsing et al., 1990). The syndactyly in Fraser syndrome is always cutaneous and most often involves fingers and toes. Its severity may vary from slight interdigital webbing to complete syndactyly. Another consideration in the differential diagnosis of syndactyly is short-rib polydactyly syndrome (SRPS) type II, Majewski (see Chapter 95). In type II SRPS, patients have polysyndactyly, short ribs, cleft lip, and short tibiae (Thomson et al., 1982).

ANTENATAL NATURAL HISTORY

Syndactyly is due to deficiency in the normal pattern of preprogrammed cell death that occurs with the radial grooves of the hand and foot plates (Ramsing et al., 1990). Under normal developmental circumstances, differentiation of the metacarpal bones and phalanges occurs in the fifth to sixth week of fetal life (Hill et al., 1987). Persistent digital fusion

Table 105-1

Differential Diagnosis of Fetal Syndactyly

Isolated
Triploidy
Acrocephalosyndactyly Type I (Apert syndrome)
Acrocephalosyndactyly Type II (Carpenter syndrome)
Fraser syndrome
Pfeiffer syndrome
Short-rib polydactyly syndrome Type II Smith–Lemli–Opitz syndrome (Majewski syndrome)
Synpolydactyly

results from failure of the tissue between the digits to degenerate at between 40 and 44 days of gestation (Schauer et al., 1990).

The *HOX* genes code for a highly conserved family of transcription factors that are essential for normal morphogenesis during embryonic life. Like most vertebrates, humans have 39 *HOX* genes that are organized into four separate clusters, known as *HOXA*, *HOXB, HOXC*, and *HOXD*. Each cluster contains 9 to 11 genes and is oriented in the same 5′ to 3′ direction (Goodman, 2002). The parts of the *HOXA* and *HOXD* gene clusters that are nearest the 5′ end are important in limb development. Synpolydactyly results from mutations in the *HOXD13* gene (Muragaki et al., 1996).

MANAGEMENT OF PREGNANCY

When syndactyly is suspected, the pregnant patient should be referred to a center with expertise in sonographic diagnosis. The fetus should undergo a thorough examination to screen for the possibility of other anatomic abnormalities. A complete family history should be obtained by a genetic counselor or geneticist. The results of second trimester maternal screening tests, if performed, should be reviewed, with particular inspection of the estriol levels, which may be low in cases of Smith–Lemli–Opitz syndrome and triploidy. A prenatal chromosome analysis should be considered to rule out a diagnosis of triploidy. It is important to diagnose triploidy, as this condition is lethal, and it carries a maternal risk of preeclampsia.

Fetal chromosomes are normal in the acrocephalosyndactyly syndromes. Craniosynostosis and abnormalities of skull shape should be specifically ruled out. Prospective parents may benefit from discussing the fetal anomalies observed with a genetic counselor and/or medical geneticist. If a diagnosis of one of the acrocephalosyndactyly syndromes is made before 24 weeks of gestation, the parents should be given the option of terminating the pregnancy. It may be helpful for the parents to see photographs of infants and children with the acrocephalosyndactyly syndromes. Care should be taken when discussing the long-term implications of the diagnosis.

Delivery by cesarean section should be reserved for standard obstetric reasons. Consideration may be given to delivering the patient at a tertiary care center to permit immediate postnatal consultation with a clinical geneticist and pediatric plastic and orthopedic surgeons.

TREATMENT OF THE NEWBORN

The newborn with prenatally diagnosed syndactyly should have a complete physical examination at birth. Consideration should be given to obtaining postnatal radiographs of the extremities and skull if clinical suspicion exists that the child has craniosynostosis. Consultation with a dysmorphologist is indicated. Typical physical features of Apert syndrome include craniosynostosis, turricephaly (a towerlike skull), a flat occiput, midface hypoplasia, ocular hypertelorism, proptosis, a parrot-beaked nose, maxillary hypoplasia, and mandibular prognathism (Narayan and Scott, 1991). In Apert syndrome, one of the characteristic features is that symmetrical syndactyly is present in all four limbs. Subcutaneous or osseous syndactyly always exists in the second through fourth digits, presenting as a large bony mass with a common nail. Partial separation may be present for the first and fifth digits.

The infant with triploidy will be severely growth restricted but may not have markedly dysmorphic features. Often infants with triploidy are mistakenly thought to have trisomy 18.

FETAL INTERVENTION

There are no fetal interventions.

SURGICAL TREATMENT

Affected children with syndactyly may require plastic surgery to improve their appearance. Consultation with a plastic or orthopedic surgeon is recommended because these children eventually require hand surgery to create a pincer grasp.

Patients affected with one of the acrocephalosyndactyly syndromes may require neurosurgical repair of the prematurely fused sutures during infancy (see Chapter 10).

LONG-TERM OUTCOME

Acrocephalosyndactyly syndromes are compatible with survival outside the womb, although the infant mortality rate is greater than 10% for Apert syndrome (Kim et al., 1986). Hydrocephaly is considered to be one of the more common associations in Apert syndrome. Approximately 48% of patients with Apert syndrome have normal or borderline intelligence (Narayan and Scott, 1991). There is no long-term outcome for triploidy because it is not compatible with extrauterine survival.

GENETICS AND RECURRENCE RISK

In general, triploidy is due to double fertilization and has a negligible recurrence risk. Apert syndrome is inherited as an autosomal dominant condition, with a 50% recurrence risk in affected individuals. Most cases represent a new mutation, possibly associated with increased paternal age (Tolorova et al., 1997). New mutations in Apert syndrome are exclusively paternal in origin (Maloney et al., 1996). Phenotypically normal individuals have given birth to more than one affected child, which implies that gonadal mosaicism exists for this condition (Parent et al., 1994). Patients affected with Apert syndrome have reproduced (Leonard et al., 1982; Narayan and Scott, 1991). Apert and Pfeiffer syndromes are associated with fibroblast growth factor receptor type 2 *(FGFR2)* mutations (see Chapter 10), so if the affected person has been genotyped, DNA diagnosis is possible in the first trimester in at-risk families (Chang et al., 1998).

First trimester prenatal diagnosis of disorders associated with syndactyly are also amenable to the diagnosis by fetoscopy (Ginsberg et al., 1994).

Carpenter and Fraser syndromes are both inherited as autosomal recessive conditions with a 25% risk of recurrence. Pfeiffer syndrome is an autosomal dominant trait with a 50% risk of recurrence. Synpolydactyly is inherited as an autosomal dominant condition, with a 50% recurrence risk. The disorder is due to expansion of polyalanine tracts within the gene. There is a genotype phenotype correlation in that the larger the expansion, the greater the number of limbs involved and more complete extent of digital duplication (Goodman, 2002).

Patients who have previously had affected fetuses or infants with syndactyly should have targeted sonographic studies in future pregnancies.

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106 CHAPTER Radial Aplasia

Key Points

- Defect occurs on the radial (formerly preaxial) side of the forearm. Findings may include absence or hypoplasia of the radius, absence or hypoplasia of the scaphoid and trapezium bones of the wrist, or abnormalities of the thumb and the first metacarpal.
- Radial deformities may be associated with hematologic abnormalities.
- Incidence is 1 in 30,000. Occurs bilaterally in 50% of cases.
- May be diagnosed as early as 14–15 weeks. Sonographically, a single forearm bone is seen with radial deviation of the hand.
- Differential diagnosis includes chromosome abnormalities, single-gene (dominant or recessive) disorders, teratogen exposure, and multiple congenital anomaly syndromes.
- Should exclude trisomy 18 by performing a karyotype.
- Delivery is recommended at a tertiary center to permit consultation with genetics, radiology, and orthopedics.
- Recurrence risk depends on underlying condition.

CONDITION

Radial aplasia is one manifestation of a spectrum of anomalies known as radial ray malformations. These may occur unilaterally or bilaterally, and either as isolated malformations or in association with other birth defects (Figure 106-1). In radial aplasia, the defect occurs on the radial (thumb) side of the forearm. Skeletal findings in radial ray malformations may include absence or hypoplasia of the radius, with associated absence or hypoplasia of the scaphoid and trapezium bones of the wrist, with or without first metacarpal and thumb abnormalities (Lamb, 1972; Brons et al., 1990).

Radial aplasia results from arrest of radial longitudinal development, which may be secondary to damage at the apical ectoderm of the limb bud occurring between 6 and 12 weeks of gestation. One hypothesis regarding its etiology is that radial aplasia may result from abnormal blood vessel development, which causes an abnormal gradient of nutrients important for the differentiation of mesenchyme into bone or muscle (Van Allen et al., 1982). In radial aplasia, bones as well as associated muscles, nerves, and joints may be affected. Other causes for the developmental arrest of the radius include maternal infectious agents and local biochemical abnormalities secondary to maternal diabetes or medication.

In many cases, a correlation exists between the specific type of radial deformity and associated hematologic abnormalities (Bay and Levine, 1988). For example, absence of the radius with presence of the thumb affects the platelets and is a characteristic finding in the thrombocytopenia–absent radius (TAR) syndrome. If both the radius and thumb are absent, the hematologic findings are more severe; aplastic anemia generally results (Bay and Levine, 1988).

INCIDENCE

The incidence of radial aplasia is approximately 1 in 30,000 livebirths (Brons et al., 1990; Sofer et al., 1983). The condition is bilateral in approximately 50% of cases (Bay and Levine, 1988).

SONOGRAPHIC FINDINGS

In radial aplasia, a single fetal forearm bone is identified, with acute radial deviation of the hand (Figure 106-2). The single forearm bone can be identified as an ulna by comparison

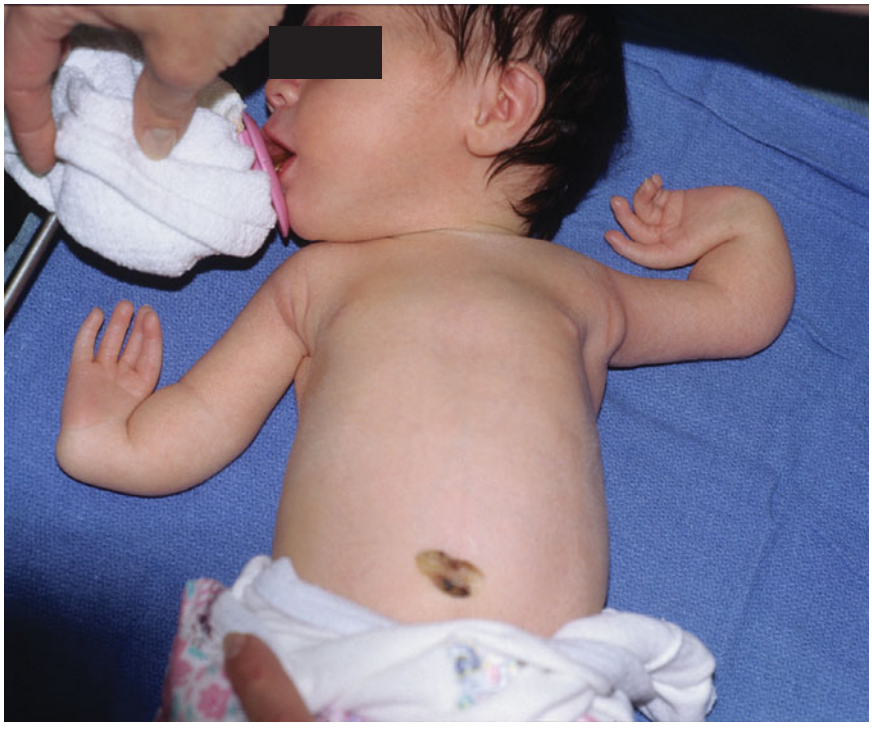

Figure 106-1 Postnatal photograph of a newborn infant with bilateral radial aplasia and absent thumbs.

with standard tables of ulnar lengths (Ylagan and Budorick, 1994). Published standards exist for normal humeral, radial, and ulnar bone lengths at different points in gestation (Jeanty et al., 1985). Detailed examination of the fetal extremities is not listed in current American College of Obstetricians and Gynecologists or American Institute of Ultrasound in Medicine (AIUM) guidelines for standard obstetric sonography (ACOG, 2008). However, examination of the extremities is critically important in the diagnosis of many genetic syndromes. The fetal limb buds may be seen sonographically as early as 8 weeks of gestation, with the limb articulations and digits becoming visible by 11 to 12 weeks of gestation (Bromley and Benacerraf, 1995).

The diagnosis of radial aplasia may be made as early as 14 to 15 weeks of gestation by noting the absence of the radius and the hand in varus position. Prolonged observation of the fetus will reveal that malposition of the hand persists during the entire sonographic examination. When the fetus moves its arms, the hand remains flexed but not rigid (Deschamps et al., 1992). More recently, three-dimensional ultrasound examination has been used to demonstrate radial agenesis in a male fetus with trisomy 18 (Huang et al., 2004).

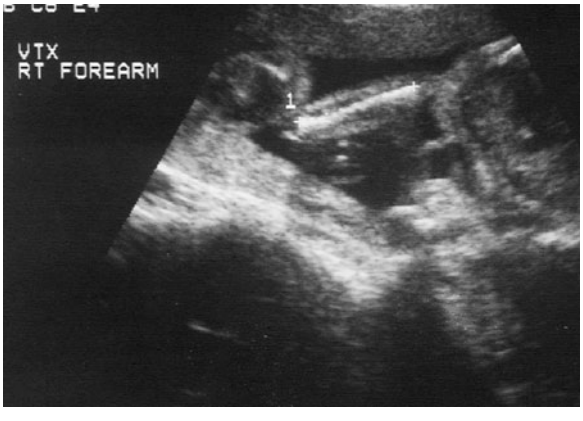

Figure 106-2 Prenatal sonographic image of a fetal right forearm, demonstrating the presence of a single bone, the ulna.

In one report, Meizner et al. (1986) described the prenatal diagnosis of an affected fetus with absence of the radius and thumb at 18 weeks of gestation. They noted shortening and bowing of the ulna. The fetal hands were clubbed and deviated laterally. An additional finding included crossed renal ectopy of the right kidney. The family history was notable for an affected father and sibling (Sofer et al., 1983; Meizner et al., 1986). In a retrospective study of seven affected fetuses and infants with radial aplasia diagnosed during the perinatal period at the University Hospitals of Amsterdam and Rotterdam, six affected patients were noted to have associated abnormalities of the central nervous system, gastrointestinal tract, kidneys, or heart (Brons et al., 1990). Three of these affected fetuses had trisomy 18. A high degree of perinatal lethality was noted in this report; however, there may have been bias of ascertainment. These authors recommended both longitudinal visualization and transverse scanning of the bones of the extremities to clearly delineate the ulna from the radius. They recommended that the best time for visualization and separate measurements of the radius and ulna was approximately 13 to 16 weeks of gestation. Many of the cases in this report were complicated by abnormalities in amniotic fluid, including both oligohydramnios and polyhydramnios. These authors emphasized, however, that special attention

should be paid to the central nervous system, heart, kidneys, vertebral column, and monitoring of fetal growth.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for conditions associated with radial aplasia is listed in Table 106-1. The conditions comprise four different categories: single-gene disorders, multiple congenital anomaly syndromes of unknown or sporadic cause, chromosomal abnormalities, and teratogen exposures. The most common chromosomal abnormality associated with radial aplasia is trisomy 18, although radial abnormalities are generally uncommon in trisomy 18 (Sepulveda et al., 1995). More commonly, a shortened radial ray is present. However, in one case of trisomy 18, upper limb defects (bilateral radial aplasia, and absent first metacarpals and thumbs) were the only sonographic abnormalities detected (Makrydimas et al., 2003). Although many authors list trisomy 13 as potentially being associated with radial aplasia, the much more common skeletal abnormality in trisomy 13 is polydactyly (see Chapter 129). In one report, a case of mosaic trisomy 22 was associated with radial aplasia (Dulitzky et al., 1981). In another case report, a translocation occurring between chromosomes 1 and 7 was associated with the presence of Wilms tumor and bilateral radial aplasia (Hewitt et al., 1991).

With regard to maternal teratogen exposure, valproic acid is the biggest concern (Verloes et al., 1990). Valproic acid is the most effective antiepileptic drug for simple petit mal seizures, which is the most commonly occurring type of epilepsy in women of childbearing age. Unfortunately, valproic acid is associated with a higher prevalence of fetal anomalies than other antiepileptic agents (Ylagan and Budorick, 1994). The risk of neural tube defects with valproic acid exposure during pregnancy is on the order of 1% to 2%. Valproic acid crosses the placenta, and the fetal serum concentration is greater than the maternal serum concentration. Limb anomalies have been reported in 47% to 65% of mothers exposed to valproic acid. These figures, however, include even minor abnormalities of the nails such as hypoplasia (Ylagan and Budorick, 1994).

In one case, a fetus with radial ray aplasia was described in a mother with a petit mal seizure disorder who took valproic acid from 2 to 8 menstrual weeks. After 8 weeks, when it was determined that she was pregnant, her therapy was changed to carbamazepine for the remainder of the pregnancy (Ylagan and Budorick, 1994). Multidrug therapy has been noted to be a primary factor associated with an increased incidence of malformations in offspring of women with epilepsy (Delgado-Escueta and Janz, 1992).

A complete family history is essential for any fetus diagnosed with radial ray aplasia. Several disorders characterized by autosomal dominant patterns of inheritance are associated with radial ray malformations. These include Holt–Oram syndrome, the acrorenal syndrome, and acrofacial dysostosis (Nager syndrome) (Paladini et al., 2003) (see Table 106-1). Many of the autosomal recessive conditions associated with radial aplasia are also associated with hematologic disturbances. The major disorders in this category include Fanconi anemia, thrombocytopenia–absent radius (TAR) syndrome, and Aase syndrome. In the TAR syndrome, thrombocytopenia results in symptomatic bleeding in more than 90% of affected cases during the first 6 months of life (Bhargava et al., 1972; Adeyokunnu, 1984; O'Flanagan et al., 1989). Cordocentesis results documenting the presence of thrombocytopenia will diagnose this condition (Boute et al., 1996; Shelton et al., 1999). The Baller–Gerold syndrome is distinguishable by the hallmark findings of craniosynostosis, short stature, and radial aplasia. In this condition, cases are divisible into two groups: those who do not have additional malformations and those who have a broad range of additional abnormalities. In Baller–Gerold syndrome, the chromosomes are normal and most patients are intellectually normal (Greitzer et al., 1974; Feingold et al., 1979; Anyane-Yeboa et al., 1980; Boudreaux et al., 1990; Galea and Tolmie, 1990). Juberg–Hayward syndrome is an autosomal recessive condition characterized by growth restriction, microcephaly, cleft lip and palate, and radial abnormalities (Couvreur-Lionnais et al., 2005). The acronym RAPADILINO stands for radial aplasia, patella absent, diarrhea, dislocated joints, little size/limb malformations, nose long, normal intelligence. To date, affected patients have been of Finnish ancestry (Kaariainen et al., 1989).

The finding of associated vertebral, cardiac, renal, or tracheoesophageal abnormalities may also lead to a presumed diagnosis of VACTERL association (Tongsong et al., 1999).

ANTENATAL NATURAL HISTORY

At 6 weeks of gestation, the upper limb buds are recognized as small bumps on the lateral side of the embryo's body. Embryonic mesenchyme induces a thickening of the covering ectoderm. This ectoderm secondarily induces mesenchymal differentiation. The proximal segment of the limb bud develops first (Deschamps et al., 1992). At 7 weeks the limb buds first become visible sonographically (Bromley and Benacerraf, 1995). At 8 weeks, the distal limb buds flatten to become the hand and foot plates. The limbs subsequently develop and flex. Development of the upper limb occurs approximately 2 days ahead of the lower limbs (Bromley and Benacerraf, 1995). By 9 weeks the fetal forearms can raise progressively above the shoulder level. The hands are often observed to cover the mouth and nose. At this point, however, sonographic differentiation of the digits is still not possible (Deschamps et al., 1992). At 10 weeks of gestation, posterior rotation of the upper limb occurs, and for the first time, individual digits can be identified. At 12 weeks, primary ossification centers of the long bones are present. By 14 weeks of gestation, the whole hand is fully formed and one can observe full movements of the fetal arm, including abduction, flexion, scratching, and movements toward the mouth. By 15 weeks of gestation, differentiation of the carpal

Table 106-1

Differential Diagnosis of Radial Aplasia

Condition	Associated Findings in Addition to Radial Aplasia	Mode of Inheritance
Single-Gene Disorders		
Aase syndrome	Cleft lip and/or palate, hypoplastic anemia	Autosomal Recessive
Acrofacial dysostosis (Nager syndrome)	Malar and mandibular hypoplasia, deafness, coloboma of lower eyelids	Autosomal Dominant
Acrorenal syndrome	Crossed renal ectopy, single kidney, ear malformations	Autosomal Dominant
Baller–Gerold syndrome	Craniosynostosis, short stature	Autosomal Recessive
Cornelia de Lange syndrome	Dwarfism, microcephaly, synophrys	Autosomal Dominant, X-linked
Fanconi anemia	Pancytopenia, microcephaly, hyperpigmentation, increased chromosome breakage	Autosomal Recessive
Holt–Oram syndrome	Cardiac abnormalities	Autosomal Dominant
IVIC (oculo-oto-radial syndrome)	Hearing impairment, external opthalmoplegia, thrombocytopenia, urogenital anomalies	Autosomal Recessive
Juberg–Hayward syndrome	Growth restriction, microcephaly, cleft lip and palate	Autosomal Recessive
Lacrimo-auriculo-dental-digital syndrome	Lacrimal duct stenosis, cupped external ear, dental anomalies	Autosomal Dominant
RAPADILINO syndrome	Absent patellae, dislocated joints, diarrhea, short stature, long nose	Autosomal Recessive
Roberts syndrome	Cardiac anomalies, cleft lip and/or palate, tetraphocomelia	Autosomal Recessive
Seckel syndrome	Dwarfism, microcephaly, mental retardation, prominent nose	Autosomal Recessive
Thrombocytopenia-absent radius (TAR)	Thrombocytopenia	Autosomal Recessive
Multiple anomalies, unknown cause		
Poland anomaly	Breast and chest wall deformities on affected side	Vascular accident
VACTERL association	Vertebral, anal, cardiac, tracheoesophageal, renal, and limb defects	Sporadic
Chromosomal abnormalities		
46,XY,t(1:7)(q42;p15)	Wilms' tumor	Chromosomal (familial)
Mosaic trisomy 22	Ectopic kidney, mental retardation	Post-meiosis nondisjunction
Trisomy 13	Polydactyly, central nervous system abnormalities, cardiac and renal abnormalities	Chromosomal
Trisomy 18	Intrauterine growth restriction, micrognathia, cardiac anomalies, clenched hand	Chromosomal
Teratogen exposure		
Thalidomide	Tetraphocomelia	Environmental
Valproic acid	Neural tube defects, vertebral and cardiac abnormalities	Environmental

bones is possible and individual phalanges are identifiable (Deschamps et al., 1992).

Any disruption in the process of limb development occurring between 6 and 12 weeks of gestation will result in a limb defect (Bay and Levine, 1988). Vascular differentiation may have a role in this process. The radial artery is the last major vessel of the arm to appear, at 39 days of embryonic life. The radial bone develops later than the ulna. The difference in timing may contribute to the increased frequency of radial versus ulnar defects observed in humans (Van Allen et al., 1982). Vasculogenesis precedes differentiation of the mesenchyme into muscle and bone. The formation of arteries does not require the presence of bone. Van Allen et al., (1982) described three different patterns of vascular abnormalities in spontaneously miscarried fetuses with radial aplasia. In type 1 cases, a single midline superficial vessel was observed, with no radial or ulnar artery. This pattern of malformation was characteristic of fetuses with acardia. In type 2 cases, absence of the radial artery was seen with or without persistence of the median artery. Other vessels were within normal limits. This pattern was observed in fetuses with multiple malformations of unknown cause. In type 3 cases, the radial artery was present but had an abnormal course. All other vessels were normal. This pattern was characteristic of TAR syndrome. These authors hypothesized that the morphogenesis of the entire limb was determined by a previously established pattern of blood vessels. They hypothesized that radial aplasia may be the result of abnormal vessel development. The early capillaries form a three dimensional network that gives the appearance of a humerus, radius, and ulna even before chondrogenesis ensues. The existing vasculature establishes gradients that are important in the determination of mesenchymal differentiation into bone or muscle. Therefore, it is not unreasonable to imply that abnormalities in vessel development will have important consequences for subsequent bone and muscle development.

FETAL INTERVENTION

There are no fetal interventions for radial aplasia.

MANAGEMENT OF PREGNANCY

Fetuses in which radial aplasia is ascertained need to have a detailed anatomic survey to specifically delineate the presence of other anatomic abnormalities. Areas of concern include the central nervous system, heart, vertebral column, gastrointestinal system, and kidneys. A complete family history should be obtained, ideally by a genetic counselor, to specifically rule out consanguinity, which may predispose the fetus to an autosomal recessive disorder. The parents should be examined for subtle malformations such as ear abnormalities (present in the acrorenal syndrome) or minor, clinically subtle hand abnormalities that may occur in the Holt–Oram syndrome. A history of teratogen exposure should be obtained from the mother, specifically with regard to valproic acid treatment during the pregnancy. Maternal diabetes should be ruled out. An amniocentesis should be performed to study the fetal karyotype. The most likely underlying chromosomal abnormality is trisomy 18. Microarray analysis should be considered to rule out the microdeletion on chromosome 1q21.1 that is associated with thrombocytopenia-absent radius syndrome (Klopocki et al., 2007). If Fanconi anemia is a consideration, karyotyping should be performed, with specific documentation of the presence of chromosomal breaks and the formation of quadriradial figures. To rule out Fanconi anemia, the chromosomes must also be studied after exposure to the clastogenic agent diepoxybutane. This is best performed by a specialty laboratory with experience in the prenatal diagnosis of Fanconi anemia.

In the setting of a positive family history for TAR syndrome, or to rule out associated hematologic abnormalities, consideration should be given to cordocentesis. Cordocentesis can provide both chromosome analysis and diagnosis of hematologic abnormalities. It is potentially useful in ruling out thrombocytopenia or early signs of aplastic anemia, such as an increased mean corpuscular volume for gestational age.

Consideration should be given to delivery of the infant by cesarean section because of the presence of bilateral flexion contractures at the elbow, which might result in dystocia. Delivery is recommended at a tertiary care center to permit early consultation with experts in clinical genetics, orthopedic surgery, and pediatric radiology.

TREATMENT OF THE NEWBORN

A complete physical examination is essential at birth. The newborn should be evaluated by individuals with experience in clinical genetics, pediatric orthopedic surgery, pediatric hematology, and pediatric radiology. Confirmatory skeletal radiography of the extremities should be performed (Figure 106-3). If a chromosome analysis was not performed prenatally, full-scale banded karyotyping with observation for chromosome breaks and a diepoxybutane study should be performed postnatally. A complete blood count with a differential and platelet counts should also be obtained to rule out Fanconi anemia, and TAR, and Aase syndromes. A subtle manifestation of aplastic anemia during the newborn period is an increased elevation in the mean cellular volume as compared with normal reference values for neonates.

SURGICAL TREATMENT

The child with radial aplasia will have displacement of the wrists and hand to the radial side of the ulna, producing a characteristic deformity (see Figure 106-1). This is initially

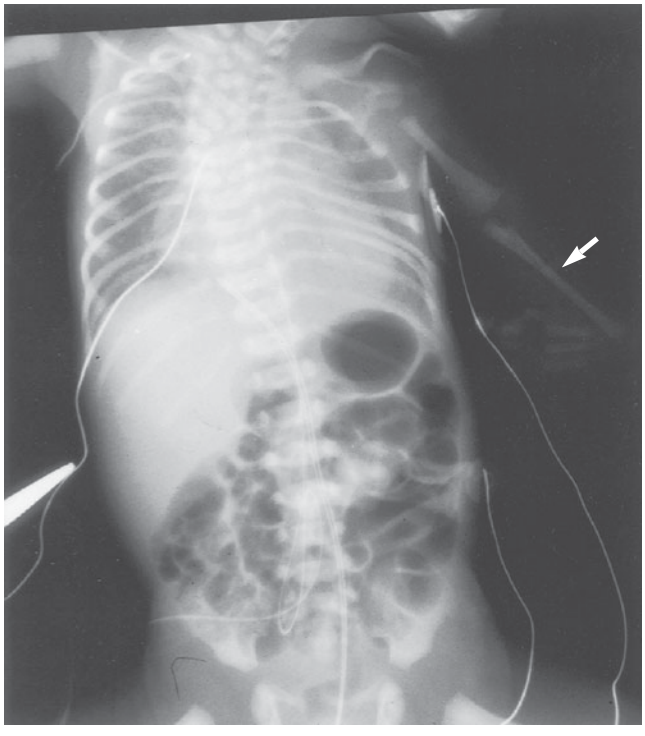

Figure 106-3 Postnatal radiograph of an infant with VATER association. Note the presence of vertebral malformations. The arrow indicates a single left forearm bone with clubbed hand.

correctable with manipulation by casts or by splinting. The soft tissues of the wrists can be tight and contracted on the radial side. This is generally due to the presence of a strong, fibrous band that replaces the absent radius. With subsequent long-bone growth, bowing of the ulna increases. Therefore, splinting is an essential part of the early treatment of radial aplasia (Lamb, 1972). The two digits on the ulnar side of the hand are almost always normal in appearance and function. The two digits on the radial side of the hand usually have some impairment in joint structure and function. Most affected children prefer to use the ulnar two digits for prehension (Lamb, 1972).

Surgical treatment depends on whether the affected patient has unilateral or bilateral radial aplasia. If the case is unilateral, the normal arm will be the functional one and the affected arm will serve only as an aid. In this case, the major goal is to improve the appearance of the affected arm. Functional outcome is a secondary consideration. In bilateral cases, the goal is to improve function to permit independent living. In general, treatment begins during the newborn period and operative intervention occurs within the first year of life. All therapies are designed to improve mobility, strength, and stability of the forearm and wrist, and to improve the dexterity of the hand and fingers (Bay and Levine, 1988). The four basic principles of treatment are (Lamb, 1972):

1. Prevent soft-tissue contractures by short casts or by creating splints for the patient to wear at night.
2. Excise the fibrous band that causes radial contractures.
3. Centralize the carpus over the ulna. This produces wrist stability with a limited range of wrist movement.
4. Pollicize the index finger (creating a thumb from the index finger by surgically migrating to the position of the thumb).

LONG-TERM OUTCOME

In one report, 10 patients were described with congenital anomalies of the radius diagnosed at birth. None of the cases were isolated. Two of the patients had TAR syndrome, 1 had VACTERL association, 1 had Holt–Oram syndrome, and 1 had Poland anomaly. All patients had concomitant abnormalities of the ulna. Four patients had associated congenital cardiac disease. Three patients had vertebral defects and 2 had abnormalities of the sacrum. Seven of the 10 cases were bilateral. Three patients had a positive family history and 2 were infants of diabetic mothers. Of the 10 patients, 5 required surgery: 3 had centralization of the carpus over the ulna, 1 had pollicization of the index finger, and 1 had local reconstructive hand surgery. In all 5 cases, the limb function improved to some degree (Bay and Levine, 1988).

GENETICS AND RECURRENCE RISK

The genetics and recurrence risk of radial aplasia depends on the underlying condition responsible for this bony abnormality. If a chromosomal abnormality was diagnosed, the recurrence risk for a condition such as trisomy 18 will be the maternal age–related risk or 1%, whichever is greater. If an unbalanced chromosomal abnormality was diagnosed, both parents need to be studied to determine whether a parental translocation was responsible for the unbalanced situation in the offspring. If a single-gene disorder was diagnosed, the recurrence risk will be 25% or 50%, depending on whether the condition is inherited as an autosomal recessive or autosomal dominant condition, respectively (see Table 106-1). The VACTERL association is considered to be sporadic, with a negligible recurrence risk. If maternal valproic acid exposure has been determined to be the underlying cause for the radial aplasia, consideration should be given to stopping the antiepileptic medication prior to conception after consultation with a neurologist. If necessary, medication can be restarted during the second trimester.

Thrombocytopenia-absent radius (TAR) syndrome has recently been shown to be the result of homozygosity for a common interstitial microdeletion of 200 kb of DNA on chromosome 1q21.1 using microarray analysis (Klopocki et al., 2007). If, following microarray analysis, a microdeletion is found in the fetus, parental studies should be performed to determine if the deletion is inherited or de novo. About 25% of TAR cases arise from de novo deletions.

In the event that the fetus or infant dies from associated malformations, a perinatal autopsy is strongly recommended to determine the underlying diagnosis.

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107 Clubfoot

CHAPTER

Key Points

- Positional abnormality of the fetal foot that results in it being fixed in adduction, supination, and varus, with concomitant soft-tissue abnormalities.
- Incidence is 1 in 1000 livebirths.
- Early amniocentesis (11–14 weeks of gestation) is associated with an increased incidence of clubfoot.
- Fetuses with clubfoot should be referred to a facility capable of performing detailed fetal sonographic anatomic evaluation. Such a targeted scan should include measurement of amniotic fluid volume, observation for presence of amniotic bands, masses or abnormalities that could crowd the fetus, and assessment of fetal movement.
- Associated abnormalities are seen in 23% to 61% of cases. More than 250 syndromes include clubfoot as one component.
- If associated anomalies are seen, consider obtaining a karyotype. If clubfoot is isolated, a karyotype is not needed.
- Treatment consists of stretching exercises, serial casting, and/or surgery. Surgery, if performed, is done at 2 to 12 months.
- Recurrence risk depends on whether a syndrome is present. If clubfoot is isolated, complete family history information is needed to quote a risk.

CONDITION

The term clubfoot refers to a positional abnormality of the fetal foot, resulting in it being fixed in adduction, supination, and varus, with concomitant soft-tissue abnormalities (Drvaric et al., 1989). The Latin term *talipes equinovarus* (*tali* = ankle, *pes* = foot, *equino* = horse, *varus* = bent inward) (abbreviated as TEV) is used interchangeably with clubfoot.

Two general categories of clubfoot are recognized. Intrinsic clubfoot describes a foot that is rigid at birth with marked atrophy, fibrosis, and abnormal bony relationships. This form of clubfoot is generally treated by surgical intervention. Extrinsic clubfoot refers to a foot that is flexible at birth, although bony relationships may be abnormal. This type of clubfoot may be corrected conservatively, with manipulation and stretching (Kawashima and Uhthoff, 1990).

Even today, the cause of clubfoot is not precisely known. Most investigators agree that clubfoot is the result of an intrauterine developmental deformity, although controversy exists as to whether the cause is primarily muscular or neurologic in origin. The chief anatomic abnormality is the deformity of the talus, which is smaller than normal. Plantar and medial deviation of the head and neck of the talus also exists. Bony malposition and subsequent development of contractures serve to keep the foot in a fixed position, resulting in forefoot adduction, midfoot supination, and hindfoot supination or equinus deformity (Drvaric et al., 1989). One hypothesis proposed for the cause of clubfoot involves a potential arrest in fetal development. The evidence for this relates to studies performed by Kawashima and Uhthoff (1990), who demonstrated that during normal embryologic development of the lower limb bud, the foot is first adducted in a position that resembles the clubfoot deformity at approximately 8 to 9 weeks of gestation (Figure 107-1) (Kawashima and Uhthoff, 1990). Movements of the fetal lower limb begin between 9 and 11 weeks of gestation. Thus, if neurologic or muscular abnormalities impede limb movement, the joints will eventually become stiff and contracted. Flexion of the fetal foot occurs to the point at which by 11 weeks of gestation it reaches a normal position (Kawashima and Uhthoff, 1990). Therefore, some investigators believe that anything that arrests development of the fetal foot at approximately 8 to 9 weeks will eventually result in a clubfoot deformity. Other theories regarding the cause of clubfoot include primary bony abnormalities, either intrinsic or because of exogenous forces acting on the bone, primary muscle imbalances, ligamentous contractures with fibrosis, peroneal nerve weakness, peroneal dorsiflexor

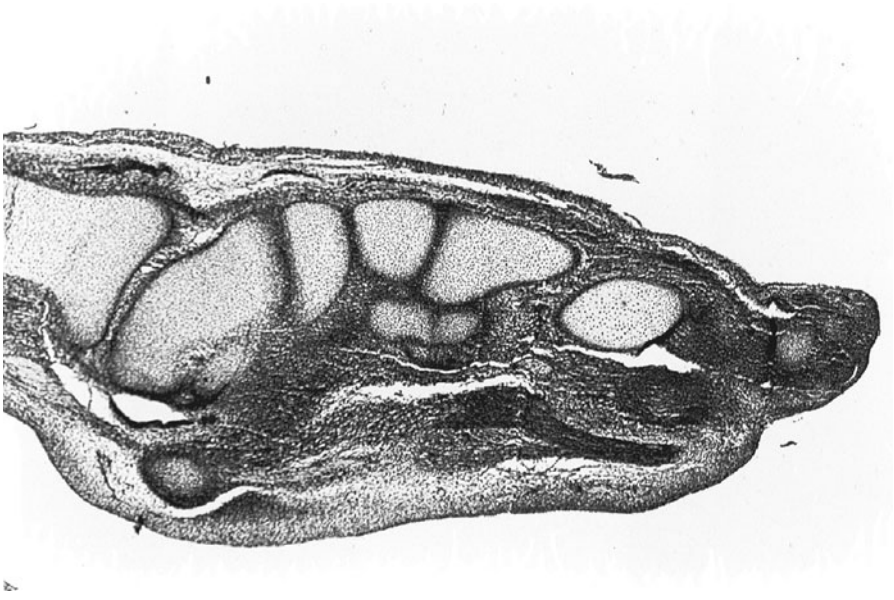

Figure 107-1 Sagittal section of the fetal foot and ankle at approximately 8 weeks of gestation, demonstrating the marked equinus angle in the normal developing early fetal foot. (*Courtesy of Professor Hans K. Uhthoff, Ottawa.*)

weakness, collagen abnormalities, neurogenic abnormalities, or the presence of subcellular retractile elements (Drvaric et al., 1989), excessive fibrous tissue resulting in a retracting fibrosis, contracture of myofibroblastlike cells enhanced by histamine release from mast cells, anomalous insertion of the Achilles tendon, tibialis anterior or peroneal tendons (Bleck, 1993), or relative delay in the growth of the tissues of the posteromedial foot and leg (Dietz, 1985).

Early amniocentesis, at 11 to 14 weeks of gestation, is associated with an increased incidence of clubfoot (Sundberg et al., 1997; Canadian Early and Mid-Trimester Amniocentesis Trial Group, 1998; Cederholm et al., 2005). Pediatric orthopedic surgeons who reviewed the data from the Canadian Early and Midtrimester Amniocentesis Trial group (CEMAT) concluded that the increase in foot deformities seen in the early amniocentesis group suggested that the period between 11 and 16 weeks is a vulnerable time (Tredwell et al., 2001). Weeks 12 to 16 are a period of maximal foot growth velocity and also a time when the fetus is developing coordinated movements, which are necessary for the development of normal synovial joints. During this period the amniotic fluid volume is also increasing exponentially. The orthopedists proposed that the loss or leakage of amniotic fluid induces a temporary fetal akinesia, which results in joint and limb deformities. The underlying mechanism is at present unknown, but has been speculated to be either a physical response or a result of maternal humoral and local microcellular response to the loss of amniotic fluid (Tredwell et al., 2001).

INCIDENCE

The incidence of clubfoot is approximately 1 in 1000 liveborn infants (Wynne-Davies, 1964a; Bakalis et al., 2002). In a study that encompassed a period of 45 years (1946–1990) in Malmö, Sweden, Danielsson (1992), determined that there were more than 128 cases of clubfoot in 137,614 livebirths that occurred over this period, yielding an incidence of 0.93 case per 1000 livebirths. In one study, the incidence of prenatally diagnosed clubfoot was 0.43% of cases (Treadwell et al., 1999). The incidence of clubfoot depends on the ethnic background of the patient. The highest incidence of clubfoot occurs in individuals of Polynesian ancestry, specifically Hawaiians and Maoris of New Zealand, who have an incidence of 6.5 to 7 cases of clubfoot per 1000 livebirths (Wynne-Davies, 1972; Drvaric et al., 1989). In all published studies, the incidence of clubfoot is more common in males than in females, with an approximate 2:1 ratio (Wynne-Davies, 1964a). In Danielsson's study, 79% of affected patients were males (the range in other studies was 64%–76%) (Danielsson, 1992). Forty-four percent of cases are bilateral (range 40%–59%) (Danielsson, 1992). When the clubfoot is unilateral, there is a slight right-sided predominance (Drvaric et al., 1989). The incidence of clubfoot is not increased with advanced maternal age (Yamamoto, 1979). In one study, a seasonal variation was demonstrated, with an increased incidence of milder forms of clubfoot occurring in babies born between November and April (Pryor et al., 1991).

SONOGRAPHIC FINDINGS

Prenatal sonographic detection of clubfoot is now common. The first prenatal diagnosis of clubfoot was reported in 1985 by Benacerraf and Frigoletto, who described five affected fetuses. Of the five fetuses, four had other associated malformations (Benacerraf and Frigoletto, 1985). These authors recommended examining the fetal lower extremity in a transverse section, in which the plantar aspect of the foot can be seen perpendicular to the shaft of the tibia (Figures 107-2 and 3). They made a diagnosis of clubfoot deformity when the foot was oriented in the same plane as the lower leg and

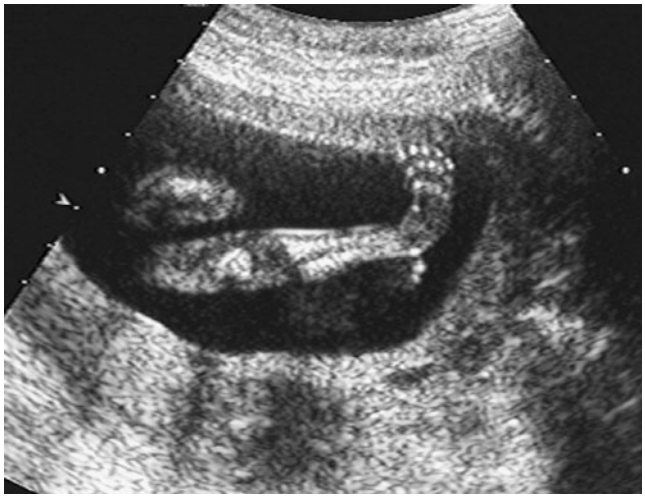

Figure 107-2 Prenatal sonogram demonstrating the visualization of the fetal foot and tibia and fibula in the same plane.

was visualized only in a plane or section parallel to the lower leg rather than perpendicular to it. Transvaginal sonography has been used to diagnose the presence of bilateral clubfeet in a female fetus at 13 weeks of gestation (Bronshtein and Zimmer, 1989). In this case, the family history was notable for maternal congenital hip dysplasia and a maternal uncle with orthopedic problems in one of his ankles during infancy. This case highlights what has been noted previously in a genetic epidemiologic study of clubfoot: A high frequency of associated connective tissue disorders, such as hernia, congenital hip dislocation, and generalized joint laxity are observed in families that have at least one affected member (Wynne-Davies, 1964a).

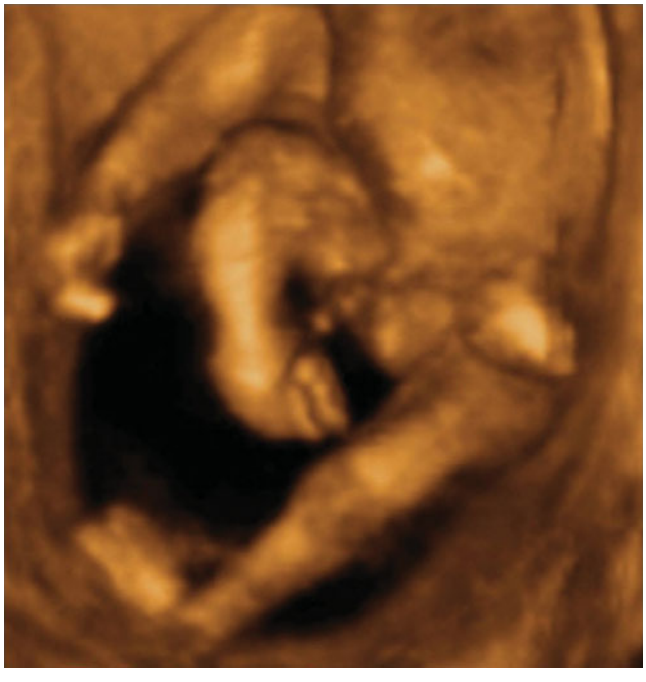

Figure 107-3 Three-dimensional surface rendered image of a fetus at 24 weeks of gestation showing bilateral clubfoot.

The presence of a clubfoot deformity may not be apparent on an early sonographic scan. For example, intrauterine progression of a clubfoot deformity was demonstrated concurrent with the worsening of hydrocephalus observed by transvaginal scanning over a period between 11 and 16 weeks of gestation (Bronshtein et al., 1992). Similarly, in a fetus with trisomy 18, early scans performed at 14 and 17 weeks of gestation did not reveal the presence of a clubfoot deformity (Bar-Hava et al., 1993). At 21 weeks of gestation, multiple sonographic abnormalities, including clubfoot, were easily observed.

The targeted anatomic scan for a fetus with clubfoot should include measurement of amniotic fluid volume; observation for the presence of amniotic bands; detailed observation for the presence of masses within the uterus that could result in an abnormal, fixed position of the fetus; evidence for uterine abnormalities that might similarly crowd the fetus, resulting in a positional deformation; and a careful observation for the presence of associated anomalies.

Using this approach, a number of studies have looked at outcome for fetuses diagnosed with clubfoot (see Table 107-1). The relatively high percentage of associated anomalies (23%–62%) reflects the fact that most of these studies were performed in high-risk referral centers. Studies involving large numbers of liveborn infants quote a 10% incidence of associated anomalies (Yamamoto, 1979). Also of note is the fact that there is a significant false-positive rate for the diagnosis of clubfoot (Bar-On et al., 2005; Mammen and Benson, 2004). While three-dimensional sonography (see Figure 107-3) is not usually needed to make or clarify the diagnosis of clubfoot, in one case it was used to help a couple visualize the problem and better understand it (Mohammed and Biswas, 2002).

DIFFERENTIAL DIAGNOSIS

Most cases of clubfoot are isolated and idiopathic. When considering the differential diagnosis, it is important to determine whether this is a familial trait, part of a syndrome, or as a result of a positional deformity. More than 250 nonchromosomal syndromes include clubfoot as one component (Rebbeck et al., 1993) (Table 107-2). Chromosomal abnormalities that are associated with clubfoot deformity include trisomy 18 (Bar-Hava et al., 1993) and deletion of chromosomes 18q, 4p, 7q, 9q, and 13q. Possible causes of positional deformity include uterine constriction due to a multiple gestation, large uterine fibroid, or severe oligohydramnios. Consideration must also be given to underlying neuromuscular disorders in the fetus, including neural tube defects, spinal muscular atrophy, muscular dystrophy, and arthrogryposis multiplex congenita (see Chapter 101). Dominantly inherited Mendelian disorders, such as Freeman–Sheldon syndrome, can be associated with clubfoot. Similarly, recessively inherited syndromes such as Smith–Lemli–Opitz, Larsen, and multiple pterygium (Ramer et al., 1988) can all be associated with clubfoot. Some of the skeletal dysplasias, for example, diastrophic dysplasia

Table 107-1

Clubfoot: Characteristics of Prenatally Diagnosed Cases

Study	Number of Fetuses with Clubfoot	Percent Bilateral	Mean age at Diagnosis (wk)	Percent Associated with Anomalies	Percent with No or Mild Treatment (Less than Casting)
Katz et al., 1999	13	69	23.6	23	0
Tillett et al., 2000	14	64	20	NG	21
Bakalis et al., 2002	107	60	18–23	48	NG
Mammen and Benson, 2004	87	52	22.2	62	NG
Bar-On et al., 2005	51	61	22.1	39	NG

NG, not given in article.

(Gollop and Eigier, 1987) are also associated with the presence of clubfoot (see Chapter 93).

The presence of clubfoot has also been reported after in utero treatment of maternal tetanus with tubocurarine. This finding has been duplicated experimentally in chickens. Clubfoot has also been documented following failed abortion attempts using sodium aminopterin (Drvaric et al., 1989).

ANTENATAL NATURAL HISTORY

The antenatal natural history for a lower extremity affected by a clubfoot deformity includes atrophy of the leg, resulting from a decrease in the size of the individual muscle fibers. Tendon sheaths in the affected extremity are frequently thickened, especially around the peroneal and tibialis posterior tendons. Eventually, during fetal life, the joint capsules become contracted at the ankle, subtalar, talonavicular, and calcaneocuboid joints (Bronshtein et al., 1992). Involved ligaments eventually become contracted. Contractures of the fascial planes and plantar fascia may also occur. The end result is that in cases of unilateral clubfoot, the entire lower limb may be shorter than the normal limb on the affected side.

There is no evidence for increased loss of pregnancy in cases of isolated clubfoot. When the clubfoot deformity is part of a more generalized syndrome, there may be an increased chance of spontaneous pregnancy loss.

MANAGEMENT OF PREGNANCY

When a diagnosis of fetal clubfoot is made antenatally, referral to a center with expertise in targeted fetal anatomy scanning is indicated. We recommend that associated abnormalities, oligohydramnios, and uterine deformities be specifically ruled out. We also recommend consultation with a genetic counselor or medical geneticist, who can obtain a complete family history and examine the parents for evidence of discrepancies in leg length and width. The presence of associated anomalies may suggest an underlying syndromic diagnosis. Controversy exists about whether to offer genetic amniocentesis for fetal karyotype when the clubfoot is isolated (Benacerraf, 1986). In one study, follow-up of 68 fetuses identified prenatally with clubfoot showed that four had abnormal karyotypes: 47, XXY, 47, XXX, trisomy 18, and trisomy 21 (Shipp and Benacerraf, 1998). However, the two fetuses with trisomy 18 and 21 had additional abnormal sonographic findings, so the clubfoot was not isolated. As described in Chapters 135 and 136 on the XXY and XXX syndromes, clubfoot is not considered part of the phenotype associated with these karyotypes. In another study performed at Tufts-New England Medical Center, we reviewed 51 cases of prenatally diagnosed isolated clubfoot (Malone et al., 2000). No cases of aneuploidy were found on either fetal karyotype evaluation or newborn physical examination. Our findings and subsequently, those of others (Bakalis et al., 2002; Mammen and Benson, 2004) suggest that invasive testing for fetal karyotype is not necessary if the fetal anatomy has been studied by an appropriately detailed sonographic anatomy survey and found to be otherwise normal.

In a study performed at the Royal Women's Hospital, Melbourne, 17 fetuses were diagnosed with isolated clubfoot (Woodrow et al., 1998). Sixteen of the seventeen had a normal karyotype and the remaining case was phenotypically normal. Six infants did not have clubfoot at birth, two infants did not require further treatment, and nine infants required casting, orthotics, and/or surgery. All infants had excellent results at 2 years of age.

Table 107-2

Conditions Associated with Clubfoot

Type of Condition	Pattern of Inheritance
Chromosome Abnormalities	Chromosomal
Neuromuscular Disorders	
Meningomyelocele	Multifactorial
Amyoplasia congenita	Sporadic
Arthrogryposis multiplex congenita	Many etiologies
Moebius sequence	Sporadic
Pena Shokeir phenotype	Many etiologies
Skeletal Dysplasias	
Campomelic dysplasia	Autosomal recessive
Diastrophic dysplasia	Autosomal recessive
Chondrodysplasia punctata, rhizomelic	Autosomal recessive
Ellis-van Creveld syndrome	Autosomal recessive
Single-gene Disorders	
Escobar syndrome	Autosomal recessive
Multiple pterygium syndrome	Autosomal recessive
Freeman–Sheldon syndrome	Autosomal dominant
Hecht syndrome	Autosomal dominant
Larsen syndrome	Autosomal recessive and dominant
Smith–Lemli–Opitz syndrome	Autosomal recessive
Meckel–Gruber syndrome	Autosomal recessive
Zellweger syndrome	Autosomal recessive

If the clubfoot is an isolated abnormality, there is no indication for delivery at a tertiary care hospital. Similarly, cesarean section should be performed only for standard obstetric indications. The parents may benefit from antenatal consultation with a pediatric orthopedic surgeon, who can counsel them regarding the expected treatment for the condition.

FETAL INTERVENTION

There is no fetal intervention for clubfoot.

TREATMENT OF THE NEWBORN

For the fetus diagnosed antenatally with clubfoot, we recommend that a complete and detailed physical examination be performed during the newborn period. We also recommend consultation shortly after birth with a pediatric orthopedic surgeon. Initial therapy consists of gentle stretching and manipulation of the affected foot or feet, followed by taping, casting, or a Denis Browne splint, which consists of adhesive strapping of shoes to a metal plate that is rotated laterally and attached to a transverse bar. The infant corrects the foot abnormality by constant kicking, which forces the foot into eversion and dorsiflexion (Bleck, 1993). With conservative management, the clubfoot that results from uterine deformation will be corrected in most cases. In cases that are due to an underlying neurologic or neuromuscular disorder, approximately one-third to one-half of cases will be corrected with physical manipulation (Drvaric et al., 1989). Casting of the foot prevents further tightening of contracted structures prior to surgery. Other authors have described even more optimistic results from conservative management. In one clinic's experience, satisfactory functional results were achieved in 89% of cases by manipulation and serial application of casts, supported by limited operative intervention (Ponseti, 1992). This author suggested that a successful nonoperatively treated clubfoot results in much better long-term function than the successfully surgically treated foot (Ponseti, 1992).

Some authors recommend obtaining an anteroposterior radiograph of the foot (Bleck, 1993). In the newborn, one can visualize only the ossification centers of the major tarsal bones, but not the key indicator of prognosis, the navicular ossification center. Other authors recommend that magnetic resonance imaging (MRI) may be more helpful to study the foot anatomy (Downey et al., 1992). MRI produces excellent images of the tendons, cartilage, and bone in the infant's hindfoot. In one study, the T_2-weighted image was demonstrated to be useful in delineating articular surfaces, but the intermediate weighting image gave the best overall image of the cartilaginous structures. Downey et al. (1992) studied the feet of 10 infants with clubfoot by MRI. This was the first study to look in great detail at the relationships between the bones in the in vivo setting. These authors observed medial angulation of the talar neck and rotation of the calcaneus with the anterior portion of the calcaneus shifting medially and the posterior portion of the calcaneus shifting laterally. They thought that the primary problem in clubfoot was a talar head and neck deformity, which resulted in the anterior calcaneus following the deformed anterior talus, thus causing a pivot about the interosseous ligament so the posterior calcaneus is forced laterally (Downey et al., 1992).

SURGICAL TREATMENT

Many different surgical approaches have been described for the treatment of clubfoot. In many ways, however, little has changed since Felix Würtz, a Basel surgeon, published the following treatment for clubfoot in 1563: "It hapneth that a child is born with crooked feet . . . Let no man be neglective if his child be thus crooked, as not to ask counsel about it; though all be not recovered which are in such cases, yet many

are cured, if not perfectly, yet may they be mended in some sort. Observe whether that joint both lie and turn easily to the place where it should be, then bind it that way, and cure it" (Würtz, cited in Dunn, 1992). All authors agree that the initial management should be nonoperative with manipulation and casting. The optimal age for initial surgical intervention is 3 to 6 months (Drvaric et al., 1989). There appears to be no advantage for surgery performed at less than 2 months of age. Ideally, however, surgery should be performed at less than 12 months of age because up to this time, the tarsal bones are still cartilaginous. Thus, maximal potential for remodeling of the joint still remains. The goal of surgery is that the patient ends up with a functional, pain-free, plantigrade foot with good mobility and no calluses and no need for modified shoes (Ponseti, 1992). Precise surgical goals consist of accurate bone realignment, resulting in talonavicular articulation and proper alignment of the bimalleolar axis with normal range of motion. Most surgical techniques consist of soft-tissue release with lengthening of the tendons. Some authors use wires to stabilize the talonavicular and talocalcaneal joints (Drvaric et al., 1989). In one approach, the contracted joint capsules are cut, the tendons are lengthened, and the bones are repositioned correctly in one stage. Specifically, this consists of a posterior ankle capsulotomy and tendon lengthenings to correct the equinus deformity, and capsulotomy of the talonavicular joint with posterior tibial tendon lengthening to shift the navicular bone laterally onto the head of the talar neck to correct the varus deformity (Bleck, 1993).

LONG-TERM OUTCOME

Prospective parents of a fetus with isolated clubfoot should be counseled that successful results of treatment, consisting of complete correction and no recurrence of the deformity with manipulation, serial casting, or surgery, varies from 60% to 95% of cases (Bleck, 1993). A good clinical prognosis exists for a female infant with a unilateral clubfoot, clinical evidence at birth of increased joint laxity, or an age at diagnosis and treatment of less than 9 months. A relatively poorer prognosis exists for an infant older than 9 months of age at the time of diagnosis and treatment. Also, the presence of a deep medial crease in the plantar arch because of a cavus deformity or evidence of marked atrophy of the leg on the affected side indicate an underlying neurologic or neuromuscular disorder.

Prospective parents should be counseled that eventual correction can be achieved with manipulation and surgery in the majority of cases, although recurrences will occur in some. Surgery is generally successful for most patients who require operative intervention, but 25% of cases may require revision surgery (Atar et al., 1992). Prospective parents should also be counseled that in unilateral cases, the corrected clubfoot will remain smaller than the normal foot. Similarly, the circumference of the calf on the affected side will be smaller than that of the contralateral calf. This will be variable in severity but will persist into adult life (Bleck, 1993; Ponseti, 1992). In general, children with corrected clubfeet can participate in almost all athletic activities and there appears to be no long-term apparent functional disability.

To document long-term outcome for patients with clubfoot, Wynne-Davies (1964b) reported on her clinical outcome studies of 84 patients (representing 121 feet) at age 10 through 35 years of life. This study was performed to determine residual disability and deformity in patients with clubfoot. These individuals were treated with casting, splinting, Denis Browne shoes with a cross bar, and eventual surgical correction if conservative management failed. She concluded that very few of these patients limited their activities because of the clubfoot. Extremely few of the patients reported any symptoms at all. Only after extensive questioning, the commonest complaint was the presence of calluses on the lateral border of the affected foot or feet. In unilateral cases, some patients had shortening of the affected leg, which on an average was 2.5 cm shorter than the contralateral leg. Nearly all the patients with the unilateral deformity had a smaller foot on the affected side (average difference 2.5 cm), but interestingly, the patients did not buy shoes of unequal size. Dr. Wynne-Davies also measured the extent of the equinus deformity, which was measured as the distance between the heel and the ground when the tibia was vertical. In 51 of 121 feet studied, there was greater than a 1.25-cm distance, but this was not described as a practical problem for the patient when the individual was wearing shoes. Overall, this long-term study indicated that there was very little residual morbidity associated with the clubfoot deformity (Wynne-Davies, 1964b).

GENETICS AND RECURRENCE RISK

The traditional teaching has been that clubfoot is inherited as a multifactorial trait (Yamamoto, 1979) or as polygenic inheritance with a threshold effect (Wynne-Davies, 1972). Evidence for the presence of a genetic background effect was demonstrated in one large-scale study of twins, in which the incidence of clubfoot was compared between monozygous and dizygous twins. In 4 of 134 (2.9%) dizygotic twins, there was concordance of the clubfoot deformity. This was greatly increased above the background incidence of 0.1% in the general population. In the monozygous twins, there was an even higher incidence of both twins being affected, 13 of 40 (32.5%) twins. Because of the increased incidence in monozygous as opposed to dizygous twins, genetic factors must have a cause in the inheritance of clubfoot; however, the trait cannot be solely genetic or the incidence in monozygous twins would have been closer to 100% (Wynne-Davies, 1972).

Using complex segregation analyses, Rebbeck et al. (1993) demonstrated that the probability of having idiopathic clubfoot was explained by Mendelian segregation of a single gene with two different alleles in the population, plus effects of other unmeasured factors shared by siblings (Rebbeck et al., 1993). This study suggests that a search for an underlying DNA abnormality in a single gene as the molecular basis of the disorder is warranted.

At present, the appropriate recurrence risk counseling for parents is as follows: If both parents are normal, and the initially affected fetus or child was male, the risk for a subsequent sibling to be affected is 2%. If both parents are normal and the original affected fetus or child was female, the risk for a subsequently affected sibling is higher, in the order of 5%. However, if one parent has a clubfoot deformity and one previous fetus or child has been affected with clubfoot, the risk for a subsequent sibling to be affected is 25% (Wynne-Davies, 1972). The appropriate prenatal diagnostic method for detection of clubfoot is antenatal sonographic examination.

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Umbilical Cord Abnormalities

108 CHAPTER

Key Points

- A variety of umbilical cord abnormalities may be sonographically detected, including short cord, lack of coiling, and cystic and vascular malformations.
- Sonographic examination of the cord should include counting the number of vessels, Doppler studies, notation of coiling, and observation of the presence of cysts, masses, and vascular malformations.
- Umbilical cord diameter increases with age.
- The major consideration in the differential diagnosis is to determine if cord abnormality is isolated or associated with anomalies or aneuploidy.
- The umbilical cord grows by tension generated by fetal movement. Short cords are associated with trisomy 21 and neuromuscular abnormalities.
- Other findings associated with aneuploidy include lack of coiling, umbilical vein varix, aneurysms, and pseudocysts. Abnormal umbilical cord diameter measurements are not currently thought to be accurate markers of aneuploidy.

CONDITION

A variety of umbilical cord abnormalities may be detected by prenatal sonography. These conditions include a short cord, lack of coiling, umbilical cord ulceration, a knot in the umbilical cord, umbilical artery hypoplasia, supernumerary vessels, and a variety of cystic and vascular malformations (Table 108-1) (Persutte and Hobbins, 1995). The most common abnormality, single umbilical artery, is discussed in Chapter 109.

INCIDENCE

An absolutely short cord (≤35 cm at term) occurs in 0.78% of pregnancies (Skupski et al., 1992). A relatively short cord (≤54 cm at term) occurs in 16.8% of pregnancies (Skupski et al., 1992). Noncoiled umbilical vessels occur in 4.3% (38 of 394 pregnancies) (Strong et al., 1993). Umbilical cord ulceration is a rare abnormality. Four umbilical vessels have been noted in 0.4% (2 of 444 pregnancies) (Aokio et al., 1997). Umbilical artery hypoplasia occurs in 1.9% of pregnancies (6 of 310 high-risk patients) (Sepulveda et al., 1992). A knot occurs in the umbilical cord in 0.3% to 2.1% of pregnancies (Sepulveda et al., 1995). Vascular malformations are rare. Tumors of the umbilical cord are extremely rare.

SONOGRAPHIC FINDINGS

Sonographic examination of the umbilical cord includes documentation of the number of vessels, Doppler velocimetry studies, and observation of coiling and looping of the cord (Figure 108-1). The umbilical cord is routinely examined in three locations: at the insertion site in the anterior abdominal wall of the fetus, at some point along the cord to determine

Table 108-1

Abnormalities of the Umbilical Cord

- Umbilical cord
  - Abnormal length and diameter
  - Neoplasms
    - Thrombosis
    - Hemangioma
    - Hematoma
    - Teratoma
  - Edema
  - Distortional abnormalities
    - Loops
    - Knots
    - Torsions
    - Twists
- Vascular malformations
  - Abnormal vessel number
  - Abnormal vascular spiraling
  - Umbilical cord varix
  - Umbilical artery aneurysm
  - Persistent right umbilical vein
- Wharton jelly
  - Aberrations in amount
  - Mucinous degeneration
- Other
  - Allantoic duct cysts
  - Omphalomesenteric duct cysts
  - Varix of the umbilical cord
  - Urachal cyst
  - Omphalocele
  - Gastroschisis

Source: Persutte WH, Hobbins J. Single umbilical artery: a clinical enigma in modern prenatal diagnosis. Ultrasound Obstet Gynecol. *1995;6:216-229.*

the number of vessels, and at the segment floating within the cavity during assessment of amniotic fluid volume (Sepulveda et al., 1995). The umbilical cord diameter can be measured. Its diameter increases with gestational age (Ghezzi et al., 2002; Rembouskos et al., 2004). An increased umbilical cord diameter was originally thought to be a marker for aneuploidy (Ghezzi et al., 2002) but this finding was disproven in a later study (Rembouskos et al., 2004).

In extremely short umbilical cords, the cord appears to be stretched tautly across the uterine cavity (Skupski et al., 1992). Color Doppler has greatly enhanced the ability to visualize abnormalities in the umbilical cord (see Figure 108-1) (Jauniaux et al., 1989). Vascular abnormalities include umbilical artery aneurysm (Siddiqui et al., 1992), umbilical vein varix (Estroff and Benacerraf, 1992; Mahony et al., 1992;

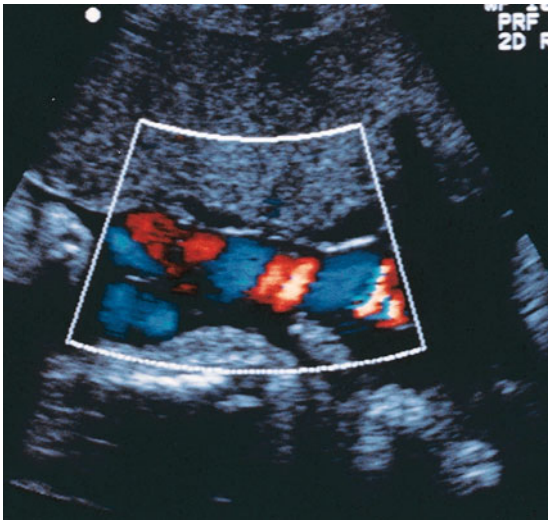

Figure 108-1 Color Doppler velocimetry studies showing the normal coiling of the umbilical cord.

Rahemtullah et al., 2001), and persistent right umbilical vein (Jeanty, 1989; Hill et al., 1994; Wolman et al., 2002). The distance between spirals (helixes) in the umbilical cord can be measured. Normally, this distance is 2 to 2.5 cm. If the distance decreases to less than 2 cm between helixes, acute torsion of the cord is possible (Collins et al., 1993). Umbilical cord knots are difficult to identify prospectively; as many as 72% of cases are missed on third trimester color Doppler studies (Sepulveda et al., 1995). Umbilical cord cysts are found in 3% of pregnancies in the first trimester; most resolve spontaneously (Weissman and Drugan 2001). When found in the second or third trimester, there is a high incidence of structural or chromosome abnormalities (Smith et al., 1996).

DIFFERENTIAL DIAGNOSIS

The major consideration in the differential diagnosis is to determine if the umbilical cord abnormality is a false-positive finding and if it is associated with other sonographically detectable abnormalities. Many umbilical cord abnormalities are descriptive. Sensitivity and specificity of diagnosis is improved by the concurrent use of Doppler studies. The differential diagnosis for umbilical cord tumors includes hemangioma and teratoma. The differential diagnosis for cystic masses includes true cysts, pseudocysts, allantoic cysts, and hematomas.

ANTENATAL NATURAL HISTORY

The umbilical cord grows by tension generated by fetal movement; Naeye (1985) has measured umbilical cord lengths of 35,779 singletons and determined that a length of at least 32 cm is necessary to prevent traction on the cord during a

vaginal delivery. The majority of umbilical cord growth occurs during the first and second trimesters. Walker and Pye (1960) demonstrated that the cord length of premature babies is similar to that of full-term babies. The mean length of a full-term newborn's umbilical cord is 60 cm. There is no correlation between umbilical cord length and parity, maternal age, maternal weight or height, presence of preeclampsia, or fetal gender, weight, length, or presenting part (Walker and Pye, 1960).

Short umbilical cords are significantly associated with low IQ values and neuromuscular abnormalities, such as the fetal akinesia deformation sequence or severe infantile spinal muscular atrophy (Naeye, 1985). In infants with trisomy 21, the average cord length is 45 cm; this is almost certainly due to in utero hypotonia, which causes decreased tension to be placed on the cord (Moessinger et al., 1982). Miller et al. (1981) studied infants with a variety of pathologic conditions. They found the most dramatically shortened cords in patients with early evidence of amnion rupture. Restriction of fetal movement was thought to be the effect of tethering by amniotic bands. The lesser degree of cord shortening seen in renal agenesis is presumably due to a later decrease in intrauterine space resulting from oligohydramnios.

Experiments on rat fetuses have confirmed that early oligohydramnios affects the cord length by limiting the intrauterine environment. Conversely, rat fetuses allowed to develop in the maternal abdomen have a cord length that is 147% greater than controls. In addition, rat fetuses with movements that are paralyzed by curare have cord lengths that are 85% of control values (Moessinger et al., 1986; Skupski et al., 1992).

Umbilical vascular coiling is established by the end of the first trimester. A sinistral (counterclockwise) rotation is present in most pregnancies (Fletcher 1993; Strong et al., 1993). The absence of the normal coiling of the umbilical cord has been identified as an antenatal risk factor for perinatal morbidity and mortality. This finding occurs in approximately 5% of fetuses (Weissman and Drugan, 2001). This so-called straight cord may be structurally weaker and more susceptible to external tension (Figure 108-2) (Strong et al., 1993). Lacro et al. (1987) noted a 10% stillbirth rate in newborns with absent umbilical coiling. In a prospective study, 38 fetuses with noncoiled umbilical vessels were identified. As compared with normal control fetuses, the noncoiled group had a significantly increased incidence of intrauterine death, preterm delivery, repetitive intrapartum fetal heart rate decelerations, operative delivery for fetal distress, meconium staining, and anatomical and karyotype abnormalities (Strong et al., 1993). Other investigators have calculated an umbilical coiling index by dividing the total number of coils observed by the length of the cord. Subjects with below the 10th percentile and above the 90th are defined as hypocoiled and hypercoiled, respectively. In one study of 635 placentas from deliveries of at least 24 weeks of gestation, Rana et al. (1995) found that subjects with hypocoiled cords had increased rates of fetal heart rate disturbances and interventional delivery. Fetuses with hypercoiled cords had a higher rate of premature delivery as compared with fetuses with normally coiled cords.

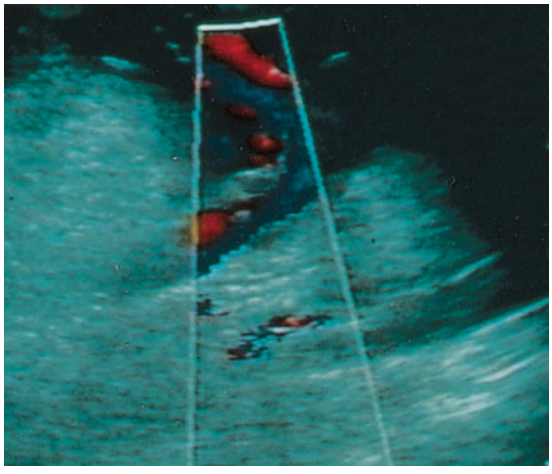

Figure 108-2 Color Doppler velocimetry studies demonstrating a straight umbilical cord. Note the lack of coiling as compared with Figure 108-1.

To our knowledge, prospective outcome studies related to a sonographic finding of umbilical cord ulceration have not yet been performed. The finding is described here because of the reported association of umbilical cord ulceration noted at birth with intestinal atresia in two infants and one stillborn fetus (Bendon et al., 1991). In two of three cases, severe in utero hemorrhage occurred from the ulcers. The intestinal atresia is the primary problem, with umbilical cord ulceration occurring as a secondary phenomenon. The following hypotheses have been proposed to account for this association: vascular reactivity, gastric reflux, and epithelial abnormalities (Bendon et al., 1991).

In one case report, an infant with four umbilical arteries and one vein was described (Beck and Naulty, 1985). The infant had multiple medical problems due to *Escherichia coli* sepsis, but ultimately survived with age-appropriate growth and development. There were no associated anomalies. The patient was shown to have triplication of the right umbilical artery.

Umbilical artery hypoplasia has been defined as a difference in the diameter between both umbilical arteries of $\geq$2 mm (Sepulveda et al., 1992). The umbilical arteries have discordant blood flow velocity waveforms in the absence of associated placental pathology. In one series, two of six affected fetuses with this finding had an adverse perinatal outcome (Dolkart et al., 1992). In another case report with pathologic follow-up of the umbilical cord after birth, no adverse effect was seen (Sepulveda et al., 1992).

Vascular malformations of the umbilical cord, such as umbilical vein varix and umbilical artery aneurysm, are rare. In one study, 25 cases of intra-abdominal umbilical vein varix were identified over a 10-year period (Rahemtullah et al., 2001). Follow-up information was available for 23 of 25 cases. Eleven of 23 cases (48%) had normal pregnancies, full-term deliveries, and normal neonatal outcome.

Three cases (13%) had preterm deliveries, and one had Kell isoimmunization. In the remaining 8 cases (35%) structural anomalies were identified. These authors recommended that a thorough fetal survey and echocardiogram be performed if an umbilical vein varix is observed. Umbilical artery aneurysm is potentially lethal in utero because of umbilical venous compression (Siddiqui et al., 1992). One case of umbilical cord aneurysm and arteriovenous fistula has been reported in association with a case of trisomy 18 (Berg et al., 2001). Cystic dilatation of the umbilical vein has been variously associated with both an increased incidence of in utero death (Mahony et al., 1992) and a normal outcome (Estroff and Benacerraf, 1992). Umbilical cord cysts develop from the remnants of the allantois or omphalomesenteric duct (Weissman and Drugan, 2001). They are usually located near the fetal insertion end of the cord and range from 4 to 60 mm in size. Pseudocysts have no epithelial lining and represent localized edema of Wharton's jelly (Kiran et al., 2003). Allantoic cysts originate from an extra-abdominal urachal system (Bunch et al., 2006).

MANAGEMENT OF PREGNANCY

When a short cord is diagnosed, detailed level II sonography is indicated to look for evidence of oligohydramnios, amniotic bands, body wall defects, neuromuscular abnormalities, and arthrogryposis. A short cord in the setting of abnormalities such as increased nuchal translucency measurement and a decreased ratio of femur to foot length may suggest trisomy 21. Fetuses with noncoiled umbilical cords may also be at increased risk for aneuploidy. In one study of 48 consecutive liveborn neonates with noncoiled umbilical vessels, four cases of trisomy (8.3%) and one case of mosaic trisomy (2.1%) were identified (Strong, 1995). However, all of these fetuses had additional anomalies detected with sonography. It is therefore unclear at present whether amniocentesis is indicated for an isolated noncoiled cord. Umbilical cord pseudocysts, if detected with other sonographic abnormalities, are strongly associated with aneuploidy and, in particular, trisomy 18 (Sepulveda et al., 1999). A good general principle is that cord abnormalities, when found with other malformations, are an indication for fetal karyotyping.

Fetuses with noncoiled umbilical cords are at increased risk for perinatal mortality; antepartum testing and early documentation of fetal lung maturity should be considered. Fetuses with evidence of bowel atresia should be monitored for sonographic findings consistent with umbilical cord ulceration and resulting hemorrhage.

Fetuses with vascular malformations such as umbilical artery aneurysm may need to be delivered as soon as lung maturity is present (Siddiqui et al., 1992). Fetuses with true knots of the umbilical cord ascertained prenatally may need to be delivered by cesarean section. In one report, a fetus with umbilical cord cysts underwent magnetic resonance imaging (MRI). The MRI suggested that the diagnosis was actually an allantoic cyst (Bunch et al., 2006).

FETAL INTERVENTION

There are no fetal interventions for umbilical cord abnormalities.

TREATMENT OF THE NEWBORN

For all of the conditions discussed here, a thorough physical examination of the newborn and the umbilical cord is indicated. Umbilical cord hemangioma is associated with a high (40%) incidence of vascular birthmarks, such as port wine stains (Daniel-Spiegel et al., 2005).

In the setting of the short cord, observation of newborn movements, with particular emphasis on the neurologic examination, is important. Tables of normal values exist for the measurement of periumbilical skin length in the newborn. These standards are useful in the neonatal diagnosis of syndromes that include umbilical dysmorphology (O'Marcaigh et al., 1992).

SURGICAL TREATMENT

There is no surgical treatment indicated for most umbilical cord abnormalities. Allantoic cyst is the prenatal presentation of patent urachus (Van der Bilt et al., 2003; Bunch et al., 2006). These umbilical cords are often grossly edematous from reflux of urine via the patent urachus. The cord is usually clamped well away from the edematous segment of cord. In the newborn period, the urachus can be surgically closed and cord remnants debrided away. Postnatally, the patent urachus needs to be resected.

LONG-TERM OUTCOME

The isolated umbilical cord findings do not need follow-up. Follow-up is indicated for associated abnormalities.

GENETICS AND RECURRENCE RISK

None of the conditions discussed, when present as an isolated finding, have implications for familial recurrence.

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109 CHAPTER Single Umbilical Artery

Key Points

- Single umbilical artery (SUA) is one of the most common malformations found in humans.
- Color Doppler techniques have improved the ability to visualize vessels in the umbilical cord, particularly in a transverse view through the fetal bladder.
- Detailed sonographic evaluation of fetal anatomy is important to determine if SUA is isolated or associated with other anomalies.
- If isolated, fetal echocardiography should be considered, but karyotype is not indicated.
- If associated anomalies are present, fetal karyotype should be obtained, with trisomy 18 being the most commonly associated aneuploidy.
- SUA is associated with increased perinatal mortality, increased chance of IUGR, and slightly increased prematurity.
- If no additional anomalies are detected, postnatal urologic radiographic investigations are not indicated.
- For surviving infants, long-term prognosis is excellent.

CONDITION

The normal umbilical cord consists of three vessels—two arteries and one vein (Figure 109-1). Single umbilical artery (SUA) refers to the congenital absence of one of the arteries. The condition was originally described by Vesalius in 1543, Fallopio in 1561, and by Bauhin in 1621 (Persutte and Hobbins 1995). The first prenatal diagnosis of SUA was made in 1980 (Jassani et al., 1980). SUA is one of the most common malformations found in humans.

INCIDENCE

In prospective studies of liveborn infants, the incidence of SUA varied from 344 in 39,773 (0.9%) to 782 in 372,066 (0.48%) births in the United States National Collaborative Perinatal Project and a Swedish registry, respectively (Froehlich and Fujikura, 1973; Lilja, 1991). The incidence was twofold to threefold higher in a survey of spontaneous abortuses (Byrne and Blanc, 1985). In most studies, the gender distribution is equal. In the National Collaborative Perinatal Project, SUA was noted in 1.2% of white infants and 0.5% of black infants (Froehlich and Fujikura, 1973). SUA occurs three to four times more frequently among twins than among singletons (Heifetz, 1984). Other conditions associated with SUA include maternal diabetes, epilepsy, hypertension, antepartum hemorrhage, polyhydramnios, and oligohydramnios (Persutte and Hobbins, 1995). Maternal age does not affect the incidence of SUA (Prucka et al., 2004).

SONOGRAPHIC FINDINGS

The normal umbilical cord contains two arteries and one vein (see Figure 109-1). SUA is easiest to demonstrate in cross-sectional images (Figure 109-2) but may also be visualized longitudinally (Figure 109-3). The most reliable technique is to use color Doppler to visualize both umbilical arteries on either side of the dome of the fetal bladder. SUA can be diagnosed in the first trimester (Rembouskos et al., 2003). Fetuses with SUA have an increased diameter of the umbilical artery with no changes in diameter of the umbilical vein (Sepulveda et al., 1996b). There may, however, be a reduction in the amount of Wharton's jelly present (Raio et al., 1999). Color flow Doppler techniques have greatly enhanced the ability to both visualize the umbilical cord (Jauniaux et al., 1989; Catanzarite et al., 1995) and measure its flow velocity waveforms (Sepulveda et al., 1996a; Ulm et al., 1997). Fetal umbilical arteries should be examined near the bifurcation of

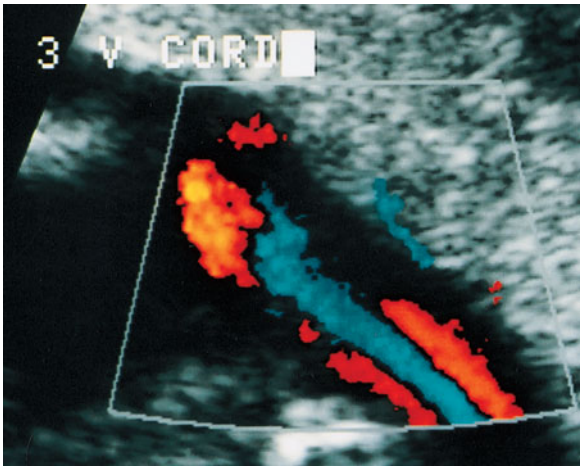

Figure 109-1 Color Doppler study demonstrating the presence of two umbilical arteries and one umbilical vein.

the aorta with color Doppler (see Figure 109-3). The intrafetal portion of the umbilical arteries may be easier to visualize than the free-floating cord. A SUA may have a diameter that approaches that of the umbilical vein. Diagnosis of SUA by sonography has a sensitivity of 64.9%, a specificity of 99.9%, and a positive predictive value of 64.9% (Jones et al., 1993).

Rembouskos et al. (2002) performed a prospective study in 717 consecutively examined singleton pregnancies undergoing chorionic villus sampling at 11 to 14 weeks to determine the incidence of SUA. Color flow mapping was used to visualize the umbilical arteries on either side of the bladder. The overall incidence of SUA was 5.9% (42/712), which is much higher than the liveborn incidence. In the 21 fetuses with SUA and normal chromosomes, 6 had major anomalies detected, including omphalocele, diaphragmatic hernia, megacystis, and scoliosis. In the 21 fetuses with SUA and an abnormal karyotype, 14 had trisomy 18, 5 had trisomy 21, and 2 had other abnormalities. In this study, the incidence of associated chromosome abnormalities in fetuses with SUA

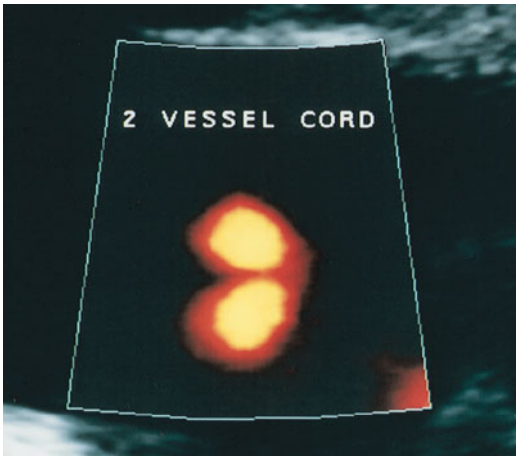

Figure 109-2 Cross-sectional view of the umbilical cord demonstrating the presence of two umbilical vessels.

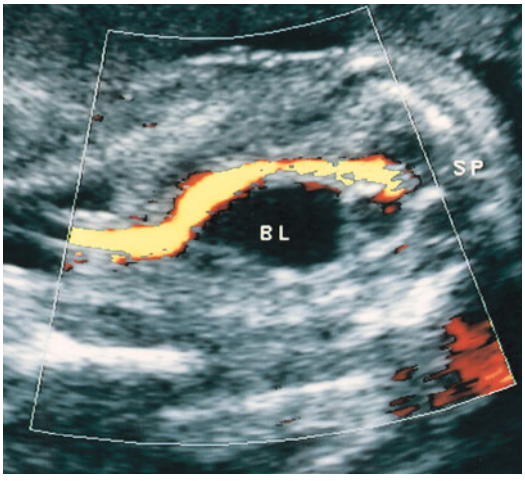

Figure 109-3 Longitudinal view of the umbilical arteries at the bifurcation of the aorta, demonstrating the presence of a single umbilical artery. BL, bladder.

was much higher (50%) than in studies performed in the second and third trimester.

DIFFERENTIAL DIAGNOSIS

Nonvisualized second umbilical artery should be ruled out. False-positive diagnoses are more likely to occur before 22 weeks of gestation.

ANTENATAL NATURAL HISTORY

The umbilical arteries develop from the allantois, a diverticulum of the yolk sac. Between 3 and 5 weeks of gestation, a transient common umbilical artery is normally present in all embryos, replacing a plexus of arteries around the allantois. Subsequently, the common umbilical artery becomes shorter, and right and left umbilical arteries advance within the body stalk (Monie, 1970). SUA can result from one of three mechanisms: primary agenesis of one of the definitive umbilical arteries, a secondary atrophy or atresia of a previously normal umbilical artery, or persistence of the common allantoic or umbilical artery. In several prospective studies of fetuses with antenatally diagnosed SUA, the left artery was absent 69% to 73% of the time. In addition, the presence of multiple anomalies and/or abnormal karyotype were seen more commonly with absence of the left artery (Abuhamad et al., 1995; Geipel et al., 2000). However, other studies do not demonstrate an association between the side of the single artery and presence of malformations (Blazer et al., 1997; Budorick et al., 2001). The risk of perinatal mortality increases when SUA is diagnosed. Much of this is due to the presence of associated congenital malformations. Independent of the presence of malformations, several studies have documented an increased chance of intrauterine growth restriction (with an

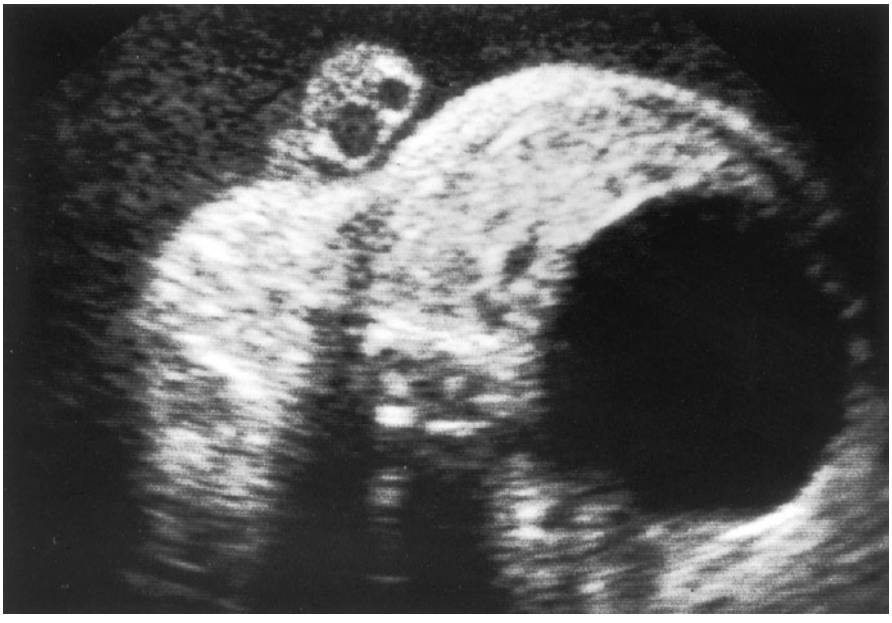

Figure 109-4 Cross-sectional view of an umbilical cord with two vessels, in association with a large simple ovarian cyst. *(Courtesy of Dr. Wolfgang Holzgreve.)*

average birth weight of less than 2.5 kg) and preterm delivery (with an average gestation of 35.9 weeks) for infants with SUA (Heifetz, 1984; Leung and Robson, 1989; Lilja, 1991; Jones et al., 1993; Gornall et al., 2003).

MANAGEMENT OF PREGNANCY

The key determinant of prognosis for a fetus with SUA is to detect the presence of associated anomalies (Table 109-1, Figure 109-4) (Csecsei et al., 1992). For this reason, detailed fetal sonographic evaluation is recommended for all cases of SUA. Some groups advocate fetal echocardiographic studies even for cases of apparently isolated SUA (Abuhamad et al., 1995; Persutte and Hobbins, 1995; Budorick et al., 2001). Other groups have not found abnormalities on echocardiography in fetuses with isolated SUA (Gossett et al., 2002). In newborns, the incidence of major malformations ranges from 17.5% to 44% (Leung and Robson, 1989). These malformations affect a wide variety of organ systems, including heart, brain, skeletal, gastrointestinal, and genitourinary systems (Table 109-1) (Froehlich and Fujikura, 1989). In fetuses with SUA, prospective studies indicate a 26% to 31% chance of associated structural anomalies (Abuhamad et al., 1995; Chow et al., 1998). The distribution of anomalies in fetuses differs from newborns in that genitourinary and cardiac anomalies are more common (Martínez-Payo et al., 2005) (Table 109-1). The documentation of associated anomalies puts the fetus at a significant risk for a chromosomal abnormality (Byrne and Blanc, 1985; Nyberg et al., 1991, 1988); prenatal karyotyping is recommended. Trisomies 13, 18, and 21 and Turner syndrome have all been reported in association with SUA (Saller et al., 1990), although trisomy 18 is the most common aneuploidy (Rembouskos et al., 2003). If the karyotype is normal but there are associated anomalies, consideration should be given to planned delivery in a tertiary care center capable of newborn resuscitation and sophisticated syndrome diagnosis. If the karyotype reveals a diagnosis incompatible with prolonged extrauterine survival, the infant can be delivered in a community hospital with pediatric consultation and

Table 109-1

Anomalies Associated with a Single Umbilical Artery

Fetuses*	**Newborn Malformations†**
Multiple congenital anomalies	Skeletal system
ADAM sequence	Cardiovascular
Urogenital malformations	Urogenital
Craniospinal malformations	Gastrointestinal
Meckel syndrome	Central nervous system
Nonimmune hydrops	Respiratory tract Integumentary (skin)

* *Data from Csécsei K, Kovacs T, Hinchliffe SA, Papp Z. Incidence and associations of single umbilical artery in prenatally diagnosed, malformed, midtrimester fetuses: a review of 62 cases.* Am J Med Genet. *1992;43:524-530.*

† *Data from Froehlich LA, Fujikura T. Follow-up of infants with single umbilical artery.* Pediatrics. *1973;52:6-13 and Leung AK, Robson WL. Single umbilical artery: a report of 159 cases.* Am J Dis Child. *1989;143:108-111.*

an antenatal agreement not to perform heroic resuscitative efforts.

Many questions arise regarding the appropriate subsequent management of a fetus with an isolated SUA. On the basis of our experience and review of the literature, prenatal karyotype is not indicated once the detailed fetal anatomical survey reveals no other abnormalities (Nyberg et al., 1991; Budorick et al., 2001). Many groups now recommend that fetal echocardiography be performed as part of the evaluation of SUA. In addition, careful attention to fetal growth during the third trimester with serial ultrasound examinations is warranted. (Nyberg et al., 1991; Khong and George, 1992; Catanzarite et al., 1995).

FETAL INTERVENTION

There are no fetal interventions indicated for SUA.

TREATMENT OF THE NEWBORN

As discussed above, the newborn with associated malformations needs delivery, treatment, and diagnostic evaluation in a tertiary care center. The newborn with isolated SUA needs no immediate treatment other than a thorough physical examination.

A somewhat controversial area has been the need for a renal workup following the demonstration of SUA. This originated from a study by Feingold (1964), who performed intravenous pyelography on 24 children with isolated SUA at birth and found genitourinary tract abnormalities in one-third of cases. These findings were confirmed by an Irish study of 112 infants who were found to have isolated SUA at delivery. In this study, 19 infants were documented with abnormal postnatal renal sonography; 8 of 112 (7.1%) had significant persisting abnormalities, with vesicoureteric reflux found in five infants (Bourke et al., 1993). The morphologic abnormalities found in three patients included megaureter, pelvic kidney, and dilation of the collecting system. These anomalies, however, would be visible on a contemporary sonographic scan. Therefore, if a detailed fetal sonographic anatomic evaluation is normal, we do not advocate confirmatory postnatal renal screening in the absence of clinical symptoms.

A more recent meta-analysis of 37 postnatal studies on SUA published over a 40-year period confirms this approach (Thummala et al., 1998). The mean incidence of associated anomalies in liveborn infants with SUA was 27% (range 22%–32%). Additional urologic studies were performed on 204 infants with apparently isolated SUA. Of these, 33 (16.2%) had some form of renal anomaly, but more than half of these anomalies were minor or self-limiting. Thummala et al. concluded that current data do not justify extensive urologic radiographic investigations for asymptomatic newborns with isolated SUA.

SURGICAL TREATMENT

There is no surgical treatment for isolated SUA. If a genitourinary abnormality is detected, consultation with a pediatric urologist is warranted. Postnatal follow-up may include renal sonography and voiding cystourethrography.

LONG-TERM OUTCOME

For surviving infants, the prognosis is excellent. The National Collaborative Perinatal Project noted that growth-restricted infants caught up with their peers (Froehlich and Fujikura, 1973). Intelligence was in the normal range. The one surprising finding was the increased incidence of inguinal hernias in survivors.

GENETICS AND RECURRENCE RISK

Isolated SUA is thought to be a developmental anomaly, with no risk for familial recurrence. In the setting of associated anomalies, it is important to make an accurate diagnosis to permit proper genetic counseling.

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Cervical Teratoma

110
CHAPTER

Key Points

- Cervical teratomas are often large, solid, and cystic lesions with calcifications.
- Polyhydramnios occurs from esophageal compression, predisposing to preterm delivery.
- Vascular malformations, including lymphangiomas and arteriovenous malformations, are the main differential diagnoses.
- The EXIT procedure is indicated to secure the airway.
- Delivery should occur in a tertiary center with expertise in the EXIT procedure.
- Cervical teratomas can arise in the thyroid. Postoperative hypothyroidism or hypoparathyroidism can occur.
- Close follow-up after resection is indicated, as residual or recurrent teratoma is at risk for malignant transformation.

CONDITION

Cervical teratoma is a rare tumor. Approximately 300 congenital cases have been described (Riedlinger et al., 2005; Oka et al., 2007). Since the first prenatal diagnosis of fetal cervical teratoma in 1978, there have been only a few dozen published reports of cervical masses detected in utero (Schoenfeld et al., 1978; Patel et al., 1982; Suita et al., 1982; Kagan, 1983; Thurkow et al., 1983; Trecet et al., 1984; Pearl et al., 1986; Cunningham et al., 1987; Hitchcock et al., 1987; Holinger and Birnholz, 1987; Roodhooft et al., 1987; Jordan and Gauderer, 1988; Kelly et al., 1990; Zerella and Finberg, 1990; Baumann and Nerlich, 1993; Liechty et al., 1997; O'Callaghan et al., 1997).

As in other teratomas, cervical teratomas are composed of tissues foreign to their normal anatomic sites. All three germ layers are represented within the tumor. Neural tissue is the most common histologic component, with cartilage and respiratory epithelium also observed (Schoenfeld et al., 1982). Thyroid tissue occurs in 30% to 40% but it is uncertain whether this represents actual involvement of the gland or ectopic thyroid tissue (Jordan and Gauderer, 1988). Theories regarding the origin of cervical teratoma include derivation from totipotential germ cells or abnormal development following cleavage of monozygous twins with fetus in feta (Ashley, 1973; Hitchcock et al., 1987).

INCIDENCE

Cervical teratomas are rare with an incidence ranging from 1 in 20,000 to 1 in 40,000 livebirths (Azizkhan et al., 1995). Cervical teratomas account for 3% to 6% of teratomas (Azizkhan et al., 1995, Jordan and Gauderer, 1988). There is no apparent relationship to maternal age or parity (Hitchcock et al., 1987). Unlike other teratomas, males and females are equally affected (Batsakis et al., 1964; Tapper and

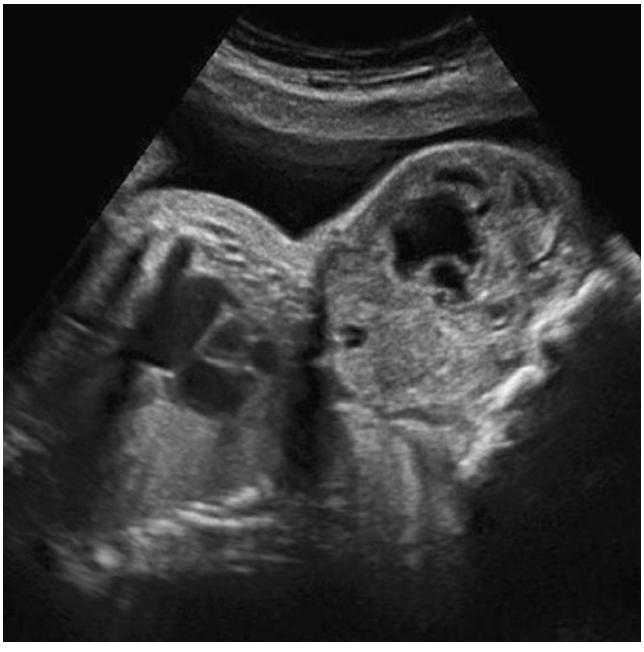

Figure 110-1 Sagittal image demonstrating cervical teratoma. Note the solid and cystic areas.

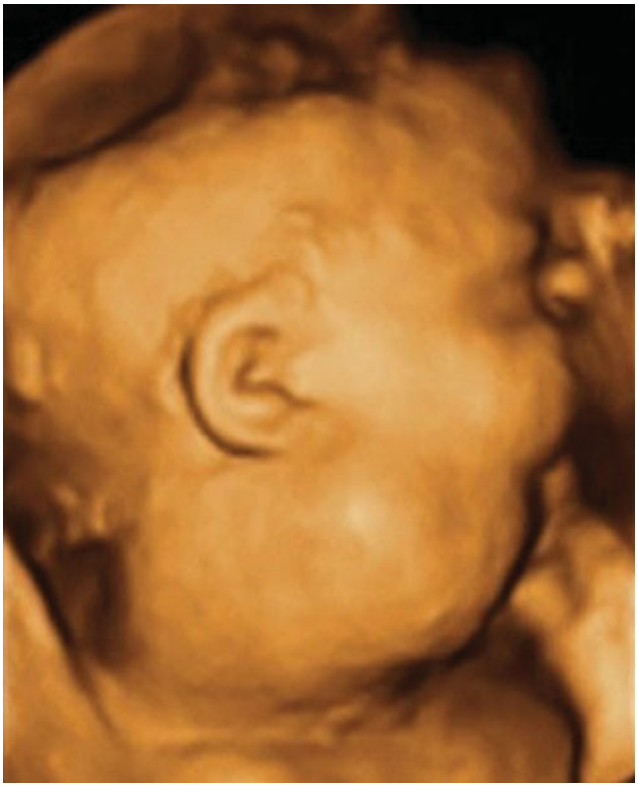

Figure 110-2 3D image revealing a mass arising from the right side of the fetal face.

Lack, 1983) and there is no racial predilection (Suita et al., 1982).

SONOGRAPHIC FINDINGS

On ultrasound examination, cervical teratomas are typically asymmetric, unilateral, mobile, and well demarcated (Figures 110-1 to 110-3). Most are multiloculated, irregular masses with solid and cystic components (Figure 110-1). As many as 50% have calcifications present (Gundry et al., 1983; Kelly et al., 1990). Calcifications may be difficult to appreciate on ultrasound examination and are more easily seen on plain radiographs (Goodwin and Gay, 1965; Hajdu et al., 1966; Suita et a1., 1982). Calcifications, when present in a partially cystic and solid neck mass, are virtually diagnostic of cervical teratoma (Gundry et al., 1983).

Cervical teratomas are usually large and bulky, typically measuring 5 to 12 cm in diameter (Silberman and Mendelson, 1960; Batsakis et al., 1964; Liechty et al., 1997; Liechty and Crombleholme, 1999; Crombleholme and Albanese, 2001). Tumor masses greater than the size of the fetal head have also

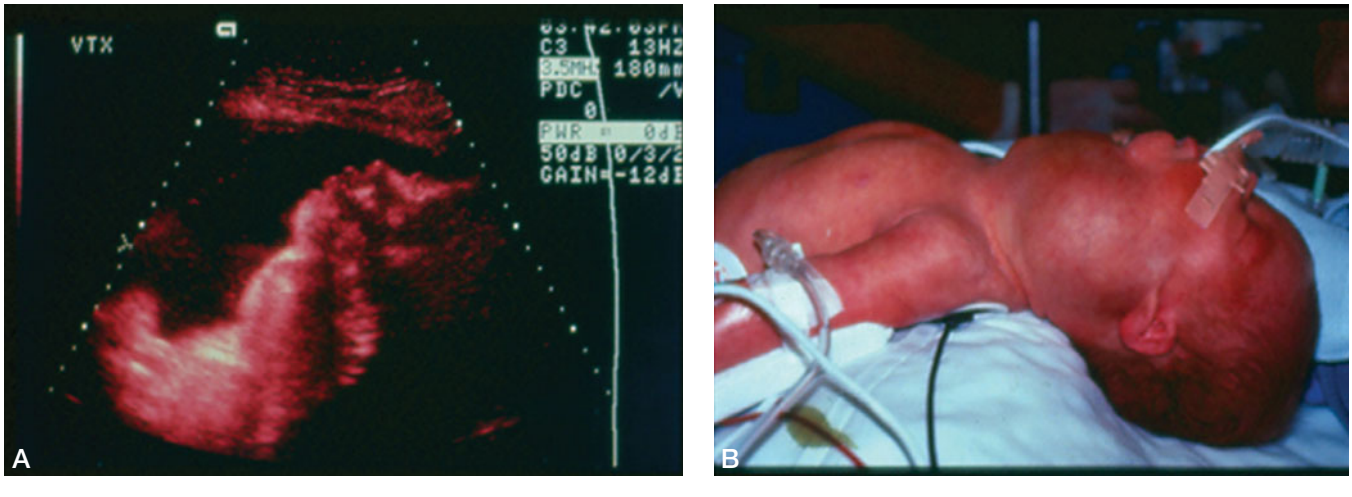

Figure 110-3 **A.** Prenatal sonographic image of a fetus in sagittal section demonstrating a complex cervical mass resulting in hyperextension of the neck due to a cervical teratoma. This has been referred to as the "flying fetus" sign, as the head extension is similar to that observed in ski jumpers when they fly off the ski jump. **B.** Postnatal appearance of the same patient.

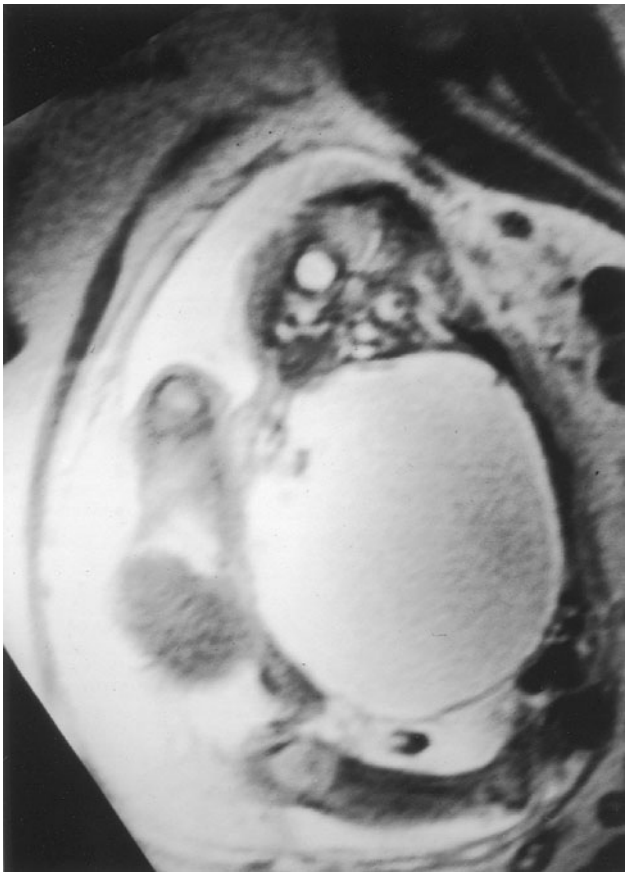

Figure 110-4 Fetal magnetic resonance image (MRI) showing a giant cervical teratoma with a huge cystic component. The cervical teratoma was larger than the fetus. *(Reprinted, with permission, from Liechty KW, Crombleholme TM, Flake AW, et al. Intrapartum airway management for giant fetal neck masses: the EXIT procedure (ex-utero intrapartum treatment). Am J Obstet Gynecol. 1997;177:870-874.)*

been reported (Figure 110-4) (Batsakis et al., 1964; Owor and Master, 1974; Jordan and Gauderer, 1988). These tumors usually extend to the mastoid process and body of the mandible, superiorly displacing the ear. Inferiorly they can extend to the clavicle and suprasternal notch or extend into the mediastinum. Posteriorly, they can extend to the anterior border of the trapezius. Involvement of the oral floor, protrusion into the oral cavity (epignathus), and extension into the superior mediastinum have also been noted in cervical teratomas (Jordan and Gauderer, 1988).

Polyhydramnios will complicate 20% to 40% of the prenatally diagnosed cases and is more commonly observed in large tumors (Bale, 1949; Lloyd and Clatworthy, 1958; Hajdu et al., 1966; Trecet et al., 1984). Polyhydramnios is thought to be due to esophageal obstruction, as has been demonstrated by contrast amniography (Rosenfeld et al., 1979; Mochizuki et al., 1986). An empty stomach may be the first sonographic clue to esophageal obstruction from cervical teratoma (Rosenfeld et al., 1979; Suita et al., 1982). Other anomalies have been reported in association with cervical teratomas, including one case each of chondrodystrophia fetalis and imperforate anus (McGoon, 1952). Hypoplastic left ventricle and trisomy 13 have also been reported in association with cervical teratoma (Gundry et al., 1983; Dische and Gardner, 1987), as has agenesis of the corpus callosum (Goldstein and Drugan, 2005). Mandibular hypoplasia may also be seen as a direct result of mass effect on the developing mandible (Liechty et al., 1997).

The fetus with a large cervical teratoma often has a marked extension of the neck due to mass effect. The cervical teratomas are deeper than the strap muscles of the neck, thus causing severe compression of the larynx, trachea, and esophagus. As noted above, esophageal compression results in polyhydramnios, and compression of the larynx and trachea can result in not only deviation and distortion of the airway, but also marked laryngotracheomalacia. The hyperextension of the fetal neck may also result in profound pulmonary hypoplasia. The hyperextended neck pulls the fetal trachea cephalad, and in severe cases the carina can be found above the level of the thoracic inlet. This pulls the lungs into the cupola of the thoracic cavities, preventing normal lung growth. Several cases of death due to profound pulmonary hypoplasia have been reported despite successful EXIT (ex utero intrapartum treatment) procedures to secure the airway (Liechty and Crombleholme, 1999; Crombleholme and Albanese, 2001).

DIFFERENTIAL DIAGNOSIS

Cystic hygroma is the most likely entity to be mistaken for cervical teratoma in cases detected prenatally (see Chapter 32). The similarities in size, sonographic findings, clinical characteristics, location, and gestational age at presentation make this distinction difficult (Batsakis et al., 1964). Cystic hygromas are typically multiloculated cystic masses with poorly defined borders that infiltrate the normal structures of the neck. This contrasts with the usually well-defined borders of cervical teratomas. Furthermore, cystic hygromas tend to be smaller than cervical teratomas, are unilateral, and more frequently involve the posterior triangle (Pearl et al., 1986).

Many other entities may resemble a cervical teratoma on sonographic imaging (Table 110-1). Amniotic fluid α-fetoprotein (AFP) has been suggested as an aid in the differential diagnosis of a cervical mass. However, maternal and fetal AFP levels may be either elevated or normal in cervical teratomas. Because fewer than 30% of cervical teratomas have an elevated AFP (Schoenfeld et al., 1982; Trecet et al., 1984), this assay is not particularly helpful in the differential diagnosis of fetal cervical masses. An elevated serum AFP level in the newborn, however, may be helpful in following the patient for signs of teratoma recurrence after successful resection. The preoperative values may be difficult to interpret, as AFP levels are high in normal newborns

Vascular malformations are another important condition in the differential diagnosis. These lesions may be both cystic and solid, like cervical teratomas, but do not have

Table 110-1

Differential Diagnosis of Cervical Teratoma

Congenital goiter
Solid thyroid tumors
Thyroid cyst or thyroglossal duct cyst
Branchial cleft cyst
Neuroblastoma
Hamartoma
Hemangioma
Lipoma
Laryngocele
Lymphangioma
Parotid tumor
Neural tube defects, such as occipital encephalocele or cervical myelomeningocele

calcifications. These lesions are often quite vascular and color flow Doppler images often reveal the extensive vascularity of these lesions. Flow through either cervical teratomas or vascular malformations can result in high-output failure, and echocardiographic assessment of combined ventricular output is indicated in all cases.

Fetal MRI has proven particularly useful in distinguishing the complex, septic, and solid teratoma from lymphangioma (see Figure 110-2) (Liechty et al., 1997; Hubbard et al., 1998). An MRI allows a larger field of view than an ultrasound and may show better tissue contrast (Figure 110-4). The T_1 and T_2-weighted imaging may allow fat to be identified within the lesion, which is more consistent with a diagnosis of cervical teratoma than cystic hygroma or vascular malformation (Hubbard et al., 1998).

ANTENATAL NATURAL HISTORY

The antenatal natural history of fetal cervical teratomas is not well defined. Although they are most often malignant in adults, the vast majority of cervical teratomas in fetuses and infants are benign (Mochizuki et al., 1986). However, rare cases of malignancies in this age group have been described with estimates of fewer than 10% of cases being malignant (Heys et al., 1967; Schoenfeld et al., 1982; Thurkow et al., 1983; Touran et al., 1989; Baumann and Nerlich, 1993; Azizkhan et al., 1995). The true malignant potential of a cervical teratoma is uncertain (Batsakis et al., 1964; Owor and Master, 1974; Watanatittan et al., 1981; Gundry et al., 1983; Pupovac, 1986; Cunningham et al., 1987). Despite the existence of primitive tissue types in the tumor and metastases to regional lymph nodes, many infants have remained free from recurrence following complete resection of a cervical teratoma. These cases suggest that malignant biologic behavior is uncommon in this population (Batsakis et al., 1964; Gundry et al., 1983; Dunn et al., 1992). Immature tissue seen on histologic examination may merely represent the immaturity of the host; thus, pathologic studies are not completely reliable in predicting the prognosis (Batsakis et al., 1964; Tapper and Lack, 1983). This is an unusual tumor that may have "benign" metastases to regional lymph nodes detected after resection of the cervical teratoma (Rothschild et al., 1994; Azizkhan et al., 1995; Oka et al., 2007).

A fetus with a cervical teratoma is at increased risk for intrauterine fetal demise and stillbirth. It has been estimated that as many as 17% die in utero and 35% die prior to surgery (Mochizuki et al., 1986; Berry, 1997; Berge et al., 2004). Because of esophageal compression, the majority of the fetuses with cervical teratoma will have polyhydramnios. The notable exceptions are small lesions and those that extend to one side without severe compression of the esophagus. The presence of a large cervical mass may result in compression of the cranial nerves. This results in loss of function, most notably the mandibular branch of the facial nerve with an attendant drop of the corner of the mouth, of the hypoglossal nerve with deviation of the tongue to the contralateral side with protrusion, and of the recurrent laryngeal nerve with paresis or paralysis of the ipsilateral vocal cord. The large cervical teratomas may compress or displace the mandible, causing hypoplasia or flaring out of the mandible from the face at odd angles, causing marked facial asymmetry.

In some cases, cervical teratomas may result in nonimmune hydrops due to the highly vascular nature of some of these lesions. In this rare circumstance, fetal demise would be anticipated without fetal surgical resection (Hirose et al., 2003).

MANAGEMENT OF PREGNANCY

Fetal cervical teratoma can profoundly affect the course of pregnancy. Repeated ultrasound examinations are indicated to monitor amniotic fluid volume, tumor size, and fetal well-being. In cases followed by serial sonography, rapid tumor growth has been noted (Hitchcock et al., 1987; Baumann and Nerlich, 1993). Stillbirth rates of 10% to 50% have been reported (Silberman and Mendelson, 1960; Hajdu et al., 1966; Hawkins and Park, 1972; Trecet et al., 1984; Roodhooft et al., 1987). There is a high incidence of preterm labor and preterm delivery, thought to be secondary to the increase in uterine size due to polyhydramnios and/or tumor. Because of the hyperextension of the neck, the so-called "flying fetus" sign (see Figure 110-1) and the often large tumor size, there is an increased incidence of malpresentation and dystocia (Owor and Master, 1974; Gonzalez-Crussi, 1982). Cesarean

section is often recommended because of the abnormal fetal position (Kagan et al., 1983; Chervenak et al., 1985; Rempen and Feige, 1985; Levine et al., 1990). Stabilization of the newborn's airway at delivery is facilitated by the assembly of a team qualified to obtain a bronchoscopic or surgical airway, if orotracheal intubation is unsuccessful (Zerella and Finberg, 1990). Currently, a fetus with cervical teratoma is best managed by the EXIT procedure, which provides time for laryngoscopy, bronchoscopy, tracheostomy, or tumor resection, if necessary, to secure the airway (Liechty et al., 1997; Crombleholme and Albanese, 2001; Marwan and Crombleholme, 2006).

Airway obstruction and respiratory compromise at birth can be life-threatening and accounts for up to 45% of the mortality seen with this abnormality. Consequently, delivery should occur at a tertiary care center with significant experience with the EXIT procedure. There have been anecdotal reports of intrapartum laryngoscopy or bronchoscopy in cases of fetal neck masses in which the fetus is delivered but the cord is not clamped (Kelly et al., 1990). Unfortunately, this procedure offers no advantage over standard cesarean section, as the removal of the fetus from the womb results in uterine contraction and cessation of the uteroplacental gas exchange (McNamara and Johnson, 1995; Liechty et al., 1997; Crombleholme and Albanese, 2001; Bouchard et al., 2002; Marwan and Crombleholme, 2006).

FETAL INTERVENTION

The ex utero partum treatment, or EXIT, procedure was specifically designed to provide time to secure an airway while preserving uteroplacental gas exchange (Figure 110-5). While Langer and Schwartz and their colleagues had each reported a case using this approach, the technique was not fully developed until it was applied in diaphragmatic hernia (Langer et al., 1992; Schwartz et al., 1993; Mychalishka et al., 1997). When tracheal clip application was applied in human fetuses with diaphragmatic hernia, it was necessary to develop a technique to allow time for neck dissection, clip removal, bronchoscopy, and intubation. Several individual case reports have described "operating on placental support" for fetal airway management, but none presented a systematic approach and correlated cord blood gases with time or placental support (Catalano et al., 1992; Langer et al., 1992; Schwartz et al., 1993; Tanaka et al., 1994; Skarsgard et al., 1996). Crombleholme et al., (1997) applied the lessons learned from use of the EXIT procedure in diaphragmatic hernia to the management of giant fetal neck masses in a small series of five patients, three with cervical teratomas and two with lymphangioma (Crombleholme et al., 1997; Liechty et al., 1997). The mean duration of the EXIT procedure was 28 minutes, with a range of 8 to 54 minutes. Direct laryngoscopy was performed in all five cases. Although orotracheal intubation was possible in two of the five, but one of the two intubations was possible only after drainage of 1800 ml of cyst fluid. In one case, massive involvement of the chest, neck, and face by the lymphangioma precluded orotracheal intubation and, in accordance with the family's wishes, a surgical airway was not attempted. In the remaining two patients, who had teratomas, there was severe distortion of the airway, rendering intubation by direct laryngoscopy impossible. In each of these cases bronchoscopy and tracheostomy were required to secure the airway. In both cases the mass effect of the tumor had pulled the thoracic trachea into the neck. In the first case this resulted in a tracheostomy 1.5 cm above the carina, and in the second case the tracheostomy was performed between the 8th and 10th tracheal rings, as this was the only available site because of mass effect of the tumor (Figure 110-6). This infant subsequently underwent resection of the mass closure of this distal tracheostomy and creation of a new tracheostomy between the 2nd and 3rd tracheal rings.

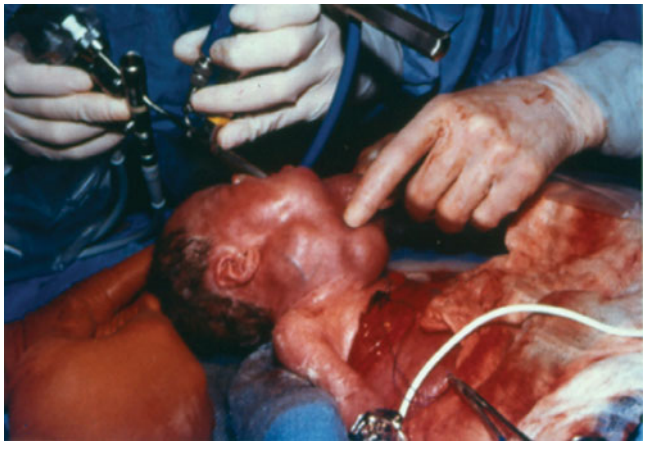

Figure 110-5 EXIT procedure being performed on a fetus with a cervical teratoma. Only the head and the upper chest are removed from the uterus to maintain uterine volume. A pulse oximetry probe is on the right hand and a bronchoscope is inserted into the airway of the fetus.

Unlike a conventional cesarean section, the EXIT procedure maintains uteroplacental blood flow and fetal gas exchange by keeping the uterus relaxed with the use of inhalational agents and the maintenance of uterine volume, by only partially exposing the fetus (Bouchard et al., 2002; Marwan and Crombleholme, 2006). This is apparent in the relatively normal venous cord blood gases seen after up to 54 minutes of uteroplacental support (Liechty et al., 1997). By preserving uteroplacental blood flow, the EXIT procedure allows for adequate time to perform multiple procedures such as direct laryngoscopy, bronchoscopy, tracheostomy, surfactant administration, and cyst decompression, some or all of which may be required to secure the airway (Figures 110-5 and 110-6).

There are a number of potential risks to the mother who undergoes an EXIT procedure. Because inhalational agents keep the uterus very relaxed, there is a risk of increased hemorrhage because of uterine atony. The risk of uterine atony and hemorrhage can be minimized through coordination between the surgeon and the anesthesiologist to decrease the concentration of inhalational anesthetic and administer oxytocin at the time of umbilical cord ligation. The use of the uterine stapling device and coordination with the anesthesiologist keeps the average intraoperative blood loss at 950 ml,

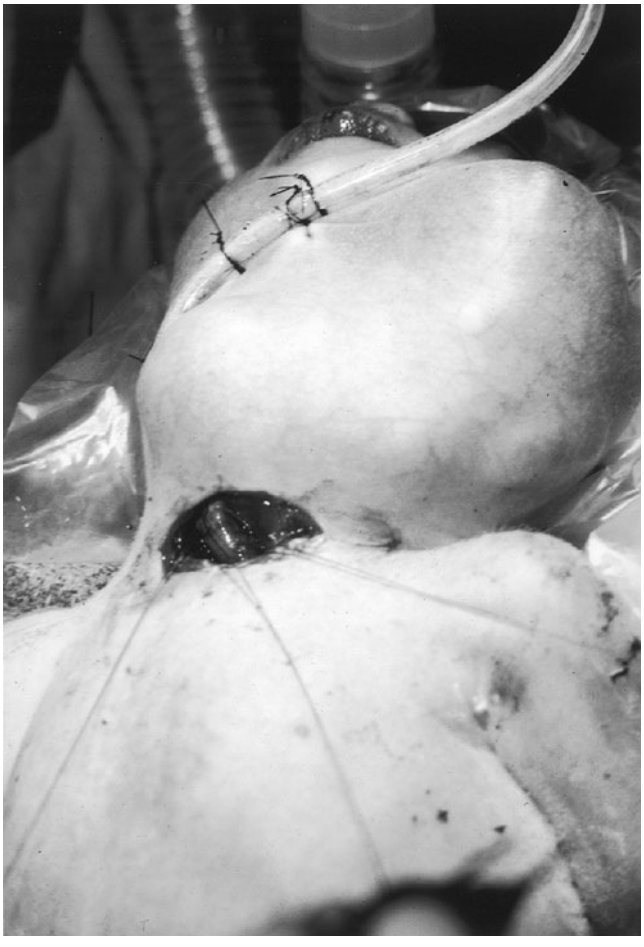

Figure 110-6 The same patient in Figure 110-5 during the EXIT procedure. The cervical teratoma had so distorted the airway that an endotracheal tube had to be tunneled through the soft tissue of the neck and entered the trachea between the 8th and 10th tracheal rings.

well within the accepted range for traditional cesarean section (Hood and Holubec, 1990).

Lower uterine segment hysterotomy is preferred for the EXIT procedure, as it allows the possibility of future vaginal delivery. However, a low anterior placenta or extremely large neck mass may make lower uterine segment section impossible. In such cases, a classical hysterotomy is necessary. This approach necessitates cesarean delivery for all future deliveries because of the risk of uterine rupture during labor. Prior to an EXIT procedure, mothers should be counseled about the possibility that future pregnancies would require cesarean delivery. In rare cases, hydrops resulting from a cervical teratoma in a fetus less than 30 weeks' gestation may necessitate open fetal surgery to resect the teratoma. To date this has been performed successfully in only one case (Hirose et al., 2003).

TREATMENT OF THE NEWBORN

Airway obstruction at birth is life-threatening and associated with a high mortality rate (Azizkhan et al., 1995). In giant fetal neck masses, this mortality is usually associated with a delay in obtaining an airway and an inability to ventilate the infant effectively. This delay can result in hypoxia and acidosis and, if the delay is greater than 5 minutes, anoxic injury may occur (Dawes, 1968). This complication is all the more tragic as most of these children have an isolated benign tumor and do well after postnatal resection.

Mortality can be as high as 80% to 100% in untreated infants, regardless of the tumor size (Silberman and Mendelson, 1960; Batsakis et al., 1964; Goodwin and Gay, 1965; Hurlbut et al., 1967; Gundry et al., 1983; Garmel and Crombleholme, 1985). Delaying surgery can result in retention of secretions, atelectasis, and/or pneumonia due to interference with swallowing (Batsakis et al., 1964; Gonzalez-Crussi, 1982). In addition, precipitous airway obstruction may occur due to hemorrhage into the tumor (Silberman and Mendelson, 1960; Batsakis et al., 1964; Hurlbut et al., 1967; Gundry et al., 1983) even in minimally symptomatic newborns. For this reason, orotracheal intubation is indicated in all patients regardless of the presence or absence of symptoms. Mortality decreases to between 9% and 17% in infants treated surgically (Silberman and Mendelson, 1960; Batsakis et al., 1964; Goodwin and Gay, 1965; Hajdu et al., 1966; Hurlbut et al., 1967; Gundry et al., 1983).

SURGICAL TREATMENT

These tumors tend to be large, disfiguring masses that displace or envelop vital structures in the neck. Extensive neck dissection and multiple procedures are often necessary to achieve the goals of complete extirpation of the tumor with acceptable functional and cosmetic results.

In a review of 18 cases of cervical and orofacial teratomas, Azizkhan and colleagues reported that life-threatening airway obstruction occurred in 7 infants (39%), 2 of whom died without ever having a secure airway (Azizkhan et al., 1995). Two neonates with prenatally diagnosed tumors, survived because tracheostomies were performed in the delivery room by an attending pediatric surgeon. Survival was observed in 15 of the 18 cases (83%). One neonate required multiple surgeries to achieve complete tumor removal. Morbidity included two cases with recurrent laryngeal nerve injury, two with hypothyroidism, and two with developmental delay and mental retardation secondary to airway obstruction and asphyxia at birth.

LONG-TERM OUTCOME

Infants with cervical teratoma are at risk for transient or permanent hypoparathyroidism and hypothyroidism. Cervical teratoma may completely replace the thyroid gland and tumor resection may result in permanent hypothyroidism. More commonly, thyroid tissue may be preserved but may not be adequately functioning and an interval of thyroxine supplementation may be necessary. Because of the massive nature

of these tumors and the difficulty in identifying parathyroid glands, transient or even permanent hypoparathyroidism may be observed. Calcium and vitamin D supplementation may be needed postoperatively. A pediatric endocrinologist should be consulted if these complications are encountered. In approximately one-third of the cases, cervical teratomas produce markedly elevated levels of AFP. However, an elevated AFP level obtained immediately postoperatively must be interpreted with caution. AFP levels in normal newborns have an enormous range, with some as high as 20,000 units during the first month of life. The AFP values progressively fall during infancy until levels of less than 10 units are obtained at the age of one. While an elevated AFP level may not necessarily be abnormal, the levels should progressively decrease during infancy. A rising AFP should alert the clinician to the possibility of teratoma recurrence. While cervical teratoma is generally a benign tumor, there is the possibility of malignant transformation, and close surveillance for tumor recurrence is essential. We recommend following AFP levels at 3-month intervals in infancy and yearly thereafter, with CT or MRI scanning twice a year for the first three years of life.

GENETICS AND RECURRENCE RISK

There has been one report of congenital cervical teratoma occurring in siblings, but no other familial cases have been described (Hurlbut et al., 1967).

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111 Liver Tumors

CHAPTER

Key Points

- Liver tumors account for only 5% of fetal and neonatal tumors.
- The most common tumor is hemangioma followed by mesenchymal hamartoma and hepatoblastoma.
- Hemangiomas can be hypoechoic, hyperechoic, or undetectable and can result in high-output failure polyhydramnios and hydrops.
- Mesenchymal hamartomas tend to be cystic lesions.
- Hepatoblastomas are typically solid and echogenic and occasionally have calcifications.
- Hepatoblastoma can be associated with Beckwith–Wiedemann syndrome, familial adenomatous polyposis coli, and rarely, trisomy 18.

Key Points (cont.)

- Alpha-fetoprotein levels may be markedly elevated in mesenchymal hamartoma and neuroblastoma.
- In utero cyst decompression, rare mesenchymal hamartomas with extremely large cysts may be considered.
- Transplacental steroids may be helpful in large hemangiomas associated with high-output cardiac failure or hydrops.
- There is increased risk of intrauterine demise and stillbirth in primary hepatic tumors.
- Neonatal management of primary hepatic tumor is complicated and should be performed at centers with appropriate expertise.

CONDITION

Tumors of the liver are rare during the perinatal period. They account for only 5% of all neoplasms that occur in the fetus and the newborn (Campbell et al., 1987; Borch et al., 1992; Broadbent, 1992; Werbe et al., 1992; Isaacs, 1997). The most common primary hepatic tumor is hemangioma, followed by mesenchymal hamartoma and hepatoblastoma (Stocker and Ishak, 1983; Isaacs, 1985; Davis et al., 1988; Davenport et al., 1995; von Schweinitz, 2003; Laberge et al., 2005; Christison-Lagay et al., 2007; Isaacs, 2007). Each has been detected prenatally by ultrasound examination and can be detected postnatally by palpation of an abdominal mass (Romero et al., 1988; Garmel et al., 1994; Isaacs, 1997; Isaacs, 2007). However, metastatic lesions are more common than primary liver tumors (Dehner, 1978; Coffin and Dehner, 1992). The most common tumor that metastasizes to the liver in the fetus and newborn is neuroblastoma, followed by leukemia, yolk sac tumor from sacrococcygeal teratoma, and rhabdoid tumor of the kidney (Dehner, 1978; Isaacs, 1985, Isaacs, 1997). The majority of hepatic hemangiomas are diagnosed before the age of 6 months and almost 50% appear within the first week of life (Dehner et al., 1975; Laird et al., 1976; Stanley et al., 1977, Dehner, 1978, Dehner, 1981, Ehren et al., 1983; Miller and Greenspan, 1985a and Miller and Greenspan, 1985b; Golitz et al., 1986; Dehner, 1987; Davis et al., 1988; Luks et al., 1991; Drut et al., 1992; Werbe et al., 1992). There have been multiple reports in the literature of hepatic hemangiomas diagnosed by prenatal sonographic examination (Nakamoto et al., 1983; Platt et al., 1983; Horgan et al., 1984; Petrovic et al., 1992; Sepulveda et al., 1993; Chou et al., 2005; Isaacs, 2007). In the report by Isaacs, reviewing reported cases in the literature and experience at Children's Hospital San Diego and Children's Hospital Los Angeles, he found that of the 194 fetal and neonatal tumors, 29% presented antenatally (Isaacs, 2007). The most common of these were hepatic hemangiomas, accounting for 117 of the 194 tumors, with 28% presenting antenatally. The most common antenatal presentation was the sonographic detection of a hepatic mass followed by anemia, hydrops, polyhydramnios, heart failure, thrombocytopenia, and disseminated intravascular coagulation (Isaacs, 2007). It is likely that more hemangiomas occur in the liver than are actually recognized, because many are asymptomatic or silent conditions that regress or are discovered as only an incidental finding on clinical imaging or postmortem examination (Dehner, 1978). Some hemangiomas, in contrast, present with hepatomegaly or a mass lesion and high-output cardiac failure, while others may be life-threatening during the perinatal period because of rupture of the hemangioma and hemoperitoneum during delivery (Dehner, 1981; Larcher et al., 1981; Miller and Greenspan, 1985a and Miller and Greenspan, 1985b; Weinberg and Finegold, 1986; Dehner, 1987; Romero et al., 1988; Stanley et al., 1989; Berry, 1993; Davenport et al., 1995). Hemangiomas have been associated with consumptive coagulopathy resulting from disseminated intravascular coagulation (DIC), sequestration of platelets causing a bleeding diathesis (Kasabach–Merritt syndrome), and anemia (Dehner, 1987; Slopeck and Lakatau, 1989; Isaacs, 1991; Berry, 1993; Isaacs, 2007). High-output cardiac failure leading to in utero demise as a result of hepatic hemangioma has been described by (Nakamoto et al. (1983); Isaacs, 2007). In a report from Stanley et al. (1989) a palpable abdominal mass and cardiac failure were the most frequent presenting findings in 20 infants diagnosed with hepatic hemangiomas. Hepatic hemangiomas can be focal or multifocal. Most focal hemangiomas occur in the right lobe of the liver (Isaacs, 2007). Associated extrahepatic hemangiomas most often occur in skin, brain, placenta, lungs, and eyes. In about 50% of newborns, hepatic hemangiomas are associated with hemangiomas of the skin and other organs (Dehner, 1978; Shturman-Ellstein et al., 1978; Larcher et al., 1981; Isaacs, 1985; Golitz et al., 1986; Dehner, 1987; Stanley et al., 1989; Berry, 1993; Leonidas et al., 1993; Davenport et al., 1995; Isaacs, 2007). The fatal combination of cutaneous and hepatic hemangiomas, hydrops fetalis, hydramnios, and premature delivery has been reported by Shturman-Ellstein et al. (1978). This case was also notable for associated placental edema and chorioangioma, with a terminal clinical course complicated by thrombocytopenia and DIC in the Kasabach–Merritt syndrome that was further compromised by respiratory distress syndrome (Shturman-Ellstein et al., 1978).

Congenital malformations may also be observed in association with hepatic hemangiomas. Werbe et al. (1992) described two such cases in stillborn infants. One infant had a 4-cm hemangioma and an encephalocele, while the other had two liver lesions in addition to encephalomyelitis, partial

gut malrotation, and single umbilical artery. In another report, congenital heart disease and prune belly syndrome, respectively, occurred with hepatic hemangiomas in two other neonates (Ehren et al., 1983). Shah et al. (1987) reported a 6-hour-old full-term female infant who died during surgery for repair of a left congenital diaphragmatic hernia and was found to have hemangioma rising from the lobe of the liver in the left thorax. Hepatic hemangiomas have also been described in association with the Beckwith–Wiedemann syndrome, placental chorioangioma, and dysmorphic kidneys (Drut et al., 1992). In the review by Isaacs, capillary and cavernous hemangioma was the most common histology, accounting for 39% of cases, followed by type I hemangioendothelioma (31%), infantile hemangiomas (24%), and angiosarcoma (7%) (Isaacs, 2007).

The second most common benign hepatic tumor that occurs during the perinatal period is mesenchymal hamartoma (Dehner, 1978; Dehner, 1981, Isaacs, 1983; Stocker and Ishak, 1983; Weinberg and Finegold, 1986; Davis et al., 1988; De Maioribus et al., 1990; Isaacs, 1991; Isaacs, 2007;). Over 33% of cases of mesenchymal hamartomas are diagnosed in infants and about 25% are in newborns. In the review by Isaacs, 23% of hepatic tumors were mesenchymal hamartomas (Isaacs, 2007). In a report by Keeling (1971), five of seven patients with this condition were of the age of 2 months or younger. The lesion was an incidental postmortem finding in three newborns, including one stillborn infant.

The pathogenesis of mesenchymal hamartoma is incompletely understood and, as the name *hamartoma* implies, it is of a developmental rather than a neoplastic origin (Dehner, 1978, Weinberg and Finegold, 1986). Lennington et al. (1993) have suggested that mesenchymal hamartomas result from anomalous blood supply to a liver lobule, leading to ischemia and subsequent cystic change and fibrosis. Consistent with this premise is the observation that some hamartomas have necrotic centers and are attached to the liver by a pedicle (Lennington et al., 1993). In addition, neither recurrence following complete resection nor malignant transformation has been reported in mesenchymal hamartomas (Dehner, 1978; Isaacs, 1983; Stocker and Ishak, 1983; Stanley et al., 1989). Mesenchymal hamartomas can readily be detected by prenatal sonographic examination (Foucar et al., 1983; Hirata et al., 1990; Wienk et al., 1990; Mason et al., 1992; Garmel et al., 1994; Isaacs, 2007). Most mesenchymal hamartomas are multicystic (70%), with the remainder being either solid or a combination of solid and cystic (Isaacs, 2007). In general, mesenchymal hamartomas are not associated with other congenital malformations (Weinberg and Finegold, 1986), but occasional exceptions have been noted, including Keeling's (1971), report of excessive oral mucus secretions and an abdominal mass. This infant was found to have a tracheoesophageal fistula with an annular pancreas in addition to the hamartoma. Stocker et al., reported that 5 of their 30 patients with mesenchymal hamartoma had various anomalies and associated conditions (Stocker and Ishak, 1983). Most mesenchymal hamartomas occur in the right lobe of the liver (90%) but up to 10% can be bilateral (Dehner, 1978; Weinberg and Finegold, 1986; Dehner, 1987; Isaacs, 2007). Hepatoblastoma is the leading primary hepatic malignant tumor occurring during the first year of life (Isaacs , 1997; Isaacs, 2007). Over half of all hepatoblastomas are diagnosed in infants, but less than 10% are found in newborns (Keeling, 1971; Exelby et al., 1974; Gonzalez-Crussi et al., 1982; Weinberg and Finegold, 1983; Weinberg and Finegold, 1986; Campbell et al., 1987; Isaacs, 1991). Among the 32 cases of fetal and neonatal hepatoblastomas reported by Isaacs, 9 were diagnosed prenatally (Isaacs, 2007).

Typically, hepatoblastoma presents as an upper abdominal mass arising from a single area, more often from the right lobe of the liver than the left (Figure 111-1). Hepatoblastoma

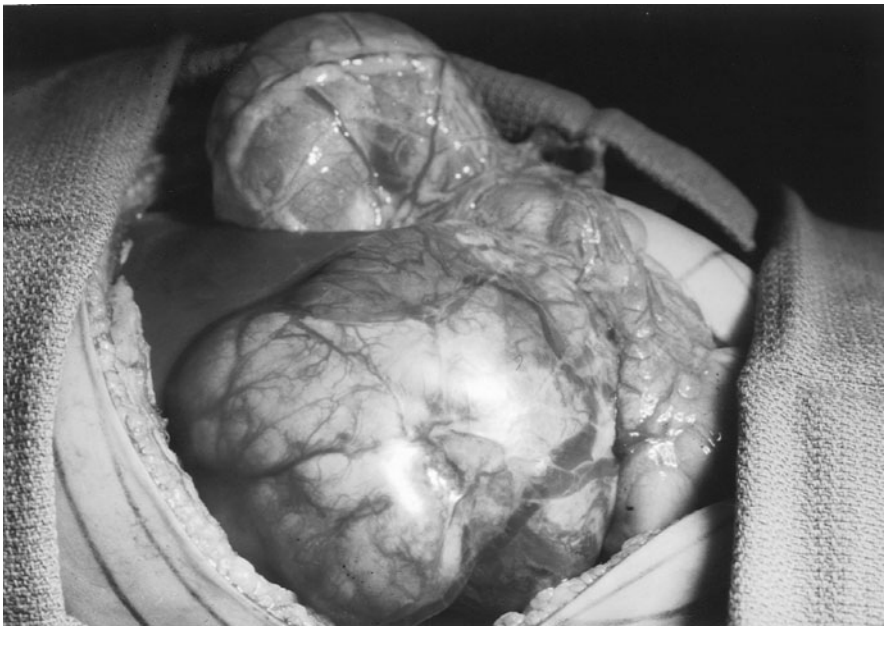

Figure 111-1 Intraoperative view of a newborn with congenital hepatoblastoma arising from the right lobe of the liver.

can be detected by antenatal sonography (van de Bor et al., 1985; Orozco-Florian et al., 1991; Garmel et al., 1994; Isaacs, 2007). In one prenatally detected case, a hepatoblastoma was responsible for compression of the inferior vena cava, leading to fetal hydrops and intrauterine death at 36 weeks of gestation (Benjamin et al., 1981). Kazzi et al. (1989) described a similar case in a newborn with hepatoblastoma that was diagnosed antenatally. Hydrops fetalis, consumptive coagulopathy associated with massive hemorrhage into the tumor, and anemia were present at birth in this fetus. Orozco-Florian et al. (1991) reported a fetus with hepatoblastoma detected antenatally that had associated nephromegaly and pancreatic nesidioblastosis consistent with the diagnosis of Beckwith–Wiedemann syndrome; however, the affected neonate did not have either macroglossia or omphalocele. In addition to neuroblastoma and leukemia, hepatoblastoma is one of the rare perinatal malignancies that can metastasize to the placenta and cause fetal death (Bond, 1976; Robinson and Bolande, 1985; Dinmick, 1991). A broad range of congenital anomalies and malformation syndromes have been reported to occur in association with hepatoblastoma. Hemihypertrophy can occur in as many as 2% to 3% of affected patients. Beckwith–Wiedemann syndrome and familial intestinal adenomatous polyposis (FAP) are the most common associated syndromes (Geiser et al., 1970; Landing, 1976; Fraumeni et al., 1978; Dehner, 1981; Weinberg and Finegold, 1986; Li et al., 1987; Kazzi et al., 1989; Hartley et al., 1990; Giardiello et al., 1991; Orozco-Florian et al., 1991; Greenberg and Filler, 1993; Rubie et al., 1993). Hepatoblastoma, in addition, has been described in siblings in a variety of clinical settings, including in fetal alcohol syndrome, in association with the maternal use of contraceptives, in trisomy 18, in patients with Wilms tumor, and in newborns with adenomatoid malformation of the renal epithelium (Landing, 1976; Khan et al., 1979; Knowlson and Cameron, 1979; Mamlok et al., 1989; Riikonen et al., 1985; Greenberg and Filler, 1993). Aicardi syndrome (infantile spasms, agenesis of the corpus callosum, and multiple ocular malformations) has been described in a 2-month-old female infant with hepatoblastoma (Tanaka et al., 1985).

No clearly defined factors have been implicated in the development of these tumors and the causes of these entities are unknown. Because of the rarity of these lesions, much remains to be learned about the prenatal sonographic findings, natural history, and optimal pregnancy management for these unusual cases.

INCIDENCE

Tumors of the liver presenting during the perinatal period are rare. Primary hepatic neoplasms account for only 0.5% to 2% of pediatric tumors (Alagille and Odievre, 1979). They comprise 5% of total neoplasms occurring in the fetus and neonate (Dehner, 1978; Wu et al., 1981; Lack et al., 1982; Stocker and Ishak, 1983; Weinberg and Finegold, 1986; DeMaioribus et al., 1990; Samuel and Spitz, 1995; von Schweinitz, 2003; Sallam et al., 2005). Hemangiomas are relatively common, occurring in as many as 1 in 100 newborns and in 1 in 5 premature infants with a birth weight less than 1000 grams (Folkman, 1984; Enjorlas et al., 1990). The specific incidence of hepatic hemangioma is not known. The annual incidence of hepatoblastoma in the United States is estimated to be 0.9 in 1 million children, with a 2:1 male predominance (Young and Jr Miller, 1975; Fraumeni et al., 1978). However Isaacs found a 1.6:1 female ratio in fetal and neonatal hepatoblastomas (Isaacs, 2007). The incidence of mesenchymal hamartoma is uncertain, but there appears to be a male predominance. The prenatal incidence of each of these hepatic tumors is unknown.

SONOGRAPHIC FINDINGS

There have been multiple reported cases of hepatic hemangiomas diagnosed prenatally by ultrasound examination (Nakamoto et al., 1983; Platt et al., 1983; Horgan et al., 1984; Petrovic et al., 1992; Sepulveda et al., 1993; von Schweinitz, 2003; Christison-Lagay et al., 2007). These lesions can be single or multiple and can appear hypoechogenic, hyperechogenic, or mixed in appearance depending on the degree of fibrosis and the stage of evolution (Nakamoto et al., 1983; Horgan et al., 1984; Gonen et al., 1989). The reported sizes of hemangiomas have ranged from 1.1 × 0.9 cm to 7.8 × 6.4 cm (Petrovic et al., 1992; Sepulveda et al., 1993). Hepatomegaly may also be seen. Polyhydramnios has been noted occasionally, which is thought to be due to either a hyperdynamic state induced by this vascular tumor or gastrointestinal tract compression secondary to mass effect (Nakamoto et al., 1983; Petrovic et al., 1992). In addition, fetal hydrops has been reported in one case by Shturman-Ellstein et al. (1978).

Mesenchymal hamartomas have also been described prenatally (Foucar et al., 1983; Stocker and Ishak, 1983; Hirata et al., 1990; Mason et al., 1992; Laberge et al., 2005). Hamartomas typically appear as an irregular cyst on ultrasound examination (Nyberg et al., 1990). Both oligohydramnios and polyhydramnios have been reported in association with mesenchymal hamartomas (Mason et al., 1992).

Hepatoblastoma develops in fetal life and is the most common primary liver malignancy in infancy and childhood, yet only rarely are cases detected prenatally (van de Bor et al., 1985; Garmel et al., 1994; Isaacs, 1997; Shih et al., 2000; von Schweinitz, 2003; Aviram et al., 2005; Catanzarite et al., 2008). Neonatal hepatoblastomas are typically solid and echogenic and calcifications may be present. Two-thirds involve only one lobe (Exelby et al., 1974). Associated anomalies have been reported in the neonate, including hemihypertrophy, Down syndrome, cardiovascular defects, and genitourinary anomalies (Gonzalez-Crussi et al., 1982). Whether most of these are chance associations is not clear. In van de Bor et al.'s (1985) case report of hepatoblastoma, polyhydramnios was

noted in association with hepatomegaly; this was because of a gastrointestinal obstruction.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of fetal hepatomegaly also usually involves splenomegaly and includes hydrops, fetal infection, anemia, metabolic abnormalities (e.g., hypothyroidism) and genetic syndromes such as Beckwith–Wiedemann and Zellweger (Schutgens et al., 1985; Nyberg et al., 1990). The differential diagnosis of prenatally diagnosed hepatic masses should include isolated nonparasitic cysts (Chung, 1986), cysts associated with polycystic kidney disease, and metastatic neuroblastoma. Gonen et al. (1989) prenatally confirmed the vascular nature of hemangioma with pulsed Doppler studies showing drainage into an enlarged hepatic vein. This technique may prove useful in a differential diagnosis of prenatally detected hepatic lesions. In addition to hemangioma, hepatoblastoma, and mesenchymal hamartomas, one should also consider the possibility of hepatic adenoma. There has been one reported case of prenatally diagnosed hepatic adenoma. Marks et al. (1990) noted a 4-cm × 4-cm hypoechoic liver mass with no associated anomalies. An autopsy confirmed the diagnosis of hepatic adenoma. Hepatic hemangioendothelioma has also been diagnosed prenatally as a cystic and solid lesion with Doppler imaging, confirming the vascular nature of the tumor (Gonen et al., 1989). While this fetus progressed to nonimmune hydrops, another case was noted to spontaneously regress (Horgan et al., 1984).

Alpha-fetoprotein (AFP) levels are markedly elevated in neonatal cases of hepatoblastoma and mesenchymal hamartoma (Exelby et al., 1974; Ito et al., 1984; Pollice et al., 1992). AFP levels can be difficult to interpret in the newborn, as this value is normally quite high. This has not yet been reported with prenatal lesions, and the usefulness of maternal serum AFP levels in the diagnosis and management of prenatally detected hepatic tumors is unknown.

ANTENATAL NATURAL HISTORY

Because of the rarity of these lesions, little is known about the antenatal natural history of hepatic tumors. Hemangiomas are histologically benign. Postnatally, the natural history tends toward spontaneous regression after infancy. However, there is great variability in severity and complications (Larcher et al., 1981). Occasionally, hemangiomas are associated with arteriovenous shunting and subsequent congestive heart failure. Heart failure and hydrops, with resultant intrauterine neonatal death, has been reported (Berdon and Baker, 1969; Nakamoto et al., 1983; Gonen et al., 1989). These cases may represent the prenatal correlate of infants with hemangiomas and arteriovenous shunting, resulting in congestive heart failure. Others have reported either no change or spontaneous resolution (Platt et al., 1983; Horgan et al., 1984; Sepulveda et al., 1993). Once the diagnosis of hemangioma is confirmed postnatally, by computed tomographic (CT) or magnetic resonance imaging (MRI) scans, the asymptomatic neonate can be treated conservatively with counseling to alert the family of potential complications (Platt et al., 1983; Horgan et al., 1984). In the absence of complications, such as heart failure, the prognosis is good (Slovis et al., 1975).

The report by van de Bor et al. (1985) of prenatally detected hepatomegaly, later found to be hepatoblastoma, described neonatal death from liver rupture. Benjamin et al. (1981) reported hepatoblastoma as a cause of intrauterine fetal death. Similarly, Robinson and Bolande (1985) reported a stillborn infant with metastases to the lungs, placenta, and cord from hepatoblastoma. Experience with infants and children is slightly more encouraging. In patients in whom complete resection is possible, the long-term survival rate is 60% (Exelby et al., 1974). However, local extension and recurrence occurs in more than 40% of patients with hepatoblastoma. Hepatoblastoma is usually fatal if it cannot be completely resected, despite preoperative chemotherapy (Gonzalez-Crussi et al., 1982).

There is one reported case of stillbirth associated with mesenchymal hamartoma, and no other fetal abnormalities potentially responsible for fetal death were noted at autopsy (Foucar et al., 1983). Laberge et al., have reported fetal demise because of mesenchymal hamartoma that was associated with placental changes of mesenchymal stem villous hyperplasia of the placenta. They noted that among 11 such cases diagnosed prenatally, 4 had died in utero. Two other fetuses with prenatally diagnosed hamartomas did well after surgical resection. This last scenario is more consistent with neonatal mesenchymal hamartoma, in which the prognosis is favorable following tumor resection (Hirata et al., 1990). However, Isaacs reported that among 45 fetuses and neonates with mesenchymal hamartoma that underwent surgery, only 76% survived. Some patients were not treated and only one-third survived, yielding an overall survival rate for mesenchymal hamartoma of 65% (Isaacs, 2007).

MANAGEMENT OF PREGNANCY

A pregnant woman carrying a fetus in which a hepatic tumor is suspected should undergo an extensive prenatal evaluation. This should include a detailed sonographic examination to define the nature of the mass, location, blood supply, and any associated anomalies. Color Doppler studies may be helpful in distinguishing hemangioma from hepatoblastoma, mesenchymal hamartoma, or adenoma. Evidence of other hemangiomas should be sought. While mesenchymal hamartoma is usually an isolated finding, associated anomalies such as tracheoesophageal fistula and annular pancreas have been reported (Keeling, 1971; Stocker and Ishak, 1983). Hepatoblastoma has been reported in Beckwith–Wiedemann

syndrome and a fetus with a hepatic tumor should be examined for evidence of organomegaly or macroglossia. Hepatoblastoma also occurs in the Aicardi syndrome, and care should be taken to rule out agenesis of the corpus callosum (Jones, 1997). Every fetus with a hepatic mass should undergo echocardiography to obtain baseline values and be followed for development of high-output cardiac physiology. Serial scans in fetuses with hepatic tumors are indicated because of the potential for the development of oligohydramnios, polyhydramnios, nonimmune hydrops, and intrauterine fetal death. Fetal MRI scanning may be helpful in establishing a diagnosis of a liver tumor as well as defining the anatomic relationship with intrahepatic structures and adjacent organs.

Pregnancies complicated by hepatic tumors should be delivered in a tertiary care center, with neonatologists, pediatric surgeons, and pediatric oncologists available. Depending on the size of the lesion, cesarean section may be necessary. Tumor rupture at the time of delivery has been reported with mesenchymal hamartoma and hepatoblastoma. Because of the vascular nature of these lesions, every effort should be made to minimize the risk of tumor rupture.

FETAL INTERVENTION

There are few indications for fetal interventions for liver tumors. However, in case of fatal fetal mesenchymal hamartomas, decompression of large cystic components was suggested as a last ditch effort to prevent fetal death from tumor growth (Laberge et al., 2005). In the case of large hepatic hemangiomas that result in high-output failure and hydrops, maternal steroid treatment should be considered.

TREATMENT OF THE NEWBORN

Once an infant with a hepatic tumor is born, attention should focus on establishing a definitive diagnosis. In the case of hepatic hemangiomas, more than 50% will have associated cutaneous hemangiomas. The infant's platelet count, fibrinogen, and fibrin split products should be checked to exclude DIC and platelet trapping. Follow-up echocardiography should be performed to exclude high-output cardiac physiology. An initial bedside ultrasound examination may be helpful in establishing the diagnosis; however, CT or MRI scans are usually indicated to more fully define these lesions.

In the newborn with a hepatic mass suspected of being a hepatoblastoma, the serum AFP level should be measured. However, values in normal term infants may be between 20,000 and 120,000 ng/mL, which may make interpretation difficult in the newborn, but even more markedly elevated AFP levels are usually seen in hepatoblastoma. Ultrasound examination is helpful in differentiating solid from cystic masses. Hepatoblastoma usually shows a large hyperechoic mass. Color Doppler imaging is also helpful in evaluating the involvement of the portal vein, hepatic veins, and the inferior vena cava.

CT or MRI scanning of the liver is helpful in defining the extent of the tumor and assessing its resectability (Figure 111-2). MRI scans give detailed information not only on

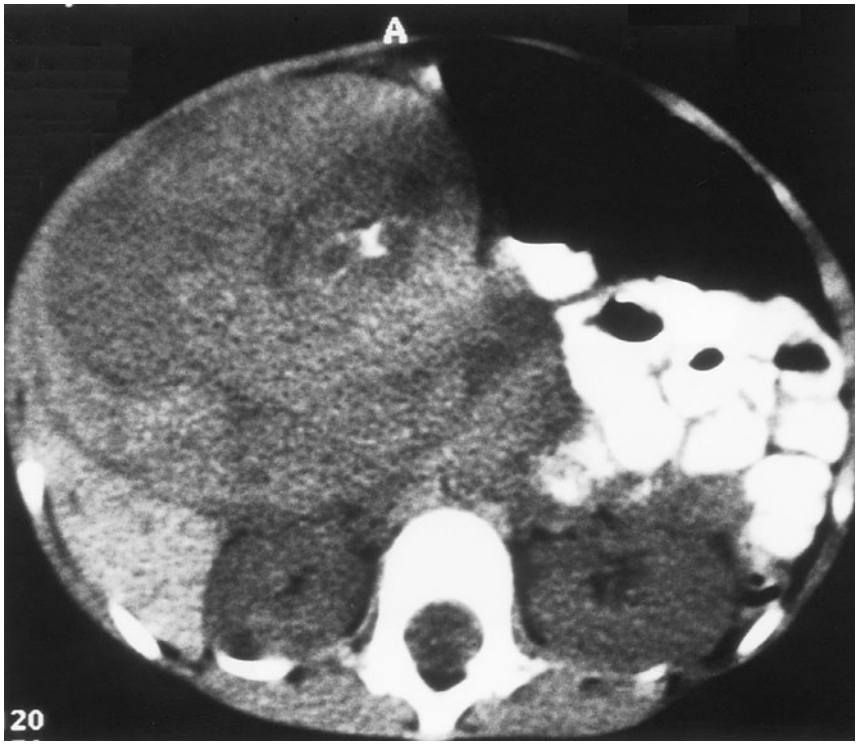

Figure 111-2 CT scan of a patient with a hepatoblastoma largely replacing the right lobe of the liver.

segmental anatomy of a hepatic tumor, but also on the vascular anatomy of the liver, making angiography unnecessary.

The distinction between hepatic hemangioma and arteriovenous malformations is an important one. Hepatic arteriovenous malformations require embolization or surgical resection and do not respond to corticosteroids or interferon gamma.

SURGICAL TREATMENT

In the experience with 34 hepatic hemangiomas causing congestive heart failure, the mortality associated with surgical resection of solitary lesions was 25%, and it was 45% when embolization was used for solitary and multiple lesions (Folkman, 1984). The mortality rate was only 20% when corticosteroids were used. Eleven patients who did not respond to corticosteroids received interferon gamma, resulting in a mortality rate of only 9%. Currently, interferon gamma is restricted to treatment of serious or life-threatening hemangiomas that fail to respond to corticosteroids, develop complications of corticosteroid administration, or have a contraindication to long-term corticosteroids (gastrointestinal bleeding, vomiting, infection), or if there is parental refusal of corticosteroids. An initial 2-week course of oral corticosteroids at 2 to 3 mg per kilogram of body weight per day is given. If the hemangioma responds, as evidenced by shrinkage, decreased turgor, pallor, or arrest of growth, then steroids are continued for 4 weeks before beginning a slow taper over 8 to 10 months (Folkman et al., 1997).

Interferon gamma is not without potential complications; recognized toxicities include fever, elevated liver function tests, transient neutropenia, and anemia. These toxicities are reversible. One worrisome complication associated with interferon gamma is the development of long tract signs and increased motor tone in the lower limbs.

The survival among fetuses and neonates with hemangiomas reported by Isaacs depended on treatment and histology. Only 78% of the 41 patients with multifocal hemangiomas were treated. Twenty-two percent were untreated, with survival rates of 75% and 56%, respectively. Among the 5 patients with type II hemangioendothelioma or angiosarcoma, 2 of the 5 operated on survived. Corticosteroids were a frequent choice of therapy for multifocal hemangiomas; all 10 patients who received them survived. Hepatic artery ligation was used successfully in 11 of 12 patients with or without steroids. In large type I hemangioendotheliomas, even biopsy can precipitate a consumptive coagulopathy, and medical therapy using steroids or even chemotherapy to shrink the lesion may be safer than surgery alone (Isaacs, 2007).

In cases of mesenchymal hamartoma, definitive treatment consists of a frozen section to confirm the diagnosis and exclude the possibility of malignancy. This is followed by complete resection of the mass. In the review by Isaacs, surgery was performed in 29 of 45 patients (64%) with 76% survival. Only one-third of those not treated survived. The fetal and neonatal survival with mesoblastic nephroma was 64% and 65%, respectively (Isaacs, 2007).

Surgical resection is the primary mode of treatment in hepatoblastoma. However, in tumors that are found to be unresectable at operative staging, a biopsy is performed to make a diagnosis and chemotherapy is begun. Reexploration for evidence of tumor regression with consideration of definitive resection occurs after several cycles of chemotherapy. In some centers a decision on resectability is made on the basis of imaging studies, and a percutaneous biopsy is obtained to make a tissue diagnosis before starting chemotherapy.

Surgical resection of liver tumors, whether hemangioendotheliomas, mesenchymal harmatomas, or hepatoblastomas, should be undertaken by experienced pediatric surgeons. In the case of hemangioendotheliomas, the involvement of multiple specialists from a Vascular Malformation and Tumor service is advisable. In the case of hepatoblastoma, the survival of the 32 cases compiled by Isaacs were stage dependent, with survival rates of 50%, 50% and 0% for stages I, III, and IV, respectively (Isaacs, 2007).

LONG-TERM OUTCOME

In hepatic hemangiomas in the absence of complications such as congestive heart failure, platelet trapping, or rupture at the time of delivery, a good prognosis can be anticipated. Most hepatic hemangiomas are asymptomatic and go unrecognized and do not develop complications. Even in the face of complications there has been significant improvement in survival because of the treatment of hepatic hemangiomas with corticosteroids and interferon gamma (Folkman et al., 1997). The natural history of hemangiomas is to progress during infancy and then to steadily regress thereafter (Folkman et al., 1997).

The long-term prognosis in mesenchymal hamartoma is excellent following complete resection. These tumors are not associated with malignant transformation and do not recur following complete resection.

There has also been steady progress in the outcome of patients treated for hepatoblastoma. The combination of surgery, chemotherapy, and liver transplantation has achieved disease-free survival rates of 100% for stage I, 75% for stage II, and 67% for stage III disease (Tagge and Tagge, 1997; Sallam et al., 2005; Tiao et al., 2005). Unfortunately, no disease-free survival has been achieved with stage IV disease.

GENETICS AND RECURRENCE RISK

Most of the hepatic lesions discussed in this chapter develop sporadically, without an associated risk for recurrence in subsequent pregnancies. There are, however, three notable exceptions associated with hepatoblastoma. Hepatoblastoma occurs in up to 10% of children with Beckwith–Wiedemann

syndrome, which is inherited as an autosomal dominant condition (see Chapter 27). There is also an increased risk of hepatoblastoma in kindreds with familial adenomatous polyposis (FAP). This is an autosomal dominant condition that predisposes to colonic adenomas and carcinomas. It is estimated that the risk of hepatoblastoma in children of patients with FAP is 0.42% (Li et al., 1987, Tagge and Tagge, 1997). DNA mutation analysis of the *APC* gene is clinically available for families with symptoms that suggest FAP. Lastly, hepatoblastoma has been reported in 4 individuals with trisomy 18 (Bove et al., 1996).

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112 CHAPTER

Mesoblastic Nephroma

Key Points

- Most common congenital renal tumor.
- Sonographically, mesoblastic nephroma is most often a unilateral solid mass with nodular densities.
- Differential diagnosis includes hydronephrosis, multicystic dysplastic kidney, and nephroblastoma (Wilms' tumor).
- Mesoblastic nephroma can be cystic in areas due to hemorrhage with cystic degeneration.
- There are 3 histologic variants: classic, cellular, and mixed.
- 50% deliver prior to 34 weeks of gestation and are associated with polyhydramnios; 23% are hypertensive.
- Surgical resection is curative – local recurrence and metastases usually associated with the cellular variant.

CONDITION

Although in general, congenital renal tumors are rare, mesoblastic nephroma is among the most common to present during the first few months of postnatal life, accounting for 50% of all renal masses in the neonate (Campagnola et al., 1998; Jones and Cohen, 2007). Mesoblastic nephroma is also known as fetal renal hamartoma, lyomyomatous hamartoma, and mesenchymal hamartoma (Wigger, 1975; Slasky et al., 1982). These tumors are composed of mesenchymal tissue, in the form of interlacing bundles of ovoid or spindle-shaped cells. Since this "classical" form of mesoblastic nephroma was reported, a cellular variant has been described that may account for a large proportion of cases. Both types can coexist in distinct areas in a given tumor; this is known as a mixed type (Joshi et al., 1986; Pettinato et al., 1989). The cellular type of mesoblastic nephroma accounts for 42% to 63% of all cases (Knezevich et al., 1998; Furtwaengler et al., 2006). The cause of mesoblastic nephroma is unknown, but it has been suggested that mesoblastic nephroma is a differentiated form of Wilms' tumor (Bolande, 1974) or a derivative of secondary mesenchyme (Wigger, 1975). Current opinion favors classification of mesoblastic nephroma as a distinct, usually benign neoplasm arising from renal mesenchyme.

There is much debate as to the nature of mesoblastic nephroma and its biologic behavior. It is estimated that 95% of patients with mesoblastic nephroma do not relapse. The majority of those that either recur locally or metastasize have the cellular variant of mesoblastic nephroma (Bolande, 1974; Howell et al., 1982). The cellular variant has the strongest evidence, given the rarity of this tumor, for associated poor prognosis with a recurrence-free survival of 85% in contrast to 100% for the classic variant (Furtwaengler et al., 2006). This biologic behavior in the cellular variant may be due to a chromosome translocation, which results in the *ETV6* sequence on chromosome 12p13 fusing with the *NTRK3* sequence on chromosome 15q25 (Argani and Beckwith, 2000; Anderson et al., 2006). These genes are thought to result in constitutive dimerization of activating tyrosine kinase mediated growth signals. This translocation is not present in the classic variant and is variably present in the mixed type (Argani and Beckwith, 2000; Anderson et al., 2006; Ahmed et al., 2007).

INCIDENCE

A mesoblastic nephroma is a rare tumor, but accounts for 3% to 10% of all pediatric renal tumors and is the most common renal tumor in infants under three months of age (Glick et al., 2004; Ahmed et al., 2007). Ninety percent of mesoblastic nephromas are diagnosed in the first year of life (Glick et al., 2004). It has been estimated that fewer than 50 cases have been described in utero (Chen et al., 2003; Jones and Cohen, 2007). The rarity of this tumor makes estimates of the incidence of this lesion difficult. In one report, there was a male predominance of 2 to 1 (Furtwaengler et al., 2006). Another

report of 29 cases found a female predominance of 1.6 to 1 (Sanstedt et al., 1985).

SONOGRAPHIC FINDINGS

Ehman et al. (1983) described the first case of mesoblastic nephroma detected prenatally by ultrasound examination—a 4-cm solid mass in the left upper quadrant of a twin fetus at 35 weeks of gestation. They also noted mild-to-moderate polyhydramnios. A nephrectomy performed after birth confirmed the diagnosis of mesoblastic nephroma. Since then, other authors have described the detection of these tumors prenatally with ultrasound imaging during the third trimester (Giulian, 1984; Romano, 1984; Geirsson et al., 1985; Howey et al., 1985; Walter and McGahan, 1985; Appuzio et al., 1986; Yamboa et al., 1986; Burtner and Willard, 1988; Boulot et al., 1989; Kuo et al., 1989; Ohmichi et al., 1989; Rempen et al., 1992; Matsumura et al., 1993; Irsutti et al., 2000; Chen et al., 2003; Won et al., 2002; Yamamoto et al., 2006). However, some of these authors did not consider the diagnosis of mesoblastic nephroma prenatally. Mesoblastic nephroma can present as a large (4 to 8 cm), unilateral renal mass with nodular densities or as diffuse renal enlargement (Figure 112-1). These tumors are predominantly solid, but cystic areas are occasionally seen (Slasky et al., 1982), most likely due to hemorrhage with subsequent cystic degeneration. Unlike Wilms' tumor, there is no well-defined capsule.

Many fetal mesoblastic nephromas are initially detected by ultrasound examination because of a discrepancy between uterine size and gestational dates due to associated polyhydramnios. Polyhydramnios has been detected in most of the published cases of mesoblastic nephroma (Giulian, 1984; Romano, 1984; Geirsson et al., 1985; Howey et al., 1985; Walter and McGahan, 1985; Appuzio et al., 1986; Yamboa et al., 1986; Burtner and Willard, 1988; Boulot et al., 1989; Ohmichi et al., 1989; Rempen et al., 1992). The mechanism of polyhydramnios is unclear (Favara et al., 1968; Howey et al., 1985; Walter and McGahan, 1985). Theories regarding cause include impaired gastrointestinal obstruction due to mass effect of the tumor (Geirsson et al., 1985; Howey et al., 1985) and increased renal blood flow or impaired renal concentrating ability (Perlman et al., 1976; Geirsson et al., 1985), with subsequent increase in fetal urine production (Ohmichi et al., 1989). No matter the cause, over 70% of fetal mesoblastic nephromas will present with polyhydramnios, which may predispose to preterm labor and delivery (Haddad et al., 1996; Glick et al., 2004; Yamamoto et al., 2006).

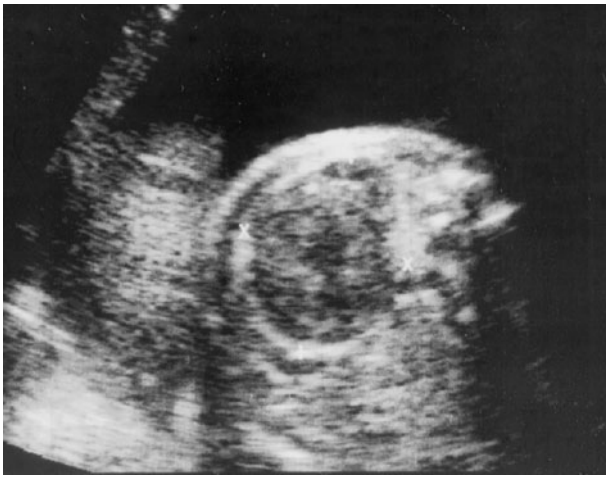

Figure 112-1 Transverse sonographic image of a fetal mesoblastic nephroma demonstrating the complex solid and cystic components of the tumor completely replacing the normal renal structure.

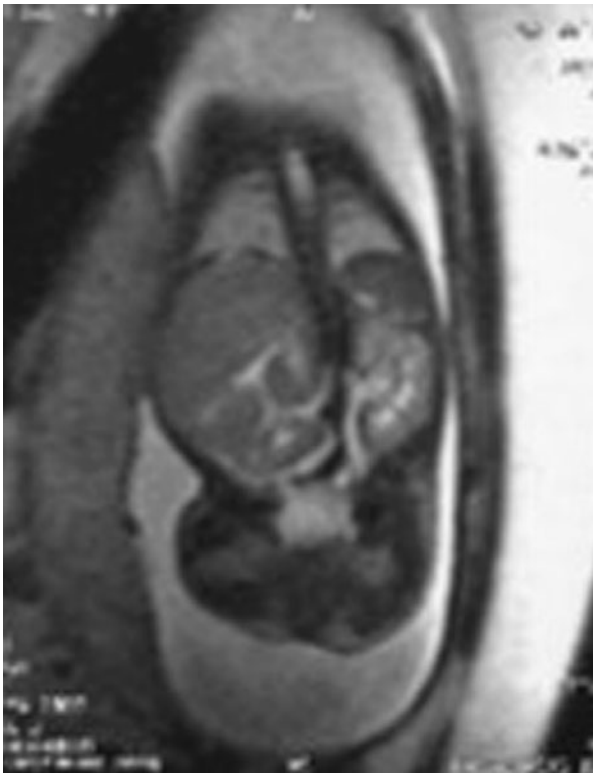

Figure 112-2 Fetal MRI demonstrating the anatomic relations of this very large mesoblastic nephroma elevating the ipsilateral liver and diaphragm, crossing the midline with the ureter visible along the medial and inferior border of the tumor.

Fetal MRI has been reported to aid in the accurate prenatal diagnosis of mesoblastic nephroma (Figure 112-2) (Matsumura et al., 1993; Irsutti et al., 2000; Won et al., 2002; Yamamoto et al., 2006). The advantages of MRI include better tissue contrast and definition of the relationship of the tumor to adjacent structures (Yamamoto et al., 2006). However, the overlap in imaging findings between mesoblastic nephroma and Wilms' tumor often preclude a definitive diagnosis without tissue histology (Toma et al., 1990; Geller et al., 1997; Applegate et al., 1999).

Associated anomalies have been reported with congenital mesoblastic nephroma; these include neuroblastoma (Blank et al., 1978) and central nervous system (Howell et al., 1982; Werb et al., 1992), genitourinary, gastrointestinal, and limb abnormalities (Howell et al., 1982).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of mesoblastic nephroma includes hydronephrosis and multicystic dysplastic kidney, which are both more common than mesoblastic nephroma and appear typically cystic on ultrasound examination. The more malignant nephroblastoma, or Wilms' tumor (see Chapter 116), may be indistinguishable from mesoblastic nephroma antenatally (Giulian, 1984; Walter and McGahan, 1985; Toma et al., 1990; Geller et al., 1997; Applegate et al., 1999). Wilms' tumor usually has a well-defined capsule and, although an embryonic tumor, is more likely to be seen in the infant or young child. Focal renal dysplasia should also be considered in the differential diagnosis (Gordillo et al., 1987; Sanders et al., 1988). In addition, diffuse nephroblastomatosis should be considered, in which case both kidneys are involved and can be seen as acoustic shadowing due to calcifications (Ambrosino et al., 1990). Infantile polycystic kidney disease can be recognized by nonvisualization of the bladder, oligohydramnios, and bilaterally enlarged echogenic kidneys (Rempen et al., 1992). Adult polycystic kidney disease can be presumed in the presence of a positive family history of this condition (see Chapter 79). Kidney enlargement in other inherited disorders, such as Meckel–Gruber syndrome, is usually bilateral.

In the differential diagnosis, one must also rule out masses extending from adjacent organs such as the adrenal gland or the liver. Solid tumors, such as neuroblastoma of the adrenal or extraadrenal neuroblastoma and extrathoracic bronchopulmonary sequestration, may be mistaken for mesoblastic nephroma. Careful sonography can usually distinguish the normal-appearing kidney adjacent to these external tumors.

Other conditions that should be considered in the differential diagnosis include rhabdoid tumor, clear cell sarcoma, angiomyolipoma and ossifying renal tumor of infancy (Marsden and Lawler, 1983; Pinto and Guignard, 1995; Lowe et al., 2000; Glick et al., 2004).

ANTENATAL NATURAL HISTORY

Mesoblastic nephromas are usually benign. In the vast majority of cases, total nephrectomy is curative. However, infiltration of adjacent structures, local recurrence, and metastases have been reported (Fu and Kay, 1973; Joshi et al., 1973; Walker and Richard, 1973; Bolande, 1974; Gonzalez-Crussi et al., 1980; Shen and Yunis, 1980; Howell et al., 1982; Steinfeld et al., 1984). These unusual cases may be due to incomplete excision (Slasky et al., 1982; Beckwith and Weeks, 1986). However, mesenchymal tumors are a heterogeneous group, with malignant tumors comprising one end of the spectrum and the majority (the benign tumors) at the other end (Gonzalez-Crussi et al., 1981; Beckwith and Weeks, 1986; Joshi et al., 1986).

Most of the tumors that recur locally or with distant metastasis fall into the cellular variant of mesoblastic nephroma (Fu and Kay, 1973; Howell et al., 1982; Ahmed et al., 2007). Recurrent disease can be local (Fu and Kay 1973) or due to distant metastases to lung (Gonzalez-Crussi et al., 1980), liver (Patel et al., 2003), heart (Vujanic et al., 1993) or brain (Heidelberger et al., 1993).

MANAGEMENT OF PREGNANCY

Because of the benign nature of most mesoblastic nephromas, if ultrasound examination convincingly shows a renal lesion, it is recommended to allow the pregnancy to go to term (Giulian, 1984). There appears to be a higher incidence of preterm labor and/or preterm rupture of membranes in pregnancies complicated by mesoblastic nephroma, as a result of associated polyhydramnios (Walter and McGahan, 1985; Haddad et al., 1996). In a review of prenatally diagnosed mesoblastic nephroma, 9 of 13 (69%) cases were complicated by preterm labor and/or preterm rupture of membranes as early as 26 weeks of gestation (Appuzio et al., 1986; Rempen et al., 1992). LeClair et al. found that almost half of newborns with mesoblastic nephroma delivered before 34 weeks' (LeClair et al., 2005). In addition, 25% of fetuses showed evidence of fetal distress prompting Cesarean section delivery. Not only were these infants delivered prematurely, but 8 required ventilatory support either due to respiratory distress syndrome or an abdominal mass that compressed the diaphragm. Therefore, due to the risks of prematurity and potential for complications related to mesoblastic nephroma, we recommended delivery of these patients in tertiary care centers to optimize care of the neonate.

Dystocia may complicate these deliveries due to the large size of these renal tumors (Yamboa et al., 1986). There has also been one report of hydrops in association with a large mesoblastic nephroma. Possible mechanisms include obstruction of the portal vein or inferior vena cava circulations, increased vascularity with subsequent arteriovenous shunting, massive hemorrhage into the tumor with resultant anemia, or some combination of these factors (Gray, 1989). Serial ultrasound examinations should be performed to monitor tumor size, amniotic fluid volume, and fetal well being. The prospective parents should be advised that the prognosis for cases of fetal mesoblastic nephroma is excellent with current surgical techniques and close postoperative surveillance for possible recurrence.

FETAL INTERVENTION

There is no fetal treatment for mesoblastic nephroma.

TREATMENT OF THE NEWBORN

The main differential diagnosis in an infant with a large heterogeneous renal mass is between mesoblastic nephroma and

malignant neoplasms, such as Wilms' tumor, clear tumor, clear-cell sarcoma of the kidney, and malignant rhabdoid tumor and ossifying renal tumor of infancy. The infant should be delivered in a tertiary care setting, with consideration given to cesarean section delivery to obviate the potential for dystocia or hemorrhage into the tumor. Once the infant has been stabilized, further preoperative evaluation should include an ultrasound examination with color flow Doppler studies to evaluate for the presence of tumor thrombus within the renal veins or inferior vena cava, as is commonly seen with Wilms' tumor, but is uncommonly associated with mesoblastic nephroma. Computed tomographic scanning of the abdomen is useful to best define the extent of the tumor and plan the surgical resection.

Careful blood pressure monitoring is indicated, as up to 23% of cases of mesoblastic nephroma will have significant hypertension due either to renin production within the tumor or altered renal perfusion by the tumor, inducing renin production by the native kidney (Malone et al., 1989). This will need to be controlled preoperatively. Hypercalcemia may also occur in mesoblastic nephroma as a paraneoplastic phenomenon due to tumor production of parathyroid hormone-like peptides or prostaglandins causing hypercalcemia (Shanbhogue et al., 1986; Jayabose et al., 1988; Yokomori et al., 1988; Tsuchida et al., 1993).

SURGICAL TREATMENT

Radical resection of the tumor is the therapy of choice, and it is usually curative (Bolande, 1974; Wigger, 1975). Although resection alone is usually curative for mesoblastic nephroma, a small percentage may have local recurrence or present later with metastases. It is thought that these local recurrences are due to inadequate resection during the primary procedure. It was observed by Beckwith and Weeks (1986) that many of the specimens of patients in whom metastases subsequently developed showed either focal or diffuse increases in cellularity, with high mitotic rates. Some have suggested that the so-called cellular or atypical congenital mesoblastic nephroma should be treated as a potentially malignant tumor (Joshi et al., 1986). However, a review of all cases of recurrent or metastatic mesoblastic nephroma demonstrated that the cellular variant is not associated with adverse outcome in infants younger than 3 months, with the exception of one instance in which incomplete removal of the tumor was documented (Beckwith and Weeks, 1986).

Because of the tendency to extend into perirenal tissues and subsequently recur, appropriate treatment of mesoblastic nephroma includes a radical surgical approach with efforts to secure wide margins of uninvolved tissue on all aspects of the specimen. In addition, the cellular variant of mesoblastic nephroma carries no adverse prognostic significance in infants younger than three months of age. However, in older infants the demonstration of increased cellularity and high mitotic rate is of some concern because a few patients with such lesions will experience local recurrence or distant metastases. Infants older than 3 months of age with the cellular variant of congenital mesoblastic nephroma should probably receive adjuvant chemotherapy, whereas in infants younger than 3 months of age, resection alone is adequate therapy (Beckwith and Weeks, 1986; Berry, 1987). The proper role for adjuvant chemotherapy mesoblastic nephroma remains controversial (Jones and Cohen, 2007) especially in infants less than 3 months of age in the presence of tumor spillage with the cellular variant. It is believed that cellular variants with genetic characteristics like *ETV-6-NTRK3* gene fusion associated with translocation between chromosomes 12 and 15 may respond better to chemotherapy (Jones and Cohen, 2007). In the setting of recurrent disease, combinations of vincristine, doxorubicin and cyclophosphamide or ifosfamide, carboplatin and etoposide have been used successfully (Ahmed et al., 2007). Chemotherapy can be used either alone or in combination with radiation therapy (Howell et al., 1982; Loeb et al., 2002).

LONG-TERM OUTCOME

Because of the potential in a small percentage of patients with these tumors for local recurrence or distant metastases, these patients need to be followed closely for evidence of recurrence so that they can be treated aggressively. It has been suggested that monthly postnatal ultrasound examinations be used to screen for local recurrence. In addition, if a patient is hypercalcemic preoperatively, calcium levels can be followed as an indicator of recurrent disease. The majority of recurrences, either local or metastatic, occur within one year.

GENETICS AND RECURRENCE RISK

Mesoblastic nephroma is not known to be familial and there is no known risk of recurrence in subsequent siblings.

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113 CHAPTER Neuroblastoma

Key Points

- Most common solid tumor in infants.
- Neuroblastomas are generally diagnosed by sonography in the third trimester, and can be cystic, solid, or both.
- The differential diagnosis includes hydronephrosis, multicystic kidney, obstructive duplex collecting system, Wilms' tumor, mesoblastic nephroma, and adrenal hemorrhage.
- Neuroblastoma in situ may be responsible for many prenatally diagnosed cystic neuroblastomas, and may be due to delayed regression of neuroblasts.
- 83% of prenatally diagnosed neuroblastomas will be localized stage I or II disease.
- Neuroblastoma is stage III or IVS in only 16% of cases.
- Poor prognostic signs, such as N-myc amplification, occur in less than 5% of cases.
- Prenatal complications such as fetal hydrops, hepatomegaly, and maternal hypertension occur rarely.

CONDITION

Neuroblastomas arise from undifferentiated neural tissue of the adrenal medulla (40% to 70%), or extraadrenal sympathetic ganglia (30% to 60%), in the abdomen, thorax, pelvis, or head and neck (Birner, 1961; Beckwith and Perrin, 1963; Schneider et al., 1965; Janetschek et al., 1984; Ferraro et al., 1988). Neuroblastic nodules appear to be normal fetal structures within the adrenal gland that regress or differentiate throughout gestation. Greater numbers of these nodules are present early in gestation than at birth or during early infancy (Turkel and Habashi, 1974; Ikeda et al., 1981; Grosfeld et al., 1993). Neuroblastic nodules were found in 100% of the adrenal glands studied in second trimester abortuses (Turkel and Habashi, 1974; Ikeda et al., 1981) (Figure 113-1). Postnatal autopsy studies of newborn and young infants who died of unrelated causes reveal nodules to be present in 0.5% to 2.5% of carefully sectioned specimens (Beckwith and Perrin, 1963; Guin et al., 1969; Grosfeld et al., 1993). These figures contrast with the incidence of symptomatic neuroblastoma of 1 in 10,000 to 1 in 30,000 children. This calls into question the clinical significance of these early lesions and the need for treatment. It is also of interest that adrenal cysts are more commonly seen in fetal neuroblastoma, but are relatively uncommon in postnatal life (Turkel and Habashi, 1974). Cystic change may also represent a phase of normal adrenal development, thus accounting for prenatal detection of sonographically apparent but possibly clinically insignificant tumors (Tubergen and Heyn, 1970) (Figure 113-2). Although these tumors may represent rests of neural tissue with persistence

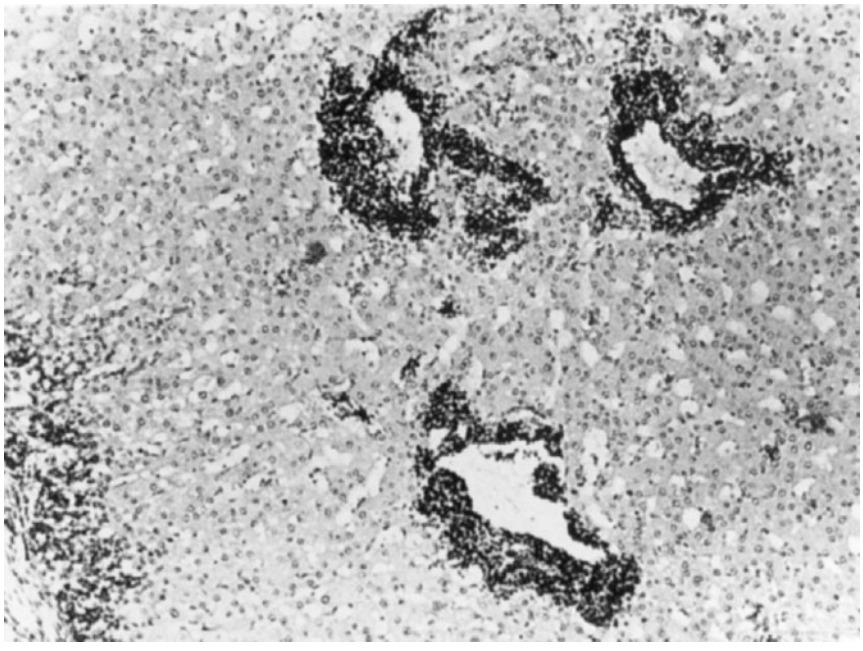

Figure 113-1 Histologic section demonstrating fetal neuroblastic nodules, or rests.

into neonatal life, the potential for malignant transformation due to defective regression or differentiation must be considered (Turkel and Habashi, 1974; Grosfeld et al., 1993). Beckwith referred to these lesions as "neuroblastoma in situ" because these aggregates of neuroblasts exhibited mitotic figures and infiltration of the adult cortex (Beckwith and Perrin, 1963).

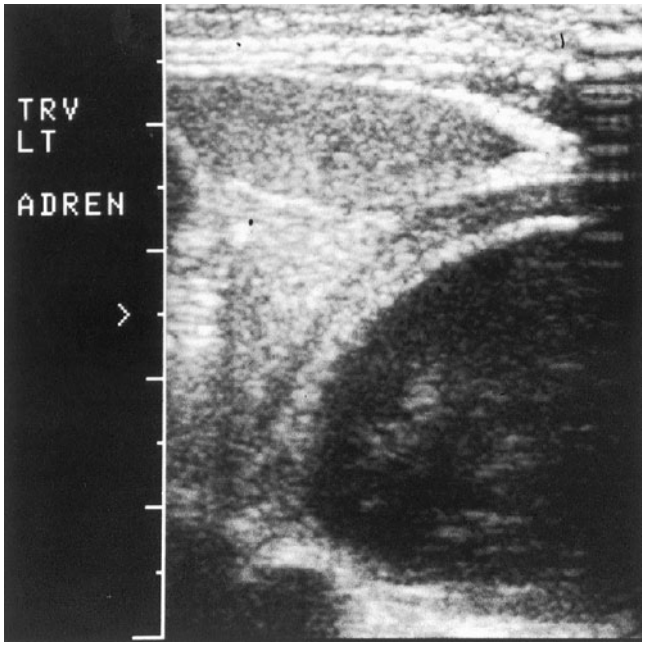

Figure 113-2 Prenatal sonographic image of an adrenal cyst from a fetal neuroblastoma. *(Reprinted, with permission, from Garmel SH, Crombleholme TM, Semple JP, et al. Prenatal diagnosis and management of fetal tumors.* Semin Perinatol. *1994b;18:350-365.)*

The results of mass infant screening programs in Japan and Canada using urinary vanillylmandelic acid (VMA) and homovanillic acid (HVA) support the view that neuroblastoma in situ may not represent clinically significant disease (Bessho et al., 1991; Murphy et al., 1991; Grosfeld et al., 1993; Woods et al., 2002). Screening infants at 6 months of age has resulted in a doubling of the incidence of neuroblastoma detected in infants. However, the expected fall in the incidence of more advanced stage neuroblastoma detected in older age groups was not seen. Furthermore, survival in the screened groups has approached 100%. The asymptomatic cases detected by screening may represent a subset of tumors destined to regress or differentiate without posing any clinical risk. This would explain both the high incidence in infants detected by screening programs and their excellent survival. The group detected by newborn screening may be the same subset of tumors detected prenatally with ultrasound examination.

In contrast, there is a subset of neuroblastoma diagnosed in utero or in newborns that does display an aggressive biologic behavior. Among the 300 cases of fetal or perinatal neuroblastoma reported, 83% were stage I or II, but there were also one each with stage III and IV disease (Fenart et al., 1983; Gadwood and Reynes, 1983; Sones, 1983; Newton et al., 1985; Atkinson et al., 1986; deFilippi et al., 1986; Giulian et al., 1986; Tovar et al., 1988; Kurtz and Hilbert, 1989; Pley et al., 1989; Forman et al., 1990; Hosoda et al., 1992; Suresh et al., 1993; Crombleholme et al., 1994a; Goldstein et al., 1994; Garmel et al., 1994b; Acharya et al., 1997; Granata et al., 2000; Sauvat et al., 2002; Nuchtern, 2006) and five with stage IVS disease (Hainaut et al., 1987; Ho et al., 1993). All children affected with stage IV disease died. In a review of congenital neuroblastoma reported between 1985 and 1991, Jennings et al. (1993) found 14 stillbirths, 44 neonatal deaths, and 2 late deaths, with only 10 survivors. Eight cases were associated with metastases to the placenta, and 1 had umbilical cord

metastases. This subset of aggressive tumors associated with such poor outcomes may be quite different from the subset detected by the Japanese screening programs (Grosfeld et al., 1993) or by prenatal ultrasound examination.

The cause of neuroblastoma is unclear, although most cases appear sporadically (Behrman, 1992). At least one hypothesis is that antenatal factors play a role, with some adverse stimulus or stimuli occurring in late pregnancy. Preterm delivery is protective, while growth restricted term infants are at risk (Johnson and Spitz, 1985). There have been reports of congenital neuroblastoma in association with maternal phenytoin and phenobarbital use (Sherman and Roizen, 1976; Allen et al., 1980). The causative effect of phenytoin in neuroblastoma has been questioned and this is most likely a coincidental finding. In addition, some epidemiologic studies have suggested an association with maternal diabetes (Chow et al., 2007) and antenatal exposure to codeine (Cook et al., 2004).

INCIDENCE

Neuroblastoma is one of the most common tumors of infancy and childhood, with a clinical incidence of between 1 in 10,000 and 1 in 30,000 individuals (Janetschek et al., 1984; Fowlie et al., 1986; Goodman et al., 1999). Gurney et al., estimated the rate of neuroblastoma in the U.S. at 58 per 1,000,000 infants per year (Gurney et al., 1997). Neuroblastoma may be more common in white children than in other ethnic groups, and more common in male than in female children (Miller et al., 1968; Turkel and Habashi, 1974; Askin and Geschickter, 1985; Behrman, 1992). It is estimated that 16% of infant neuroblastomas are diagnosed in the first month of life and 41% within the first three months (Goodman et al., 1999).

SONOGRAPHIC FINDINGS

Since the first case of prenatally detected neuroblastoma was reported by Fenart et al., 300 cases of neuroblastoma have been suspected or diagnosed by prenatal ultrasound examination (Nuchtern, 2006; Fenart et al., 1983). All have been visualized during the third trimester of pregnancy (Fenart et al., 1983; Gadwood and Reynes, 1983; Sones, 1983; Janetschek et al., 1984; Newton et al., 1985; Atkinson et al., 1986; deFilippi et al., 1986; Fowlie et al., 1986; Giulian et al., 1986; Hainaut et al., 1987; Ferraro et al., 1988; Tovar et al., 1988; Kurtz and Hilbert, 1989; Pley et al., 1989; Forman et al., 1990; Hosoda et al., 1992; Liyanage and Katoch, 1992; Ho et al., 1993; Jaffa et al., 1993; Jennings et al., 1993; Suresh et al., 1993; Crombleholme et al., 1994a; Garmel et al., 1994b; Goldstein et al., 1994; Acharya et al., 1997; Granata et al., 2000; Sauvat et al., 2002). The sonographic findings described by these studies were quite variable. The primary tumor is often small (only a few millimeters or centimeters in greatest diameter). Ninety percent of cases involve the adrenal gland, creating difficulties in distinction between the mass itself and the upper pole of the ipsilateral kidney. Cystic and solid areas within the mass are typically seen, which may be related to hemorrhage and necrosis of the tumor (Atkinson et al., 1986). Purely cystic lesions have also been reported in fetal neuroblastoma and may indicate a more favorable prognosis (Atkinson et al., 1986; Kurtz and Hilbert, 1989; Crombleholme et al., 1994a; Garmel et al., 1994b; Hamada et al., 1999; Petit et al., 2001; Lopez Alvarez-Buhilla et al., 2002; Tanaka et al., 2003; Athanassiadou et al., 2005). Occasionally, calcifications can be seen within the tumor (Potter, 1961; Fowlie et al., 1986; Giulian et al., 1986). Calcifications within neuroblastomas are often described as microcalcifications with acoustic shadowing (Kurtz and Hilbert, 1989; Gorincour et al., 2003). The tumor is usually well encapsulated and may displace the kidney inferiorly and laterally but preserves the renal outline (Figure 113-3A and B). If arising in the sympathetic ganglia, the mass may be seen in the chest, cervical region, or intra-abdominal paravertebral locations. Cervical lesions sufficiently large to compromise the fetal airway have been reported (Gorincour et al., 2003), as have large retroperitoneal masses presenting as flank masses that are readily palpable on physical examination (Nagasako et al., 2004).

Occult neuroblastomas are rarely metastatic, but prenatal detection of liver metastases has been reported (Liyanage and Katoch, 1992; Jaffa et al., 1993; Nagasako et al., 2004). A suprarenal mass associated with hepatomegaly is highly suggestive of the diagnosis of neuroblastoma. Likewise, if a liver mass is seen on prenatal ultrasound examination, one needs to carefully examine all neural crest regions, especially in the renal and suprarenal areas, to rule out a primary tumor locus (Jaffa et al., 1993). Several cases have been reported with neuroblastoma metastatic to the placenta and umbilical cord. Careful imaging of the placenta and umbilical cord is also indicated because of reports of metastases to these areas. Fetoplacental metastases have been also reported in monochorionic twins with a primary tumor detectable in only one twin, with both having simultaneous evidence of metastatic disease (Adaletli et al., 2006).

Occasionally, ultrasound examination may also reveal polyhydramnios and/or hydrops (Falkinburg and Kay, 1953; Forman et al., 1990). Although the underlying mechanism is unknown, numerous hypotheses have been proposed, including hepatomegaly with subsequent mechanical obstruction of the umbilical vein or vena cava (Moss and Kaplan, 1978; Van der Slikke and Balk, 1980), compromised liver function with resultant hypoproteinemia (Adzick and Harrison, 1994); metastatic involvement of the placenta with placentomegaly and hydrops (Janetschek et al., 1984), tumor infiltration of bone marrow with subsequent anemia and heart failure (Moss and Kaplan, 1987), or arrhythmia and heart failure due to catecholamine release (Moss and Kaplan, 1987).

Malformations have occasionally been noted in association with neuroblastoma in children, including microcephaly, hydrocephaly, absence of the corpus callosum,

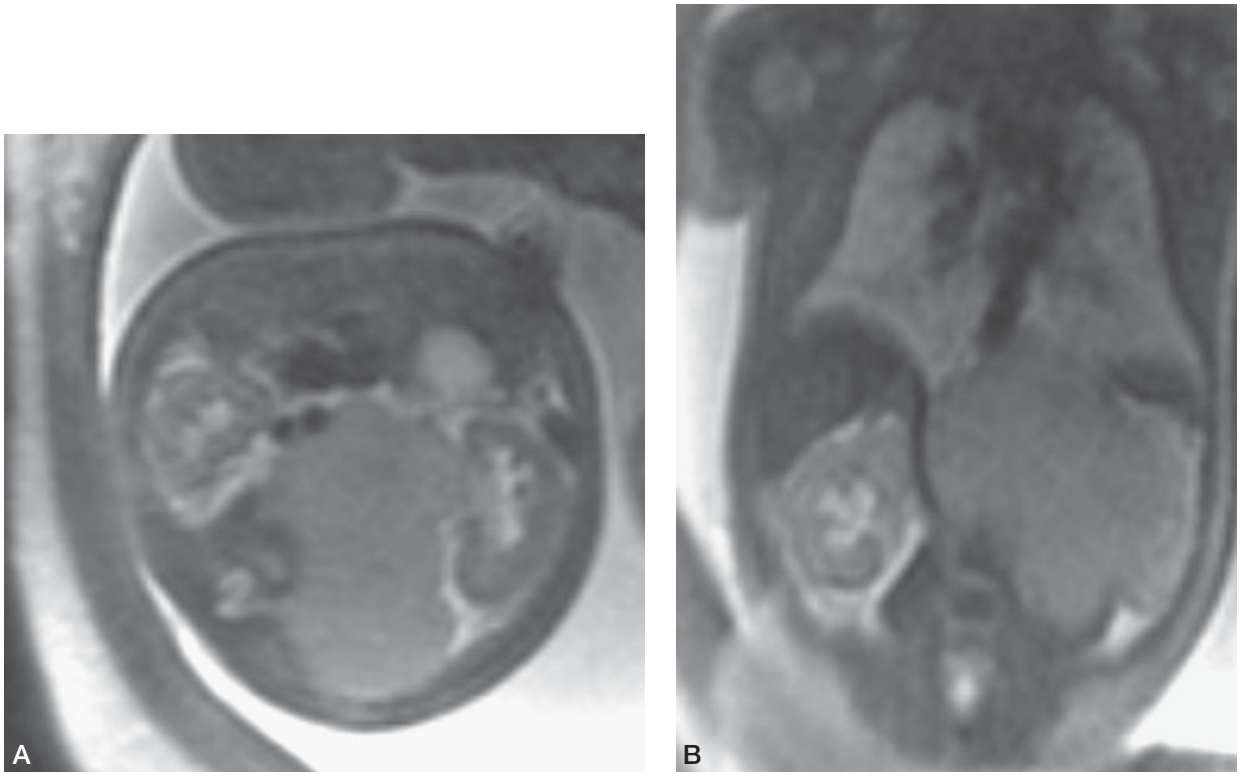

Figure 113-3 **A.** Axial image on fetal MRI of a large neuroblastoma arising from the retroperitoneum. **B.** Coronal image of same fetus demonstrating very large neuroblastoma.

cleft lip and palate, tracheoesophageal fistula, heart defects, skeletal abnormalities, genitourinary abnormalities, polydactyly, and single umbilical artery (Potter and Parrish, 1942; Kouyoumdjian and McDonald, 1951; Bodian, 1963; Berry et al., 1970; Andersen and Hariri, 1983). A consistent pattern of associated anomalies has not been demonstrated however, and the majority have been isolated cases of fetal neuroblastomas (Miller, 1966; Sy and Edmonson, 1968; Berry et al., 1970).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis in neuroblastoma is extensive, as these tumors can be found in the adrenal gland and elsewhere along the sympathetic ganglia. The involvement of the adrenals can be mistaken for hydronephrosis, multicystic kidney, or upper-pole cystic dysplasia seen in obstructive duplex collecting systems, Wilms' tumor or mesoblastic nephroma unless a clear distinction from the adjacent kidney is made. Less common entities are outlined in Table 113-1. Demonstration of low-impedance waveforms by color Doppler studies and flow mapping may be helpful in differentiating neuroblastoma from adrenal hemorrhage (Goldstein et al., 1994). If the liver is involved, hamartoma, hepatoblastoma, and hemangioma must be considered. Subdiaphragmatic extralobar pulmonary sequestrations are predominantly left-sided, solid, with echogenic appearance and occur only one-third

Table 113-1

Differential Diagnosis of Fetal Suprarenal Mass or Cyst

Adrenal hematoma
Duplex collecting system with dysplastic changes
Neuroblastoma
Extralobar bronchopulmonary sequestration
Liver cyst
Hepatoblastoma
Lymphangioma
Mesenteric cyst
Meconium cyst
Splenic cyst

as frequently as neuroblastomas (Curtis et al., 1997). A case report of a solid neck mass seen prenatally on ultrasound examination was found postmortem to be consistent with either primary or metastatic cervical neuroblastoma (Gadwood and Reynes, 1983). In this case, the differential diagnosis included cystic hygroma, neural tube defect, cervical teratoma, and goiter. In one case report of cerebral neuroblastoma, the differential diagnosis included teratoma, glioblastoma, and craniopharyngioma. Prenatal tumor biopsy confirmed the diagnosis of neuroblastoma (Suresh et al., 1993).

ANTENATAL NATURAL HISTORY

Our understanding of the antenatal natural history of prenatally diagnosed neuroblastoma is still evolving, and much remains uncertain. The incidence of adrenal neuroblastoma in situ at neonatal autopsy has been reported to occur in 1 of 40 patients dying from unrelated causes (Grosfeld et al., 1993). The majority of occult neuroblastomas are most likely developmental variants, which regress spontaneously before becoming clinically evident, or differentiate into benign ganglioneuromas (Beckwith and Perrin, 1963; Miller et al., 1968; Turkel and Habashi, 1974; Pley et al., 1989).

Among the 300 reported cases of fetal or perinatal neuroblastoma, the vast majority developed in the adrenal glands, with rare cases of intrathoracic, intracranial tumor, or an unknown primary site (Gadwood and Reynes, 1983; deFilippi et al., 1986; Jaffa et al., 1993; Ho et al., 1993; Suresh et al., 1993; Acharya et al., 1997; Granata et al., 2000; Sauvat et al., 2002). Eighty-three percent of these neuroblastomas were stage I or II, only 16.6% were stage III, IV, or IVS (Gadwood and Reynes, 1983; Newton et al., 1985; Hainaut et al., 1987; Kurtz and Hilbert, 1989; Liyanage and Katoch, 1992; Ho et al., 1993; Jaffa et al., 1993; Suresh et al., 1993; Acharya et al., 1997; Granata et al., 2000; Sauvat et al., 2002). It is interesting that in two patients initially diagnosed and treated as stage I postnatally, hepatic metastases developed and later evolved to stage IV (Fenart et al., 1983; Ferraro et al., 1988). One patient with neuroblastoma initially diagnosed and treated as stage II later had hepatic and bone marrow metastases, which evolved into stage IVS (Ho et al., 1993). These cases underscore the need for close postoperative surveillance, even in patients with stage I disease. Hydrops developed in three fetuses with stage IV or IVS and liver metastases (Gadwood and Reynes, 1983; Newton et al., 1985; Hainaut et al., 1987). In addition, hypertension and preeclampsia reportedly developed in three pregnant women, thought to be induced by catecholamines secreted from functional tumors although it was not documented (Newton et al., 1985; Pley et al., 1989; Jennings et al., 1993).

The two most important factors in the prognosis of clinical neuroblastoma are the age of the patient at diagnosis and the stage of the disease. The overall survival is only 10% to 20% in children presenting after 1 year of age, but is greater than 90% in patients younger than 1 year of age at the time of diagnosis (Estroff et al., 1991; Grosfeld et al., 1993). Patients with disease at an earlier stage and well-differentiated tumors have a better prognosis than those with disease at a more advanced stage and poorly differentiated tumors. Early diagnosis is important in identifying patients prior to 1 year of age and at an early stage of disease. The increasing use of prenatal ultrasound imaging may allow diagnosis at a younger age and earlier stage with the hope of improved survival. The caveat is that the clinical significance of fetal neuroblastoma remains unknown. It is not clear that the natural history of fetal neuroblastoma parallels that of clinical neuroblastoma presenting later in life. The true prenatal natural history of fetal neuroblastoma may never be determined because potentially malignant tumors are rarely managed expectantly. The Children's Oncology Group is conducting a clinical trial of expectant observation for infants with small stage I neuroblastomas diagnosed either prenatally or within the first 6 months of life (Nuchtern, 2006). Because of this we may be subjecting neonates, many of whom have biologically benign lesions, to unnecessary risks of surgery and chemotherapy.

MANAGEMENT OF PREGNANCY

Serial ultrasound examinations to assess tumor size, amniotic fluid volume, and fetal well-being play an important role in pregnancy management. A search should also be made for evidence of metastatic spread. An attempt should be made to stage the disease prenatally by sonographic examination. The presence of extensive hepatic metastases places the fetus at markedly increased risk for the development of hydrops. Significant and rapid tumor growth has been noted in at least two reports and may not be predictable (Janetschek et al., 1984; Fowlie et al., 1986). Others have reported an association with placentomegaly and hydrops, with subsequent death in utero or during early neonatal life (Potter and Parrish, 1942; Birner, 1961; Anders et al., 1973; Van der Slikke and Balk, 1980; Gadwood and Reynes, 1983; Newton et al., 1985; Hainaut et al., 1987; Jaffa et al., 1993). Because of the poor prognosis, delivery is recommended if hydrops develops. In one case, the rapid growth of the component of the neuroblastoma extending into the spinal canal resulted in irreversible paralysis (Nagasako et al., 2004). The authors speculated that early delivery to prevent cord compression might have prevented paralysis.

Dystocia at delivery has been reported due to liver enlargement with capsule rupture and subsequent hemoperitoneum (Hagstrom, 1929; Askin and Geschickter, 1985; Birner, 1961; Potter, 1961). Cesarean section should be considered to avoid tumor hemorrhage during labor when the neuroblastoma is large, as has been reported by Murthy, Weinberg, and others (Weinberg and Radman, 1943; Murthy et al., 1978; Jaffa et al., 1993). However, Ho et al. (1993) reported no peripartum delivery complications in their series. We recommend an ultrasound examination late in gestation to evaluate the likelihood of dystocia and the need for cesarean section.

Maternal symptoms related to fetal catacholamine production, including sweating, flushing, palpitations and hypertension, have been reported during the third trimester of pregnancy (Voute et al., 1970; Newton et al., 1985). Development of hypertension is a potential complication in pregnancies associated with either a functioning fetal adrenal tumor or a hydropic fetus (Nicolay and Gainey, 1964; Voute et al., 1970; Newton et al., 1985). Early delivery may be indicated if maternal health is jeopardized. Delivery should take place at a tertiary care center, with neonatologists, pediatric surgeons and oncologists available.

It has been suggested that a 24-hour maternal urine assay or amniocentesis for fetal urinary catecholamine metabolites (VMA, HVA) may be helpful when the prenatal diagnosis of neuroblastoma is unclear or the cause of maternal hypertension is suspected (Zambotti et al., 1975; Newton et al., 1985; Crombleholme et al., 1994a; Garmel et al., 1994b). However, most neuroblastomas are nonfunctional, and thus far, amniotic fluid catecholamine studies have not been helpful in establishing the prenatal diagnosis of neuroblastoma (Hosoda et al., 1992). Therefore, in the absence of maternal or fetal complications, no invasive diagnostic testing is warranted, but serial examinations of the mother and fetus are recommended (Crombleholme et al., 1994a; Garmel et al., 1994b).

FETAL INTERVENTION

There is currently no indication for fetal intervention in fetal neuroblastoma. However, if fetal or maternal complications arise, early delivery should be considered in cases of catecholamine-induced hypertension or fetal hydrops. Early delivery may be warranted if ultrasound or MRI demonstrates intraspinal extension of the tumor. If the neuroblastoma is rapidly growing, the spinal extension may cause cord compression and urgent delivery may be warranted.

TREATMENT OF THE NEWBORN

An infant with a prenatal diagnosis of suspected fetal neuroblastoma should undergo a detailed physical examination. In cases of stage IVS disease, bluish subcutaneous nodules (the so-called "blueberry muffin" sign) from metastatic neuroblastoma may be seen all over the infant's body. The blood pressure should be noted prior to and during palpation of the suspected tumor mass. Among postnatal neuroblastomas, approximately 20% may release vasoactive peptides on palpation. The abdomen should be gently palpated to discern an abdominal mass and its relationship to other viscera. The liver should be assessed for size and evidence of metastases. Similarly, gentle palpation of a cervical mass will offer clues to histology and relationship to adjacent structures.

The newborn with suspected congenital neuroblastoma should have plain radiography of the abdomen, chest, or neck region (depending on tumor location). Neuroblastoma has characteristic finely stippled calcifications. A postnatal ultrasound examination may be useful to correlate with prenatal findings. Chest radiography should be performed to exclude pulmonary metastases. In most instances a computed tomographic (CT) scan is indicated to more accurately stage the disease and define the extent of the primary tumor (Figure 113-4).

Urine should be collected for spot measurement of catecholamines and tumor metabolites, including epinephrine, norepinephrine, dopamine, VMA, and HVA. Baseline liver function tests should be determined in all patients even without evidence of hepatic metastases. Serum ferritin and neuron-specific enolase should be assayed, as they have

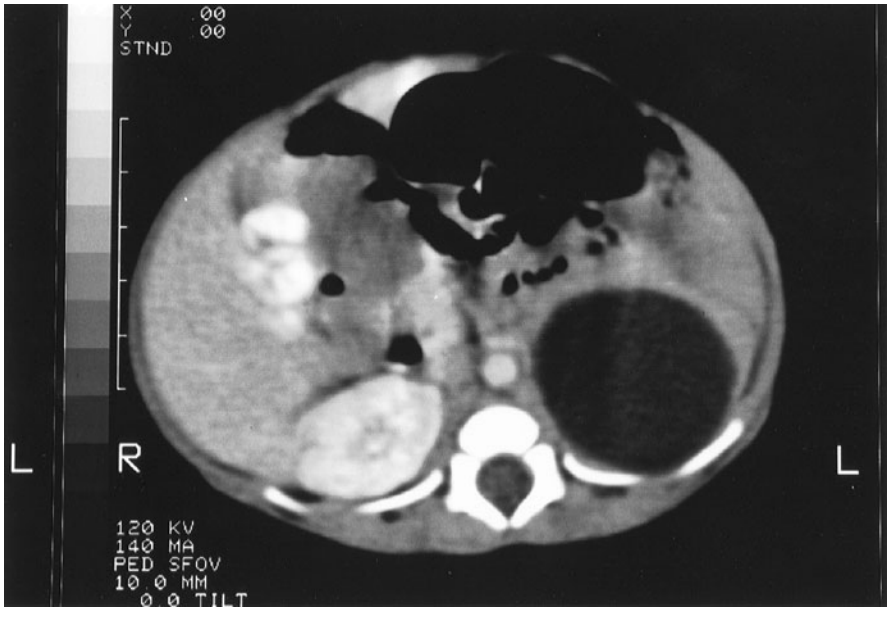

Figure 113-4 CT of newborn diagnosed with fetal neuroblastoma.

prognostic significance in patients less than 1 year of age. As part of the preoperative staging, a technetium-99m bone scan, and bone marrow aspiration and biopsy should be performed. ^{123}I-MIBG and ^{99m}Tc-MDP scintigraphy can be useful in identifying metastatic disease (Sauvat et al., 2002; Kushner, 2004).

The child should undergo surgery for biopsy, staging, and resection of the primary tumor, if possible without jeopardizing adjacent structures. Similarly, in stage IVS disease, resection of the primary tumor is indicated. This will provide tissue for determination of N-*myc* amplification and DNA ploidy. In stage IVS disease, with the presence of diploid DNA complement and N-*myc* amplification, chemotherapy is indicated. In the absence of these findings, observation alone is indicated. The treatment of neuroblastoma depends on the clinical staging. In stage I (primary with regional or distant metastases) or stage II (regional lymph node metastases but no distant metastases), surgery alone is sufficient. But in stage III (tumor extends beyond midline and bilateral lymph nodes may be involved) or stage IV (distant metastases) preoperative chemotherapy is indicated.

LONG-TERM OUTCOME

The newborn with congenital neuroblastoma may initially present with stage I disease that subsequently progresses. This does not represent disease recurrence but rather a delayed presentation of metastases, which results in restaging to stage IVS or IV, which requires chemotherapy. As with all pediatric oncology patients, close long-term follow-up is essential even after completion of therapy to ensure early detection of recurrence. Overall, the long-term survival in prenatally diagnosed neuroblastoma is over 90% (Nuchtern, 2006).

GENETICS AND RECURRENCE RISK

Several cytogenetic abnormalities can be seen in neuroblastoma, including deletion of the short arm of chromosome 1, abnormal chromosome fragments known as "double minutes" (DMs, N-*myc* amplification), and integrated homogeneously staining regions (HSRs) (Brodeur et al., 1981; Brodeur and Fong, 1989). The chromosome 1p deletion may represent loss of a tumor suppressor gene involved in neuroblastoma, while the DMs and the HSRs may represent gene amplification. Neuroblastomas can be familial, but no characteristic genetic syndrome or congenital anomaly is associated with a predisposition for this tumor. The proto-oncogene N-*myc* was found initially because it was amplified in neuroblastoma cell lines (Schwab et al., 1983). N-*myc* amplification (3- to 300-fold) is found in primary neuroblastoma and is associated with advanced stages of disease, rapid progression, and poor outcome (Brodeur et al., 1984; Seeger et al., 1985; Brodeur, 1990). Neuroblastomas with favorable prognoses are diagnosed early in life, at an early stage, with hyperdiploid karyotypes, and without abnormalities of chromosome 1p or N-*myc* amplification (Jennings et al., 1993). More than 90% of perinatal neuroblastomas have a DNA index of >1, which is associated with a better prognosis in infants (Acharya et al., 1997; Granata et al., 2000; Sauvat et al., 2002). In addition, less than 5% of perinatal neuroblastomas have N-*myc* amplification (Acharya et al., 1997; Granata et al., 2000; Sauvat et al., 2002).

Familial cases of neuroblastoma have been observed in siblings, identical twins, and one case in which the mother and child were both affected (Pendergrass and Hanson, 1976; Emery et al., 1983; Grotting et al., 1983; Gorincour et al., 2003). Neuroblastoma has also been reported in patients with the Beckwith–Wiedemann syndrome, pancreatic islet-cell dysplasia, and infants born to mothers taking phenytoin. There have also been occasional reports of familial neuroblastoma. One report involved four or five siblings, which suggests that some neuroblastomas may be inherited as an autosomal dominant trait (Dodge and Benner, 1945; Chatten and Voorhees, 1967). There is also an increased incidence of neuroblastoma in infants with the fetal alcohol syndrome (Seeler et al., 1979; Kinney et al., 1980). Neuroblastoma has also been reported in infants with both rectosigmoid and total colonic Hirschsprung's disease (Carachi et al., 1982; Michna et al., 1988).

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114 CHAPTER Retinoblastoma

Key Points

- Most common intraocular tumor of childhood, with only a few cases diagnosed antenatally.
- Retinoblastoma develops in cells that have mutations in both copies of the gene *RB1*, which is located on chromosome 13q14.
- Retinoblastoma may be nonheritable or heritable. When familial, a single RB1 mutation is inherited as an autosomal dominant condition. Tumor formation then requires a second mutation. Heritable forms are predisposed to second malignancies, such as sarcoma.
- Prenatal sonography is an extremely insensitive screening technique for families at risk for recurrence. DNA diagnosis is definitive if the RB1 mutation is known.
- In fetuses with a suspected retinoblastoma and negative family history, work-up should include chromosome analysis with FISH probes for 13q14 deletion, level II sonography, and delivery in a tertiary setting.
- Many postnatal treatment options exist, including radiation, enucleation, and chemotherapy.

CONDITION

Retinoblastoma is the most common intraocular tumor of childhood (Donaldson et al., 1993). It is a malignant tumor that arises from the embryonic neural retina. This tumor is thought to be congenital, although it may not be recognized at birth. Although it usually presents during early childhood, there has been at least one report of retinoblastoma diagnosed in utero (Maat-Kievit et al., 1993). Retinoblastoma occurs in both sporadic and inherited forms, with the hereditary type predisposing to other malignant tumors (Abramson et al., 1984; Murphree and Benedict, 1984; Roarty et al., 1988; Wilson et al., 1996). Retinoblastoma is usually characterized by rapid growth, enlarging over a period of only weeks to destroy increasing amounts of the retina. The tumor can fill the eye, either by direct enlargement or by growth of tumor seeds. Once the globe is filled by the tumor, orbital and intracranial extension may occur. Retinoblastoma has been said to have a spontaneous regression rate of 1%, but this figure is sometimes confused with two separate processes (Gallie and Phillips, 1982). In the first process there is true regression after an enlarged intraocular tumor becomes totally necrotic. The tumor subsequently atrophies, resulting in a small, disorganized blind eye. The second process occurs in a functional eye as a benign variant of retinoblastoma, which has been termed "retinocytoma" or "retinoma" (Gallie and Phillips, 1982; Marga et al., 1983; Zimmerman, 1985). These tumors are usually composed of viable, benign-appearing tumor cells with a high degree of photoreceptor differentiation. On ophthalmoscopic examination, retinomas have an appearance similar to retinoblastomas that have undergone regression following radiotherapy. Despite the presence of the retinoma, vision is usually normal, but the genetic implications are the same as for retinoblastoma.

The majority of cases of retinoblastoma are diagnosed while the tumor remains confined to the eye. In contrast, in prenatal diagnosis, because of the insensitivity of sonographic evaluation of the eye, to be detected there must be gross extension to the orbit (Maat-Kievit et al., 1993). The most common postnatal sign in retinoblastoma is leukokoria of one or both eyes, which has been termed the "cat's-eye reflex" but which parents described as an unusual appearance of the eye (Donaldson et al., 1993). The next most common presenting sign is strabismus, which occurs when the tumor arises in the macula, causing loss of central vision and, therefore, loss of the fusional reflex so that the eye may drift, resulting in esotropia or exotropia. Other less common signs are orbital inflammation, hyphema, fixed pupil, and heterochromic irides. Vision loss is not a typical symptom at presentation because young children do not report unilaterally decreased vision. In addition, intraocular tumors are not painful unless secondary glaucoma or inflammation is present. Between 20% and 30% of cases are bilateral at the time of initial diagnosis. In these cases the disease is often multifocal, with several tumors in each eye. The presentation in utero is that of a sonographically detected ocular mass, which is irregular and echogenic, with extension beyond the orbit itself.

INCIDENCE

The incidence of retinoblastoma is estimated to be 1 in 15,000 to 1 in 34,000 livebirths (Devesa, 1975; Shields and Shields, 1990; Salim et al., 1998). The estimated frequency of bilateral cases of retinoblastoma in children is between 20% and 30% (Donaldson et al., 1993). There is no known racial or gender predisposition for this tumor. Retinoblastoma is a congenital tumor and is present at birth, although it is not often recognized at that time. Eighty percent of cases are diagnosed before the age of 3 to 4 years, with a mean time of presentation at 2 years of age. Bilateral retinoblastoma typically becomes clinically apparent earlier; the average age at diagnosis is 12 months (Shields and Shields, 1990). In rare cases, multiple congenital anomalies may be seen in association with retinoblastoma. However, these cases represent only 0.05% of cases of retinoblastoma reported in the United States (Jensen and Miller, 1971). The reported anomalies include congenital heart disease, cleft palate, Bloch–Sulzberger syndrome, infantile corital hyperasthosis, dentinogenesis imperfecta, incontinentia pigmenti, and familial congenital cataracts (Green, 1985).

SONOGRAPHIC FINDINGS

Only a few cases of retinoblastoma have been antenatally diagnosed (Maat-Kievit et al., 1993; Salim et al., 1998; Kodzov et al., 2002; Lehman, 2003). In the case reported by Maat-Kievit et al. (1993), a fetus at 21 weeks of gestation had an oval-shaped mass protruding from the right side of the face (Figure 114-1). The tumor was an irregular echogenic mass measuring 8 × 6 × 3 cm. The tumor was covered by a thin membrane with an echolucent rim between the membrane

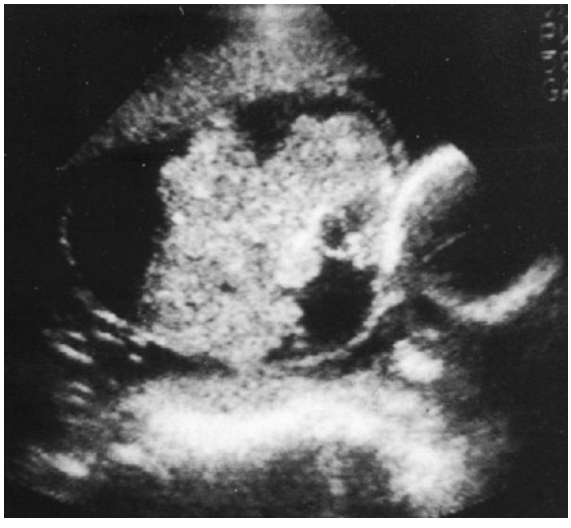

Figure 114-1 Fetus at 22 weeks of gestation with a large tumor originating from the right eye. (*Reprinted from Maat-Kievit JA, Oepkes D, Hartwig NG, et al. A large retinoblastoma detected in a fetus at 21 weeks of gestation.* Prenat Diagn. *1993;13:377-384. Copyright John Wiley & Sons Limited. Reproduced with permission.*)

Table 114-1

Differential Diagnosis of Facial/Orbital Tumors Detected by Prenatal Sonographic Studies

Epignathus Sonolucent and (highly) echogenic areas Irregular shape Localization: nasopharyngeal area
Cephalocele Intracranial abnormalities, hydrocephaly, skull defect Smooth, rounded shape Localization: skull
Hemangioma Echogenic or sonolucent areas Pulsations, flow (Doppler) Localization: oral cavity
Myoblastoma Echogenic with small sonolucent areas Multilobular shape Localization: oral cavity
Dacryocystocele Sonolucent Small cyst Localization: inferomedial to the orbit
Retinoblastoma Irregular, echogenic, surrounded by sonolucent area Oval shape, covered by membrane Localization: eye

Source: Maat-Kievit JA, Oepkes D, Hartwig NG, et al. A large retinoblastoma detected in a fetus at 21 weeks of gestation. Prenat Diagn *1993;13:377-384.*

and the tumor. The majority of the face was obscured by the tumor. The tumor deformed the normal anatomy of the facial bones, and the contralateral orbit could not be seen. The differential diagnosis of a facial tumor detected by prenatal ultrasound examination and the features that distinguish them are listed in Table 114-1. It should be noted that ultrasound examination is an extremely insensitive screening technique for heritable retinoblastoma in families at risk for recurrence. In these cases, percutaneous umbilical blood sampling, CVS, or amniocentesis to obtain fetal tissue is recommended, as DNA-based prenatal diagnosis is available.

DIFFERENTIAL DIAGNOSIS

The case of retinoblastoma diagnosed at 21 weeks of gestation was found to have a very large oval-shaped mass protruding from the right side of the fetal face (Maat-Kievit et al., 1993). Histologic studies confirmed the diagnosis of retinoblastoma with extension beyond the orbit with an 8 × 6 × 3-cm mass rounded by a transonic area covered by a thin membrane. Because of the location and the size of this tumor the differential diagnosis included most causes of facial tumors (see Table 114-1). Epignathus is a tumor that grows through the floor of the mouth, is usually quite irregular in shape, and is localized primarily in the nasopharyngeal area. Although it has a heterogeneous appearance, with sonolucent and highly echogenic areas, its location usually distinguishes it from retinoblastoma. Encephalocele (see Chapter 12) is usually associated with intracranial abnormalities, such as hydrocephalus and calvarial defects. It is usually smooth, contoured, round in shape, and localized to the skull. In contrast, hemangiomas are usually readily identified by color flow Doppler studies, which show significant blood flow within the tumor mass. Myoblastomas are ordinarily localized to the oral cavity and tend to be echogenic, with other sonolucent areas within it. Dacryocystocele may be more difficult to distinguish from retinoblastoma because of its proximity to the eye. It is usually localized in the inframedial aspect of the orbit. Retinoblastoma is an irregular echogenic mass that may be surrounded by the sonolucent area that arises specifically from the eye (see Figure 114-1).

ANTENATAL NATURAL HISTORY

Retinoblastoma is a congenital tumor that arises from embryonic neural crest cells. In most newborns, as well as fetuses, retinoblastomas remain undetected until ophthalmologic symptoms arise during childhood (Liebman and Gellis, 1966; Gallie and Phillips, 1982; Abramson et al., 1983). It is thought that the onset of retinoblastoma must be after the transformation and first differentiation of the nervous layer of the pars optica of the retina in the fifth to eighth weeks of embryogenesis (England, 1983). In the case reported by Maat-Kievit et al. (1993), the fetus presented at 21 weeks with a large mass extending beyond the orbit. This suggests that the tumor cells must have undergone enormous mitotic activity to create such a large tumor in a brief time. This is not the usual presentation of retinoblastoma, which may not be detected for the first several years of life. Whether the natural history of retinoblastoma presenting prenatally is distinct from more typical cases that present in early childhood is unknown.

MANAGEMENT OF PREGNANCY

Fetuses in which retinoblastoma is suspected should be referred to a tertiary care center capable of anatomic sonographic diagnosis of the fetus. Level 2 sonograms should be obtained to exclude the possibility of associated congenital anomalies, including cleft palate and congenital heart disease. Because of the potential for associated congenital heart disease, if any abnormalities are detected on four-chamber view of the heart, or the outflow tracts or abnormalities in

cardiac axis are detected, formal echocardiography is indicated. Chromosome analysis should be considered to look for deletions in chromosome band 13q14. FISH probes are available specifically for this region. If a deletion is found, the parental chromosomes also need to be analyzed.

If retinoblastoma is detected prior to 24 weeks of gestation, the parents should be counseled about the option of terminating the pregnancy. No treatment options are currently available in utero, and the parents should be informed that a retinoblastoma of a sufficient size to be detected sonographically places the fetus in a very poor prognostic category. Postnatal survival with tumors of this nature is poor, with only a third of the eyes being salvageable, and the cure rate is less than 25%.

Although data regarding the management of the pregnancy are scarce, as few cases have been diagnosed prenatally, consideration should be given to delivery at lung maturity for immediate postnatal therapy. It is unclear if cesarean section is warranted and should be based on an assessment of the size of the tumor close to the time of delivery. Delivery should be planned in a tertiary care setting, with pediatric ophthalmologists, oncologists, and radiation therapists available to plan the treatment of the newborn.

FETAL INTERVENTION

There is no fetal treatment for retinoblastoma. However, in a fetus with an RB1 mutation that had sonographically detected tumors, preterm delivery was induced to initiate postnatal treatment (Gallie et al., 1999).

TREATMENT OF THE NEWBORN

The neonate should be carefully examined for the presence of associated anomalies. An ophthalmologic consultation should be obtained to assess the extent of the tumor, as well as the contralateral eye. Molecular genetic testing should be performed on peripheral blood to identify the two RB1 mutations that inactivated both *RB1* alleles. If no mutations are detected in the blood and the eye(s) requires enucleation, tumor DNA should also be studied.

SURGICAL TREATMENT

The goals of treatment are first, to preserve life and second, to preserve sight. Retinoblastoma cure rates exceed 90% with current treatment methods (Shields and Shields, 1990). Specific treatment approaches vary from center to center, and increasing attention is now focused on preservation of visual function. Enucleation of the eye is considered when there is no hope for useful vision, even if the tumor is thought to be eradicated. A cosmetic disadvantage of this approach is that in children younger than 3 years of age the orbit ceases to grow normally after the eye is removed, and as the face of the infant grows the orbit looks increasingly sunken (see Chapter 29). External beam radiation therapy produces the same appearance due to inhibition of bone growth. The indication for cryotherapy and photocoagulation are similar; however, both techniques can successfully treat only small lesions, less than 3 mm in diameter and 2 mm thick. Episcleral plaque radiotherapy may be superior to external beam irradiation in delivering a higher local tumor radiation dose with considerably lower orbital and facial radiation and may be used in solitary tumors less than 8 mm in thickness.

Retinoblastomas are considered radiosensitive. The purpose of radiation therapy for retinoblastomas is control of local disease while preserving vision. Because the majority of patients will have multiple tumors in one or both eyes and these tumors may be multifocal in origin, radiation fields must include the entire geographic extent of the retina, the anterior border of which is the ora serrata. In an attempt to preserve vision, external beam or episcleral plaque radiotherapy has become the treatment of choice for the majority of children with retinoblastoma. Any eye that has a chance for useful vision should be considered for radiation therapy rather than enucleation. The results of chemotherapy treatment for intraocular retinoblastoma have been disappointing because intraocular penetration of systemic drugs is poor and tumors often express the membrane glycoprotein p170 and become drug-resistant (Chan et al., 1989). Adjuvant chemotherapy has been tested in children with group V disease (tumors involving more than half the retina or with vitreous seeding) after enucleation, with no survival advantage over enucleation alone (Abramson, 1985). Chemotherapy is best restricted to patients with extraocular disease or regional or distant metastases (Pizzo et al., 1985).

After initial treatment, patients must be examined closely for tumor regrowth, extraocular extension, and/or vitreous seeding, and additional radiation, laser, cryotherapy, or adjuvant chemotherapy may be indicated in these cases.

Coordinated follow-up between the ocular oncologist and the primary care specialist is essential because of the likelihood of retinoblastoma recurrence, treatment-associated morbidity, and development of a second tumor that is not retinoblastoma.

LONG-TERM OUTCOME

Patients with heritable retinoblastoma have an increased risk for developing other malignancies (Abramson et al., 1984; Roarty et al., 1988; Wilson et al., 1996). In one study, 13% of patients with retinoblastoma, treated by radiation therapy, had second malignancies. Seventy percent of these tumors were in and 30% outside the irradiation field (Abramson et al., 1984). In the same study, there were 23 patients who did not receive radiation therapy and 5 of these had second malignant tumors. These tumors were predominately sarcomas, with osteosarcoma the tumor most frequently reported. The incidence of second malignant tumors appears to increase with time, with a 20% incidence after 10 years. This rises to 50% at 20 years, and at 30 years it approaches 90% (Abramson et al., 1984).

There is considerable controversy regarding the true rate of second malignancy in retinoblastoma survivors. Long-term follow-up studies vary widely with respect to long-term incidence, with reported rates of second malignancy between 25% and 90% at 30-year follow-up. Because of the increasing risk of the development of a second tumor, patients should be examined periodically by the primary care physician. In particular, patients with bilateral retinoblastoma are always at risk for the development of second tumor; the longest reported interval is 57 years between primary retinoblastoma diagnosis and second tumor presentation (Wilson et al., 1996).

GENETICS AND RECURRENCE RISK

Retinoblastoma develops in cells that have mutations in both copies of *RB1*, the retinoblastoma locus, which is located on chromosome 13q14 (Sparkes et al., 1980). Cytogenetic analysis has revealed that there is a deletion of band 13q14 in 5% to 10% of patients with retinoblastoma (Howard, 1982; Lemieux and Richer, 1990). Genetic and physical mapping indicates that the retinoblastoma gene is closely linked to the genetic locus for esterase D, which maps exactly to this region (Sparkes et al., 1983; Lee and Lee, 1986; Squire et al., 1986).

RB1 is the only gene known to be associated with retinoblastoma. *RB1* is 200,000 base pairs in size and it encodes a protein of 928 amino acids. The *RB1* gene product is a nuclear phosphoprotein with DNA-binding activity that is expressed in many different types of cells (Lee et al., 1987). RB1 protein forms complexes with viral oncoproteins of several DNA tumor viruses (DeCaprio et al., 1988; Whyte et al., 1988). Many studies have suggested that the RB1 protein plays a role in the regulation of cell growth (Chan et al., 1989).

Retinoblastoma may be either nonheritable or of the heritable type that shows an autosomal dominant inheritance pattern with a high degree of penetrance (Nussbaum and Puck, 1976; Vogel, 1979). If there is a positive family history, genetic counseling becomes more straightforward because this is clearly a heritable case of retinoblastoma (Cavenee et al., 1986; Yandell et al., 1989; Draper et al., 1992). In sporadic cases, which include the majority of patients, this may be either heritable or nonheritable. Bilateral sporadic cases are always heritable, and each child of the affected patients who survive will have a 50% risk of having retinoblastoma. Unilateral sporadic cases may be either heritable or nonheritable, with empiric risk studies revealing a 10% to 12% risk of having heritable type and that the first child of a survivor has a 5% to 6% chance of having the disease (Vogel, 1979). If normal parents have one affected child, the risk of their next child having a retinoblastoma is approximately 1% if the first child has a unilateral tumor and 6% if the child has bilateral tumors. To rule out the possibility that one parent is silently clinically affected with an unsuspected retinoblastoma, both parents should have ophthalmologic examinations to facilitate accurate genetic counseling.

DNA-based prenatal diagnosis is available for families in which one parent is affected with a heritable RB1 mutation (Wiggs et al., 1988). For these families a 50% recurrence risk exists. DNA analysis is much more accurate than prenatal sonography (Dryja et al., 1989; Gallie et al., 1991; Naumova and Sapienza, 1994). Preimplantation genetic diagnosis of retinoblastoma is also available for families at risk for the disease to screen embryos prior to embryo transfer (Girardet et al., 2003; Xu et al., 2004; Thornhill, 2005).

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115 CHAPTER

Sacrococcygeal Teratoma

Key Points

- Sacrococcygeal teratomas (SCTs) arise from a totipotent stem cell in Henson's node.
- Most SCTs are large, complex, solid, and cystic masses but may have intrapelvic or intra-abdominal extension.
- Ultrasound alone will make the diagnosis, but fetal MRI will help define anatomic relations, and echocardiographs will evaluate high-output state.
- SCTs that are >10 cm, solid, highly vascular, or rapidly growing are at highest risk for hydrops.
- Fetal surgery may be an option in cases that develop early signs of hydrops.
- Cesarean section is usually indicated for large SCTs due to risk of rupture and exsanguination.
- SCTs are usually benign but can have immature elements or rests of malignant yolk sac tumor.
- Close serial follow-up for at least 3 months for tumor recurrence is indicated with serial α-fetoprotein levels, physical exam, and imaging studies.

CONDITION

Sacrococcygeal teratoma (SCT) is defined as a neoplasm composed of tissues from either all three germ layers or multiple foreign tissues lacking an organ specificity arising in the sacrococcygeal region (Gross et al., 1951; Mahour et al., 1975). Because of the multiple cell lineages that characterize these tumors, it was previously suggested that SCT was of germ cell origin or a form of fetus in fetu (Theiss et al., 1960; Linder et al., 1975). Early theories suggested a "twinning accident" with incomplete separation during embryogenesis and abnormal development of one fetus (Waldhausen et al., 1963; Ashley, 1973; Cousins et al., 1980). In support of this theory, several authors have noted a family history of twinning in many SCT patients (Hickey and Layton, 1954; Grosfeld et al., 1976; Gross et al., 1987). However, more recently, SCT has been thought to arise from a totipotent somatic cell originating in Hensen's node (Gross et al., 1987). This node is a caudal cell mass in the embryo that appears to escape normal inductive influences (Bale, 1984). Others hypothesize that SCT is derived from totipotent cells in reproductive gland anlage (Abbott et al., 1966).

SCT has been classified by the relative amounts of presacral and external tumor present [American Academy of Pediatrics Surgery Section (AAPSS) Classification (Table 115-1 and Figure 115-1)] (Altman et al., 1974). The utility of this classification scheme lies in the relationship between stage and timing of diagnosis, ease of resection, and malignant potential. Type I SCT is evident at birth, is usually easily resected, and has a low malignant potential. Similarly, types II and III SCT are recognized at birth, but resection may be difficult, requiring both an anterior and a posterior approach. In type IV SCT, the diagnosis may be delayed until it becomes symptomatic at a later age. Malignant transformation has frequently occurred by the time a type IV SCT is diagnosed.

Table 115-1

AAPSS Staging Classification of Sacrococcygeal Teratomas

Type	Description
I	Completely external; no presacral component
II	External component and internal pelvic component
III	External component and internal component extending into abdomen
IV	Completely internal and no external component

Adapted from Altman RP, Randolph JG, Lilly JR. Sacrococcygeal teratoma: American Academy of Pediatrics Surgical Section Survey 1993. J Pediatr Surg. *1974;9:389-398.*

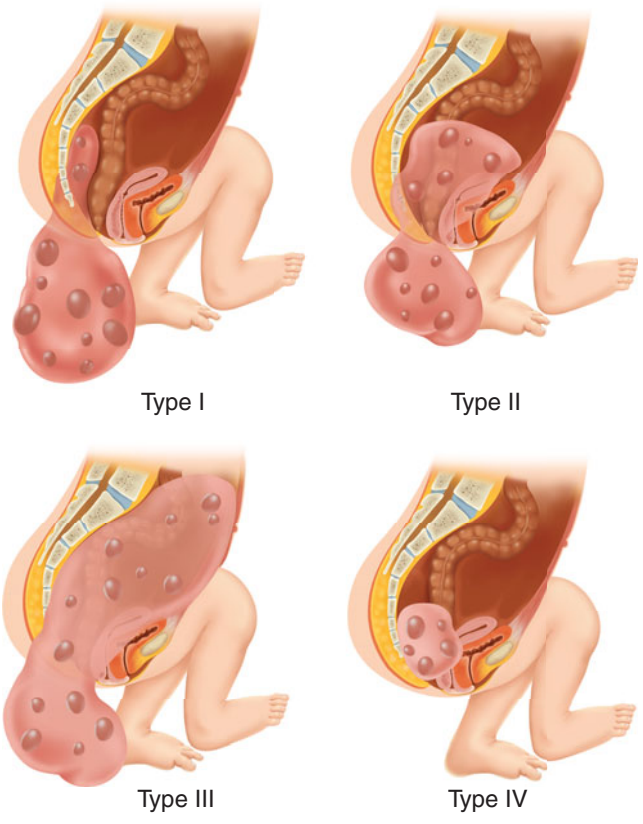

Figure 115-1 AAPSS classification of the different types of sacrococcygeal teratoma, based on the location of the tumor. (*Reprinted, with permission, from Holzgreve W, Flake AW, Langer JC. The fetus with sacrococcygeal teratoma. In: Harrison MR, Golbus MS, Filly RA, eds.* The Unborn Patient. *Philadelphia: WB Saunders; 1991:461*).

INCIDENCE

SCT is one of the most common tumors in newborns; however, it is still rare, occurring in 1 in 23,000 to 1 in 40,000 livebirths (Schiffer and Greenberg, 1956; Altman et al., 1974; Tapper and Lack, 1983; Forrester and Merz, 2006). Females are four times more likely to be affected as males, however, malignant change is more frequently observed in males (Abbott et al., 1966; Conklin and Abell, 1967; Carney et al., 1972; Fraumeni et al., 1973; Altman et al., 1974).

SONOGRAPHIC FINDINGS

Retrospective prenatal diagnosis of SCT was first made in the mid-1970s, and the first prospective prenatal diagnosis was reported by Horger and McCarter in 1979. They described a 13-cm complex mass at the caudal end of the fetus, with solid and cystic areas and bizarre internal echoes associated with polyhydramnios. This typical prenatal sonographic appearance has been confirmed by other authors (Figure 115-2) and approximately 60 cases of prenatally diagnosed SCT have been reported (Seeds et al., 1982; Grisoni et al., 1988; Bond et al.,

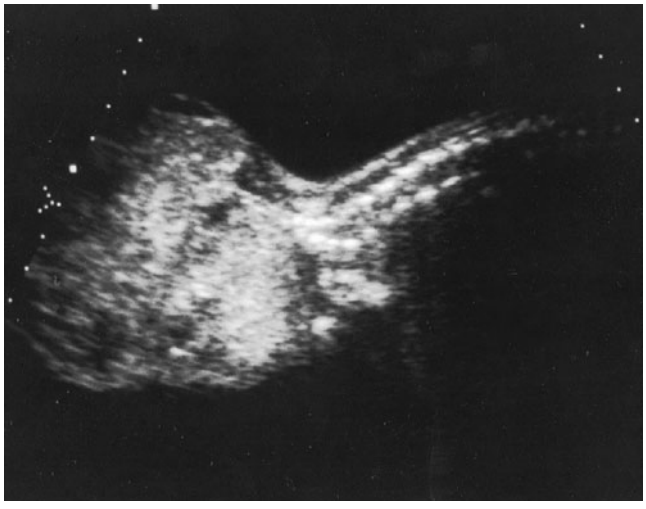

Figure 115-2 Prenatal sonographic image demonstrating large type II sacrococcygeal tumor in a 23-week-old fetus. In this view, the intrapelvic extent of the tumor cannot be seen.

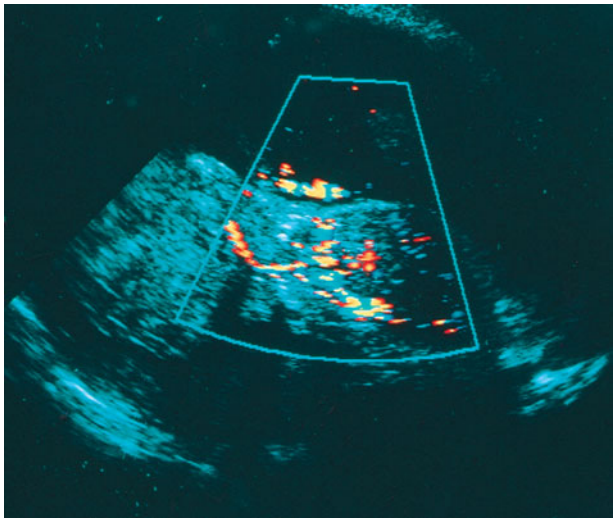

Figure 115-3 Color flow Doppler study of the same fetus shown in Figure 115-1 demonstrating the vascularity of the tumor.

1990). The most common clinical presentation is uterine size greater than dates, initiating an ultrasound examination (Seeds et al., 1982). To date, the earliest diagnosis of SCT that has been made is 12 3/7 weeks of gestation (Roman et al., 2004).

SCTs can grow at an unpredictable rate to tremendous dimensions. Several case reports note fetal tumors as large as 25 by 20 cm (Heys et al., 1967; Weiss et al., 1976). These tumors are generally exophytic (AAPSS type I), but may extend retroperitoneally displacing pelvic (type II) or abdominal structures (type III) (Litwiller, 1969).

Most SCTs are solid or mixed solid and cystic, consisting of randomly arranged irregularly shaped cysts (Seeds et al., 1982; Chervenak et al., 1985). Purely cystic SCT has also been described prenatally (Seeds et al., 1982; Hogge et al., 1987). Calcifications can be seen microscopically, although the majority are not visible on prenatal ultrasound examination. Most prenatally diagnosed SCTs are extremely vascular, which is easily demonstrated with the use of color flow Doppler studies (Figure 115-3). Three-dimensional power Doppler has been suggested to demonstrate the large vascular volume in SCT (Sciaky-Tamir et al., 2006). Polyhydramnios has been noted in most cases of prenatally diagnosed SCT, and—although the mechanisms for this are not known—it is likely secondary to renal hyperfiltration occurring as a result of high-output state (Chervenak et al., 1985).

Hepatomegaly, placentomegaly, and nonimmune hydrops have also been seen in association with SCT and appear to be secondary to high-output cardiac failure (Heys et al., 1967; Cousins et al., 1980; Gergely et al., 1980; Kapoor and Saha, 1989; Bond et al., 1990; Flake, 1993; Hedrick et al., 2004). High-output failure may be due to tumor hemorrhage or arteriovenous shunting within the tumor (Cousins et al., 1980; Flake et al., 1986; Alter et al., 1988; Schmidt et al., 1989; Bond et al., 1990). Some authors have attributed heart failure with subsequent hydrops to severe fetal anemia secondary to tumor hemorrhage (Alter et al., 1988). However, normal fetal hematocrits have also been reported, suggesting that congestive heart failure is more often due to high-output cardiac failure from arteriovenous shunting within the tumor (Schmidt et al., 1989). The demonstration of heart failure or hydrops on ultrasound examination is usually a preterminal event (Flake et al., 1986; Kuhlmann et al., 1987; Bond et al., 1990).

Controversy exists regarding the presence of associated anomalies and the need for chromosome analysis. The incidence of coexisting anomalies is 11% to 38%, primarily involving the nervous, cardiac, gastrointestinal, genitourinary, and musculoskeletal systems (Hickey and Layton, 1954; Schiffer and Greenberg, 1956; Carney et al., 1972; Fraumeni et al., 1973; Altman et al., 1974; Izant and Filston, 1975; Gonzalez-Crussi et al., 1978; Ein et al., 1980; Holzgreve et al., 1985; Kuhlmann et al., 1987; Werb et al., 1992). Several authors postulate that at least some of these anomalies are related to tumor development. Others have reported an increased incidence of spinal deformities (Ewing, 1940; Gruenwald, 1941; Alexander and Stevenson, 1946; Bentley and Smith, 1960; Wilson et al., 1963; Carney et al., 1972). Most authors agree with Berry et al.'s (1970) observation that local abnormalities such as rectovaginal fistula and imperforate anus are thought to be directly related to tumor growth during fetal development. Aneuploidy has not been reported with SCT and we do not recommend amniocentesis for karyotype analysis unless there are multiple anomalies, advanced maternal age, or fetal surgery is contemplated.

Fetal MRI has emerged as an adjunctive imaging modality that can provide important anatomical detail in cases of SCT (Avni et al., 2002; Hedrick et al., 2004; Nassenstein et al., 2006). MRI may be particularly useful in defining the pelvic component of SCT and impact on other pelvic structures (Garel et al., 2005). In cases in which fetal surgery is being considered, fetal MRI provides a broader field of view than

ultrasound and may be helpful in operative planning. In cases in which SCT has a pelvic component or there is polyhydramnios, oligohydramnios, hydronephrosis or hydrocolpos, fetal MRI may provide additional information on the anatomical relationships not apparent on ultrasound alone (Danzer et al., 2006). Fetal MRI in cases of cystic SCT may be particularly helpful in excluding myelomeningocele from the differential diagnosis (Yoon and Park, 2005; Danzer et al., 2006).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of SCT includes lumbosacral myelomeningocele, which invariably demonstrates a spinal defect. Myelomeningoceles have a cystic or semicystic rather than a solid appearance and do not contain calcifications. Examination of the fetal brain is helpful in establishing the diagnosis, as most fetuses with lumbosacral myelomeningocele will have associated cranial findings. Rarer entities that mimic SCT include neuroblastoma, glioma, hemangioma, neurofibroma, cordoma, leiomyoma, lipoma, melanoma, and any of 50 tumors or malformations reported in the sacrococcygeal region (Table 115-2) (Lemire and Beckwith, 1982; Sebire et al., 2004; Tanaka et al., 2005).

Biochemical markers such as α-fetoprotein (AFP) and acetylcholinesterase are not reliable in distinguishing SCTs from other abnormalities (Holzgreve et al., 1987). It has been suggested, however, that AFP can be used to differentiate benign from malignant tumors, as marked elevations of AFP may reflect the presence of a malignant endodermal sinus component to the tumor (Tsuchilda et al., 1975; Grosfeld et al., 1976; Gonzalez-Crussi et al., 1978; Gonzalez-Crussi, 1982). AFP levels can be extremely high in normal newborns, limiting the utility of this marker to distinguish benign from malignant lesions (Ohama et al., 1997).

Table 115-2

Tumors and Malformations of the Sacrococcygeal Region*

Subcutaneous lipoma
Teratoma
Endodermal sinus tumor
Neuroblastoma
Ganglioneuroma
Myxopapillary ependymoma
Fibromatosis
Neurofibroma
Ependymoma
Giant cell tumor of sacrum
Leiomyoma
Lymphoma
Rhabdomyosarcoma
Mesenchymoma
Wilms' tumor in teratoma
Paraganglioma
Glomus tumor
Lumbosacral lipoma
Tail appendage
Hamartoma
Hemangioma
Hemangioendothelioma
Teratoma in meningomyelocele
Myelocystocele
Meningocele

** This table lists reported tumors and malformations of the sacrococcygeal region in postnatal patients. Not all have been diagnosed prenatally. Source: Lemire RJ, Beckwith JB. Pathogenesis of congenital tumors and malformations in the sacrococcygeal region.* Teratology *1982;25:201-213.*

ANTENATAL NATURAL HISTORY

The antenatal natural history of prenatally detected SCT is not as favorable as that of SCT presenting at birth. Well-defined prognostic factors for SCT diagnosed postnatally, as outlined in the AAPSS classification system, do not necessarily apply to fetal cases (Altman et al., 1974; Bond et al., 1990) (see Table 115-1). While the mortality rate for SCT diagnosed in the newborn is at most 5%, the mortality rate for fetal SCT approaches 50% (Flake et al., 1986; Bond et al., 1990; Flake, 1993; Hedrick et al., 2004).

Most SCTs are histologically benign. The incidence of malignant elements present in fetal SCT has ranged from 7% to 30% (Hedrick et al., 2004; Heerema-McKenny et al., 2005). Malignancy appears to be more common in males, especially with solid versus complex or cystic tumors (Schey et al., 1977). The presence of histologically immature tissue does not necessarily signify malignancy (Carney et al., 1972; Gonzalez-Crussi, 1982). Calcifications occur more often in benign tumors but may also be seen in malignant tumors and are unreliable indicators of malignant potential (Hickey and Layton, 1954; Waldhausen et al., 1963; Grosfeld et al., 1976; Schey et al., 1977; Horger and McCarter, 1979). Although there is one reported case of malignant yolk sac differentiation in a fetal SCT, there has not been a case of metastatic teratoma in a neonate with a prenatally diagnosed SCT (Holzgreve et al., 1985; Flake, 1993).

The prenatal history of SCT is quite different from the postnatal natural history. Flake et al. (1986) reviewed 27 cases of prenatally diagnosed SCT. Five cases were electively terminated and 15 of the remaining 22 died, either in utero or shortly after delivery. The majority of these patients presented between 22 and 34 weeks of gestation with a uterus large for gestational age secondary to severe polyhydramnios. The presence of hydrops and/or polyhydramnios was associated with intrauterine fetal death in seven of seven cases. The International Fetal Medicine and Surgery Society reported a mortality rate of 52% among cases of prenatally diagnosed

SCT (Bond et al., 1990). When SCT was seen in association with placentomegaly or hydrops, all affected fetuses died in utero. The indication for ultrasound examination was also found to be a predictive factor. If SCT was an incidental finding, the prognosis was favorable at any gestational age. However, if the ultrasound examination was performed for maternal indications, 22 of 32 fetuses died. In addition, diagnosis prior to 30 weeks was associated with a poor outcome.

Sheth et al. (1988) also reported significant perinatal mortality associated with SCT, with only 6 survivors among 15 cases diagnosed prenatally. Three of four cases associated with hydrops were rapidly fatal. The sole survivor was salvaged by emergency cesarean section at 35 weeks. This series was unusual because three cases had severe obstructive uropathy and secondary renal dysplasia. A more favorable outcome was reported by Gross et al. (1987) in which 8 of 10 fetuses with prenatally diagnosed SCT survived. However, no fetus had hydrops or placentomegaly, and the two nonsurvivors were electively terminated.

Hydrops in SCT is usually, but not always, fatal. Nakoyama et al. (1991) reported survival in two fetuses with SCT presenting with hydrops at 27 and 30 weeks of gestation. In addition, Robertson et al. (1995) were able to salvage a hydropic fetus at 26 weeks of gestation by staged resection of the SCT in the neonatal period (Figure 115-4). In this case, acute rapid growth of the SCT led to polyhydramnios and preterm delivery. After delivery, the newborn was noted to be in a high-output state from shunting through the tumor. In a staged resection, the tumor was initially devascularized by ligation of both internal iliac arteries. Twenty-four hours later, the external portion of the mass was resected. The infant subsequently underwent resection of the intrapelvic portion of the tumor at 3 months of age, and did well.

Hedrick et al. (2004) reviewed their experiences with 30 cases of prenatally diagnosed SCT and reported 4 terminations, 5 fetal deaths, 7 neonatal deaths, and only 14 survivors (47%). Among the 26 patients continuing the pregnancy, 81% experienced obstetric complications including polyhydramnios ($n = 7$), oligohydramnios ($n = 4$), preterm labor ($n = 13$), pre-eclampsia ($n = 4$), gestational diabetes ($n = 1$), HELLP syndrome ($n = 1$), and hyperemesis ($n = 1$).

Sonographic features of SCT such as size, AAPSS classification, solid or cystic composition, or presence or absence of calcifications have not been predictive of either fetal survival or future malignant potential (Altman et al., 1974; Flake, 1993). One exception to this may be the unilocular cystic form of SCT, which has a relatively favorable prognosis because of benign histology and limited vascular and metabolic demand (Horger and McCarter, 1979; Mintz et al., 1983). The growth of the SCT in relation to the size of the fetus is also unpredictable and may increase, decrease, or stabilize as gestation proceeds. However, a rapid phase of tumor growth usually precedes the development of placentomegaly and hydrops.

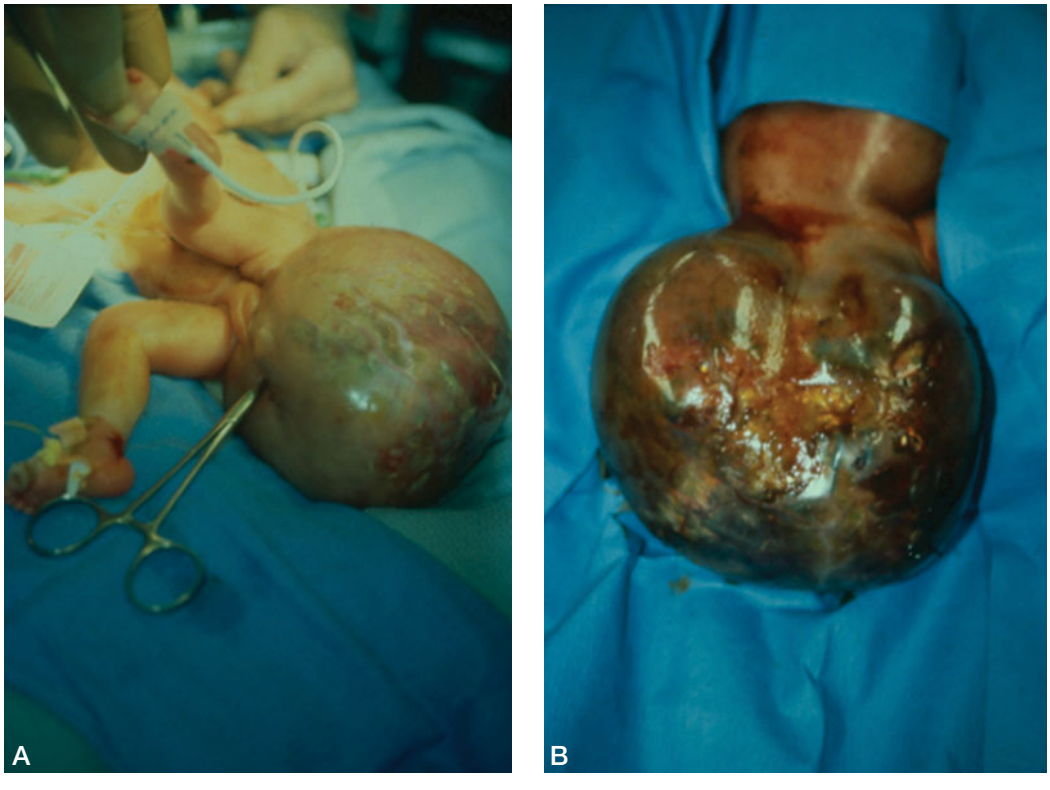

Figure 115-4 Postnatal photograph of a 26-week-gestation premature newborn with a large SCT. **A.** The SCT has distorted the perineum so that the anus is in a plane anterior to the genitalia. The tip of the clamp is in the anal orifice. **B.** The same tumor following devascularization.

Highly vascular lesions are more likely to undergo rapid tumor growth and to be associated with the development of placentomegaly and hydrops. The prenatal mortality, unlike postnatal mortality, is not due to malignant degeneration, but to complications of tumor mass or tumor physiology (Flake et al., 1993). The tumor mass may result in malpresentation or dystocia, which in turn may result in tumor rupture and hemorrhage during delivery. Dystocia has been reported in 6% to 13% of cases in postnatal series (Giugiaro et al., 1977; Musci et al., 1983; Gross et al., 1987). SCTs may also spontaneously rupture in utero leading to significant fetal anemia or death (Sy et al., 2006). The most important benefit of prenatal diagnosis is prevention of dystocia by elective or emergency cesarean section. Tumor mass effect may also result in uterine instability and preterm delivery because of uterine distention (Flake et al., 1986; Bond et al., 1990). Massive polyhydramnios is frequently seen in large fetal SCT, which also predisposes to uterine irritability and preterm delivery.

SCT may occur in twins further complicating the prenatal management. In Hedrick et al.'s series, 10% of the cases occurred in twin gestations (Hedrick et al., 2004). The presence of SCT in a twin gestation increases the risk of preterm delivery. Because SCT is associated with an increased risk of fetal death, intrauterine demise of a monochorionic twin with SCT places the surviving unaffected co-twin at risk of adverse neurologic outcome (Ayzen et al., 2006).

The physiologic consequence of fetal SCT depends on the metabolic demands of the tumor, blood flow to the tumor, and the presence and degree of anemia. The features of the SCT—whether cystic or solid, size, and rate of growth—all affect the metabolic demands of fetal SCT. While classically thought to derive its blood supply from the middle sacral artery (Smith et al., 1961), these large tumors often parasitize blood supply from the internal and external iliac systems. This may result in vascular "steal" from the umbilical artery blood flow to the placenta. As an SCT outgrows its blood supply, tumor necrosis may occur leading to tumor rupture and hemorrhage. The high-output cardiac failure in fetal SCT can be diagnosed by fetal echocardiography and Doppler study (Flake et al., 1986; Langer et al., 1989; Schmidt et al., 1989). When hydrops develops in fetuses with SCT, all have dilated ventricles and dilated inferior venae cavae due to increased venous return from the lower body (Flake, 1993). Serial sonographic examinations in fetal SCT often show progressive increases in combined ventricular output and descending aortic flow velocity. In general, placental blood flow is decreased by the vascular steal by the SCT (Schmidt et al., 1989; Flake, 1993) and may lead to the finding of end-diastolic flow reversals in the umbilical artery.

Benachi et al. (2006) have suggested a prenatal prognostic classification system based on tumor diameter, vascularity, and rapidity of growth. In a group of 44 fetal SCTs divided into group A (tumor <10 cm, absent or mild vascularity and slow growth), group B (tumor ≥ 10 cm, pronounced vascularity or high output cardiac failure and rapid growth), and group C (tumor ≥ 10 cm, predominantly cystic lesion with absent or mild vascularity and slow growth). Groups A and C did well with gestational age at delivery of 38 and 37 weeks, respectively while group B delivered prematurely at 31 weeks of gestation. There was no mortality in either group A or C but was 52% for group B. The newborns in group B also have a much longer length of stay postnatally (Benachi et al. 2006). Postnatal measurements of umbilical arterial blood gases before and after removal of a large SCT demonstrate that the tumor acts as a large arteriovenous shunt.

MANAGEMENT OF PREGNANCY

Although the primary cause of death in neonatal SCT is malignant invasion, in prenatal SCT the complications of prematurity or exsanguinating tumor hemorrhage at delivery predominate (Flake et al., 1986; Bond et al., 1990; Adzick and Harrison, 1994). Weekly sonographic examinations should be performed during pregnancy to assess amniotic fluid index, tumor growth, fetal well-being, and early evidence of hydrops (Chervenak et al., 1985; Langer et al., 1989). Serial Doppler echocardiographic evaluations should be performed in all patients to detect early signs of high-output state, as evaluated by an increased diameter of the inferior vena cava (should be >1 cm), increased descending aortic flow velocity (>120 cm/s) (Alter et al., 1988; Flake, 1993; Bahlmann et al., 2001), or increased combined ventricular output (>500 mL/kg/min for CVO) (Bahlmann et al., 2001). Evidence of the earliest signs of heart failure, placentomegaly, and/or hydrops should be sought, as these may progress rapidly and are harbingers of preterminal events (Langer et al., 1989). Bond et al. (1990) reported a uniformly fatal outcome when SCT was associated with placentomegaly and/or hydrops. Flake et al. (1986) reported seven of seven fetal deaths in pregnancies complicated by placentomegaly and hydrops.

Weekly amniocenteses to determine pulmonary maturity are recommended by some physicians after 36 weeks of gestation, with delivery once fetal lung maturity is established (Adzick and Harrison, 1994). Many pregnancies complicated by SCT do not reach this gestational age however. Warning signs and symptoms of preterm labor should be stressed at prenatal visits, and limitation of activity, treatment, and cervical checks may be indicated (Garmel et al., 1994).

The recommended mode of delivery is determined by the size of the tumor. Vaginal delivery may be possible with some small tumors (Grisoni et al., 1988; Flake, 1993). Complications of vaginal delivery, however, have included fetal death after rupture, avulsion, or asphyxia (Schiffer and Greenberg, 1956; Heys et al., 1967; Grosfeld et al., 1976; Giugiaro et al., 1977; Chervenak et al., 1985; Holzgreve et al., 1987; Werb et al., 1992). Cesarean delivery is recommended to avoid trauma-induced hemorrhage or dystocia, especially in large (>5–10 cm) tumors (Chervenak et al., 1985; Gross et al., 1987; Hogge et al., 1987; El-Qarmalaui et al., 1990; Flake, 1993). The size of the tumor may also influence the type of uterine incision. A large tumor may warrant a classical uterine incision, especially in a preterm infant (Chervenak et al., 1985).

Dystocia has been reported when the diagnosis of SCT was unsuspected in as many as 6% to 13% of cases (Hickey and Layton, 1954; Schiffer and Greenberg, 1956; Seidenberg and Hurwitt, 1958; Lowenstein et al., 1963; Hickey and Martin, 1964; Abbott et al., 1966; Lu and Lee, 1966; Heys et al., 1967; Desai, 1968; Kowalski and Sokolowska-Pituchowa, 1968; Werner and Swiecicka, 1968; Litwiller, 1969; Weiss et al., 1976; Seeds et al., 1982; Tanaree, 1982; Edwards, 1983; Mintz et al., 1983; Musci et al., 1983; Varga et al., 1987; El-Shafie et al., 1988; Johnson et al., 1988). Transabdominal and transvaginal aspirations of large cysts have been attempted with variable results to facilitate delivery in the face of significant dystocia (Abbott et al., 1966; Desai, 1968; Litwiller, 1969; Weiss et al., 1976; Tanaree, 1982; Edwards, 1983; Mintz et al., 1983; Musci et al., 1983; El-Shafie et al., 1988; Johnson et al., 1988). Cyst decompression has also been used to treat maternal discomfort, and in one case cyst amniotic shunting was used to treat bladder outlet obstruction due to tumor compression (Garcia et al., 1998; Kay et al., 1999; Jouannic et al., 2001). It is hoped that prenatal detection of SCT will prevent such unforeseen emergencies (Musci et al., 1983).

Fetal SCT is sometimes associated with maternal complications. The mother should be observed for signs and symptoms of pre-eclampsia, such as the "mirror syndrome" described by Nicolay et al. in association with SCT and hydrops (Nicolay and Gainey, 1964; Cousins et al., 1980; Flake et al., 1986; Coleman et al., 1987; Langer et al., 1989; Bond et al., 1990). Delivery should be performed in a tertiary care center, with neonatologists and pediatric surgeons available.

FETAL INTERVENTION

The uniformly dismal outcome in fetuses with SCT complicated by placentomegaly and hydrops has been the impetus for resection of this tumor in utero. Harrison was the first to attempt antenatal resection of an SCT (Langer et al., 1989). In this first case, a fetus was noted to be markedly hydropic with a significantly elevated combined ventricular output (972 mL per kilogram of body weight per minute) at 24 weeks (Langer et al., 1989; Flake, 1993). In addition, the mother had mild hypertension, edema, and proteinuria. Preterm labor developed that was controlled with tocolytic agents. At surgery, the exophytic portion of the tumor was dissected free of the anus and rectum and amputated at its base with a stapling device. Despite the resection, the fetus remained hydropic, with an elevated combined ventricular output of 869 mL per kilogram of body weight per minute. Percutaneous umbilical cord blood sampling showed the fetal hematocrit to be only 16%. This was increased to 27% by blood transfusion. The fetus subsequently improved significantly, with sonographic resolution of hydrops, and a decrease in descending aortic flow to 524 mL/kg of body weight per minute. However, the maternal mirror syndrome progressed to pulmonary edema and on postoperative day 12 a 26-week-gestation fetus was delivered by cesarean section and died of pulmonary immaturity at 6 hours of age. The mother's illness resolved within 2 days. Autopsy showed no evidence of hydrops and no residual tumor.

A second case was attempted at 26 weeks of gestation, when dramatic enlargement of the tumor resulted in early hydrops, elevated combined ventricular output, and severe polyhydramnios (Flake, 1993). The surgery went uneventfully, and the base of the tumor was stapled to excise the exophytic portion and reverse the hyperdynamic state. The fetus did well until postoperative day 8, when irreversible preterm labor developed and the fetus was delivered by emergency cesarean section. Because the histology of the resected specimen was interpreted as an immature teratoma grade III/III, with predominance of neuroepithelial elements and foci of yolk sac differentiation, resection of residual tumor was attempted on the 13th day of postnatal life. During dissection of the presacral space the baby experienced complete cardiovascular collapse due to a paradoxical air embolism. The histology of the tumor revealed grade III/III immature teratoma, but the residual tumor was more mature than the previous tumor specimen and contained no foci of yolk sac differentiation.

The first successful resection of fetal SCT with long-term survival was reported by Adzick et al. (1997). At 25 weeks of gestation a type II SCT had rapid enlargement and development of polyhydramnios and placentomegaly, with associated maternal tachycardia and proteinuria suggesting impending maternal mirror syndrome (Figure 115-5). At surgery, the exophytic portion of the tumor was dissected free of the anus and rectum and the base of the tumor excised with a thick tissue stapling device (Figure 115-6). The mother and fetus did well postoperatively, with resolution of hydrops and placentomegaly within 10 days. Pathology of the tumor showed grade III/III immature teratoma without evidence of yolk sac differentiation. At 29 weeks of gestation preterm labor prompted cesarean delivery. Postnatally, the female infant underwent resection of the coccyx and surrounding tissue at 2 months of age, but no residual tumor was found. She did well until 1 year of age when AFP levels became elevated to 22,000 ng/mL and she presented with pleural effusions, lung nodules, and a recurrent buttock mass from a metastatic yolk sac tumor. She has had an excellent response to chemotherapy. Hedrick et al. subsequently reported their experience with four open fetal surgeries for SCT with all four surviving the procedure to delivery at an average gestational age of 29 weeks (range 27.6–31.7 weeks). There was one neonatal death due to premature closure of the ductus arteriosus thought to be secondary to indomethacin exposure as a tocolytic following fetal surgery. Other complications experienced in these fetal surgery patients included embolism resulting in renal infarction and multiple jejunal atresias ($n = 1$), chronic lung disease ($n = 1$), and development of metastatic endodermal yolk sac tumor ($n = 1$) (Hedrick et al., 2004).

While clinical experience remains limited, there have been other cases of SCT successfully resected in utero at the University of California, San Francisco and at Cincinnati Children's Hospital. For the fetus with a large SCT associated

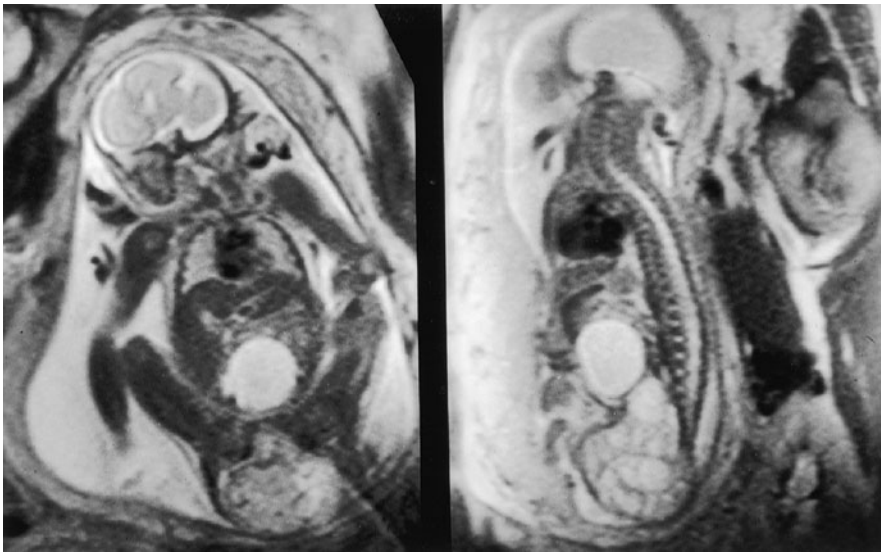

Figure 115-5 Fetal magnetic resonance imaging scan demonstrating in coronal (*left*) and sagittal (*right*) sections a fetus at 25 weeks of gestation with type II SCT. The large intrapelvic portion of tumor has completely blocked the bladder outlet, causing megacystis. The fetal urine is detectable by the presence of contrast dye. (*Reprinted, with permission, from Quinn TM, Hubbard AM, Adzick NS. Prenatal magnetic resonance imaging enhances fetal diagnosis.* J Pediatr Surg. *1998;33:553-558.*)

with early signs of hydrops or placentomegaly, resection in utero remains a viable option. Primary resection of the external portion of the tumor was performed with interval resection of the pelvic extension of SCT. This approach may be useful in managing the common association of prematurity, large tumor, and hyperdynamic state. Because the primary cause of fetal mortality and morbidity is the vascular shunting through the tumor, there have been attempts to embolize or devascularize the tumor using radiofrequency ablation (Paek et al., 2001; Lam et al., 2002). In a report of four patients

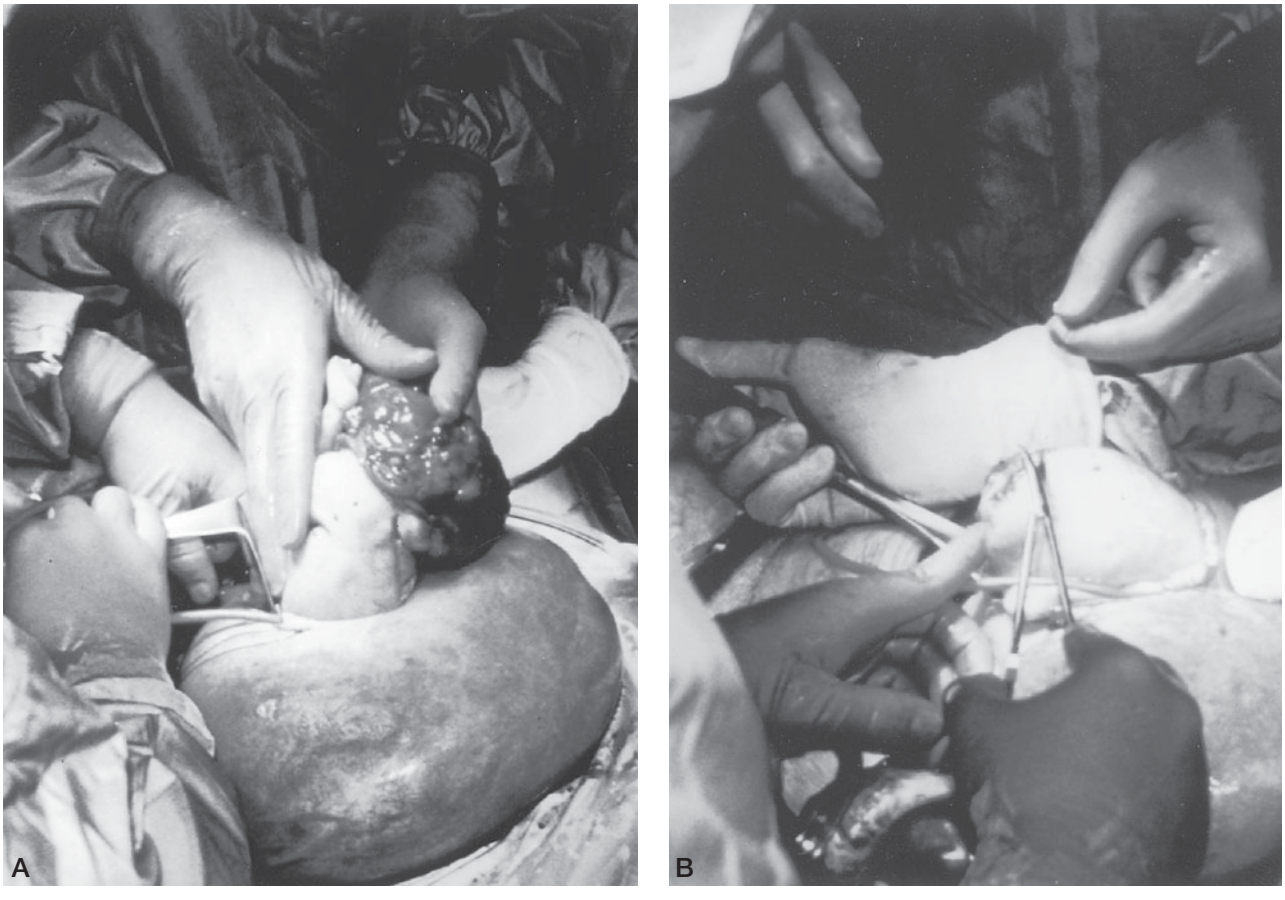

Figure 115-6 Intraoperative view of a 25-week-gestation fetus undergoing resection in utero. **A.** The ruptured tumor and lower extremities of the fetus are delivered from the wound. **B.** The fetal buttock wound is closed immediately following resection. (*Reprinted, with permission, from Adzick NS, Crombleholme TM, Morgan MA, Quinn TM. A rapidly growing fetal teratoma.* Lancet. *1997;349:538.*)

treated with radiofrequency ablation, two fetuses died secondary to hemorrhage after a significant portion of the tumor mass was ablated. The remaining two fetuses delivered at 28 and 31 weeks gestation with evidence of extensive necrosis of pelvic and perineal structures, necessitating extensive reconstructive surgery (Ibrahim et al., 2003). The uncontrolled nature of the energy delivered by the radiofrequency ablation device prevents its safe application in SCT, and this treatment modality has been abandoned.

TREATMENT OF THE NEWBORN

A neonatologist should attend the delivery and be prepared to provide respiratory support. Careful handling of the infant is important to prevent exsanguinating hemorrhage into the tumor. Excellent venous access is paramount should hemorrhage in the tumor occur, and umbilical artery and umbilical venous catheters should be placed. The infant should be started on pressor agents such as dopamine or dobutamine to support the heart in its hyperdynamic state. Transfusion may be necessary immediately postnatally because hemorrhage into the tumor may have occurred during the delivery.

Severely premature infants should be intubated and treated for respiratory distress with surfactant-replacement therapy. Echocardiography should be obtained to assess the cardiac status of the newborn. Abdominal ultrasound examination can be performed at the bedside to assess the intrapelvic extent of tumor. If there is no high-output state then there is no urgency to resect the tumor, and attention should focus on the treatment of respiratory distress and correction of anemia. If a hyperdynamic state exists with an elevated cardiac output, attention should focus on supporting the newborn heart with inotropic agents and urgent resection of the SCT.

SURGICAL TREATMENT

The goal of this resection is reversal of the high-output state, and this can usually be accomplished by resection of the exophytic portion of the tumor. Aortic occlusion by vessel loop to minimize hemorrhage when resecting an SCT in a severely premature infant has been effective in this setting (Robertson et al., 1995). Preoperative angiography and embolization and radiofrequency ablation have been used successfully as adjuncts to surgical resection of large vascular SCTs (Cowles et al., 2006). As with fetal resection of SCT, SCT resection in a premature infant should focus on eliminating the cause of the high-output state, not necessarily complete tumor resection. This can be accomplished by utilization of a thick tissue stapling device at the base of the SCT. If residual pelvic tumor remains, the urgency of resection can be guided by the pathology. The presence of yolk sac differentiation would necessitate earlier resection. In the absence of yolk sac differentiation, however, several months of growth of the infant can facilitate subsequent resection of the coccyx and the intrapelvic portion of the tumor. An abdominoperitoneal approach may be required for resection of the pelvic tumor. The operating table should be kept in a slight reverse Trendelenburg position to prevent air embolism (Seeds et al., 1982).

Staged resection may also be considered. In one report, a fetus in a high-output state due to an SCT 1.5 times its size underwent initial devascularization via ligation of the middle sacral and internal iliac arteries that eliminated the hyperdynamic high-output state and returned cardiac output to normal (Robertson et al., 1995). Thirty-six hours later, primary resection of the residual tumor was performed. The infant subsequently underwent resection of the intrapelvic portion of the tumor at 2 months of age, and is now 4 years of age and free of disease.

Massive hemorrhage is an important cause of neonatal death in large vascular SCTs undergoing resection. Coagulapathy resulting from massive hemorrhage may be an important contributing factor. Recombinant factor VIIa has been used successfully in this setting (Girisch et al., 2004).

LONG-TERM OUTCOME

The long-term outcome in newborns with SCT is generally excellent. The most important prognostic factor for SCT appears to be the age at diagnosis (Conklin and Abell, 1967). When the diagnosis is made prior to 2 months of postnatal age, or excision is performed prior to 4 months of age, the malignant potential is only 5% to 10% (Gross et al., 1951; Hickey and Layton, 1954; Waldhausen et al., 1963; Donnellan and Swenson, 1988). This increases to 50% to 90% if the diagnosis is delayed until after 2 to 4 months of age (Hickey and Layton, 1954; Altman et al., 1974).

The mortality in a newborn with SCT is, however, not primarily due to malignant potential, but rather from difficulty in resection, and possibility of tumor hemorrhage (Altman et al., 1974; Schey et al., 1977; Alter et al., 1988; Grisoni et al., 1988). Gestational age at diagnosis may also affect prognosis, as fetuses diagnosed with SCT after 30 weeks of gestation tend to fare better than those diagnosed earlier (Schey et al., 1977; Flake et al., 1986; Kuhlmann et al., 1987). Cystic tumors may carry a better prognosis, most likely because of the lower incidence of tumor hemorrhage or vascular steal (Hogge et al., 1987). Prompt excision of both the tumor and the coccyx is thought to be essential to prevent recurrence (Gross et al., 1987). Delay may result in infection, hemorrhage, pressure necrosis, and malignant degeneration (Holzgreve et al., 1985).

Although SCTs are usually benign, they are prone to recurrence and have malignant potential. Surveillance for tumor recurrence is essential postoperatively. In SCTs, AFP levels are a useful marker for possible recurrence; a consistent downward trend in values should be observed until normal levels are reached by 1 year of age. We currently recommend that all newborns with SCT have serum AFP levels measured and physical examinations performed, including digital

rectal examinations every 3 months. Such surveillance is recommended for at least 3 years (Barreto et al., 2006). If the SCT was nonfunctional, postnatal pelvic sonographic examinations should be obtained at similar intervals. Once the serum AFP level normalizes, usually by 1 year of age, then MRI should be obtained on at least a yearly basis. Any increase over previous AFP values should prompt investigation for possible recurrence.

Factors that were thought to increase risk of recurrence of SCT or malignant yolk sac tumor were immature and malignant histology or incomplete resection. The chances of this recurrence was estimated at 11% by Derikx et al. (2006). Recurrence of the tumor does not necessarily indicate recurrence of malignancy. It should be treated as a premalignant lesion and excised. Even with malignant transformation of SCT, results with current chemotherapeutic regimens have achieved excellent survival rates. Misra et al. (1997) reported survival rates of 88% with local disease and 75% even in the face of distant metastases.

If the pathologic examination of the SCT reveals microscopic rests of endodermal sinus tumor it remains controversial as to whether chemotherapy is indicated (Heerema-McKenney et al., 2005). Older studies suggested any amount of yolk sac tumor presaged a poor prognosis and aggressive treatment was indicated (Valdiserri and Yunis, 1981; Rescorla et al., 1998). More recent studies suggest the presence of yolk sac tumor, foci of fetal lines, and immature endodermal glands in the SCT are associated with an increased risk of recurrent yolk sac tumor (Hawkins et al., 1993; Heifetz et al., 1998). Those recurrences however are amenable to modern combination chemotherapy with excellent survival (Rescorla et al., 1998; Marina et al., 1999; Huddart et al., 2003; Heerema-McKenney et al., 2005; De Backer et al., 2006). As there is no consensus on this issue, the decision to treat microscopic rests of yolk sac tumor with combination chemotherapy will vary from institution to institution.

There is limited long-term outcome data in SCT patients. Fortunately, with benign SCT, there is usually no serious bowel or bladder dysfunction after surgery and most neonates do well following resection (Litwiller, 1969; Tapper and Lack, 1983; Gross et al., 1987). Neurogenic bladder, however, is not an uncommon sequela in SCTs with a large pelvic component. Ozkan et al. reported a series of 14 cases of neurogenic bladder with high grade reflux with abnormal bladder and urethral function following resection of SCTs (Ozkan et al., 2006). Similarly postoperative urologic sequelae in SCT have been ranged from 20% to 30% (Kirk and Lister, 1976; Lahdenne et al., 1992; Carr et al., 1997). Urologic functional recovery has been documented with increasing age (Engelskirchen et al., 1987; Carr et al., 1997). Bittmann and Bittman found 33% had impaired bowel and bladder function. The frequency of anorectal dysfunction has ranged up to 40% (Engelskirchen et al., 1987; Malone et al., 1990; Wooley, 1993; Boemers et al., 1994). The most common long-term complication after SCT resection was cosmetic dissatisfaction with operative closure (Bittmann and Bittmann, 2006). Some children may experience subtle gait abnormalities as a result of SCT and its resection (Zaccara et al., 2004).

GENETICS AND RECURRENCE RISK

Some cases of SCT appear to be familial, with a suggestion of an autosomal dominant inheritance (Hunt et al., 1977; Gonzalez-Crussi, 1982). Familial SCTs are more often type IV SCTs and can be easily missed (Gopal et al., 2007). While only 10% of nonfamilial SCTs are presacral, 100% of familial SCTs are presacral. Familial cases have a male to female rate of 1:1 compared to 1:3 ratio in nonfamilial cases. Familial cases can be associated with anorectal malformations, most commonly anal stenosis, and can present as part of Currarino's triad (presacral tumor, anorectal malformation, and sacral anomaly) (Currarino et al., 1981). The familial cases are more likely to be associated with a "scimitar sacrum" and are usually benign (Gopal et al., 2007).

There have been rare cases of chromosomal abnormalities reported in patients with SCT including distal 10q trisomy syndrome (Batukan et al., 2007), mosaic trisomy of the long arm of chromosome 1 (Wax et al., 2000), and de novo translocation between chromosome 2 and 7 (Le Caignec et al., 2003).

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116 Wilms' Tumor

CHAPTER

Key Points

- Wilms' tumor is a common cause of renal neoplasms in children but is rarely diagnosed in utero.
- The main differential diagnosis in Wilms' tumor is mesoblastic nephrosis.
- Wilms' tumor may present in utero as part of Perlman syndrome (ascites, polyhydramnios, hepatomegaly, macrosomia, and Wilms' tumor).
- Wilms' tumor may present as part of recognized genetic conditions including Beckwith–Wiedemann syndrome, Denys–Drash syndrome, WAGR syndrome, Fanconi anemia, and Simpson–Golabi–Behmel syndrome.
- Excellent survival is achieved with current therapies including surgery, chemotherapy, and in some cases radiation therapy.

CONDITION

Renal neoplasms account for approximately 10% of all malignant tumors in children (Breslow and Beckwith, 1982). Nephroblastoma (Wilms' tumor) accounts for 80% of renal neoplasms in children, while other tumor types, such as anaplastic sarcoma, clear cell sarcoma, rhabdoid tumor, and renal cell carcinoma account for the rest. Wilms' tumor has a peak incidence at 2 to 3 years of age, but it can present from fetal life to adulthood (Breslow et al., 1988a,b). However, neonatal Wilms' tumor is unusual, with only 5 cases reported to the National Wilms' Tumor Study among 3340 reported between 1969 and 1984 (Hrabovsky et al., 1986; Ritchey et al., 1995). Several cases now have been diagnosed in utero (Giulian, 1984; Ritchey et al., 1995; Applegate et al., 1999; Vadeyar et al., 2000; Cavicchioni et al., 2005).

Nephroblastoma is a tumor that arises within the kidney and consists of a variety of embryonic tissues such as glomeruli and tubules, spindle cells, smooth and skeletal muscle fibers, cartilage, and bone. Wilms' tumor is associated with

many genetic conditions, including Beckwith–Wiedemann, Denys–Drash, Klippel–Trenaunay syndromes and neurofibromatosis and the WAGR complex (Wilms' tumor, aniridia, genitourinary malformations, and mental retardation) (King, 1993), suggesting a genetic predisposition to Wilms' tumor (Jadresic et al., 1990). However, the most common presentation of Wilms' tumor is an asymptomatic abdominal mass. Abdominal pain, hematuria or malaise, weakness, anorexia, and weight loss may also be presenting symptoms.

Fetal Wilms' tumor may present as part of Perlman syndrome, which is characterized by familial nephroblastomatosis, fetal ascites, polyhydramnios, hepatomegaly, macrosomia, and Wilms' tumor (Greenberg et al., 1986; Perlman, 1986). Wilms' tumor in Perlman syndrome occurs in the absence of chromosomal abnormalities, enzymatic defects, or somatic conditions known to be associated with Wilms' tumor. Nephroblastomatosis may present as either diffuse or discrete rests of abnormally persistent embryonic renal blastema. In some instances, this condition is believed to be a premalignant precursor of Wilms' tumor (Kulkarni et al., 1980; Stone et al., 1990). Nephroblastomatosis has been defined by Ambrosino et al. (1990) as either persistent metanephric blastema in infants over 36 weeks of gestation or the presence of persistent metanephric blastema in an abnormal location and/or quantity in younger fetuses. Nephrogenic rests occur as two main types, perilobar and intralobar (Beckwith et al., 1990). Nephroblastomatosis occurs in four patterns: perilobar only, intralobar only, combined, and universal or panlobular (Beckwith et al., 1990). The diffuse, panlobar type is characterized by diffuse superficial blastemal tissue that surrounds and compresses the normal parenchyma. In contrast, in the multifocal, perilobar, or intralobar types, nodular renal blastoma is found in the subcapsular cortex and in the deep cortex above the columns of Bertin. In autopsy series of infants younger than 3 months of age, perilobular nephrogenic rests were observed in 0.87% and intralobular in 0.1% (Beckwith et al., 1990). In contrast, 41% of unilateral Wilms' tumors are associated with nephrogenic rests and 99% of synchronous bilateral Wilms' tumors were associated with nephrogenic rests (Beckwith et al., 1990). Nephroblastomatosis is considered a precursor of Wilms' tumor, especially when it is of the multifocal type (Kulkarni et al., 1980; Ambrosino et al., 1990, Stone et al., 1990). Diffuse hyperplastic perilobar nephroblastomatosis is a distinct entity presenting as massively enlarged kidneys or kidneys that maintain their normal architecture and lack necrosis (Shamberger, 2005). A third of these will go on to develop Wilms' tumor (Barbosa et al., 1998).

INCIDENCE

Relatively few cases of Wilms' tumor have been diagnosed prenatally. However, our current understanding of the disease suggests that at least the predisposition to developing Wilms' tumor is present before birth. The incidence of Wilms' tumor is thought to be 1 in 8000 to 10,000 livebirths, with an estimated 8 cases in 1 million children younger than the age of 15 years (Kramer, 1985; Breslow et al., 1993; Miller et al., 1995). The fetal and neonatal incidence of the disease is unknown. In 50% of cases the left kidney is affected, in 45% of the cases the right is affected, and in 5% the tumor is bilateral. The tumor can be seen in association with specific anomalies, including aniridia (8.5 in 1000 cases), hemihypertrophy (25 in 1000 cases), cryptorchidism (28 in 1000 cases), and hypospadias (18 in 1000) (Breslow et al., 1988a,b).

SONOGRAPHIC FINDINGS

The sonographic features of Wilms' tumor may be indistinguishable from those of mesoblastic nephroma. Both present as complex masses that arise from or may completely replace the normal kidney. These tumors are predominantly solid, but cystic areas also can be seen. There may be a well-defined pseudocapsule in Wilms' tumor as opposed to mesoblastic nephromas (Figure 116-1A) (Giulian, 1984; Walter and McGahan, 1985). In mesoblastic nephroma, polyhydramnios is a feature of most cases that have been reported (Yambao et al., 1986). Few antenatally detected cases of Wilms' tumor have been described thus far, so it is uncertain if polyhydramnios may also occur in association with Wilms' tumor. Magnetic resonance imaging (MRI) may be used to enhance anatomic delineation of a renal mass (Figure 116-1B) (Tomá et al., 1990). Fetal MRI provides a larger field of view with better appreciation of the impact of a large Wilms' tumor on adjacent structures (Figure 116-1A and 116-1B). Three cases of prenatally diagnosed nephroblastomatosis have been reported (Ambrosino et al., 1990; Gaulier et al., 1993). One was the stillborn product of a 28-week gestation complicated by polyhydramnios, ascites, pleural effusion, nephromegaly, and calcific foci in one kidney. The second case similarly showed polyhydramnios, homogeneous nephromegaly, and calcific foci within the kidney. The lungs of both fetuses were hypoplastic. The kidneys at autopsy showed diffuse nephroblastomastosis and were thought to represent Perlman syndrome. The third case occurred within a multicystic dysplastic kidney.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of a fetal renal mass includes hydronephrosis (see Chapters 80–83) and multicystic dysplastic kidney (see Chapter 78). While far more common, the typical cystic appearance of hydronephrosis and multicystic dysplastic kidney easily distinguishes them from Wilms' tumor. However, mesoblastic nephroma (see Chapter 113) may be indistinguishable from Wilms' tumor (Giulian, 1984; Walter and McGahan, 1985; Garmel et al., 1994). Focal renal dysplasia should also be considered in the differential diagnosis (Gordillo et al., 1987; Sanders et al., 1988) as well as masses

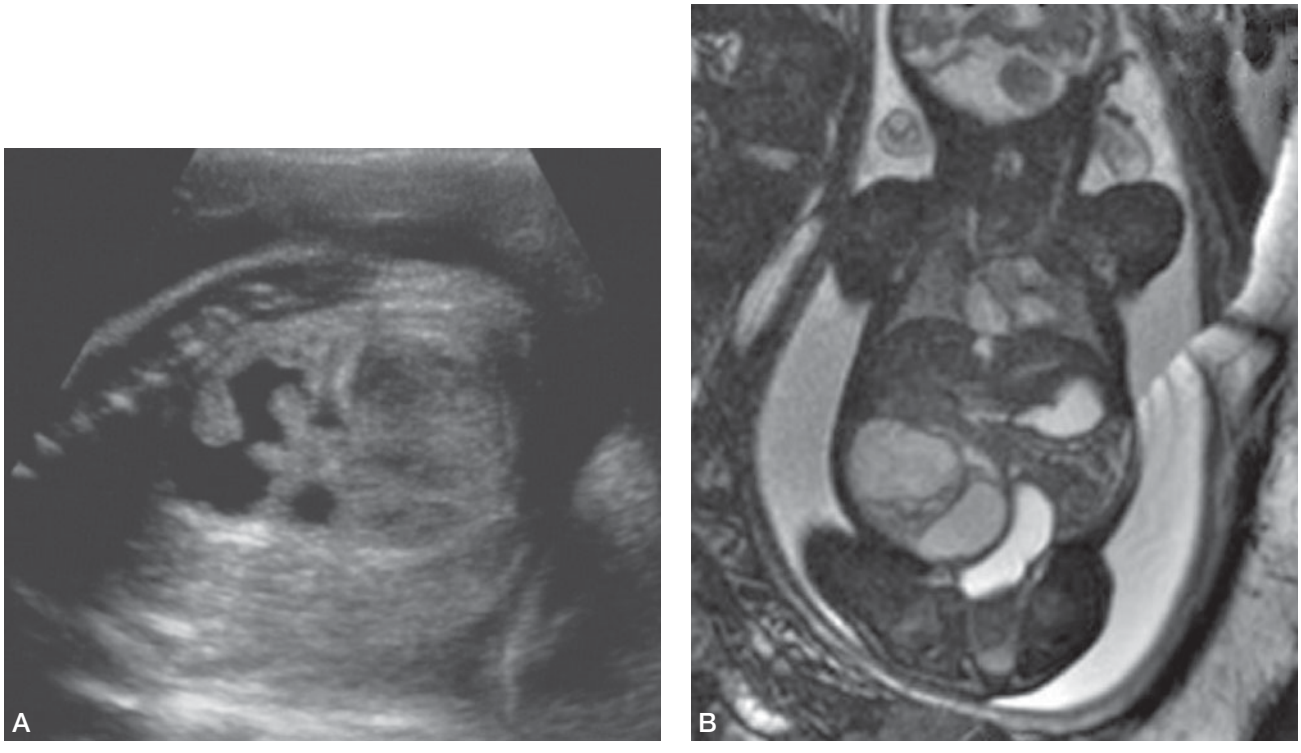

Figure 116-1 **A.** Fetal saggital sonographic image at 33 weeks of gestation demonstrating a large complex echogenic mass with well-defined borders arising from the right renal fossa displacing the bladder and extending across the midline with large cystic components. **B.** Coronal T_1-weighted MRI image of the same fetus, showing the mass to be hypointense relative to the liver, displacing the liver superiorly and the bladder to the left. The contrast in signal intensity in solid and cystic components is apparent.

extending from adjacent organs such as the adrenal gland or liver. In addition, nephroblastomatosis occurring in multicystic dysplastic kidney was detected by prenatal ultrasound examination as a renal mass may be difficult to distinguish from a Wilms' tumor (Gaulier et al., 1993). Nephroblastomatosis tends to maintain more normal renal architecture, and there are no cases of necrosis or cystic degeneration (Barbosa et al., 1998).

ANTENATAL NATURAL HISTORY

The antenatal natural history of Wilms' tumor remains undefined because of the infrequent prenatal ascertainment of these tumors.

MANAGEMENT OF PREGNANCY

The fetus with a suspected renal tumor should undergo a detailed sonographic evaluation to detect associated anomalies and clues to the cause of the mass. The features of Perlman syndrome, including fetal ascites, hepatomegaly, macrosomia, and polyhydramnios should be sought. A family history of Wilms' tumor should also be excluded. The contralateral kidney should be closely examined for anomalies or masses.

Because of the possibility of polyhydramnios in mesoblastic nephroma (the main consideration in the differential diagnosis) as well as in Perlman syndrome, these pregnancies should be followed closely, as polyhydramnios may precipitate preterm labor and premature birth. These tumors seldom achieve a size that might preclude vaginal delivery; however, an ultrasound examination should be done close to term to assess this possibility. Fetal MRI may be helpful in defining the anatomy and potentially in assisting in the differential diagnosis (Figure 116-1B).

FETAL INTERVENTION

No fetal intervention is necessary in Wilms' tumors.

TREATMENT OF THE NEWBORN

Physical examination of the newborn should confirm the presence of an abdominal mass. The affected newborn's blood pressure should be monitored, as 50% of Wilms' tumors may have associated hypertension. Associated anomalies (aniridia, cryptorchidism, and hypospadias) or physical signs of Beckwith–Wiedemann syndrome (macrosomia and macroglossia) should be excluded. A diagnostic work-up for

the presence of metastases should include chest radiography and abdominal computed tomographic (CT) scanning. Abdominal ultrasound should be obtained to evaluate tumor thrombus within the renal vein and the inferior vena cava.

A newborn with suspected Wilms' tumor should undergo an exploratory laparotomy for radical nephroureterectomy and exploration of the contralateral kidney to exclude synchronous bilateral lesions. If a complete resection is achieved and the histology reveals mesoblastic nephroma, no further treatment is indicated. In the National Wilms' Tumor Study-5 protocol, in cases of stage I Wilms' tumors that weigh less than 550 g in a patient younger than 2 years of age, a complete surgical resection is all that is necessary (Larsen et al., 1990; Green et al., 1994; Ritchey, 1998). In other tumors, adjuvant treatment with chemotherapy and radiation therapy is planned according to stage of disease and histology as defined by the National Wilms' Tumor Study. Expected long-term survival rates of >90% for localized cancers and approximately 70% for metastatic disease are achieved with current treatment regimens (Pritchard-Jones, 2002).

LONG-TERM OUTCOME

The long-term outcome for infants with Wilms' tumor depends on histology and stage of the tumor. In general, the 4-year survival of all patients with favorable histology approaches 90% (Haase and Ritchey, 1997; Pritchard-Jones, 2002). Unfavorable histology includes Wilms' tumors with anaplasia, and two other distinct renal tumors—clear cell sarcoma of the kidney and malignant rhabdoid tumor of the kidney. Anaplasia is present in approximately 4.5% of tumors and is more common in older children, with a peak incidence of 5 years. Stage I anaplastic tumors have a biologic behavior similar to stage I patients with a favorable histology with similar survival and relapse rates (Shochat, 1997). The survival rate in patients with focal anaplasia, stages II to IV, was 100%. However, this is a small percentage of patients with anaplasia. The 4-year survival of patients with diffuse anaplasia was only 52% (Shochat, 1997). The 4-year survival is 75% for patients with clear cell sarcoma of the kidney, and 25% for malignant rhabdoid tumors (D'Angio et al., 1989).

One concern for patients undergoing treatment for Wilms' tumor is the potential for the development of second malignant neoplasms. Li et al. (1983) reported that in 11 (2%) of 487 children treated at the Dana–Farber Cancer Institute second primary malignancies developed 7 to 34 years after treatment. The National Wilms' Tumor Study has reported similar findings, with 1% of survivors having a second malignancy at 10 years (Breslow et al., 1988b). These malignancies ranged from leukemia or lymphoma to hepatocellular carcinoma and soft tissue sarcomas. Children with Wilms' tumor who are long-term survivors require ongoing surveillance for the development of a second malignant neoplasm during their adult life.

Other late effects in Wilms' tumor survivors are problems with hypertension, fertility and pregnancy, and low birth weight infants. Haddy et al. (2007) found that as many as 70% of Wilms' tumor patients develop hypertension or prehypertension. Green et al. (1982) reviewed the reproductive histories of 36 Wilms' tumor survivors and found a significant increase (6.7%) in the perinatal mortality of their offspring. This was thought to be primarily the result of prematurity and the low birth weight of infants born to mothers who had previously undergone abdominal radiation. The risk of low birth weight infants in this group of patients was 30%. Li et al. (1987) observed similar problems in 34 of 114 pregnancies in female Wilms' tumor survivors who underwent radiation. Because of the increased risk in mothers who are Wilms' tumor survivors, prenatal counseling and referral to a maternal and fetal medicine specialist is recommended when pregnancy is contemplated (Byrne et al., 1988).

GENETICS AND RECURRENCE RISK

Recent advances suggest that there are hereditary and nonhereditary forms of Wilms' tumor, depending on whether the initial mutational event occurred in a germ cell or a somatic cell (Knudson and Strong, 1978) (Table 116-1). Younger patients; those with aniridia, genitourinary anomalies, and bilateral disease; and familial cases have been considered to be in the hereditary group. It has been estimated that this group accounts for 20% of cases of Wilms' tumors. Of the patients registered with the National Wilms' Tumor Study, 1% of the cases have at least one family member similarly affected (Breslow and Beckwith, 1982).

Patients with Wilms' tumor and aniridia, genitourinary anomalies, and mental retardation (WAGR) syndrome frequently demonstrate a deletion of band 11p13 (Francke et al., 1979; Kofous et al., 1984). The loss of function of a recessive tumor suppressor gene located in the 11p13 region may be responsible for the development of Wilms' tumor. Call et al. (1990) have identified a *WT1* (Wilms' tumor) gene from the 11p13 region. *WT1* invades a zinc finger transcription factor then acts by binding to other DNA sequences that control the expression of renal genes. *WT1* acts as a classic tumor suppressor gene and the XXXX type allele is somatically inactivated in tumors occurring in individuals with constitutional *WT1* mutations or deletions (Haber et al., 1991). *WT1* appears to be essential for normal development of the kidney and genitourinary tract. However, *WT1* mutations occur in fewer than 10% of cases. A second gene, *WT2*, has been identified at the end of chromosome 11p in association with the Beckwith–Wiedemann syndrome locus. In addition, a third Wilms' tumor locus has been suggested by lack of linkage to either *WT1* or *WT2* in the rare families affected with Wilms' tumor (Grundy et al., 1988; Strong et al., 1988). Other genes and chromosomal abnormalities have been identified at the 11p15 locus and on chromosome 16q (Waley et al., 1990; Maw et al., 1992). The sporadic form of Wilms' tumor is not

Table 116-1

Conditions with an Increased Risk of Wilms' Tumor

High Risk (>20%)
- WT1 deletions (including WAGR syndrome)
- Truncating and pathogenic missense WT1 mutations (including Denys–Drash syndrome)
- Familial Wilms' tumor
- Perlman syndrome
- Mosaic variegated aneuploidy
- Fanconi anemia D1/biallelic BRCA2 mutations

Moderate Risk (5–20%)
- WT1 intron 9 splice mutations (Frasier syndrome)
- Beckwith–Wiedemann syndrome caused by 11p15 Uniparental disomy, isolated H19 hypermethylation, or of unknown cause
- Simpson–Golabi–Behmel syndrome caused by GPC3 mutations/deletions

Low Risk (<5%)
- Isolated hemihypertrophy
- Bloom syndrome
- Li–Fraumeni syndrome/Li–Fraumeni-like syndrome
- Hereditary hyperparathyroidism-jaw tumor syndrome
- Mulibrey nanism
- Trisomy 18
- Trisomy 13
- 2q37 deletions

Adapted from Scott H, Stiller CA, Walker L, et al. Syndromes and constitutional chromosomal abnormalities associated with Wilms' tumour. J Med Genet. 2006;43:705-715.

associated with recurrence in subsequent pregnancies. However, approximately 20% of patients with Wilms' tumor are at risk for recurrence in a sibling. These pregnancies should be closely observed by ultrasound examination and amniocentesis should be considered for genetic testing.

Familial cases of Wilms' tumor account for 1% to 2% of cases. Putative tumor genes have been identified in some of these cases as FWT1 with a link to chromosome 17q12-21 (Rahman et al., 1996) and FWT2 linked to chromosome 19q13.3-q13.4 (McDonald et al., 1998). Grundy et al. (1994) have found that loss of heterozygosity on chromosome 16q in Wilms' tumor, which occurs in 15% to 20% of cases, is associated with 3.3-fold greater rate of relapse and 12-fold greater incidence of mortality compared to cases without these changes.

Most Wilms' tumors diagnosed in the newborn or infant are stage I or II and the long-term prognosis appears to be excellent, with a survival rate of 95% (Ritchey et al., 1995). Not only is survival influenced by the early stage of neonatal Wilms' tumor, but also unfavorable histology is rare in patients younger than 2 years of age (Isaacs, 1997). It is important to emphasize, however, that the rarity of neonatal Wilms' tumor precludes definitive statements regarding survival.

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Malformations in Twins

117
CHAPTER

Key Points

- Congenital malformations occur more commonly in twins as compared with singleton gestations and are an important contributor to the increased perinatal mortality associated with multiple gestations.
- The incidence of congenital anomalies is thought to be more common in monozygotic compared with dizygotic twin pregnancies.
- Antenatal ultrasound examination is used to detect malformations in twin pregnancies.
- The antenatal natural history will depend on the malformation diagnosed, whether or not it is discordant, and the chorionicity of the pregnancy.
- The management will be influenced by the type of abnormality, whether or not it is concordant, the gestational age when diagnosed, and chorionicity.
- Counseling of parents depends on the type of abnormality and the prognosis for the anomalous twin as well as on the likely outcome for the normal co-twin.
- Three management options are available in this situation: expectant management, selective termination of the anomalous fetus, and termination of the entire pregnancy.
- Expectant management of a twin pregnancy discordant for an abnormality is associated with an increased risk for preterm delivery.
- The method chosen for selective termination will depend on chorionicity. Intracardiac injection of potassium chloride is safe in dichorionic twins, while cord occlusive techniques are necessary for monochorionic pregnancies.
- Treatment of neonatal twins with malformations will depend on the particular malformation.
- The recurrence risk for malformations seen in twin pregnancies will depend on the specific abnormality.

CONDITION

When congenital malformations occur in a multiple gestation, management decisions can be difficult for both parents and physicians because the fates of such sibling fetuses are necessarily linked. Given that the incidence of multiple gestations is increasing in industrialized countries, primarily because of assisted reproductive technologies (Jewell and Yip, 1995), the management dilemma for twins with malformations will also inevitably increase. Congenital malformations occur more commonly in twins as compared with singleton gestations and are an important contributor to the increased perinatal mortality associated with twin gestation. Some malformations in twins are inherent to the monozygotic twinning process, such as acardiac twinning, conjoined twins, and twin-to-twin transfusion syndrome. These

malformations are discussed separately (see Chapters 119–121). Other malformations in twins are deformation abnormalities, such as clubfoot, which result from the crowding of the intrauterine environment.

INCIDENCE

Using data from the British Columbia Health Surveillance Registry, the incidence of congenital malformations in twin pairs was estimated at 6% (Schinzel et al., 1979). In this series, the incidence of congenital anomalies was 2.5 times more common in monozygotic twins than in dizygotic twins or singletons. The incidence of chromosomal abnormalities is increased twofold in dizygotic twins as compared with age-matched singleton pregnancies, but the incidence of nonchromosomal abnormalities is not increased (Drugan et al., 1996).

In one series of 1424 twin pairs, 445 pairs were monozygotic, 26 of which (6%) had congenital malformations (Cameron et al., 1983). Even among monozygotic twin pairs with malformations, however, the majority of fetuses will be discordant for the abnormality, with only 6 of the 26 twin pairs (23%) concordant (Cameron et al., 1983). In another registry of 4490 twins, there was a 50% increase in incidence of congenital malformations among twins as compared with singletons, 4.9% versus 3.3%, respectively, with this increase almost entirely limited to same sex—and therefore presumably monozygotic—twin pairs (Layde et al., 1980).

The incidence of open neural tube defects in twins is controversial. In one study from California and Norway, anencephaly and encephalocele, but not meningomyelocele, were found more commonly in twins as compared with singletons (Windham et al., 1982). In a national survey from England and Wales, there was a threefold increased incidence of anencephaly in twins as compared with singletons, while the incidences of encephalocele and meningomyelocele were similar in twins and singletons (Doyle et al., 1991). In a further study from Spain, the incidence of anencephaly was 0.1% for twins as compared with 0.03% for singletons, and this increase was almost entirely in same-sex twin pairs (Ramos-Arroyo, 1991). However, in a study from Northern Ireland, the incidence of anencephaly was decreased in twins, while the incidence of meningomyelocele was similar to that of singletons (Little and Nevin, 1989a). The incidence of congenital cardiovascular malformations was also found to be modestly increased in twins as compared with singletons, 0.9% versus 0.7%, with the increase again being confined to same-sex twin pairs (Little and Nevin, 1989b).

SONOGRAPHIC FINDINGS

The ability of sonographic examination to detect congenital malformations in twin pregnancies has not been adequately evaluated, with no large patient series available for review. In one series of 33 fetuses from twin pregnancies with anomalies, none of the 8 cardiac anomalies were diagnosed prenatally, while 11 of 20 (55%) other major anomalies and none of the 12 minor anomalies were diagnosed prenatally (Allen et al., 1991). In another series of 24 fetuses with anomalies, it was concluded that by using serial ultrasonography in a tertiary care center it may be possible to achieve an 88% detection rate, with 100% specificity, in the prenatal diagnosis of anomalies in twin pregnancies (Edwards et al., 1995). However, almost 40% of fetuses with anomalies in this series were not diagnosed until 24 weeks of gestation or later, when options for management are more limited. It has also been suggested that up to 88% of cases of Down syndrome in twin pregnancies could be detected by combining risks derived from maternal age and sonographic nuchal translucency thickness measurement at 10 to 14 weeks of gestation (Sebire et al., 1996).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis following the prenatal diagnosis of a congenital malformation in a twin pregnancy is extensive and is dependent on the particular abnormality that is suspected. For differential diagnoses for individual malformations, the corresponding chapters in this textbook should be consulted. Judging from the few published series of sonographic diagnosis of congenital malformations in twins, there is a high degree of specificity involved in the correct prenatal identification of anomalies (Allen et al., 1991; Edwards et al., 1995).

ANTENATAL NATURAL HISTORY

Specific information on the antenatal natural history of individual malformations is available in the corresponding chapters in this textbook. The history of such pregnancies becomes even more complicated when, as in the majority of cases, there is discordance for the malformation in question. In a series of 14 expectantly managed twin gestations in which only one fetus had a congenital malformation, Malone et al. (1996) found a significantly increased (20%) risk of preterm delivery in such pregnancies, in addition to the baseline risk of prematurity already seen with normal twin gestations. This was attributable to the presence of a fetus with an anomaly. Birth weight was significantly lower, and both cesarean delivery rate and perinatal mortality rate were increased in anomalous twin pregnancies as compared with control twins. These data were subsequently confirmed by Alexander et al. (1997) and Gul et al. (2005), both of whom found both lower gestational age at delivery and lower birth weight in their small series of expectantly managed anomalous twin pregnancies as compared with control twins.

MANAGEMENT OF PREGNANCY

When both fetuses in a twin pregnancy are concordant for malformations, subsequent management of that pregnancy

is straightforward and should involve both the usual obstetric management of twin gestations and any required interventions for the particular malformation. However, pregnancy management becomes considerably more complex when one twin has a congenital malformation but the co-twin is normal. Counseling of parents depends on the type of abnormality and the prognosis for the twin with the anomaly as well as on the likely outcome for the normal co-twin. Three management options are available in this situation: expectant management, selective termination of the anomalous fetus, and termination of the entire pregnancy (Malone and D'Alton, 1997; Rustico et al., 2005). Selective termination of an anomalous twin is described in detail under "Fetal Intervention."

For pregnancy management, we recommend karyotyping for twins with malformations. As already described, parents should be counseled that expectant management of an anomalous twin pregnancy is associated with an increased risk of preterm delivery. In addition to the risk of prematurity, expectant management can also be complicated by intrauterine death of the anomalous fetus, which can have profound implications for the well-being of the normal co-twin, especially in a monochorionic twin gestation. If one fetus in a monochorionic twin pair dies, there may be a greater than 20% risk to the remaining co-twin of developing multicystic encephalomalacia, leading to profound neurologic handicap (Pharoah and Cooke, 1997; Pharoah and Adi, 2000). This risk is present from the moment of the death of the first twin, and may not be predictable, even by intensive surveillance with sonographic examination or fetal heart rate monitoring. Therefore, serious consideration should be given to delivering the twins if an anomalous fetus in a monochorionic gestation appears to be in a premorbid condition. This decision will depend on the gestational age, so that the risks of neurologic morbidity associated with expectant management are balanced against the iatrogenic risk of prematurity associated with delivery. If an anomalous twin in a monochorionic twin pair has already died in utero, close fetal surveillance for the surviving co-twin is recommended, although it must be realized that this may not prevent neurologic morbidity, which may already have occurred. Similarly, delivery immediately after diagnosis of the intrauterine death of one twin may not protect against neurologic morbidity in the surviving co-twin. Delivery at 37 weeks, or after measuring lung indexes consistent with maturity, is reasonable in such situations.

Antenatal surveillance of twin gestations complicated by congenital malformations should follow the usual recommended fetal surveillance practices for normal twin pregnancies. This includes serial sonographic examinations every 3 to 4 weeks, from approximately 18 weeks for fetal growth, or every 2 weeks if growth restriction or growth discordance greater than 20% is present. More intensive fetal surveillance with nonstress tests and Doppler velocimetry is recommended for cases of growth restriction or significant growth discordance. Additional fetal testing may also be indicated depending on the particular type of congenital malformation present.

The decision on location of delivery will depend entirely on the nature of the congenital malformation, presence of associated anomalies, and availability of postnatal therapies. With regard to mode of delivery, the choice between vaginal and cesarean delivery will also be dictated by the individual malformation and fetal prognosis. This is described in detail in the appropriate section in the chapters describing each abnormality. In addition, the usual obstetric indications for determining mode of delivery of normal twin gestations may also apply. Typically, all vertex/vertex twins are candidates for vaginal delivery, while most obstetricians perform a cesarean delivery if the presenting twin is nonvertex. When the presenting twin is vertex and the second twin is nonvertex, a vaginal breech delivery of the second twin is generally acceptable if the estimated fetal weight is greater than 1500 g. There are insufficient data to confirm the optimal mode of delivery when a nonvertex second twin weighs less than 1500 g.

FETAL INTERVENTION

The main fetal intervention available for twin gestations in which one fetus has a congenital malformation is selective termination. Whether selective termination is considered a reasonable option will depend on the severity of the anomaly, the chorionicity of the gestation, and the moral and ethical beliefs of the parents (Table 117-1). Selective termination may appear unreasonable in the case of minor congenital malformations. It has also been argued that selective termination should not be performed in cases of lethal anomalies, because it is difficult to justify the additional risk to the normal fetus of an invasive procedure designed to terminate a co-twin that is already nonviable (Stone and Berkowitz, 1995). An exception may be the presence of polyhydramnios in a twin gestation discordant for anencephaly because such pregnancies are at much higher risk of preterm delivery than are normal twin pregnancies (Sebire et al., 1997). Another option in the case of twins discordant for anencephaly is to perform serial amnioreduction if polyhydramnios develops, with the goal of reducing the risk of preterm delivery (Sebire et al., 1997).

Table 117-1

Common Indications for Selective Fetal Reduction in Monochorionic, Diamniotic Twin Gestations

1. TRAP sequence
2. Severe fetal malformations in one twin
3. Early severe intrauterine fetal growth restriction in one twin
4. Early severe TTTS when laser therapy not an option
5. Chromosomal abnormality in heterokaryotypic twins

Determining chorionicity is vital prior to considering selective termination of an anomalous fetus in a twin pregnancy. This can be determined sonographically by identifying fetal gender, observing the thickness of the dividing membranes, or observing separate placentae. Alternatively, at the time karyotyping is performed, the amniocyte culture can also be used as a source of fetal DNA for zygosity testing (Norton et al., 1997). Monozygous twins will have identical DNA polymorphisms at all loci analyzed, whereas dizygous twins will differ.

Before performing the termination procedure, it is essential to confirm that the targeted fetus has the abnormality in question. This identification is fairly straightforward if a structural abnormality is present. However, in cases of chromosomal abnormality without obvious structural malformation, there may be some doubt about correct identification of the anomalous fetus, especially if some time has passed since karyotyping or if careful intrauterine mapping was not performed initially. In cases in which there is some doubt regarding fetal identification, it is recommended to perform repeat chromosomal analysis using rapid techniques (such as fluorescence in situ hybridization or fetal blood sampling) immediately before selective termination.

Several techniques have been successfully used to perform selective termination in the second trimester. These include cardiac puncture, removal of the anomalous twin at hysterotomy, cardiac puncture with intracardiac injection of calcium gluconate, air embolization through the umbilical vessels with fetoscopic guidance, and intracardiac injection with potassium chloride (Aberg et al., 1978; Beck et al., 1981; Kerenyi and Chitkara, 1981; Rodeck et al., 1982; Antsaklis et al., 1984; Chitkara et al., 1989). The latter has gained widespread acceptance for both selective termination and multifetal pregnancy reduction procedures in dichorionic twins due to its proven safety and efficacy (Evans et al., 1999).

Evans et al. reported the outcome of 402 selective termination procedures from four countries and eight centers using ultrasound-guided intracardiac injection of potassium chloride (Evans et al., 1999). The overall results were excellent, with delivery of one or more viable infants in more than 90% of cases. Similarly, Eddelman and colleagues reported favorable outcomes in 200 selective termination cases performed in one institution (Eddelman et al., 2002). This study included 164 twins, 32 triplets, and 4 quadruplets. The average gestational age at the time of the procedure was 19 2/7 weeks, with a range of 12 to 23 6/7 weeks. The indications for selective termination included chromosomal abnormalities, structural anomalies, Mendelian disorders, placental insufficiency, and cervical incompetence. The overall unintended pregnancy loss rate was 4%, with losses being fivefold higher in triplets than in twins. The average gestational age at delivery was 36 1/7 weeks and 84% delivered after 32 weeks of gestation.

Selective termination by potassium chloride injection is contraindicated with monochorionic gestations because death of the unaffected twin occurs in 80% to 100% of cases within several days of termination of the anomalous fetus (Golbus et al., 1988; Evans et al., 1994; Challis et al., 1999). Other methods of performing selective termination of an anomalous fetus in a monochorionic twin pair have been described, but all are considered experimental at this time. Each of these experimental techniques must ensure rapid occlusion of the umbilical vessels of the anomalous fetus to prevent acute hypotension and subsequent mortality or neurologic morbidity in the normal fetus (Malone and D'Alton, 1997). Successful techniques that have been described to date include hysterotomy (Robie et al., 1989), fetoscopic cord ligation (Figure 117-1) (Crombleholme et al., 1996; Quintero et al., 1996), fetoscopic laser ablation of umbilical vessels (Hecher et al., 1996), and percutaneous injection of absolute alcohol (Denbow et al., 1997) into the intra-abdominal umbilical vessels (Tables 117-2 and 117-3; Figures 117-1 to 117-4).

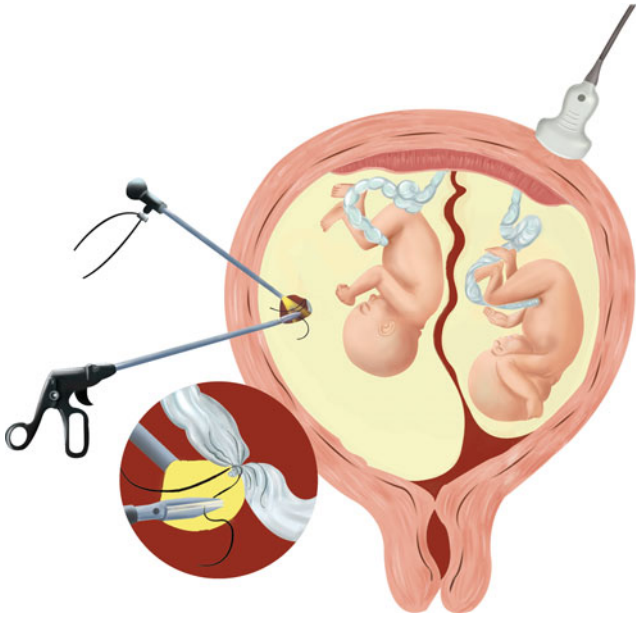

Figure 117-1 Diagram of fetoscopic cord ligation technique used in the selective termination of a twin fetus with a malformation.

TREATMENT OF THE NEWBORN

The treatment of neonatal twins with malformations is entirely dependent on the type of abnormality and is described for each abnormality under the appropriate "Treatment of the Newborn" section in this textbook.

SURGICAL TREATMENT

As with treatment of the newborn, neonatal surgery is also entirely dependent on the type of abnormality and is described for that abnormality under the appropriate "Surgical Treatment" section in this textbook.

Table 117-2

Published Cases of Mechanical Cord Ligation in Monochorionic Pregnancies

Author	Indication	Procedure wk/ Delivery wk	Number of Ports/Size	Technical Success	PPROM <32 wk	Neonatal Survival	Clinical Success*	Comments
Young, 2001	Mono-mono HLHS	19/19	Fetoscopic ligation	No	—	No	No	Incorrect cord ligated
Gallot, 2003	TTTS	27.5/29	USG-guided ligation	Yes	No	Yes	No	
	TTTS	24/35.5		Yes	No	Yes	Yes	
	TTTS	27/30		Yes	Yes	No	No	NND with ascites
	TTTS	23.5/23.5		Yes	—	No	No	
Galinkin, 2000	Acardiac twin	24/38	Hysterotomy	Partial	No	Yes	Yes	Unsuccessful fetoscopy, performed "mini-hysterotomy"
Quintero, 1996	TTTS	23/26	1/12 g	Yes	No	Yes	No	PTD
	TTTS	23/25	2/10 g, 12 g	Yes	Yes	Yes	No	Subchorionic hematoma
	Acardiac twin	23/23	1/12 g	No	Yes	No	No	IUFD after alcohol injection
	Acardiac twin	19/36	2/12 g	Yes	Yes	Yes	Yes	Re-seal of PPROM
	Acardiac twin	23/30	1/10 g	Yes	Yes	Yes	No	PPROM with PTL/PTD
	Acardiac twin	18.5/37	2/12 g, 10 g	Yes	No	Yes	Yes	
	Acrania	16.5/33	2/12 g, 10 g	Yes	No	Yes	Yes	PPROM with PTL/PTD
	Acardiac twin	25/25	2/5 mm	Yes	Yes	No	No	NND DOL 27 secondary to cystic fibrosis
	Acardiac twin	20/32	3/5 mm, 10 g	Yes	No	Yes × 2	Yes	Quadruplets, induction for oligohydramnios
	Acardiac twin	25/30	1/10 g	Yes	No	Yes	No	PTL/PTD
	Acardiac twin	23/26	1/10 g	No	—	No	No	Intraoperative bleeding and delayed IUFD
	Acardiac twin	20/24	2/12 g	Yes	—	No	No	Intraoperative bleeding and delayed IUFD
	Acardiac twin	20/26	2/10 g	Yes	—	No	No	Delayed IUFD with possible cord accident
Willcourt, 1995	Acardiac twin	24/29	2/10 mm	Yes	No	Yes	No	PTL/PTD
Lemery, 1994	Acardiac twin	23/36	1/5 mm	Yes	No	Yes	Yes	
Lemery, 1995	Acardiac twin	24.5/30	1/5 mm	Yes	Yes	Yes	No	PTL/PTD; developmental delay
Summary	22 cases	Median interval to delivery—5 wk		Technical success 18/22 (82%)	PPROM <32 7/16 (44%)	Neonatal survival 14/22 (64%)	Clinical success 7/22 (32%)	

**Clinical success defined as delivery of liveborn infant following 32 weeks.*
Mono-mono, monoamnionic/monochorionic; HLHS, hypoplastic left heart syndrome; TTTS, twin-to-twin transfusion syndrome; PPROM, preterm premature rupture of membranes; NND, neonatal demise; PTL, preterm labor; PTD, preterm delivery; DOL, day of life; IUFD, intrauterine fetal demise.

Table 117-3

Published Cases of Thermocoagulation Techniques for Cord Occlusion

Author	Indication	Number of Cases	Method	Technical Success	PTL or PPROM <32 wk	Neonatal Survival	Clinical Success*	Comments
Ville, 1994	Acardiac twin	4	Laser	2/4	2/4	4/4	2/4	Failed laser × 2, IUT × 1
Hecher, 1997	Acardiac twin	1	Laser	1/1	0/1	1/1	1/1	
Arias, 1998	Acardiac twin	1	Laser	1/1	0/1	1/1	1/1	
Rodeck, 1998	Acardiac twin	4	Monopolar	4/4	0/4	4/4	4/4	32 wk PTD with developmental delay
Deprest, 2000	Acardiac twin TTTS	5 5	Bipolar	10/10	3/10	8/10	7/10	PPROM at 19 wk had VTOP, IUFD following PPROM × 1
Nicolini, 2001	TTTS Dis anomalies Acardiac twin	9 6 2	Bipolar	17/17	3/17	13/17	11/17	IUFD <24 h with intraoperative bleeding NND at 1 mo with ICH
Quintero, 2002	Acardiac twin	1	Laser	1/1	0/1	1/1	1/1	
Tsao, 2002	Acardiac twin	13	RFA	13/13	1/13	12/13	11/13	NND delivered at 24 wk
Sydorak, 2002	Dis anomalies	6	Harm. scalpel × 4 (laser × 3) RFA × 2	5/6	1/6	5/6	4/6	IUFD after persistent flow noted following RFA
Taylor, 2002	TTTS	15	Bipolar	14/15	3/15	13/15	9/15	Delivery for abruption with NND DOL 7
Sepulveda, 2003	Acardiac twin	2	Monopolar	2/2	1/2	1/2	0/2	IUFD with cord entanglement
Summary		Total cases 74		Technical success 70/74 (95%)	PTL or PPROM <32 wk 14/74 (19%)	Neonatal survival 63/74 (85%)	Clinical success 51/74 (69%)	

**Clinical success defined as delivery of liveborn infant following 32 weeks.*
TTTS, twin-to-twin transfusion syndrome; Dis, discordant; IUT, intrauterine transfusion; ICH, intracranial hemorrhage; RFA, radiofrequency ablation; NND, neonatal demise; Harm, harmonic; DOL, day of life; IUFD, intrauterine fetal demise.

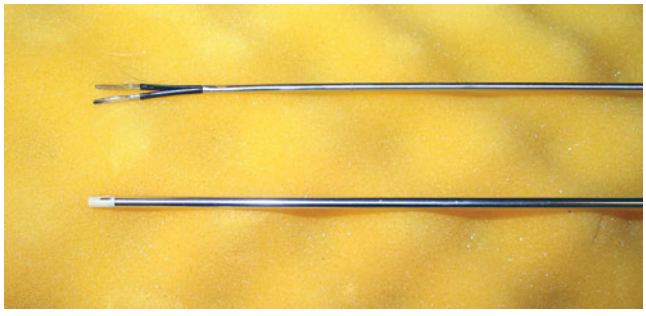

Figure 117-2 Bipolar forceps (2–3 mm) with laparoscopic sheath (Karl Storz, Tuttlingen, Germany) utilized for cord cauterization in selective termination in monochorionic twins.

LONG-TERM OUTCOME

No data are available on the long-term outcome of normal co-twins following selective termination of an anomalous twin. The long-term outcome of anomalous fetuses that are managed expectantly is also entirely dependent on the type of abnormality and is described for each abnormality under the appropriate "Long-Term Outcome" section in this textbook.

GENETICS AND RECURRENCE RISK

The recurrence risk for malformations seen in twin pregnancies varies greatly depending on the particular abnormality. For deformations such as clubfoot that probably occur as a result of crowding of the intrauterine environment, the risk of recurrence is relatively small. For malformations such as acardiac twinning and twin-to-twin transfusion syndrome, which occur secondary to vascular communications across a monochorionic placenta, the recurrence risk is also relatively small. Recurrence risks for other abnormalities are described under the "Genetics and Recurrence Risk" sections in the relevant chapters in this textbook.

Figure 117-3 Radiofrequency device (RadioTherapeutics, Sunnyvale, CA) in sheath (*left*) and deployed (*right*) for cord coagulation in selective termination in monochorionic twins.

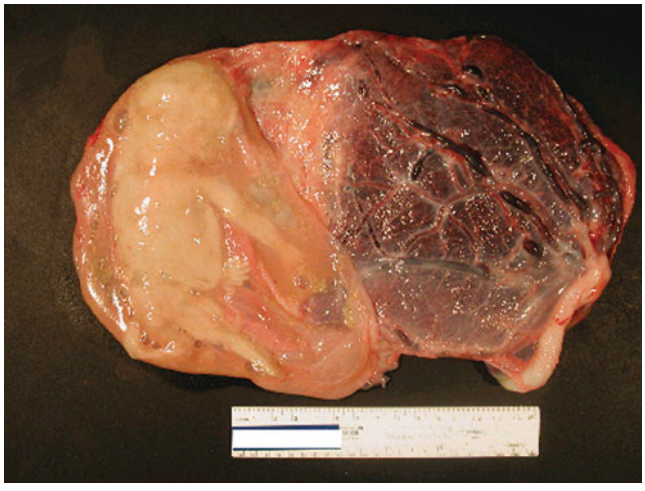

Figure 117-4 Fetus papyraceus and monochorionic twin placenta of pregnancy delivered at term following radiofrequency cord ablation procedure at 17 weeks for discordant abnormality in one twin. (*Reprinted with permission from Shevell et al. Radiofrequency ablation in a monochorionic twin discordant for fetal anomalies.* Am J Obstet Gynecol. *2004;190:575-576*)

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118 CHAPTER Intrauterine Death in One Twin

Key Points

- Intrauterine fetal death (IUFD) of one twin in the first trimester is common and is known as a "vanishing twin."
- Although a "vanishing twin" may be associated with vaginal spotting, it is not associated with adverse perinatal outcomes for the surviving twin.
- Single IUFD in the second and third trimester is less common and is more likely to be associated with complications for the surviving co-twin.
- When single IUFD occurs in a monochorionic pregnancy, it is associated with a worse prognosis, including up to 20% incidence of significant neurologic morbidity for the surviving co-twin, such as multicystic encephalomalacia.
- Sonographic assessment of a single IUFD in a twin pregnancy should include determination of chorionicity, the accuracy of which may be limited in the second and third trimesters.

Key Points (cont.)

- If a certain diagnosis of chorionicity is needed for pregnancy management, DNA studies on amniocytes may be needed.
- Management of a case of single IUFD depends on gestational age and chorionicity.
- Preterm labor and delivery is often associated with single IUFD. Otherwise, expectant management is suggested if the gestational age is less than or equal to 37 completed weeks and there are no indications for delivery.
- Surviving co-twins in a monochorionic pregnancy should be evaluated postnatally for neurologic sequelae.

CONDITION

The intrauterine fetal death (IUFD) of one twin occurs most commonly during the first trimester. This phenomenon is known as a "vanishing twin" (Landy and Weingold, 1989). Although this may be associated with vaginal spotting, the loss of one conceptus is often not clinically recognized, and the prognosis for the surviving twin is excellent (Landy et al., 1986; Samuels, 1988; Prompeler et al., 1994).

Single IUFD in the second or third trimesters is much less common. Single IUFD is observed more often in association with monochorionic than with dichorionic placentation. When it occurs in a monochorionic gestation it may be associated with a worse outcome for the surviving co-twin.

The etiology of IUFD in a multiple pregnancy may be similar to singletons or unique to the twinning process. IUFD may be caused by genetic or anatomical anomalies, abruption, placental insufficiency, cord abnormalities such as a velamentous cord insertion, infection, and maternal disease including diabetes and hypertension (Ogunyemi et al., 1998; Collins, 2002; Craven and Ward, 2002; Simpson, 2002). In monochorionic pregnancies, IUFD may result from complications of the twin-to-twin transfusion syndrome (TTTS). Most often, the smaller, donor twin dies, but IUFD can occur in the larger recipient twin (D'Alton and Simpson, 1995). In addition, monoamniotic twins are at increased risk of cord entanglement and subsequent IUFD (Colburn and Pasquale, 1982). Similar to singletons, the etiology of IUFD often remains elusive (Santema et al., 1995).

Single IUFD in a multiple gestation can adversely affect the surviving fetus or fetuses in two ways: (1) risk for multicystic encephalomalacia and multiorgan damage in monochorionic pregnancies and (2) preterm labor and delivery in both dichorionic and monochorionic twins resulting in prematurity.

Multicystic encephalomalacia (cystic lesions in the cerebral white matter distributed in areas supplied by the anterior and middle cerebral arteries) is associated with profound neurologic handicap. The risk of multicystic encephalomalacia following single IUFD in a monochorionic pregnancy may be as high as 20% for the surviving co-twin (Melnick, 1977; Wessel and Schmidt-Gollwitzer, 1988; Yoshida and Matayoshi, 1990; Dudley and D'Alton, 1986; Eglowstein and D'Alton, 1993; D'Alton and Simpson, 1995; Pharoah and Cooke, 1997; Pharoah and Adi, 2000).

Two theories have been suggested to explain the pathophysiology of multiorgan damage in surviving monochorionic twins. One theory is based on the premise that the retained demised fetus produces thromboplastic materials that traverse the anastomoses between the placentas resulting in disseminated intravascular coagulation. This would lead to infarction and cystic change in numerous organ systems including the kidneys, lungs, spleen, liver, and brain (Bulla et al., 1987). Although several autopsy reports have supported this hypothesis (Moore et al., 1969; Yoshioka et al., 1979; Szymonowicz et al., 1986), this mechanism of injury is no longer thought to be plausible.

The current widely accepted theory suggests that blood from the surviving twin may rapidly "back-bleed" into the demised twin through placental anastomoses, a form of acute fetofetal transfusion (Fusi et al., 1991). The demised twin may become congested while the surviving twin may become anemic. If the hypotension is significant, the surviving twin is at risk for ischemic damage to vital organs (D'Alton et al., 1984; Fusi et al., 1991; Okamura et al., 1994).

In 1991, Fusi et al. reported a case where cerebral and renal lesions were pathologically confirmed in a deceased neonate who had experienced IUFD of a co-twin. Autopsy demonstrated acute blood transfusion from the surviving twin to the IUFD. Hematocrit at delivery was consistent with anemia (Fusi et al., 1991). Fusi's case suggests the need for intervention before IUFD in monochorionic twins to avoid permanent multiorgan damage. Nicolini et al. further supported this concept when they described eight monochorionic pregnancies complicated by a single IUFD (Nicolini et al., 1998). Five of the eight pregnancies underwent blood sampling prior to IUFD. Four of these five who had died were not anemic prior to death and neither were their co-twins. All survivors sampled within 24 hours following the death of their co-twin were anemic.

Since the injury seems to occur at the time of IUFD, immediate delivery of the co-twin following single IUFD in a monochorionic pregnancy does not seem to improve outcomes but rather adds to the risk of prematurity. Perfectly timed intravascular transfusion of blood or fluid immediately prior to the death of the moribund twin has been suggested as a therapeutic intervention to improve outcomes (Fusi

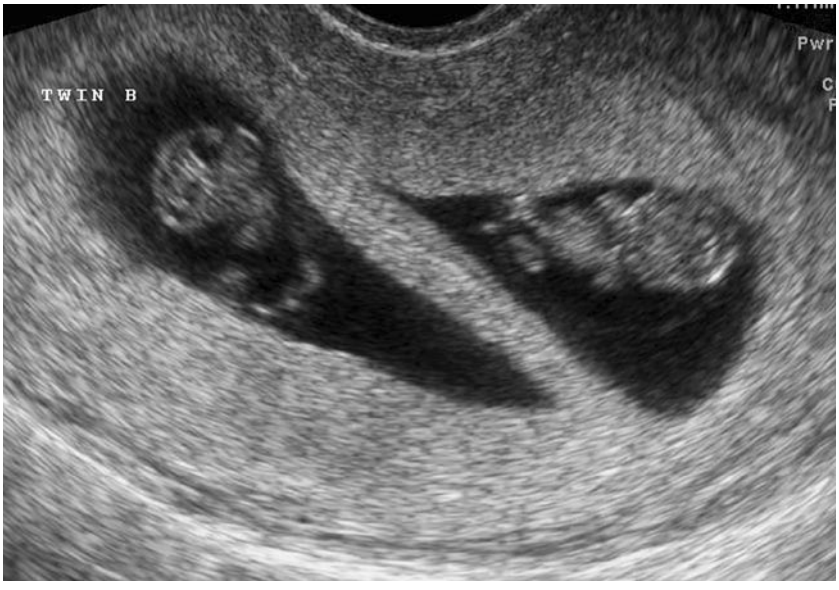
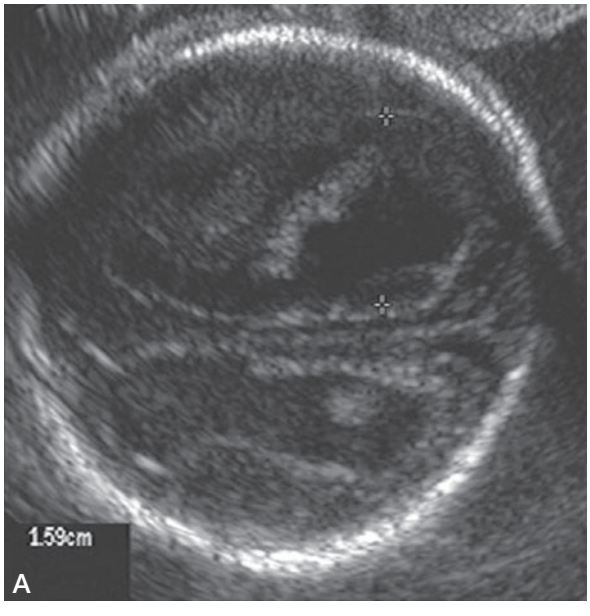


Figure 118-1 Sonographic image of monochorionic twins showing absence of "twin peak" and thin dividing membrane.

et al., 1991; Nicolini et al., 1998; Nicolini and Poblete, 1999). In our opinion, this is unproven and very unlikely to have any significant clinical role.

It is unclear at which gestational age IUFD in a monochorionic pregnancy may result in adverse sequelae for the surviving co-twin. It is often taught that the risk for multicystic encephalomalacia begins in the late second and third trimesters (D'Alton and Simpson, 1995). Neuropathology has not been able to pinpoint the exact timing of insult (D'Alton and Dudley, 1989). According to Pharoah et al., it is possible that early demise ("vanishing twin") in a monochorionic pregnancy secondary to acute and early TTTS could be an explanation for a portion of cases of unexplained cerebral palsy (Pharoah and Cooke, 1997; Pharoah and Adi, 2000). Until further research is completed, this theory can neither be supported nor refuted (Blickstein, 1998).

Of note, we recently reported a case of an IUFD of one twin at approximately 13 weeks in a monochorionic gestation that resulted in multicystic encephalomalacia in the surviving twin. Ultrasound and Magnetic Resonance Imaging (MRI) were performed at approximately 21 weeks demonstrating the neuroradiological pathology (Figures 118-1 and 118-2). The patient was counseled regarding the poor prognosis and opted for termination. The multicystic encephalomalacia was confirmed by pathology, although the exact timing of the injury could not be determined (Weiss et al., 2004).



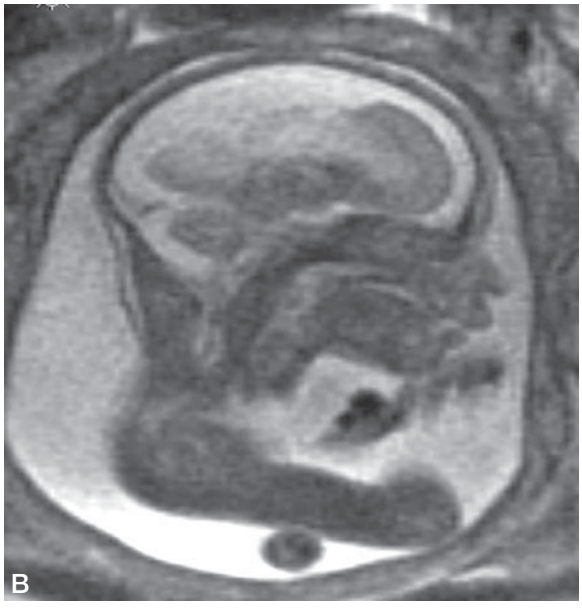


Figure 118-2 A case of monochorionic diamniotic twins, in which co-twin demise occurred at 13 weeks; follow-up ultrasound at 21 weeks demonstrating mild ventriculomegaly. (*With permission Weiss, et al. Multicystic encephalomalacia after first trimester intrauterine fetal demise in monochorionic twins.* Am J Obstet Gynecol. *2004;190:563-565.*)

In addition, studies have demonstrated that IUFD of one twin can result in preterm delivery in both monochorionic and dichorionic pregnancies (Carlson and Towers, 1989; Peterson and Nyholm, 1999). In a study by Carlson and Towers of 17 twin pregnancies complicated by IUFD, 76% of these pregnancies were delivered before 37 weeks. Eighty-six percent of the patients delivering prematurely presented in active labor (Carlson and Towers, 1989). This is almost double the background incidence of reported preterm delivery in twins.

Besides fetal risks, there is a theoretical possibility for maternal consumptive coagulopathy in twin pregnancies complicated by single IUFD (Anderson et al., 1990). It has been established that retention of a dead fetus for 4 to 5 weeks in a singleton pregnancy results in an increased risk of maternal consumptive coagulopathy (Pritchard and Ratnoff, 1955; D'Alton and Simpson, 1995). It was originally estimated that there was a 25% incidence of maternal disseminated intravascular coagulation when fetal death occurred in multiple gestations (Landy and Weingold, 1989). However, only a few cases of laboratory evidence rather than clinical evidence of coagulopathy have been reported under these circumstances, and the 25% incidence is likely an overestimation (Anderson et al., 1990; Carlson and Towers, 1989; D'Alton and Simpson, 1995). In one series of 16 pregnancies complicated by IUFD of one twin, no cases of maternal disseminated intravascular coagulation were found (Fusi and Gordon, 1990). In another series, transient fibrin-split products and hypofibrinogenemia were found in 2 of 20 cases of single IUFD in twins, neither of which was clinically apparent or required medical therapy (Eglowstein and D'Alton, 1993). It is also reassuring to note that no cases of clinically significant coagulopathy have been reported in the extensive literature on selective termination and multifetal pregnancy reduction.

INCIDENCE

Ultrasound during the first trimester has demonstrated that the incidence of twins is greater than previously presumed (Landy and Weingold, 1989). Single IUFD in the first trimester may occur in up to 50% of cases of twin pregnancies (Varma, 1979).

Single IUFD of one fetus in a multiple gestation in the second or third trimesters is much less common complicating approximately 0.5% to 6.8% of twin pregnancies (Benirschke, 1961; Litschgi and Stucki, 1980; D'Alton et al., 1984; Hanna and Hill, 1984; Enbom, 1985; Carlson and Towers, 1989; Fusi and Gordon, 1990; Kilby et al., 1994; Johnson and Zhang, 2002). Monochorionic twins are at increased risk for single IUFD compared to dichorionic twins. It is estimated that there is a threefold to fourfold increase in intrauterine death with monochorionic twins as compared with dichorionic twins (Burke, 1990; Kilby et al., 1994). It is interesting to note that because of increasing use and success of assisted reproductive technologies, the incidence of monochorionic twins is increasing and may be greater than 10 times the spontaneous rate (Blickstein, 2005).

In addition, a single fetal death is also more common among twins with a structural abnormality (Kilby et al., 1994). Demise of both fetuses in a twin pregnancy has been reported infrequently (Rydhstroem, 1996). In high-order multiples, however, demise of a single fetus may be more common. Studies have indicated single IUFD rates ranging from 4.3% to 17% in triplet pregnancies (Gonen et al., 1990; Borlum, 1991; Johnson and Zhang, 2002).

SONOGRAPHIC FINDINGS

The sonographic findings in single IUFD in twin pregnancy vary, depending on whether there is an identifiable cause for the death and on the interval between the death and performance of the ultrasound examination. Sonographic assessment should include complete biometric and anatomic assessments of the dead and surviving twins, an assessment of amniotic fluid volume, evaluation of the cord insertion sites, and determination of chorionicity. If the fetal death is due to placental insufficiency associated with maternal medical disease, there may be evidence of intrauterine growth restriction. Sonographic examination may reveal a fetal abnormality or a placental abruption as a causative factor. Sonographic features of TTTS should also be searched for, as described in Chapter 119.

The determination of chorionicity is important for the counseling and treatment of patients with single IUFD. It is optimal if chorionicity was established early in pregnancy. If chorionicity has not been documented previous to the IUFD, an attempt at determining chorionicity by ultrasound is necessary. If two separate placentas are visualized or the fetuses are of unlike gender, the pregnancy is dichorionic. If only one placenta is identified and the fetuses are of the same sex, the separating membrane should then be examined. If two layers are present the placentation is monochorionic. If three or four layers are visualized, the placentation is dichorionic (D'Alton and Dudley, 1989). Membrane thickness has been used to assess chorionicity, with a thin membrane indicating monochorionicity and a thick membrane indicating dichorionicity (Barss et al., 1985). However, there is some concern that a membrane may appear both thin and thick at different times during the same ultrasound examination and at different gestational ages (Hertzberg et al., 1987; Samuels, 1988; D'Alton and Dudley, 1989). The "twin peak" sign, identified on ultrasound examination by the presence of a triangular projection of placental tissue between the layers of the separating membrane, has been suggested to provide reliable evidence of dichorionicity (Figure 118-3). The absence of the twin peak sign does not help to determine chorionicity, which limits its usefulness as a clinical marker.

Sonographic examination may not establish the diagnosis of chorionicity with absolute certainty in a portion of cases. If an accurate diagnosis of chorionicity is needed, in

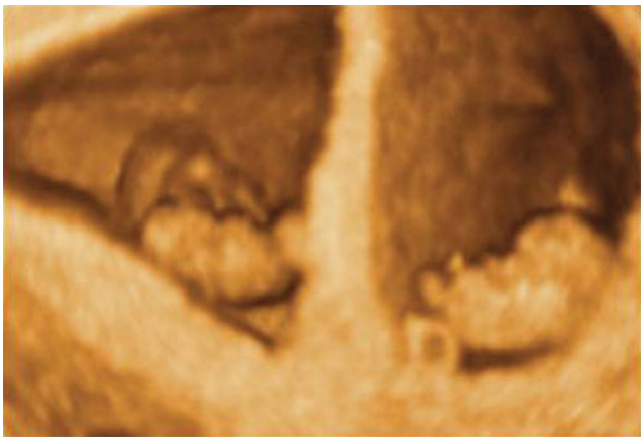


Figure 118-3 Sonographic image of dichorionic twins demonstrating "twin peak" sign.

the presence of a single placenta and same-sex fetuses, DNA studies on amniocytes may be considered (Norton et al., 1997).

DIFFERENTIAL DIAGNOSIS

There is no differential diagnosis for this condition.

ANTENATAL NATURAL HISTORY

An accurate assessment of the antenatal natural history of multiple pregnancies complicated by single IUFD is hampered by the lack of a large prospective study (Landy and Weingold, 1989). Most of the available data are biased by either case reports or small retrospective series dealing with unfavorable outcomes (Enbom, 1985). Many cases will not pose a management problem because labor will already have begun by the time the diagnosis is made. However, some patients will remain pregnant with one or more surviving fetuses, which may create a management dilemma. Elective delivery is not recommended before 37 weeks of gestation for the surviving co-twin of a stillbirth in utero unless antenatal surveillance is suggestive of fetal compromise. Similarly, close fetal surveillance after the diagnosis of single IUFD in monochorionic twins cannot guarantee a good outcome for the surviving fetus.

In 14 cases in Landy and Weingold's (1989) series, expectant management was instituted in an attempt to delay delivery in order to benefit the surviving co-twin. The interval between diagnosis of fetal death and delivery ranged from 2 to 12 weeks. One of the survivors had neurologic deficits, and 11 of the 14 pregnancies were delivered before 37 weeks of gestation. In addition to the 14 cases identified by Landy, Santema et al. identified from 8 reports 123 cases that were managed expectantly (Santema et al., 1995). The overall incidence of neurologic morbidity was 12%, and the mortality rate for the surviving twin was 4.3%.

MANAGEMENT OF PREGNANCY

Referral to a tertiary care perinatal unit is advised when single IUFD in a multiple gestation is diagnosed. In many cases, labor will already have started, and in others coexisting maternal illness or placental abruption may make it necessary to deliver the surviving fetus or fetuses (D'Alton et al., 1984). Clinical management depends on gestational age, fetal lung maturity, and detection of in utero compromise of the surviving twin. The goal is to optimize outcome for the surviving twin while avoiding prematurity and its potential adverse sequelae. The optimal treatment for IUFD in multiples is not well established due to the paucity of cases. Recommendations are based on case reports, case series, and expert opinion (Enbom, 1985; Landy and Weingold, 1989; Eglowstein and D'Alton, 1993; Johnson and Zhang, 2002). Management protocols can be divided into (1) pregnancies complicated by IUFD prior to viability and (2) pregnancies complicated by IUFD once viability has been achieved.

If IUFD occurs in a viable pregnancy, management is similar for both dichorionic and monochorionic pregnancies. Patients with monochorionic pregnancies should be counseled about the risk for multicystic encephalomalacia, but no interventions are available to impact on this risk.

It is difficult to predict in utero which cases of surviving monochorionic twin will have cerebral injury. The nonstress test and the biophysical profile give insight into the physiological status of the fetus as reflected in the autonomic nervous system. Although ultrasound may be suggestive of multicystic encephalomalacia, ultrasound of the fetal brain cannot make the definitive diagnosis (D'Alton and Simpson, 1995). MRI, however, may have a role in detecting multicystic encephalomalacia antenatally (D'Alton and Dudley, 1989; Weiss et al., 2004). We recommend that an MRI is scheduled approximately 2 to 3 weeks after the diagnosis of IUFD in a monochorionic pregnancy. Patients in the late second trimester who may be considering pregnancy termination may request an MRI earlier than the usual 2- to 3-week interval to allow for radiological changes to become evident. While it is uncertain if a normal MRI soon after diagnosis of IUFD definitively rules out brain pathology, it provides some reassurance, in our opinion.

We suggest that IUFD in monochorionic and dichorionic twin pregnancies is managed utilizing a straightforward protocol. A single course of antenatal corticosteroids is administered if delivery is anticipated within 7 days and the gestational age is between 24 and 34 completed weeks (Hashimoto et al., 2002). In monochorionic pregnancies, surviving fetuses are monitored with weekly biophysical profiles and nonstress tests (D'Alton and Simpson, 1995).

Antenatal surveillance for dichorionic pregnancies complicated by IUFD is controversial. We monitor these pregnancies weekly with nonstress tests and biophysical profiles since they have a history of unexplained stillbirth. If other abnormalities such as intrauterine growth restriction or oligohydramnios are concomitant, fetal testing is intensified.

In most cases, elective delivery is scheduled at approximately 37 weeks of gestation. If lung maturity is documented, delivery may be scheduled earlier. Nonreassuring fetal status results in immediate delivery. Vaginal delivery is not contraindicated, and cesarean delivery is reserved for routine obstetric indications (Fusi and Gordon, 1990). At delivery, umbilical cord blood gas and hematocrit measurements are performed. Autopsy is offered for the stillborn fetus. The placenta is sent for pathological examination. In addition, the pregnancy history is communicated to pediatric colleagues. Careful pediatric follow-up is suggested for the offspring of monochorionic pregnancies complicated by IUFD. It is recommended that these neonates be followed for any signs or symptoms of cerebral impairment and for any indications of other vital organ damage (Rydhstroem and Ingemarsson, 1993).

If IUFD occurs in a previable dichorionic pregnancy, the patient is managed expectantly until 37 weeks of gestation. Fetal surveillance and a single course of antenatal steroids are considered once viability is achieved.

Monochorionic pregnancies complicated by IUFD before viability are challenging. It is recommended that patients be counseled regarding the risk of multiorgan injury including multicystic encephalomalacia. Ultrasound imaging and fetal MRI may be helpful. Some patients may opt to terminate the entire pregnancy, while others may desire expectant management. Once the surviving co-twin reaches viability, these patients should be managed according to the recommendations described above.

In addition to fetal risks, IUFD in a multiple gestation may lead to maternal complications. When IUFD occurs in a multiple pregnancy, baseline maternal hematological laboratory results are obtained including a prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen level, and platelet count. If these values are within normal limits, further laboratory surveillance is not performed. Of note, mothers with IUFD in one twin do not appear to be at increased risk of infection due to a retained twin (Carlson and Towers, 1989). Dystocia secondary to the demised fetus has been reported infrequently. Cesarean delivery rates seem to be increased in patients with single IUFD because of nonreassuring fetal status (Carlson and Towers, 1989).

It is well known that IUFD in singleton pregnancies may cause feelings of loss, sadness, anxiety, and guilt (Hughes et al., 2002). The psychological impact of fetal loss in multiple pregnancies has not been well studied (Bryan, 2003). In fact, bereavement may be underestimated because there is a shift in focus to the living offspring (Bryan, 1995, Bryan, 2002). As a result, we suggest that patients with a multiple pregnancy complicated by IUFD are offered psychological and/or bereavement counseling.

FETAL INTERVENTION

No fetal intervention is recommended in cases diagnosed before 37 weeks in cases in which a single IUFD has already been documented.

In known monochorionic pregnancies with impending death of one twin, preterm delivery may be indicated in order to prevent neurologic injury to the survivor or potentially to salvage both twins. In a monochorionic twin pregnancy with a gestational age of greater than 28 weeks, the risk of neurologic handicap to the surviving twin in the case of death of the co-twin may be higher than the risk of prematurity. Delivery should be considered if it appears likely that one fetus is about to die in utero. If chorionicity is unclear and the death of one twin seems imminent, it is necessary to weigh the risks and benefits to each twin of expectant management versus early delivery. If dichorionicity can be clearly demonstrated, there is no benefit to the healthy, appropriately grown co-twin of elective preterm delivery in cases in which the smaller twin is likely to die.

In addition, selective termination of a fetus that has a significantly increased risk of demise in a monochorionic gestation may be considered, in an effort to protect the healthy co-fetus or fetuses (Crombleholme et al., 1996). The usual method of intracardiac KCl injection is contraindicated in monochorionic pregnancies. Alternative cord occlusive methods should be considered, such as fetoscopic cord ligation or fetoscopic ablation of communicating placental vessels. We have reported a case of radiofrequency cord ablation in one member of a monochorionic twin pregnancy discordant for a cystic hygroma, hydrops, and Turner's syndrome, which was thought to be at significant risk of IUFD. The normal co-twin was delivered at term and had a normal neonatal course (Shevell et al., 2004). At 2-year follow-up, the surviving co-twin was neurologically intact.

Indications for considering a fetoscopic cord ligation procedure to prevent neurologic handicap in twins include anomalies incompatible with life in monochorionic pregnancies at a previable gestational age or significant growth discordance in monochorionic gestations at a previable gestational age. Fetoscopic cord occlusive techniques in monochorionic pregnancies are further explored in Chapter 117.

The optimal gestational age at which to deliver uncomplicated monochorionic twin pregnancies to prevent single IUFD is an unanswered question, which remains an area of controversy. Barigye et al. recently reported the prospective risk of fetal death in uncomplicated monochorionic diamniotic twin pregnancies managed at a single tertiary care referral center (Barigye et al., 2005). Patients were excluded from the study if the pregnancy was complicated by TTTS, monoamnionicity, IUGR, growth discordance, structural anomalies, and TRAP. Conjoined twins and high-order multiples were

also excluded. The prospective risk of fetal death was calculated by determining the number of IUFDs that occurred within a 2-week block divided by the number of continuing uncomplicated monochorionic twin pregnancies during that same time period. There were 10 unexpected deaths (3 double IUFDs and 4 single IUFDs) for a total of 7 (4.6%) of the 151 seemingly uncomplicated monochorionic diamniotic pregnancies. These IUFDs occurred predominantly during the late preterm gestation, at a median gestational age of 34 weeks and 1 day. There were no significant differences between the IUFD affected pregnancies and the unaffected pregnancies with regard to antenatal indicators of IUGR and TTTS. The authors concluded that despite intensive fetal surveillance, uncomplicated monochorionic diamniotic twin pregnancies are at risk for unexpected intrauterine death. As a result, the authors suggested that after 32 weeks of gestation, the prospective risk for fetal death in these pregnancies might be eliminated by elective preterm delivery. Nonetheless, the risks of prematurity are not negligible at 32 weeks of gestation. Balancing the risk of iatrogenic preterm birth in an *apparently* uncomplicated monochorionic twin pregnancy with the risk of double IUFD or single IUFD with the concomitant risk of multicystic encephalomalacia for the surviving co-twin is challenging (Cleary-Goldman and D'Alton, 2005). One option may be to offer delivery of these *apparently* uncomplicated monochorionic twins at approximately 34 to 35 weeks of gestation following antenatal corticosteroid administration and thorough counseling regarding the risks of expectant management versus elective preterm delivery. This may be a reasonable approach to this dilemma until larger, prospective observational studies have been conducted to better elucidate the natural history of these high-risk pregnancies.

TREATMENT OF THE NEWBORN

All surviving infants of a monochorionic pregnancy following single IUFD should be evaluated postnatally for neurologic injury, and a thorough neurological assessment should be performed. Pediatric follow-up to assess growth and development is advisable. Otherwise, no additional special precautions or investigations are required.

SURGICAL TREATMENT

There is no requirement for neonatal surgical evaluation for surviving infants of multiple gestations following single IUFD, unless additional anomalies are present in the survivors.

LONG-TERM OUTCOME

The literature regarding the clinical significance of single IUFD in twins spans more than 40 years and includes more than 500 cases, most of which do not address long-term outcome for the survivor. In one series of 188 confirmed monozygous twin pairs, there were 7 in utero deaths (Melnick, 1977). Five of the seven co-twin survivors had normal head circumference and psychomotor development. Head circumferences ranged between the 35th and 97th percentiles, and the IQs were all within 1 SD of the mean for sex, race, and zygosity. One co-twin died at 2 months, and postmortem studies revealed necrosis of the white matter of the cerebellum. A different co-twin had a head circumference at the third percentile from 1 to 7 years of age, but psychomotor development at 1, 4, and 7 years was normal (Melnick, 1977).

In another series of 206 pregnancies with death of at least one twin before delivery, follow-up for 8 years or more after birth revealed that three twins (5%) had cerebral palsy or mental retardation (Rydhstroem and Ingemarsson, 1993). All three were second twins and of the same sex as their co-twins.

In a more recent study reviewing birth certificate data from United Kingdom, 434 gender-concordant twin pregnancies were found in which intrauterine demise of one fetus had occurred (Pharoah and Adi, 2000). The prevalence of cerebral palsy among surviving fetuses was 10.6% and the prevalence of other neurologic injury was 11.4%. The main limitation, however, of such birth certificate data is the inability to be sure of the prevalence of monochorionicity among the gender-concordant pairs. In a literature review of 119 monochorionic twin pregnancies complicated by a single intrauterine fetal demise, 9% of surviving fetuses subsequently died in utero, a further 10% subsequently died in the neonatal period, and 24% had serious neonatal morbidity, including porencephaly, multicystic encephalomalacia, renal cortical necrosis, and small bowel atresia (Nicolini and Poblete, 1999).

GENETICS AND RECURRENCE RISK

There is unlikely to be an increased risk above the baseline risk of single IUFD if future pregnancies involve multiple gestations.

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119 CHAPTER Twin-to-Twin Transfusion Syndrome

Key Points

- The twin-to-twin transfusion syndrome (TTTS) is a complication of monochorionic multiple gestations resulting from vascular communications in the placenta (chorangiopagus), such that one twin is compromised and the other is favored.
- The prognosis is poor, with a perinatal mortality rate ranging from 60% to 100% for both twins.
- TTTS is almost exclusively found in monochorionic twins and is estimated to occur in 5% to 15% of monochorionic twin pregnancies.
- Sonographic criteria for the diagnosis of TTTS include: (1) like sex, (2) monochorionic twins, (3) polyhydramnios in one sac, oligohydramnios in the other sac with or without characteristic Doppler or echocardiographic changes.
- Expectant management is not recommended due to poor perinatal outcomes associated with the disorder.
- Treatment depends on the gestational age and severity at diagnosis.
- Current treatment options for severe TTTS include: (1) serial reduction amniocentesis, (2) amniotic septostomy, (3) laser ablation of the anastomoses, and (4) intrafetal radiofrequency ablation.
- Laser ablation appears to be a promising treatment for severe TTTS diagnosed in the midtrimester. Nonetheless, further studies are still needed to assess long-term pediatric outcome.

CONDITION

The twin-to-twin transfusion syndrome (TTTS) is a complication of multiple gestation resulting from imbalanced blood flow through vascular communications in the placenta (chorangiopagus), such that one twin is compromised and the other is favored. The prognosis is poor, with a perinatal mortality rate ranging from 60% to 100% for both twins (Rausen et al., 1965; Cheschier and Seeds, 1988; Gonsoulin et al., 1990).

The earliest description of TTTS may have been in the book of Genesis. At the birth of Esau and Jacob it was recorded that "the first one came out red," possibly describing the birth of a polycythemic twin. In 1752, William Smellie reported the injection of the umbilical artery of one twin with the injection material flowing out of the vessel of the co-twin.

Research in the area of vascular anastomoses in twin placenta in the late 1800s was dominated by the German obstetrician Friedreich Schatz, who described four types of vascular connections within monochorionic placentas:

1. Superficial connections between capillaries.
2. Superficial arterial connections between large vessels.
3. Superficial venous connections between large vessels.
4. Vascular communications between capillaries in the villi.

He described three circulatory systems in monochorionic twins. The first two were the circulations in either twin. The third circulation consisted of the arteriovenous communications bridging the two fetal circulations below the placental surface (Schatz, 1882).

Schatz proposed that when superficial artery-to-artery and vein-to-vein anastomoses are absent or insufficient, imbalances may occur in the common circulation of the twins. Such imbalances favor the transfer of blood from one twin to the other and result in TTTS. A study demonstrating fewer anastomoses from placentas complicated by TTTS (Bajoria et al., 1995) confirms Schatz's observations from the late 1800s. Ten placentas from pregnancies with evidence of midtrimester TTTS diagnosed using ultrasound criteria were compared with 10 placentas from pregnancies without TTTS. Placentas from pregnancies with TTTS had significantly fewer anastomoses than did those without TTTS, both overall and for each of the different types (arterioarterial, venovenous, and arteriovenous). Whereas multiple anastomoses were present in all controls, only one TTTS placenta

had more than a single communication. Anastomoses in the TTTS group were more likely to be of the deep than the superficial type.

Because of the putative major role of intertwin anastomoses, most investigations of TTTS have been directed toward study of the monochorionic diamniotic placental vasculature. Studies generally have identified a paucity of anastomoses as a prominent risk factor in the development of TTTS. Paucity, especially of deep anastomoses, leads to fewer chances for volumetric balance in cross-circulation between the twins. Larger numbers of superficial chorionic anastomoses, particularly arterioarterial (A-A) connections, appear to confer relative protection against the development, early onset, or severity of TTTS (De Lia et al., 2000; Umur et al., 2002a; De Paepe et al., 2005; Harkness and Crombleholme, 2005; Lewi et al., 2007). However, the "protective effect" of these A-A anastomoses remains somewhat controversial. Venovenous (V-V) connections comprise a lower percentage of anastomotic types found in monochorionic diamniotic gestations and have been associated with poorer perinatal outcome. V-V anastomoses are seen in 20% of monochorionic diamniotic placentas, A-A in 75%, and A-V in 70% by clinical and pathologic studies, but fetoscopic studies have shown that 95% of anastomoses are A-V (De Lia et al., 2000; Crombleholme et al., 2007). However, some investigators have proposed that V-V anastomoses may provide compensatory reversal of blood flow in some situations (De Lia, 2000). Presumably, as the recipient's central venous pressure rises with hypervolemia and ensuing congestive failure, the V-V anastomoses may be "protective" to both twins by helping to alleviate right ventricular failure in the recipient and theoretically shunting blood back to the venous system of the donor. The relatively fewer numbers of V-V connections, in addition to their anatomy and lower pressure differential, may be determinants of how effectively they contribute to balancing intertwin blood flow.

Some researchers' observations that the average numbers of superficial vascular connections are not significantly different between gestations involving severe TTTS and those that do not (Bermudez et al., 2002) and the fact that 80% to 90% of monochorionic diamniotic twins do *not* develop TTTS has led other investigators to propose that more than quantitative differences in the number of anastomoses is involved in the pathogenesis TTTS. Recent evidence suggests that vascular diameter and resistance and the pattern of chorionic plate vascular branching are important factors. Umur et al. (2002a,b) using a complex mathematical computer model, determined that, for a given radius, an A-A anastomosis has lower resistance than the equally sized afferent artery of an A-V anastomosis, which might explain the apparent protective effect of A-A anastomoses noted in most studies of TTTS. By their calculations, blood flow could be balanced more efficaciously through an A-A anastomosis than through oppositely directed A-V anastomoses, even though the pressure gradient in the A-V anastomoses was greater.

De Paepe et al. (2005) studied the chorionic plate branching pattern in monochorionic diamniotic placentas from gestations without TTTS and those affected by severe TTTS. They found that gestations involving severe TTTS were more likely to exhibit magistral pattern (a chorionic vascular pattern composed of relatively large caliber, sparsely branching vessels that extended from the cord insertion site to the placental periphery without significant diminution in diameter), or a mixed magistral and diffuse pattern than unaffected gestations (60% vs. 44%). The presence of a magistral pattern, even when mixed with the more favorable disperse pattern, was also associated with higher incidences of other placental anatomic features implicated in the development of TTTS, such as unequal distribution of vascular territory and marginal or velamentous cord insertions. In addition, donor twins were more than twice as likely to have the magistral or mixed pattern as recipients, and when one or both twins had the magistral or mixed pattern, the average number of intertwin anastomoses was fewer. These investigators suggested that the predominance of magistral and mixed patterns in the donor twins' placentas may be related to the observations that magistral patterns in singleton placentas are associated with absent end-diastolic blood flow (AEDF) in the umbilical arteries (UAs). AEDF has been attributed to the effects of a smaller peripheral vascular tree that results in increased vascular resistance to forward flow from the UAs. The low end-diastolic flow in the donor's UAs combined with the magistral/mixed pattern might result in preferential routing of blood flow through anastomoses to the recipient twin. Thus, evidence supplied by the various placental structural studies of TTTS indicates vascular resistance, cross-sectional area, and other hemodynamic factors are contributing elements in the development, timing of clinical onset, and severity of TTTS (Luks et al., 2005).

Unequal sharing of the placental disc is an additional risk factor for the development of TTTS (Benirschke et al., 2006; Lewi et al., 2007). However, when and how disk inequality develops is unclear. The early developing chorionic villous tree may connect preferentially to the vasculature of the umbilical cord of one twin over that of the other. With unequal division of the inner cell mass, one embryo may develop a larger heart and, thereby, greater stroke volume and cardiac output such that its perfusion of the developing villous tree is initially more robust (Benirschke et al., 2006). However, others have proposed that unequal sharing may reflect abnormalities of placentation. Not all twin pairs that have TTTS exhibit significant growth discordance, and there is evidence that abnormalities of placentation may be relatively more responsible for the growth discordance in TTTS than imbalances in intertwin transfusion (Wee et al., 2006). Approximately 20% of cases of TTTS have concomitant evidence of placental insufficiency that usually, but not always, affects the donor twin (Habli et al., 2008). The combination of placentation anomalies, flow inequalities, and fetal response may determine whether the donor's placental territory appears grossly pale and bulky [with edematous large villi containing increased Hofbauer (chorionic villous macrophage) cells and nucleated fetal erythrocytes characteristic of fetal anemia] or whether it is pale and atrophic-appearing with small villi (Kraus et al., 2005; Faye-Petersen et al., 2006; Kaplan, 2007). Conversely, the recipient's

parenchymal territory usually is deep red-brown and firm due to villous congestion, but it also may show microscopic villous edema if the fetus is in congestive failure.

Marginal and velamentous cord insertions and single UA are associated with increased risks of the development and severity of TTTS (Fries et al., 1993; De Paepe et al., 2005; Benirschke et al., 2006; Kaplan, 2007). Of note, although diamniotic monochorionic twins comprise 20% of twin gestations, they have significantly increased rates of cord anomalies over diamniotic dichorionic twins, with more than 50% of marginal cord insertions, more than 40% of velamentous cord insertions, and nearly 50% of all single UA cases occurring in monochorionic diamniotic twins (Redline et al., 2001). Diamniotic monochorionic twins, therefore, are at constitutively increased risks for the underlying morbidity and mortality associated with cord compression, cord accident with thrombosis, and vessel rupture. Such cord events could compound any underlying risks of chorangiopagus, especially for the donor twin. Donor twins are more likely to have velamentous cord insertion than are recipients (Mari et al., 2000).

The asymmetric, bidirectional intertwin exchange of blood and its biochemical components results in hemodynamic, osmotic, and physiologic changes in the fetuses (Jain and Fisk, 2004; Harkness and Crombleholme, 2005; Luks et al., 2005; Benirschke et al., 2006). Hypovolemia and decreased renal blood flow in the donor may cause a number of renal structural and functional aberrations, especially in severe TTTS, including renal tubular degeneration and cellular apoptosis, loss of glomeruli or reduction in tubular number, and maldevelopmental progression to renal dysgenesis (Kilby et al., 2001; De Paepe et al., 2003). Renal hypoperfusion also has been linked to activation of the renin-angiotensin system (RAS) (Mahieu-Caputo et al., 2000; Kilby et al., 2001; Mahieu-Caputo et al., 2001) and elevated antidiuretic hormone concentrations (Bajoria et al., 2004) in the donor. Donors have hyperplasia of juxtaglomerular apparatuses, with increased numbers of renin-secreting cells (Kilby et al., 2001) and upregulation of renin synthesis (Mahieu-Caputo et al., 2000), which are presumed to represent adaptive responses to restore euvolemia. However, in severe TTTS, activation of the RAS and associated elevations in angiotensin II (AT II) likely result in AT II-mediated fetal vasoconstriction that further compromises renal blood flow, leading to worsening oliguria and oligohydramnios. Increased fetal adrenal production of aldosterone may play a contributing role (Mahieu-Caputo et al., 2000; Kilby et al., 2001; Mahieu-Caputo et al., 2001; Bajoria et al., 2004). Bajoria et al. (2004) recently found that donors' plasma and amniotic fluid concentrations of vasopressin were threefold higher than those of their co-twin recipients (monochorionic diamniotic twins that did not have TTTS had higher concentrations than the recipients in TTTS, but they were not discrepant or as elevated as the donors in TTTS). Thus, good evidence suggests that the oligohydramnios of the donor twin is a consequence of poor renal perfusion due to net hypovolemia, but it is exacerbated by vasoconstriction, mediated by AT II/vasopressin. Fetal vasoconstriction also may reduce placental blood flow to the villous tree, which may contribute to growth restriction in the donor (Mahieu-Caputo et al., 2000, 2001; Kilby et al., 2001).

In severe cases of TTTS, hypervolemic recipients have renomegaly and glomerulomegaly consistent with increased renal blood flow, and immunohistochemical studies have revealed they have downregulation of the RAS, with markedly reduced numbers of renin-secreting cells and renin synthesis (Mahieu-Caputo et al., 2000, 2001; Kilby et al., 2001). However, they have paradoxically high concentrations of renin and aldosterone, and the cardiomegaly, cardiomyopathy, hypertension, and nephrosclerosis seen in recipients in TTTS are insufficiently explained by hypervolemia alone. Such observations are supportive evidence for transfer of these and possibly other vasoactive effectors from the donor to the recipient across placental anastomoses. The hemorrhagic necrosis and microangiopathic lesions seen in kidneys from recipients in severe TTTS also may be related to transanastomotic passage of hormones from the donor (Mahieu-Caputo et al., 2001, 2005). Low concentrations of antidiuretic hormone in the recipient, together with elevated renin concentrations secreted by the donor, are likely responsible for worsening hypervolemia and polyuria/polyhydramnios in recipients. Maternal sequelae of fetal elevations in vasoactive substances have been appreciated recently. Elevated fetal renin-AT II values have been associated with maternal pseudoprimary hyperaldosteronism (Gussi et al., 2007), and it is possible that these contribute to changes in maternal perfusion of the placental bed.

In addition to anastomotic transfer of vasoactive mediators, increased cardiac synthesis and secretion of natriuretic peptides (NPs) have been linked to the progression of TTTS. NPs are a family of biochemical mediators that normally regulate blood pressure and body fluid homeostasis through their diuretic, natriuretic, and vasodilatory effects as well exerting antiproliferative effects on cardiovascular/mesenchymal tissue. Exploration of their role in the pathogenesis of adult cardiac hypertrophy and cardiomyopathy has led to greater appreciation of their importance in normal embryofetal development and their role in cardiomyopathy in the recipient twin in TTTS. In the fetus, in contrast to the adult, both atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) hormones are normally at high circulating concentrations and are expressed at high concentrations in the ventricles (in the normal adult, they are expressed at low concentrations in cardiac atria and ventricles, respectively). Their release is stimulated primarily by increased myocardial stretch and volume overload, hyperosmolality, and hypoxia, and vasoconstrictors, such as AT II, vasopressin, and endothelin-1 (ET-1), have been shown to result in their increased expression and secretion. ANPs and BNPs appear to be integral to embryonic fetal salt and water and blood pressure regulation, and the peptide system is likely functional by midgestation. ANP and BNP also appear to be important mediators of cardiogenesis because of their inhibitory effects on myocardial and fibroblast cell proliferation. Their effects on fetal aldosterone concentrations are unknown, but they suppress aldosterone synthesis in the adult. A third NP, c-type natriuretic peptide

(CNP), which is found in adult genitourinary, pituitary, and brain tissues, is not produced in any significant quantity in the fetal or adult heart, although it is secreted by the placenta. Placental production of NPs (ANP, BNP, CNP) affects vasorelaxation in the fetoplacental vasculature and likely helps regulate blood supply to and within the fetus.

Bajoria et al. (2002, 2003) demonstrated that recipient twins in TTTS have higher concentrations of ANP, BNP, and ET-1 than their co-twin donors or monochorionic diamniotic twins without TTTS and that high concentrations of BNP and ET-1 are particularly correlated with cardiac dysfunction in the recipient. They suggested that these compounds might be used as early markers of cardiac compromise. It is plausible that the immaturity of the fetal kidney and its inability to concentrate urine may be exacerbated by the vasodilatory and diuretic effects of BNP and ANP released due to hypervolemia and contribute to polyuria/polyhydramnios or be compounded by BNP stimulation due to AT II transferred from the donor. Increased ANP concentrations in blood and amniotic fluid have been detected in recipients in TTTS, greater than donor twin's and uncomplicated monochorionic diamniotic twin pair's values. Increases in ANP also are related directly to increases in amniotic fluid volumes, and markedly increased immunostaining for ANP localizes predominantly to the heart and cytoplasm of the distal convoluted tubules of the kidneys of recipients when compared with measurements for donor twins. These data are supportive evidence that polyhydramnios in the recipient twin occurs as a consequence of ANP-mediated increases in fetal urine output due to ANP expression in both cardiac and renal tissues (Bajoria et al., 2001).

Cardiac hypertrophy with cardiac dilatation is seen in recipients in TTTS and likely is due to the increased cardiac preload and increased afterload pressures due to hypertension (Mahieu-Caputo et al., 2001, 2003). Of note, ventricular hypertrophy predominates and dilatation is comparatively "mild," with right ventricular compromise preceding and generally exceeding that of the left ventricle (Harkness and Crombleholme, 2005). Although the right ventricle is the primary "workhorse" of the fetal heart, and fetal myocardium can proliferate, other developmental factors likely contribute to the myocardial mural thickening detected by ultrasonography. Fetal myocardium is "stiffer" than the adult heart. The fetal myocardium has a greater percentage of noncontractile elements (60% vs. 30% in the mature heart) and relatively delayed removal of calcium from troponin C, and the ventricles have a shorter phase of early passive diastolic filling and a greater reliance on atrial contraction. Fetal lamb studies have shown that after 4 to 5 mm Hg, further atrial preload does not result in increased stoke volume. Thus, the fetal heart is inherently and mechanically less efficient, is less able to increase stroke volume, and displays impaired relaxation (Szwast and Rychik, 2005). These effects may represent, in part, disruption of the NP system, which has been shown to be NP receptor-dependent in murine models. NP receptor-deficient, Npr1−/− knockout mice develop hypertension, cardiac hypertrophy, and fibrosis. The absence of the receptor effectively inhibits vasorelaxation despite elevated concentrations of BNP and ANP. Moreover, cardiac hypertrophy can result independently of the presence of hypertension because the lack of receptor does not permit inhibition of myocardial proliferation/enlargement and fibroplasia.

Recipient twins are at increased risk for right ventricular outflow tract obstruction and pulmonary valvar stenosis/atresia with intact ventricular septum (Harkness and Crombleholme, 2005). The progressive hypertrophy, reduced systolic function, and tricuspid valvar insufficiency lead to progressive decline in flow across the pulmonary valve. In a case in which the infant underwent surgical repair, the trileaflet semilunar valvar anatomy was identified as normal except for adhesions of the coapted leaflets. Thus, the pulmonary valvar stenosis/atresia in recipient twins seems to represent a unique form of "acquired congenital heart disease" and not a primary malformation (Harkness and Crombleholme, 2005). ANP/BNP signaling interruption may play a significant role in the generation of cardiac hypertrophy and dysfunction (Cameron and Ellmers, 2003). The right and left ventricular myocardium have embryologic differences, and the number of NP receptors in the right ventricle may be inherently lower; once proliferation and hypertrophy ensue, the right ventricle may become progressively more vulnerable to the effects of preload, afterload, and pressors.

Although cardiac dysfunction is more common and more dramatic in recipients, decreased cardiac performance and injury also may occur in donor twins in TTTS (Harkness and Crombleholme, 2005; Luks et al., 2005). Protracted increase in cardiac demands and energy expenditure, due to continued transfusion of the co-twin, and hypoxemia and acidemia, due to the anemia and probable shrinking efficiency of placental function, contribute to reduced cardiac function and growth restriction in the donor (Luks et al., 2005). Umbilical arterial end-diastolic forward (AEDF) blood flow diminishes to become absent (Mahieu-Caputo et al., 2003; Umur et al., 2003; Jain and Fisk, 2004; Luks et al., 2005; Wee et al., 2006). Hydrops from high-output cardiac failure can ensue in the donor due to loss of oncotic pressure from chronic transfusion (Luks et al., 2005) and hypoproteinemia due to passive hepatic congestion and reduced hepatic synthesis that reflects reduced blood delivery to the liver (due to splanchnic vasoconstriction and relative preservation of blood shunting through the ductus venosus with effective bypass of the liver) and placental insufficiency with reduced nutritional supply.

INCIDENCE

Vascular communications occur in all monochorionic but rarely in dichorionic placentas. TTTS is therefore almost exclusively found in monochorionic twins. TTTS is estimated to occur in 5% to 15% of monochorionic twin pregnancies (Rausen et al., 1965; Benirschke and Kim, 1973). Lage et al. (1989) described a case of TTTS resulting from vascular anastomoses within a fused dichorionic twin placenta. Robertson

and Neer (1983) reported two cases of TTTS in dichorionic pregnancies.

The true incidence of TTTS is difficult to ascertain. TTTS may occur very early during the second trimester, with loss of both fetuses; in midgestation or at term. It is of most concern to the perinatologist when it occurs in midsecond trimester, when the syndrome results in polyhydramnios, often with spontaneous rupture of membranes, or in spontaneous labor that leads to premature delivery. Because TTTS can have such a wide spectrum of clinical presentation, in many cases the diagnosis may go unrecognized.

SONOGRAPHIC FINDINGS

Wittmann et al. (1981) and Brennan et al. (1982) have suggested the sonographic criteria for the diagnosis of TTTS, including: (1) significant size disparity in fetuses of the same sex, (2) disparity in size between two amniotic sacs, (3) disparity in size of the umbilical cords, (4) single placenta, and (5) evidence of hydrops in either fetus or findings of congestive cardiac failure in the recipient. However, discordant growth is a common complication of twin pregnancies, and causes other than TTTS exist for discordant amniotic fluid volumes. The criterion of a birth weight difference of greater than 20% for the diagnosis of TTTS is based on the belief that the donor twin becomes growth restricted as a result of anemia and hypoalbuminemia. However, Sherer et al. (1994) reported a case of acute intrapartum TTTS so severe as to cause the death of both twins. In this report, the birth weights of the infants differed by only 2%.

In some cases, the discordance in amniotic fluid volume is so great that the amnion adheres to the smaller baby, so that it appears "stuck" to the wall of the uterus (Figure 119-1). In this situation it may be extremely difficult to visualize the dividing membrane between the twins. The "stuck twin" phenomenon is not pathognomonic for TTTS; it may also result from structural fetal anomalies, congenital infection, chromosomal abnormalities, or ruptured membranes (Patten et al., 1989). In contrast, the co-twin moves freely in a normal or increased amniotic fluid volume (see Figure 119-1). On ultrasound examination, signs of hydrops fetalis are occasionally found in the recipient (Brennan et al., 1982), rarely in the donor (Rausen et al., 1965), and exceptionally in both (McCafee et al., 1970).

In addition to measuring biometry and amniotic fluid volume, Doppler velocimetry can be used to confirm the diagnosis of TTTS. Nonetheless, studies have provided conflicting results. Farmakides et al. (1985) reported two cases in which UA waveforms of the twins were discordant and concluded that simultaneous observation of high- and low-resistance UA systolic/diastolic (S/D) ratios was suggestive of TTTS. Meanwhile, Giles et al. (1985) found no difference in interpair S/D ratios in eight cases where the diagnosis was documented or strongly suspected. Pretorius et al. (1988) also reported eight cases of TTTS and found no consistent pattern in Doppler studies. Five of the eight pregnancies resulted in fetal or neonatal death of both twins. In these cases of perinatal loss, one or both of the twins had either absent or reversed diastolic flow. The authors concluded that, while abnormal Doppler studies are not helpful in identifying the donor from the recipient twin, it invariably predicts a poor outcome. Data from the Australian and New Zealand TTTS Registry support these observations (Dickinson and Evans, 2000). Ishimatsu et al. (1992) were also unable to identify any distinctive findings in the UA blood flow velocity waveforms in patients with TTTS. However, the presence of cardiomegaly in five recipient

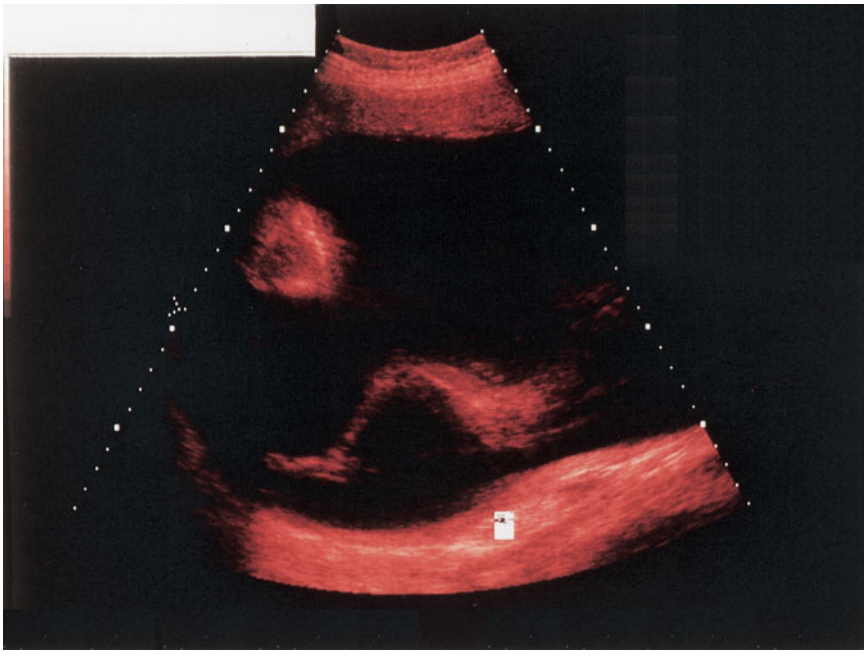

Figure 119-1 Prenatal sonographic image demonstrating a "stuck" twin in the upper left section of the image and the co-twin in a sac with polyhydramnios.

twins, with tricuspid regurgitation and a biphasic umbilical vein waveform in three others, led these authors to suggest that these findings may be more diagnostic than UA Doppler velocimetry and representative of the hemodynamic changes that occurring in TTTS. It is interesting to note that AA anastomoses can be identified using Doppler ultrasound as early as the first trimester, and absence of these anastomoses has been found to be associated with an increased risk for TTTS (Jain and Fisk, 2004).

A staging system for TTTS has been developed by Quintero et al. (1999) for the purpose of categorizing disease severity and standardizing comparison of different treatment results. In Stage I there is oligohydramnios, but the donor twin bladder is visible; in Stage II the bladder of the donor twin is no longer visible; in Stage III abnormal Doppler studies are evident (i.e., absent/reversed end-diastolic velocity in the UA, reversed flow in the ductus venosus, or pulsatile flow in the umbilical vein); Stage IV is complicated by hydrops; and in Stage V one or both fetuses have died.

Taylor et al. (2000) applied the Quintero staging system to a population treated with serial amnioreduction (AR), septostomy, and selective reduction alone or in combination and found no significant influence of staging at presentation on survival in their conservatively treated group. Survival was significantly poorer when stage increased rather than decreased. These authors concluded that the Quintero staging system should be used cautiously for determining prognosis at the time of diagnosis, suggesting that it may be better suited for monitoring disease progression. A subsequent larger study from the same institution, however, showed that Quintero stage at presentation, at first treatment, and at worst stage did, in fact, predict both perinatal (overall number of fetuses surviving of the total number of fetuses treated) and double survival (number of pregnancies with two survivors), but not survival of any twin (number of pregnancies with survival of one or both twins) (Taylor et al., 2002). Duncombe et al. (2003) also showed a correlation of Quintero stage at initial presentation and perinatal survival.

The Quintero staging system, although useful in describing the progression of TTTS along the clinical spectrum of severity, has potential limitations in guiding therapy. For patients who present at Stage I with only amniotic fluid discordance, it may be difficult to know with certainty if they actually have TTTS. Patients who have Stage II presentation usually are believed to be in the early stages of the disease. The use of echocardiography to identify findings of recipient TTTS cardiomyopathy can confirm the diagnosis in Stage I cases when it may be in doubt. In addition, echocardiographic findings can alert the clinician to more advanced disease than the Quintero Stage suggests. The largest group of patients tends to fall into Stage III, but this stage comprises a very broad spectrum of severity. At one end are patients whose only hemodynamic derangement is abnormal UA Doppler velocimetry, and at the other end of the spectrum are patients in whom the recipient twin has severe, end-stage, twin–twin cardiomyopathy. These latter patients may be premorbid but without the development of hydrops (Stage IV disease). The Quintero staging system is heavily weighted toward findings in the donor twin. The absence of a visible bladder in the donor upstages the case to Stage II. The critical Doppler abnormalities that are required for Stage III almost always are observed in the donor twin. Critical Doppler waveform abnormalities in the recipient twin are rare until end-stage TTTS has been reached. In addition, there is no assessment of the TTTS cardiomyopathy, which only occurs in the recipient and has a profound impact on survival of the recipient (Harkness and Crombleholme, 2005; Michelfelder et al., 2007; Habli et al., 2008).

The Fetal Care Center of Cincinnati has used fetal echocardiographic assessment of the recipient twin to stage patients (Table 119-1). This is in keeping with the view that TTTS is a fundamentally hemodynamic derangement. Fetal echocardiography can distinguish degrees of severity among the broad spectrum of severity in Stage III TTTS and identify sicker patients in Stages I and II. Echocardiographic features include the presence and severity of atrioventricular valvar incompetence, ventricular wall thickening, and ventricular function, as assessed by the Tei Myocardial performance index (Barrea et al., 2005; Ichizuka et al., 2005). In recent reviews of experience with the Cincinnati staging system, 20% to 55% of Quintero Stage I and II patients were upstaged to Stage III disease based on echocardiographic findings (Michelfelder et al., 2007; Habli et al., 2008). The impact of TTTS cardiomyopathy on recipient twin survival had been demonstrated by Shah et al. (2008) in patients treated by fetoscopic laser who were stratified by cardiovascular profile score and in the National Institutes of Health TTTS trial in which echocardiographic findings of TTTS were the single most important predictor of adverse recipient survival (Crombleholme et al., 2007; Shah et al., 2008). The upstaging of patients from Stage II to Stage III may influence counseling about treatment options. These echocardiographic features also are used to assess response to therapy. If a patient is treated initially with AR or microseptostomy, fetal echocardiography can be used to assess progression of TTTS despite therapy and as an indication for selective fetoscopic laser photocoagulation (Crombleholme et al., 2006, 2007; Habli et al., 2008).

Intrauterine cardiac dysfunction and hemodynamic derangements lead to ischemic brain lesions, including white matter infarction and leukoencephalopathy, intraventricular hemorrhage, hydranencephaly, and porencephaly, which can be detected by prenatal ultrasonography (Denbow et al., 1998; De Lia et al., 2000; Mari et al., 2000; Taylor et al., 2000; Kline-Fath et al., 2007). Up to 8% of TTTS cases have evidence of CNS injury on fetal magnetic resonance imaging (MRI) at the time of presentation prior to treatment. Such CNS findings range from ischemic or hemorrhagic changes in the brain to marked dilation of the cerebral venous sinuses due to central venous hypertension. The latter has been shown to correlate with worse survival when detected in TTTS (Kline-Fath et al., 2007). When these lesions are seen in surviving twins of instances of co-twin death [66% of cases

Table 119-1

Cincinnati Modification of the Quintero Staging System and the Sequence of Progressive Events in Untreated TTTS

Stage	Donor	Recipient	Recipient Cardiomyopathy
I	Oligohydramnios (DVP <2 cm)	Polyhydramnios (DVP >8 cm)	No
II	Absent bladder	Bladder seen	No
III	Abnormal Doppler finding	Abnormal Doppler finding	None
IIIa			Mild*
IIIb			Moderate*
IIIc			Severe*
IV	Hydrops	Hydrops	
V	Death	Death	
Variables/cardiomyopathy	Mild	Moderate	Severe
AV regurgitation	Mild	Moderate	Severe
RV/LV thickness	>+2 Z-score	>+3 Z-score	>+4 Z-score
MPI	>+2 Z-score	>+3 Z-score	Severe biventricular dysfunction

** Definition of recipient cardiomyopathy in the Cincinnati TTTS staging system. AV = atrioventricular; DVP = deepest vertical pocket; LV = left ventricle; MPI = myocardial performance index; RV = right ventricle.*

with intrauterine death involve demise of the donor twin (Weisz et al., 2004)], they have been attributed to sudden acute TTTS (De Lia et al., 2000; Kraus et al., 2005) through arterioarterial (A-A) anastomoses (De Lia et al., 2000). Due to the shared placental circulation, if one co-twin dies, there is an acute fall in blood pressure that causes placental resistance to decrease. This decrease in resistance across the placental vascular connections can result in reduced cerebral perfusion pressure and ischemic injury in the brain of the surviving twin. Quintero et al. (2002) reported endoscopic evidence of fetofetal hemorrhage from a recipient to donor twin within 3 hours of the spontaneous demise of the donor, noting endoscopic and middle cerebral artery Doppler evidence of paradoxic anemia in the recipient and erythrocythemia in the donor. TTTS can result in significant neurologic damage, with 5% to 27% of surviving twins having evidence of CNS sequelae on postnatal MRI or ultrasonography (De Lia et al., 1995; Ville et al., 1995; Hecher et al., 1999; Senat et al., 2004; Kraus et al., 2005). Brain injury, however, can occur in TTTS even when both twins survive. When both twins survive, neurologic damage in the recipient may be related to secondary polycythemia and venous stasis. In the donor, neurologic injury may be due to anemia and hypotension.

Multiorgan ischemic sequelae also are seen. Renal failure occurs in 48% of survivors compared with 14% of aged-matched controls (Jain and Fisk, 2004). Renal cortical necrosis, intestinal atresia, and cutis aplasia may be seen in one or both twins (Denbow et al., 1998; Luks et al., 2001; Carr et al., 2004). Limb necrosis and other ischemic lesions and hemolytic jaundice in the surviving recipient twin may be related to hyperviscosity (erythrocythemia) (Carr et al., 2004) or thromboembolic phenomena due to placental chorangiopagus vessels (Margono et al., 1992).

Diamniotic monochorionic twins are at increased risk for structural cardiac anomalies in at least one twin; 7% of monochorionic diamniotic twins have congenital heart defects (CHD) (Manning and Archer, 2006) compared with the overall prevalence of 0.5% seen in neonates (Bahtiyar et al., 2007). Bahtiyar et al. (2007), in their multistudy review of the prevalence of CHD in monochorionic diamniotic twins, found an overall ninefold increased risk for CHD over singletons, a 15- to 23-fold higher risk of CHD with TTTS over that of singletons, and a 2.78 times more frequent occurrence of CHD in the setting of TTTS compared with no TTTS. These overall and relatively increased risks are probably related to the greater frequency of abnormalities of placentation and the umbilical cord in monochorionic diamniotic gestations and their relative predominance in TTTS, respectively. However, the etiopathogenesis of cardiovascular malformations is poorly understood, even in singletons. Thus, the increased prevalence of cardiac malformations in monochorionic diamniotic twins, and especially in those pairs affected by TTTS, probably represents a complex interaction among many variables such as fetal blood flow fluctuations, vascular endothelial growth factors (VEGFs) and other mediators, the process of twinning itself, unequal sharing of the placenta, and inherent genetic factors.

The most common defects in monochorionic diamniotic twins are ventricular septal defect (VSD), pulmonary

stenosis, and atrial septal defect. The prevalence of VSDs in TTTS, although higher, is not remarkably different from that in uncomplicated monochorionic diamniotic gestations (0.024 and 0.019, respectively). The detection of VSDs may represent sites of ischemic necrosis or excessive natriuretic proteins during early embryonic life. However, the membranous septum is a complex structure that has numerous embryologic components effecting its closure and VSDs, together with patent ductus arteriosus, are the most common cardiac defects in infancy. The pathogenesis of VSD is unclear, but its mildly increased incidence in TTTS infants may be related to a combination of factors, including its relatively greater general frequency and the increased risk of ischemia in TTTS due to abnormal placentation or ischemia due to hypovolemia. Bahtiyar et al. (2007) postulated that because recent studies indicate that the cause of CHD is partly due to aberrant angiogenic factors such as VEGF, the increased prevalence of CHD in TTTS may represent the deleterious effects of angiogenic factors. VEGF is upregulated in ischemia, and Dor et al. (2001) found that VEGF is specifically upregulated during normal heart development in the atrioventricular field of the heart, soon after the onset of endocardial cushion formation. Premature induction of myocardial VEGF prevents formation of endocardial cushions in animal models.

The prevalence of pulmonary stenosis is fourfold greater in gestations involving TTTS compared with those not involving TTTS (0.028 vs. 0.007), and atrial septal defects (0.024) are seen only in twins who have experienced TTTS (Bahtiyar et al., 2007). However, these summations do not specify co-twin status (donor or recipient), although pulmonary stenosis presumably represents the recipient population. The original studies also do not separate donor or recipient twin status, so it is difficult to assess the potential relationship of atrial septal defects to fetal volume status or circulating mediators and angiogenic factors. Presumably, high-output failure in the donor twin or right ventricular outflow tract obstruction in the recipient both could result in increased shunting through the foramen ovale and acquired incompetence of the interatrial septum (passive enlargement such that the septum primum does not adequately cover the foramen ovale). It is unclear whether the clinically diagnosed "atrial septal defects" represent a true primary deficiency of tissue (due to ischemic necrosis, increased apoptosis, mesenchymal failure) or excessive secondary dilatation of the foramen due to shunt overload as the right ventricle fails. Recently, transposition of the great arteries has been identified in a recipient twin, but the donor additionally had a vein of Galen malformation. Although the coexistence of the lesions might reflect a common causal mechanism, their etiopathogenesis(es) is unclear (Steggerda et al., 2006).

CHD in donor twins appears to be very rare, but left-sided obstructive lesions might be expected due to complications of hypovolemia. However, of the 830 monochorionic diamniotic gestations reviewed by Bahtiyar et al. (2007), the only instances of coarctation of the aorta or hypoplastic left ventricle (left-sided obstructive lesions) were isolated to two cases that did not have TTTS. Thus, although the prevalence theoretically would be expected to be higher in donor twins in TTTS and small twin size correlates with the presence of structural defects in monochorionic diamniotic twins (Bahtiyar et al., 2007), the pathogenesis of these rarely encountered lesions appears to represent more than unusual sequelae of diminished blood flow.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for TTTS includes discordant severe IUGR, discordant structural fetal anomalies, congenital infection, chromosomal abnormalities, and ruptured membranes. The antenatal diagnosis is based on ultrasound findings. Nevertheless, there have been attempts to devise more definitive diagnostic techniques. Fisk et al. (1990) described fetal blood sampling in six cases compromised by TTTS. Difference in hemoglobin concentration of 5 g per deciliter was found in only one pregnancy. Confirmation of a shared circulation was achieved in two pregnancies by transfusing adult Rh-negative red cells into the smaller fetus and then detecting them by Kleihauer–Betke testing in blood aspirated from the larger fetus. Bruner and Rosemond (1993) further reported successful fetal blood sampling in six of nine cases with the ultrasonographic diagnosis of TTTS. Hemoglobin difference was present in only one case. Shared circulation was demonstrated and confirmed in four (44%) of those initially identified by ultrasonographic criteria through the transfusion of O-negative red cells into the small twin and the performance of Kleihauer–Betke analysis on blood obtained from the larger twin. The author concluded that the currently accepted prenatal criteria are insufficient for the diagnosis of TTTS and suggested that the sonographic findings of marked growth discordance with oligohydramnios, polyhydramnios, monochorionic placenta, and like gender should more accurately be described as the twin oligohydramnios/polyhydramnios sequence.

The injection of intravascular pancuronium bromide has been suggested as an alternative to the injection of adult red cells to confirm TTTS (Tanaka et al., 1992). Paralysis of both fetuses can be detected through the examination of fetal heart rate tracings. There is an absence of accelerations noted with a reduction in fetal heart rate variability and a persistent tachycardia seen following pancuronium injection.

TTTS is generally diagnosed during the neonatal period by demonstration of a hemoglobin difference of greater than 5 g per deciliter (Rausen et al., 1965; Tan et al., 1979) and a difference in birth weight between twins of greater than 20% (Tan et al., 1979). Untimely umbilical cord clamping of either donor or recipient, erythropoietic changes, and reversed intrapartum shunting may result in false-positive and false-negative diagnosis when the determination is based on hemoglobin disparity alone. The cutoff value between normal and abnormal intertwin birth weight differences also remains controversial (Blickstein, 1990). In fact, all the classically accepted neonatal criteria of discordant hemoglobin, hematocrit, and weight have been challenged.

Danskin and Neilson (1989) found that hemoglobin differences of greater than 5 g per deciliter occur at similar rates in twins with dichorionic and monochorionic placentation. They reported birth weight differences greater than 20% equally in monochorionic and dichorionic pregnancies. Wenstrom et al. (1992) reviewed 97 cases of pathologically proven monochorionic twin pregnancies and observed all combinations of weight and hemoglobin/hematocrit discordance. Of 97 twin pairs, 34 were discordant for weight, and in half of these the hemoglobin and hematocrit were concordant. In 18% of cases the smaller twin had the higher hematocrit, and in 32% the smaller twin had the lower hematocrit. The authors concluded that weight and hemoglobin/hematocrit discordance is common in monochorionic twins and in itself is not sufficient for a diagnosis of TTTS. Conflicting information regarding both the fetal and neonatal hematologic criteria for the diagnosis of TTTS, together with the potential risk inherent in fetal blood sampling, has led us to avoid this procedure at our institution for the definitive diagnosis of TTTS.

ANTENATAL NATURAL HISTORY

TTTS occurs in acute and chronic forms. In early pregnancy an acute transfusion may result in an early fetal death, resulting in the so-called vanishing twin syndrome. Later in pregnancy, TTTS may cause death of one or both twins (Figure 119-2). Sometimes, a rapid transfer of blood from one twin to the other occurs during delivery. In such cases the twins are similar in weight and length, but one is polycythemic and hypervolemic and the other is anemic and hypovolemic.

In the chronic form of TTTS, the transfusion of blood from one twin to the other occurs over an extended period during the pregnancy. In chronic TTTS, the donor twin is generally hypovolemic and shows varying degrees of growth restriction. TTTS and placental insufficiency occur together in up to 20% of cases. In severe cases, the donor may die in utero and present at delivery as a fetus papyraceous. The recipient twin is hypervolemic, often larger than the donor, and may develop cardiac hypertrophy and congestive heart failure. Because of increased urine output, severe polyhydramnios frequently develops in the recipient twin that may predispose to premature delivery. Oligohydramnios is generally associated with the donor twin. The organ changes seen in donor twins in chronic TTTS resemble abnormalities observed in malnourished singletons. Weights of the heart, liver, spleen, thymus, and fetal adrenal cortex are proportionately smaller in the donor than in the recipient twin and suggest antenatal malnutrition (Naeye, 1965) (Figure 119-3). A much higher concentration of atriopeptin (atrionatriuretic peptide) has been reported in the serum from the recipient twin as compared with the donor twin in two cases of severe transfusion syndrome. More recently, Habli et al. have found that brain atrial natriuretic peptide (BNP) is significantly elevated in 130 cases of TTTS (Habli and Crombleholme, 2009). The

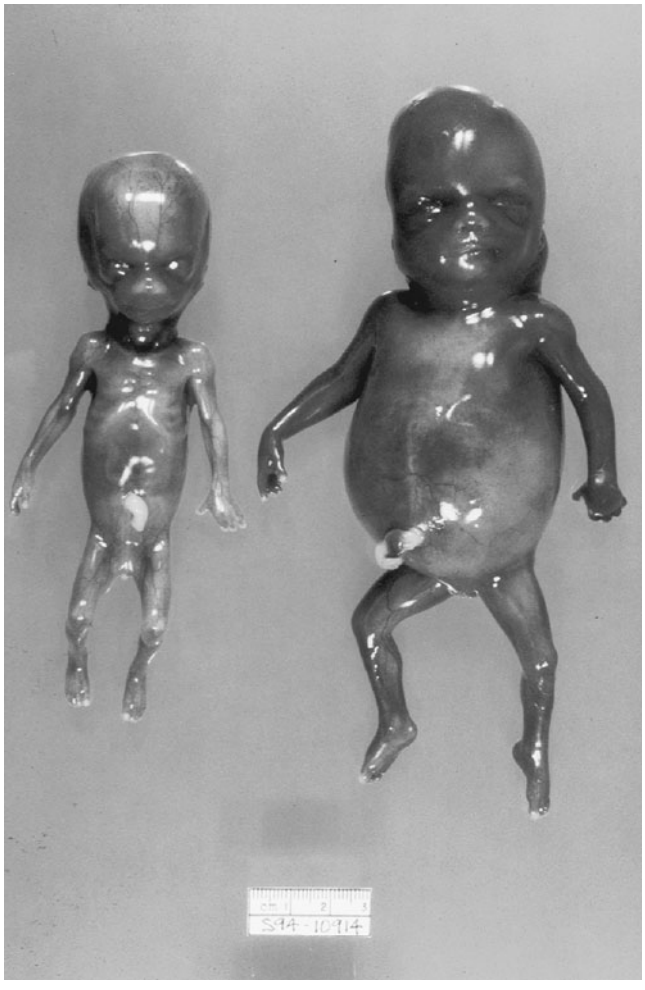

Figure 119-2 Death of both twins in midgestation as a result of twin-to-twin transfusion syndrome. The smaller, growth-restricted donor twin is on the left and the larger recipient twin on the right. (*Courtesy of Dr. Joseph Semple.*)

elevated BNP levels were found to correlate with Cincinnati stage of TTTS cardiomyopathy (Habli and Crombleholme, 2009). One may infer from this that atriopeptin plays a role in the pathophysiology of the syndrome (Nageotte et al., 1989). Atriopeptin, produced by mammalian atria and BNP produced by the ventricles, are peptides that promote diuresis and vascular changes. In TTTS, atriopeptin and BPN released from the heart of the recipient may lead to increased urine output that results in polyhydramnios and vascular changes that in turn lead to hydrops (Nageotte et al., 1989, Habli and Crombleholme, 2009). Untreated, the natural history of TTTS is associated with a 60% to 100% mortality rate for both twins in severe or chronic cases (Benirschke and Kim, 1973; Cheschier and Seeds, 1988).

MANAGEMENT OF PREGNANCY

In the assessment of discordant growth in twins in utero it is important to differentiate TTTS from isolated growth failure

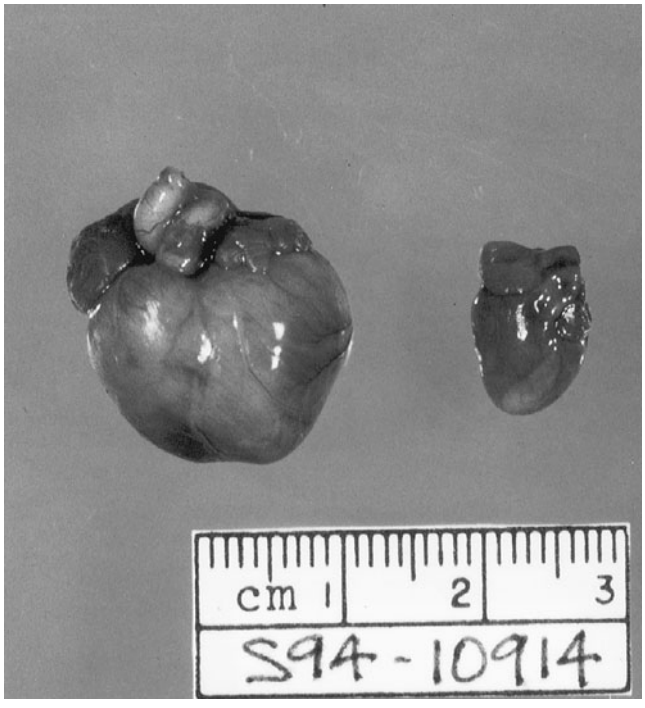

Figure 119-3 At the right is the paler, smaller heart of the donor fetus. At the left is the plethoric, larger heart of the recipient fetus.

of one twin. The cause of stuck twin syndrome includes twin-to-twin transfusion, fetal anomalies, placental insufficiency, and possibly abnormal cord insertion. A detailed anatomic survey is recommended to rule out any associated congenital abnormalities. Such a survey may be difficult if the fetus is stuck because of substantial oligohydramnios, which impairs ultrasonic visualization. Color Doppler studies are useful to visualize where the cord inserts into the placenta. In cases of TTTS, echocardiographic assessment of both donor and recipient twins is recommended and the Cincinnati staging system can be used to stratify TTTS cardiomyopathy into mild moderate and severe. In addition, we routinely perform ultrafast fetal MRI to evaluate the fetal brains for signs of ischemia, hemorrhage or dilated venous sinuses that may be present in up to 8% of cases of TTTS at presentation (Kline-Fath et al., 2007). It is our practice to perform amniocentesis to exclude a chromosomal abnormality. Amniotic fluid is also sent for cytomegalovirus culture because of the reported association of stuck twin syndrome with viral infections. The definitive antenatal diagnosis is one of exclusion, and therapy is usually based on a presumptive diagnosis. It is our practice to inform patients of the various available treatment options, summarized in Table 119-2.

Delivery should be performed at a tertiary care center because most cases deliver less than 32 weeks' gestation. Vaginal delivery may be attempted in cases in which TTTS has been diagnosed. It is critical to monitor the heart rates of both fetuses. A sinusoidal pattern on the fetal heart rate tracing may be a sign of fetal anemia. Of eight cases of TTTS monitored through labor by Goldberg et al. (1986), two pairs experienced severe fetal distress requiring emergency cesarean section. In another case, the recipient died of presumed intrapartum TTTS (Goldberg et al., 1986). The incidence of cesarean delivery in TTTS was reported to be 44% in Reisner et al.'s series (1993), but this has not been reported in other recent series.

Cord hematocrits should be measured at the time of delivery. Initial examination of the placenta should be performed by the obstetrician after delivery. Classically, the placenta of the donor twin looks pale and atrophied in comparison to that of the recipient twin that is red and hypertrophied. Because postnatal demonstration of transplacental vascular connections is an important criterion for the definitive diagnosis of TTTS, the placenta should be sent to the pathology department for further studies. Because many cases involve deep vascular shunts rather than superficial connections, vascular injection is necessary to exclude such connections (Blickstein, 1990).

Table 119-2

Options Available for the Treatment of TTTS

Observation only
Medical therapy Indomethacin Digoxin Nifedipine
Serial amniocentesis with echocardiographic surveillance
Amniotic septostomy
Selective reduction by radiofrequency ablation or cord coagulation
Fetoscopic laser treatment Selective fetoscopic laser photocoagulation Nonselective fetoscopic laser photocoagulation

FETAL INTERVENTION

Due to the poor perinatal outcomes associated with the disorder, expectant management of TTTS is not recommended except in incipient cases that do not meet criteria for TTTS (Fox et al., 2005). Treatment depends on the gestational age at diagnosis. Patients with early onset TTTS may opt for selective termination of one twin (usually the donor) or termination of the entire pregnancy. If TTTS develops later in pregnancy, treatment may be less aggressive depending on the disease severity and gestational age.

In the midtrimester, aggressive management is recommended. Medical management with digoxin has been

attempted but has not shown to be effective (De Lia et al., 1985). Indomethacin is contraindicated due to reports of fetal demise (Jones et al., 1993). Current treatment options for severe TTTS include: (1) serial reduction amniocentesis, (2) amniotic septostomy, and (3) laser ablation of the anastomoses.

In serial reduction amniocentesis, an 18-gauge spinal needle is placed into the polyhydramniotic sac under ultrasound guidance (Malone and D'Alton, 2000; Johnsen, 2004). Provided the patient can tolerate the procedure, amniotic fluid is withdrawn until the fluid level returns to normal (DVP <5 cm). Amnioreduction is repeated as often as necessary to maintain a near normal amniotic fluid volume. The mechanism by which this procedure restores the amniotic fluid balance has not been elucidated. Removing excess fluid from the sac with polyhydramnios may result in decreased pressure on the other sac or the placenta. This, in turn, may result in increased placental perfusion to the stuck twin with secondary improvement in its amniotic fluid. Studies have cited perinatal survival rates of 37% to 83% following this procedure (Malone and D'Alton 2000). The wide range in perinatal survival may be due to reporting bias, small sample sizes, and variation in the timing and amount of fluid removed. Large registries of TTTS pregnancies however, have reported survivals of 60% to 65% (Dickenson and Evans, 2000; Mari et al., 2001).

Amniotic septostomy is another option (Malone and D'Alton, 2000; Johnson et al., 2001). In this procedure, a 20-gauge spinal needle is inserted through the dividing membrane under ultrasound guidance. The amniotic fluid, then, sometimes equilibrates across the disrupted membrane. Similar to serial AR, the mechanism of action of this technique is unknown. It is possible that the defect in the membranes allows the donor to swallow a sufficient volume of fluid to augment its circulating blood volume, secondarily increasing its urine output. Studies regarding the effectiveness of this treatment modality have been conflicting. In one report of 12 cases, pregnancy was prolonged by 8 weeks with an 83% survival rate (Saade et al., 1998). In another report of 14 patients (7 managed by serial AR and 7 with amniotic septostomy) no differences in overall survival were noted. The septostomy patients, however, delivered significantly later. In another report, all three of the treated pregnancies were lost within 5 days secondary to preterm premature rupture of membranes (Pistorius and Howarth, 1999). In a more recent study by Saade et al., 32 patients were randomized to septostomy and 31 to AR. Similar outcomes were noted between the groups. Both groups had 65% survival (Saade et al., 2002). Because septostomy can result in an iatrogenic monoamniotic pregnancy that has its own inherent complications and risks, the procedure has been criticized. Likewise, comparing AR to septostomy is challenging because both procedures utilize AR, and, serial AR can be complicated by inadvertent septostomy.

Laser ablation of placental anastomoses is another invasive treatment option that has been utilized to correct the underlying pathophysiology of TTTS. Reported perinatal survival rates have ranged from 53% to 69% (Malone and D'Alton, 2000). De Lia et al. (1990) developed the technique for intrauterine ablation of vascular communications in the placenta with a fetoscopically directed neodymium-YAG laser. Three women who were carrying twins and who were at risk of pregnancy loss from acute hydramnios underwent the procedure at 18, 22, and 22.5 weeks of gestation. Four of the six infants survived. De Lia et al. subsequently reported 26 patients with a mean gestational age of 20.8 weeks at the time of treatment. One patient has surviving triplets, eight have surviving twins, nine have a single survivor (two neonatal and seven fetal deaths occurred in this group and eight have no survivors). The cases with survivors were delivered for obstetric indications at a mean of 32.2 weeks. Fifty-three percent of the fetuses survived with 96% (27 of 28) developing "normally" at a mean age of 35.8 months. An identical survival rate of 53% was reported in a second series involving 45 cases of TTTS (Ville et al., 1995). The median interval between the endoscopic laser procedure and the delivery was 14 weeks. De Lia et al.'s surgical technique consisted of laparotomy (7- to 10-cm skin incision) under general anesthesia and insertion of a 3.85 × 2.9-mm fetoscope sleeve into the uterus. The technique has not gained widespread acceptance because of its invasive nature. Ville et al. (1995) described the percutaneous insertion of a 2-mm fetoscope into the amniotic cavity using continuous ultrasound visualization under local anesthesia.

The goal of coagulation of all superficial placental vessels is to interrupt the vascular communication between the circulation of the two fetuses (Figure 119-4). This direct treatment of the underlying pathophysiology of TTTS has been cited as a major advantage over other techniques (De Lia et al., 1995; Ville et al., 1995).

In a series of 132 pregnancies with TTTS managed by fetoscopic laser ablation of placental vessels, 55% of infants survived, and there was at least one survivor in 73% of the cases (Ville et al., 1998). The rate of neurologic handicap after 12 months of follow-up was 4%, which was lower than the authors' previous experience with serial reduction amniocentesis. The authors concluded that serial reduction amniocentesis appears to provide similar overall survival results, but there was less neurologic morbidity in the laser group.

In a study of TTTS from Germany, 73 patients at a single center were prospectively treated with fetoscopic laser ablation, while 43 patients at a separate center were prospectively treated with serial reduction amniocentesis (Hecher et al., 1999). Patients in the fetoscopic laser group had a higher proportion of pregnancies with at least one survivor, fewer fetal deaths, higher gestational age at delivery, and fewer cases of abnormal sonographic findings in the brain of survivors. It was therefore concluded that fetoscopic laser ablation is a more effective treatment for TTTS than serial reduction amniocentesis.

Senat et al. (2004) recently published the results of the European prospective multicenter randomized controlled study of endoscopic laser (semiselective technique) versus

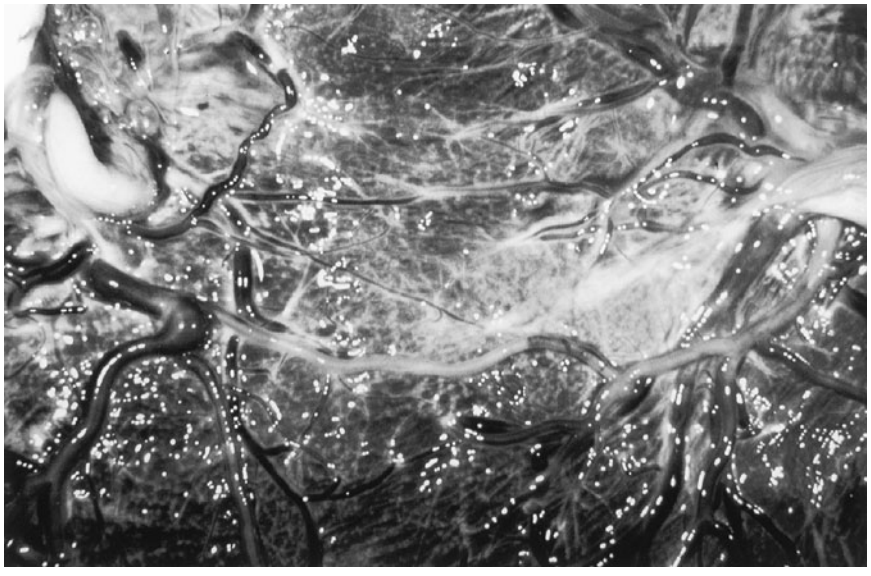

Figure 119-4 Vascular anastomoses in monochorionic twins. (*Courtesy of Dr. Joseph Semple.*)

serial AR for the treatment of severe TTTS. All patients were between 15 and 26 weeks' gestation. Interim analysis demonstrated a significant benefit to the laser group. As result, the study was stopped after 142 patients had been randomized. Compared to the AR group, the laser group had a higher likelihood of survival of at least one twin to 28 days of life (76% vs. 56%) and 6 months of age (76% vs. 51%). The median gestational age at delivery was significantly greater in the laser group than in the AR group (33.3 weeks vs. 29.0 weeks). Thirty patients in the laser group (42%) and 48 in the AR group (69%) delivered before 32 weeks. Neonates from the laser group also had a lower incidence of periventricular leukomalacia and were more likely to be free of neurologic imaging abnormalities at 6 months of age (52% vs. 31%).

The overall survival in the laser arm was 57%, which was consistent with survival rates in previous reports of nonselective fetoscopic laser treatment (53%) (De Lia et al., 1995; Ville et al., 1995). This rate is significantly lower, however, than the survival reported with selective fetoscopic laser photocoagulation (SFLP) (64–68%) (Hecher et al., 1999; Dickinson and Evans, 2000). Of particular concern is the poor survival observed in the AR arm of 39%, which is significantly lower than previously reported (60–65%) (Elliott et al., 1991; Pinette et al., 1993; Dickinson and Evans, 2000; Mari et al., 2001). Antenatal, peripartum, and neonatal care was provided by the referring hospital, and lack of standardization may explain some of these differences (Fisk and Galea, 2004). The decreased survival in the AR group may reflect the higher pregnancy termination rate in the AR group (16 vs. 0 in the laser group). The terminations were requested after the diagnosis of severe fetal complications. It would be instructive to know whether these women were offered cord coagulation as a means of rescuing one baby (Dickinson and Evans, 2000). Reliable assessment of neurologic outcome is critical when assessing efficacy of treatment for TTTS. Although the rate of abnormality on neurologic imaging was lower in the laser group (7% vs. 17%), long-term neurodevelopmental assessment has revealed no difference in outcome between survivors treated by fetoscopic laser and those treated by AR (Ortqvist et al., 2006).

The National Institutes of Health (NIH)-sponsored TTTS trial is the only other prospective randomized trial comparing survival among those receiving AR versus SFLP (Crombleholme et al., 2007). This trial differed from the Eurofoetus trial in several important aspects. First, to qualify for the NIH Trial, the TTTS had to fail to respond to a qualifying amniocentesis. The rationale for this requirement was to eliminate those who were more likely to respond to AR, the so-called "single amnio paradox." Second, patients were candidates only if the TTTS presented earlier than 22 weeks of gestation, and no Stage I patients were candidates for the trial. These two requirements were substantially different from the Eurofoetus trial in which women were randomized into the trial up to 26 weeks of gestation, and 52% of those entered were Stage I (Senat et al., 2004).

The NIH study was stopped early, after 42 women were randomized, when the Trial Oversight Committee detected a trend in adverse outcome affecting the recipient twin in one treatment arm and recommended to the Data Safety Monitoring Board that the trial be stopped to allow biostatistical analysis of the adverse trend. Results of the NIH TTTS trial showed no statistically significant difference in overall neonatal survival to 30 postnatal days (60% vs. 43% p = NS) or neonatal survival of one or both twins in the same pregnancy (75% vs. 65%, p = NS) in cases of severe TTTS treated by either AR or SFLP. Despite these overall results, a statistically significant worse fetal survival was observed among recipient twins in pregnancies treated by SFLP compared with those treated by AR. This apparent conundrum can be accounted for by recipient fetal losses in the SFLP arm being balanced by increased treatment failures among recipients in the AR arm. These results suggest that, in these highly selected cases of

severe TTTS, neither treatment is superior to the other. Once TTTS reaches this degree of severity, the mortality among recipients is considerable, but the losses may occur at different times, depending on treatment. The impact of TTTS severity on fetal survival is supported further by the significantly worse fetal survival among recipient twins in Stages III and IV compared with those in Stage II. One of the strongest predictors of recipient demise is echocardiographic evidence of TTTS cardiomyopathy. The losses of fetal recipients treated by SFLP usually occur within 24 hours of the procedure. In contrast, the recipients treated by AR are not lost following the procedure, but there is progressive TTTS cardiomyopathy, as reflected by more recipients in the AR arm meeting criteria to be declared treatment failures. Taken together, these data suggest a disproportionate impact of TTTS cardiomyopathy on recipient survival in advanced stages of TTTS no matter what treatment they receive.

Recently, Rossi and D'Addario (2008) reported a Cochrane review of TTTS with a meta-analysis that included data from both the Eurofoetus and NIH trials. The conclusion drawn from this analysis was that SFLP of TTTS is preferred over AR when it is available and AR is preferred when SFLP is not available. The results of this analysis likely are skewed toward fetoscopic laser based on the small numbers of individuals included from the NIH trial ($n = 42$) compared with the number included from the Eurofoetus trial ($n = 142$).

AR is readily available, less costly, and less invasive; laser therapy is only available at select institutions and requires specialized training. Although it makes sense to use AR where treatment options give similar results, it would be prudent to move promptly to laser therapy if rigorous studies can prove that this therapy has better short- and long-term outcomes in the setting of advanced disease.

For patients who respond to AR, the overall survival rate has been 88% (Crombleholme et al., 2006). In those cases in which echocardiographic progression is detected despite AR, the overall survival rate when SFLP is performed is 80%. The difference in survival between responders to AR and those who progress to SFLP is not statistically significantly different, suggesting that survival was not compromised by an initial trial of AR before progressing to SFLP.

TREATMENT OF THE NEWBORN

Both acute and chronic cases of TTTS must be managed expeditiously by trained neonatologists. Because the incidence of prematurity is so high, many complications of prematurity are present, including the need for respiratory support, transfusion, and supplemental glucose. Specific problems unique to newborn cases of TTTS include severe anemia in the donor and severe polycythemia and hypervolemia in the recipient newborn. Either one or both twins may have hydrops. Exchange transfusions may be necessary to correct the anemia and polycythemia. If TTTS cardiomyopathy is present, ionotrophic support may be indicated for the recipient twin. Echocardiographic assessment should be performed in any recipient with TTTS cardiomyopathy.

SURGICAL TREATMENT

No surgical treatment has been described for newborns with TTTS.

LONG-TERM OUTCOME

One of the concerns associated with in utero treatment for TTTS is that prolongation of pregnancy might produce survivors with excessive neonatal or infant complications (Mahony et al., 1990). If one fetus dies in utero, the surviving twin is at risk for multiorgan damage including severe neurologic compromise. Even if both twins survive, the pathophysiology of TTTS can result in adverse neurological sequelae to one or both (Cincotta et al., 2000; Dickinson and Evans, 2000; Mari et al., 2001; Sutcliffe et al., 2001; Banek et al., 2003; Lopriore et al., 2003; Dickinson et al., 2005).

In older literature, thrombocytopenia has been suggested as a cause of cataracts, impaired hearing, and growth restriction of the donor twin (Corney and Aherne, 1965). Intrauterine growth deficiency of the brain (Naeye, 1963) and profound neonatal hypoglycemia (Reisner et al., 1965) have been implicated as a cause for cerebral impairment of the donor, resulting in subsequent lower intelligence as compared with the recipient twin. Cardiomyopathy and associated cardiac dysfunction has been reported (Mahony et al., 1990; Elliott, 1992). In one study, five of five recipient twins were found to have cardiomegaly and tricuspid regurgitation prenatally; four had cardiac dysfunction after birth (Zosmer et al., 1994). In Elliott's (1992) experience there were two cardiac abnormalities in 12 fetuses (one critical aortic stenosis, one cardiopathy). Renal cortical necrosis (Dimmick et al., 1971; Feingold et al., 1986) and brain infarction have been reported in the donor twin (Mahony et al., 1990). These complications have also been described in the surviving co-twin of intrauterine fetal death in utero. The mechanism may be hypovolemia and ischemic injury in the smaller donor twin (Elliott, 1992).

Although much attention has focused on the effect of treatment on survival in TTTS, the neurologic morbidity among survivors frequently is underappreciated. The International Amnioreduction Registry tracked 223 women who had TTTS diagnosed before 28 weeks' gestation and were treated with serial aggressive AR (Mari et al., 2001). Of those infants who survived to 4 weeks of age and underwent clinically indicated cranial ultrasonography, 24% of recipient (26/109 scanned) and 25% of donor twins (22/88 scanned) had abnormal findings. Findings included severe intraventricular hemorrhage, ventricular dilation, cerebral echogenic foci, cerebral cysts, and periventricular leukomalacia among

other less common lesions. Eighty infants died before reaching 4 weeks of age, and how many of these would have had abnormal imaging if cranial ultrasonography had been performed is unknown. Among patients in the TTTS Registry from Australia and New Zealand, most of whom had been treated with AR, the rate of abnormal cranial ultrasonography findings was similar at 27.3% (Dickinson and Evans, 2000). The rate of periventricular leukomalacia in this group was 10.8%, which is particularly important due to the association of this lesion with cerebral palsy. In another small series of patients treated with AR, the rate of abnormal neonatal cranial ultrasonography findings was as high as 58% (Denbow et al., 1998). It is important to recognize, however, that neuroimaging does not always correlate with neurodevelopmental outcome. An infant who has normal findings on head ultrasonography and MRI can be neurodevelopmentally devastated, and an infant who has evidence of leukoencephalomalacia on imaging studies can be neurodevelopmentally intact.

Only a few studies have reported longer-term neurodevelopmental outcome. When interpreting these studies, it is important to appreciate the neurodevelopmental outcome in monochorionic twins who do not have TTTS. The incidence of severe neurodevelopmental abnormalities in monochorionic twins without TTTS is 6% (Lopriore et al., 2003). TTTS survivors who develop neurologic handicap and mental retardation do not always have abnormal neonatal ultrasonography results. Similarly, not all children who have abnormal ultrasonography findings have clinically significant neurodevelopmental deficits. In one small study that followed TTTS survivors for a mean of 6.2 years (range, 4–11 years), the incidence of cerebral palsy was 26% (5/19 infants) in the group treated by serial AR. All of these children had abnormal mental development in addition to motor deficits. Of note, three of the five children had normal findings on neonatal head ultrasonography. In the combined cohort of children whose mothers had been treated with AR or conservative treatment, 22% (5/23) who did not have cerebral palsy or abnormal mental development had mild speech delay and required special education. One limitation to this and other studies is the lack of a comparable conservatively treated cohort group. Given the improved survival of TTTS babies who receive AR and other treatment modalities, however, it is unlikely that such a cohort ever will be available for comparison.

Studying infants from pregnancies complicated by TTTS and treated with AR, Mari et al. (2001) detected a rate of cerebral palsy of 4.7% (2 of 42 infants) in those children who survived to more than 24 months of age. One reason for the lower incidence of cerebral palsy than in the study by Lopriore et al. (2003) may be related to the latter study group having more severe disease, with all the patients diagnosed before 28 weeks' gestation versus up to 33 weeks' gestation in the study by Mari et al. Of note, in the Mari study, nine survivors had mild speech or motor delay.

Wee et al. (2005) studied the long-term neurologic outcome of 52 children from 31 TTTS pregnancies who survived to more than 18 months, most of whose mothers had been treated with AR. The comparison was a regional cohort of term and preterm infants, with most born very preterm. In addition, the TTTS babies were compared with matched singleton and twin control groups. The mean intelligence quotient (IQ) of TTTS survivors was significantly lower than the comparison cohort, due primarily to a 13-point IQ reduction in those children born before 33 weeks' gestation. There was no difference in the rate of cerebral palsy (5.8% for TTTS vs. 4.9% for very preterm twins vs. 3.3% for very preterm singletons) or behavioral test results in the TTTS survivors. This was a small study, however, and not sufficiently powered to demonstrate differences in cerebral palsy. Still, these researchers appropriately raise the issue that studies evaluating long-term neurologic outcome in TTTS need to consider that most TTTS pregnancies are delivered very preterm as well as the fact that twins generally are more likely to experience neurologic compromise.

Even fewer studies have examined the long-term outcome of survivors of TTTS treated with intrauterine laser photocoagulation therapy. Banek et al. (2003) reported that in 89 such children, 78% showed normal development at a median age of 22 months. Eleven percent had minor neurologic abnormalities, including strabismus, mildly delayed motor development, or mildly abnormal speech. The remaining 11% suffered significant neurologic deficiencies, including cerebral palsy, hemiparesis, and spastic quadriplegia. Of note, significantly more children in the neurologically impaired groups were born very preterm. Also of importance, two infants from the most severely affected group had abnormal brain scan results before laser treatment. The findings of this study are consistent with those of Sutcliffe et al. (2001) who reported a cerebral palsy rate of 9% in children after in utero treatment with laser therapy for TTTS. Graef et al., (2006) in a report of 167 TTTS survivors who had been treated by fetoscopic laser, found normal neurodevelopmental testing results in 86.8% of cases, with 7.2% of infants having minor neurologic deficiencies and 6% having major neurologic deficiencies such as cerebral palsy, hemiparesis, and quadriplegia. These findings were not unlike those in follow-up of monochorionic twins without TTTS (Adegbite et al., 2004), and the most severely affected children were delivered prior to 28 weeks' gestation, suggesting an important influence of gestational age on neurodevelopmental outcome. Similarly, Ortqvist et al. (2006) reported the neurodevelopmental outcome of 114 survivors treated in the Eurofoetus trial in which 13.2% had evidence of a major neurodevelopmental abnormality. However, there was no difference between those who had been treated by laser and those treated by AR. Perinatal factors, including gestational age at delivery and Apgar score, correlated with adverse outcome.

Of note, earlier and more sensitive antenatal detection of central nervous system injury (Crombleholme, 2003; Quarello et al., 2007) has been reported recently with the adjunct use of MRI techniques. MRI has enabled the detection of cerebral venous sinus dilatation and more clearly delineated central nervous system lesions. The improvements in antenatal detection may result in further improvements in clinical

management (Crombleholme, 2003) and reduced morbidity and its severity in survivors.

GENETICS AND RECURRENCE RISK

There are no reports of recurrence of TTTS in the literature.

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Twin Reversed Arterial Perfusion Sequence

120 CHAPTER

Key Points

- Twin reversed arterial perfusion (TRAP) sequence, also known as acardia, is a rare anomaly unique to multiple gestation in which one twin has an absent, rudimentary, or nonfunctioning heart (acardiac twin) and the other twin is normal (pump twin). TRAP sequence has been associated with adverse perinatal outcomes.
- The placentation in the majority of acradic twins is monochorionic diamniotic.
- The fundamental requirement for the TRAP sequence is the development of arterial-to-arterial vascular anastomoses between the umbilical arteries of twins early in embryogenesis.
- The diagnosis is made with ultrasound. The features useful in the diagnosis of acardia include absence of normal cardiac structure and cardiac movement and variable structural abnormalities.
- The malformations found in cases of acardia include growth abnormalities, partial or complete absence of the cranial vault, anencephaly, holoprosencephaly, absent or rudimentary facial features, absent or rudimentary upper and/or lower limbs, absent lungs and heart, gastrointestinal atresia, omphalocele, gastroschisis, and absent liver, pancreas, spleen, and kidneys.
- The pump twin is usually morphologically normal, and the risk of aneuploidy is 9%.
- The goal of antepartum management of a pregnancy complicated by the TRAP sequence is to maximize outcome for the structurally normal pump twin.
- In the absence of poor prognostic features (twin weight ratio >0.70, elevated combined ventricular output, elevated cardiothoracic ratio, congestive cardiac failure, polyhydramnios), expectant management with serial sonographic evaluation is reasonable.
- Intrafetal radiofrequency ablation of the cord of the acardius when indicated by above criteria is associated with 95% pump twin survival.

CONDITION

Twin reversed arterial perfusion (TRAP) sequence, also known as acardia, is a rare anomaly unique to multiple gestation in which one twin has an absent, rudimentary, or nonfunctioning heart. Schatz (1898) classified acardia into two main groups: hemiacardius (imperfectly formed heart) and holoacardius (absence of heart). Das (1902) subdivided acardia into four groups: acardius acephalus, acardius amorphus or anideus, acardius acormus, and acardius anceps or paracephalus (Table 120-1). Simonds and Gowen (1925) added a further subgroup: acardius myelacephalus.

Contemporary authors have considered these classifications meaningless because the pathogenesis is probably similar for all cases (Benirschke and Kim, 1973; Van Allen et al., 1983). Van Allen et al. recommended *twin reversed arterial perfusion sequence* to describe all acardiac fetuses. The TRAP sequence denotes a common pathophysiology for all forms and leads to an explanation of how a gradation of abnormalities can be produced (Van Allen et al., 1983). The fundamental requirement for the TRAP sequence is the development of arterial-to-arterial vascular anastomoses between the umbilical arteries of twins early in embryogenesis. The importance of vascular arterial anastomosis as the pathophysiology for acardia was first elucidated in 1879 by Ahlfeld. The embryo with the hemodynamic advantage becomes the pump twin. The pump twin retrogradely perfuses the other twin with deoxygenated blood along the umbilical artery/arteries to the iliac artery/arteries to the abdominal aorta. The lower limbs and abdominal organs supplied by the iliac arteries and

Table 120-1

Classification of the Conditions of Acardia

Acardius acephalus: This is the most frequent variety, responsible for 60% to 75% of cases (Lachman et al. 1980). The head is absent but the trunk and limbs are more or less well developed (Das 1902; Robie et al. 1989; Simonds and Gowen 1925).
Acardius acormus: This is a very rare type of acardia in which there is development of the fetal head only (Robie et al. 1989). The head is usually directly attached to the placenta via a cord arising in the cervical region (Das 1902; Kappelman 1944; Simonds and Gowen 1925).
Acardius amorphus or anideus: This type of acardia occurs in about 20% of cases (Lachman et al. 1980). The defect consists of an irregular, skin-covered mass of bone, muscle, fat, and connective tissue without the external form of a fetus (Das 1902; Kappelman 1944). The umbilical cord is inserted anywhere on the surface.
Acardius anceps or paracephalus: The head is poorly formed, but trunk and limbs are fairly well developed (Das 1902; Simonds and Gowen 1925). This form is sometimes included with the acephalus group.
Acardius myelacephalus: This form consists of an amorphous mass, with some development of one or more limbs (Kappelman 1944; Simonds and Gowen 1925).

abdominal aorta preferentially receive a better blood supply and usually develop better than the upper part of the body (Van Allen et al., 1983). TRAP occurs in monochorionic pregnancies, and previous theories of polar body fertilization to explain acardius in sex discordant twins have been discounted (Bieber et al., 1981; Fisk et al., 1996). In addition, the TRAP sequence is more common in monozygotic triplets than in monozygotic twins (James, 1977; Healey, 1994). Some authors have suggested a slight female preponderance in acardiac twins while other studies have not supported this idea (James, 1977; Healey, 1994).

The members of a TRAP sequence are known as the perfused twin and the pump twin. The perfused twin in a TRAP sequence is an example of the impact of vascular disruption on morphogenesis. Multisystem malformations, as well as unusual body form, are found in the perfused twin. Figure 120-1 illustrates the gradation of loss of normal body form ranging from an amorphous appearance to an individual with more severe abnormalities found in the upper part of the body. The malformations found in cases of acardia include growth abnormalities, partial or complete absence of the cranial vault, anencephaly, holoprosencephaly, absent or rudimentary facial features, absent or rudimentary upper and/or lower limbs, absent lungs and heart, gastrointestinal atresia, omphalocele, gastroschisis, and absent liver, pancreas, spleen, and kidneys (Van Allen et al., 1983). Of 33 acardiac fetuses with a known karyotype, 11 (33%) were abnormal (Healey, 1994). The karyotypic abnormalities included monosomy, trisomy, deletions, mosaicism, and polyploidy. The pattern of structural abnormalities found in the perfused twins with abnormal karyotypes is not appreciably different from those with normal karyotypes (Van Allen et al., 1983). Van Allen et al. suggested that the abnormal karyotype is not responsible for the malformation complex, but rather that it contributes to the discordant development between twins, increasing the likelihood of reversal of arterial blood flow if an anastomosis occurs.

The presence of an acardiac twin requires a "pump" twin to provide circulation for itself as well as its acardiac co-twin. In many cases the acardiac twin is almost equal in size to the normal twin (Figure 120-2). The pump twin is usually morphologically and genetically normal. In a review of 34 pump fetuses with a known karyotype, 3 (8.8%) were abnormal as a result of trisomy (Healey, 1994). The pump twin may show evidence of the physiologic consequence of fetal cardiac overload and congestive heart failure with hepatosplenomegaly. The principal perinatal problems associated with acardiac twinning are pump twin congestive heart failure, polyhydramnios, and preterm delivery (Moore et al., 1990).

The reported fetal/neonatal mortality in the pump twin is substantial ranging from 50% to 75% (Gillim and Hendricks, 1953; Napolitani and Schreiber, 1960; Van Allen et al., 1983; Moore et al., 1990; Sogaard et al., 1999). One factor thought to be contributing to the high perinatal mortality rate is the increased cardiac demands placed on the pump twin to perfuse the acardiac twin (Sullivan et al., 2003).

Premature delivery is another important factor determining the prognosis for the pump twin (Figure 120-2) (Van Allen et al., 1983; Moore et al., 1990; Healey, 1994). In one study where approximately 55% of acardiac pregnancies resulted in fetal or neonatal death, approximately one quarter of the pregnancies delivered after 36 weeks. Preterm delivery and the attendant long-term morbidities complicated the remaining quarter (Moore et al., 1990).

INCIDENCE

The incidence of the TRAP sequence is estimated as 1% of monozygotic twins, with birth estimates ranging from 1/35,000 to 1/50,000 births (Gillim and Hendricks, 1953; Napolitani and Schreiber, 1960; D'Alton and Simpson, 1995). Acardia was observed in 1 of 606 twin pregnancies, and the rate of twins was calculated at 1 in 86.5 births in the United States (Gillim and Hendricks, 1953). Van Allen et al. (1983) have suggested these figures to be a gross underestimate of

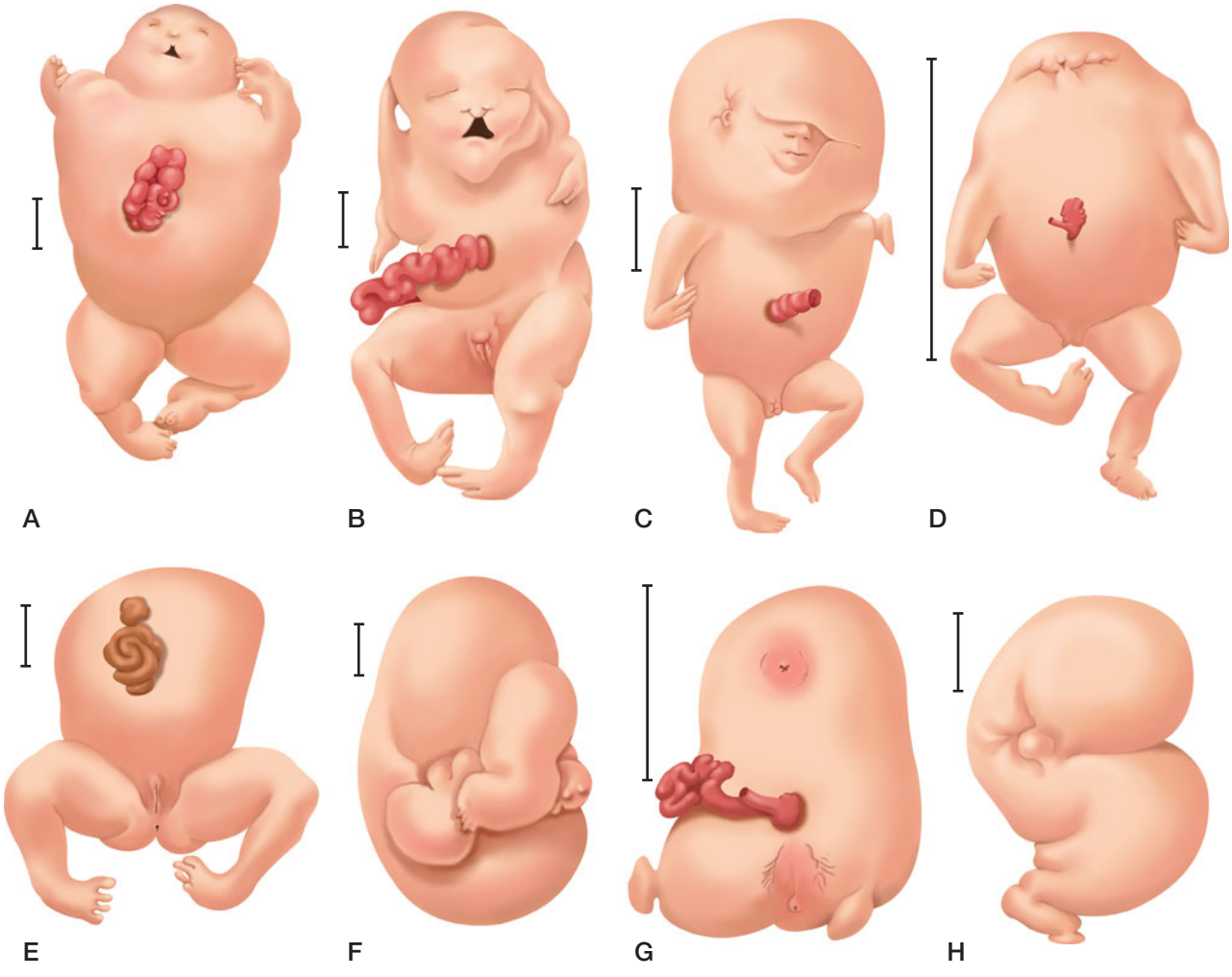

Figure 120-1 Gradation of loss of normal body form in acardia.

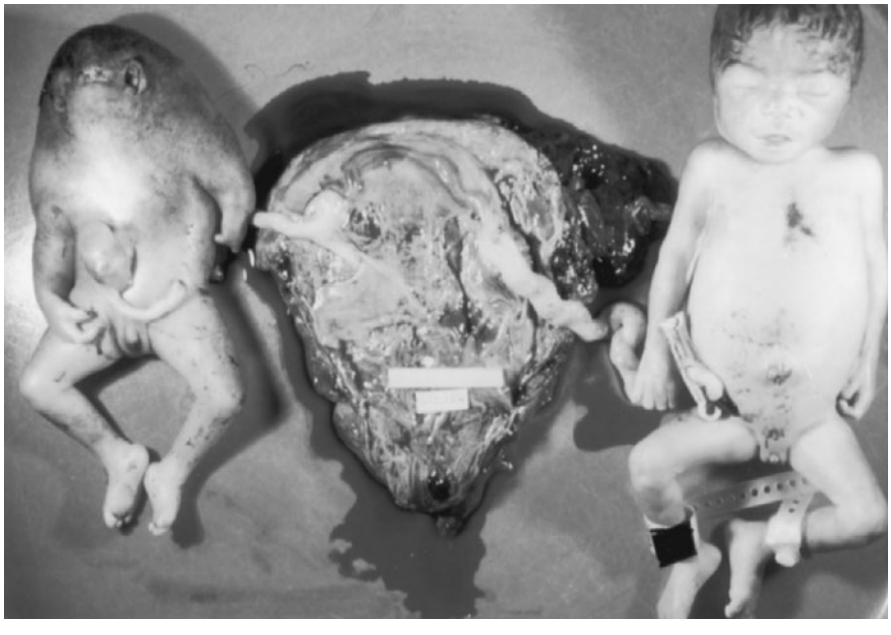

Figure 120-2 An acardiac fetus and its pump twin delivered at 26 weeks of gestation following spontaneous premature labor.

the true frequency of the TRAP sequence because most cases go unrecognized due to early pregnancy loss. In contrast, an analysis of data from the Eurocat Network (European Registration of Congenital Anomalies and Twins) gave a prevalence of acardia of 0.064 in 10,000 births, which is much lower than were previous estimates in the literature (Haring et al., 1993).

SONOGRAPHIC FINDINGS

Antenatal diagnoses of the TRAP sequence have been reported in the literature since 1980. Ultrasonographic features useful in the diagnosis of acardia include absence of normal cardiac structure and cardiac movement and variable structural abnormalities. Common structural abnormalities identified in the acardiac fetus include anencephaly, omphalocele, and absence of upper limbs. Most cases have edematous soft tissue, and large cystic hygromalike spaces are commonly identified in the skin (Mack et al., 1982).

The placentation is most commonly monochorionic diamniotic (74%), in which a thin membrane will be seen dividing the sac of the acardiac fetus from the pump fetus (Healey, 1994). Monoamnionicity is present in approximately 24% of cases (Healey, 1994). In exceptional cases, dichorionicity may be diagnosed (Healey, 1994). Polyhydramnios is common as are abnormalities in the umbilical cord or in its insertion (Dashe et al., 2001). The umbilical cord will demonstrate a single umbilical artery in approximately two thirds of cases, and in one-third the number of cord vessels will be normal (Healey, 1994). A velamentous insertion of the cord or a conjoined cord insertion may be present (Dashe et al., 2001).

Measurement of the acardiac twin should be performed, because the ratio of the weight of the acardiac twin to that of the pump twin is useful to predict pregnancy outcome. Because of the structural abnormalities, the biometric parameters of biparietal diameter, abdominal circumference, and femur length may not be available or reliable in an acardiac fetus. This problem of the antenatal determination of the acardiac twin's weight has been addressed by Moore et al. (1990). The dimensions and weights of 23 acardiac twins were used for the analysis. A second-order regression equation (weight [g] $= -1.66 \times$ length $+ 1.21 \times$ length^2) was computed and was predictive of acardiac weight with the use of its longest linear measurement ($r = 0.79$; $P < 0.001$; SEE $= 326$ g). When the actual and equation-predicted weights were compared, the mean error ($\pm$SE) in prediction was 240 ± 156 g. Careful Doppler examination of the acardiac fetus may also demonstrate reversal of flow in the umbilical artery of the acardiac fetus, with flow going from the placenta toward the acardiac fetus (Figure 120-3) (Benson et al., 1989; Malone and D'Alton, 2000).

The pump twin should have a detailed structural survey performed because trisomy has been reported in up to 9% of cases (Healey, 1994) and sonographic features typical

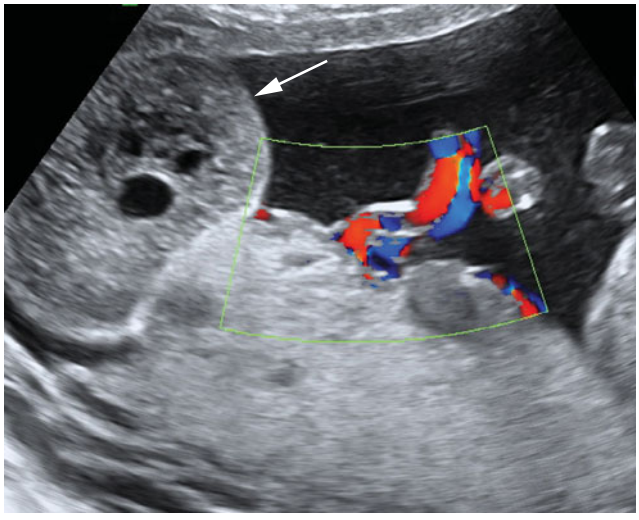

Figure 120-3 Prenatal ultrasound image of TRAP pregnancy at 22 weeks with amorphous mass (*arrow*) connected through placental surface vessel from umbilical cord of pump fetus.

of a trisomic fetus may be identified. Fetal echocardiography is helpful in detecting early signs of in utero congestive heart failure in the pump twin. Atrial and ventricular enlargement can be an initial feature of impending cardiac decompensation and can be measured using M-mode by obtaining a transverse view through the cardiac chambers (Allan, 1986; DeVore, 1987). The ventricular fractional shortening capacity can also be calculated using M-mode with the formula $(D - S)D \times 100$, where D is the diastolic and S is the systolic ventricular size. A low value is indicative of poor cardiac contractility. A pericardial effusion may be present and is a sign of congestive heart failure. Tricuspid regurgitation, demonstrated by Doppler studies of the tricuspid valve, is also a sign of congestive heart failure (Silverman et al., 1985; Shenker et al., 1988). Combined ventricular output (CVO) can be measured to determine if the pump twin is in a high output state. In TRAP sequence at a gestational age too early to determine CVO, Kinsel-Ziter et al. have demonstrated a good correlation of increased CVO with increased cardiothoracic ratio (Kinsel-Ziter et al., 2009).

Doppler studies should be performed in both the acardiac and pump twins. Verification of circulatory reversal by pulsed Doppler sonography of the acardiac twin can be documented with reversed direction of flow in the umbilical artery and vein (Pretorius et al., 1988; Sherer et al., 1989; Benson et al., 1989; Donnenfeld et al., 1991; Langlotz et al., 1991; Dashe et al., 2001). In one recent study by Dashe et al., between, 1990 and 1997, Doppler studies were performed in 6 monochorionic pregnancies complicated by the TRAP sequence. Pulsatile vessels in the umbilical vessels of the acardiac and pump twins were insonated. Reversal of flow was demonstrated in all cases. Resistive index values were calculated, and the difference in resistive index between the pump and acardiac twin was evaluated. In the acardiac twins, no

ratio of systolic to diastolic velocity or resistive index value was associated with a good or with a poor prognosis for the pump twin. In the pump twins, resistive index differences >0.20 between the pump and the acardiac twins were associated with good outcomes, while resistive index differences <0.05 were associated with poor outcomes (Dashe et al., 2001).

DIFFERENTIAL DIAGNOSIS

The acardiac fetus may be mistaken for an anencephalic fetus. The sonographic features of absent trunk region in addition to increased soft tissue in the body aid in the correct diagnosis (Billah et al., 1984).

The TRAP sequence has been mistaken for intrauterine fetal death (IUFD) of one twin in a multiple gestation (Malone and D'Alton, 2000). Evidence of growth in the "dead" fetus and a "twitching" noted on repeat ultrasound examination has allowed the diagnosis of an acardiac twin to be made (Cardwell, 1988). In a severely macerated fetus, the skeletal and visceral forms are more differentiated, and the soft-tissue edema is less advanced than in a case of acardia (Mack et al., 1982). The use of color flow Doppler can assist in differentiating between single IUFD in a co-twin and the TRAP sequence (Malone and D'Alton, 2000). Pulsed Doppler examination has been used to demonstrate reversed flow through the umbilical artery of the acardiac twin (Pretorius et al., 1988).

ANTENATAL NATURAL HISTORY

The principal perinatal problems associated with acardiac twinning are pump twin congestive heart failure, maternal polyhydramnios, and preterm delivery. The antenatal diagnosis of TRAP can be made only through sonographic examination and has been reported in the literature only since 1980. Large series of acardiac twins have attempted to identify factors prognostic of favorable outcome for the pump twin (Moore et al., 1990; Healey, 1994).

In the series of 49 cases reported by Moore et al. (1990), one third of fetuses were delivered before they were viable. In this study, viability was defined as delivery at or beyond 25 weeks of gestation. Of the potentially viable 33 cases, 4 (12%) ended in death of the pump twin in utero. The overall perinatal mortality was 55% and was primarily associated with prematurity (Table 120-2).

Polyydramnios was a major maternal complication, occurring in 46% of all acardiac pregnancies, and it was strongly associated with preterm labor and congestive heart failure in the pump twin. Eighty-two percent of patients with polyhydramnios experienced preterm labor requiring hospital admission and treatment, as compared with 22% of pregnancies with normal amniotic fluid ($P < 0.01$). Polyhydramnios was observed in 78% of pump twins with congestive heart failure as compared with 13% of those in whom congestive heart failure was not confirmed ($P < 0.001$). The perinatal outcome was strongly related to the ratio of the weight of the acardiac twin to that of the pump twin. The mean overall ratio of the twin weights was 52 ± 42%. The twin weight ratio was more than 70% in 25% of cases. When this characteristic was present, the incidence of preterm delivery was 90%, polyhydramnios 40%, and congestive cardiac failure in the pump twin 30%, as compared with 75%, 30%, and 10%, respectively, when the ratio was less than 70% (Moore et al., 1990).

In the series by Healey (1994), of 5 cases at Monash Medical Centre and a review of 184 case reports in the literature from 1960 to 1991, the overall perinatal mortality for the pump fetus was 35% in twins and 45% in triplets. Factors associated with a significant increase in perinatal mortality for the pump fetus included delivery before 32 weeks of gestation, the acardius anceps form of acardia, and the presence of arms, ears, larynx, trachea, pancreas, kidney, or small intestine in the acardiac fetus.

Nonetheless, a more recent study questioned the poor prognosis associated with pregnancies complicated by TRAP

Table 120-2

Perinatal Complications of 49 Pregnancies with Acardiac Twinning

Delivery mode	
Spontaneous abortion	18%
Elective	14%
Cesarean section, all cases	38%
Cesarean section, potentially viable cases	58%
Pump twin	
Male/female	57%/43%
Malpresentation	29%
Major structural anomaly	9%
Hydramnios	46%
Congestive heart failure	53%
Previable	32%
Liveborn	59%
Premature (<37 wk)	35%
Gestational age at delivery (wk)	29 ± 7
Birth weight (g)*	
Acardiac	651 ± 571
Pump twin	1378 ± 1047

** Mean ± SD.*

Source: Moore TR, Gale S, Benirschke K. Perinatal outcome of 49 pregnancies complicated by acardiac twinning. Am J Obstet Gynecol. 1990;163:907-912.

and explored the role of expectant management (Sullivan et al., 2003). Ten cases of antenatally diagnosed acardiac twins delivered between 1994 and 2001 in one community were evaluated. All cases were managed expectantly. Nine women delivered a healthy pump twins. There was one neonatal death. The mean gestational age at delivery was 34.2 weeks and the mean weights of the pump and acardiac twins were 2279 g and 1372 g, respectively. The authors concluded that neonatal mortality of pump twins in antenatally diagnosed acardiac twin pregnancies may be considerably less than reported, and expectant management with close antepartum surveillance may be an option.

MANAGEMENT OF PREGNANCY

The goal of antepartum management of a pregnancy complicated by the TRAP sequence is to maximize outcome for the structurally normal pump twin. Management of acardiac twin gestations is controversial. When the diagnosis is made, the gestational age should be documented by maternal history and standard biometric measurements of the pump fetus. The high and low risk factors for perinatal mortality in the pump fetus must be evaluated through sonographic examination. In the absence of poor prognostic features (twin weight ratio >0.70, elevated CVO, increased C:T ration, congestive cardiac failure, polyhydramnios), expectant management with serial sonographic evaluation is reasonable (Malone and D'Alton, 2000). Additional factors that place the pregnancy at high risk for perinatal mortality include features of acardius anceps demonstrating the presence of arms, ears, larynx, trachea, pancreas, renal tissue, and small intestine. Rapid growth of the acardiac twin may also be a sign of poor outcome (Brassard et al., 1999).

Features that indicate a lower risk include features of acardius amorphous with absence of arms, legs, brain, esophagus, trachea, and omphalocele (Healey, 1994). Karyotyping of the pump twin should be offered because as many as 9% of pump twins have an abnormal karyotype (Healey, 1994).

Various techniques have been used to interrupt the vascular communication between the twins in an effort to improve outcome of the normal pump twin. These methods have included hysterotomy with physical removal of the acardiac twin, ultrasound guided injection of thrombogenic materials into the umbilical circulation of the acardiac twin, ligation of the umbilical cord of the acardiac twin under fetoscopic guidance, and intrafetal radiofrequency cord ablation (Simpson et al., 1983; Van Allen et al., 1983; Robie et al., 1989; Ash et al., 1990; Porreco et al., 1991; Holzgreve et al., 1994; Quintero et al., 1994; Challis et al., 1999; Tsao, 2002; Livingston et al., 2007). Steroids should be given if delivery is expected between 24 and 34 weeks of gestation (NIH Consensus Development Panel, 1995). Preterm labor should be suppressed with tocolytic agents.

Delivery at a tertiary care hospital is recommended because of the risk of preterm delivery and congestive cardiac failure in the pump twin. The vaginal route is the preferred mode of delivery. The indications for cesarean include the standard obstetric reasons. In Moore et al.'s series, abnormal presentation and fetal distress necessitated cesarean delivery in more than half of the potentially viable pregnancies.

Medical management with maternal administration of digoxin or indomethacin has been reported, but there are no significant case series on these management strategies. The use of maternal digitalization to treat cardiac failure in the pump twin was reported by Simpson et al. in 1983. Marked edema of the trunk in the normal twin was present. Fetal ascites, pleural effusion, or cardiomegaly was not demonstrated. Serial ultrasound examinations demonstrated resolution of the edema and continued normal growth of the viable fetus. Delivered at 34 weeks, the normal twin weighed 1860 g. The acardiac twin weighed 1810 g. No subsequent reports of this digoxin therapy for acardia have been reported.

Ash et al. (1990) reported the use of indomethacin in an acardiac pregnancy complicated by polyhydramnios at 21 weeks. No evidence of cardiac failure was visualized in the pump twin. Indomethacin, 50 mg daily, was given to treat the symptomatic polyhydramnios because of the high risk of premature labor. The indomethacin was continued for 8.5 weeks. Oligohydramnios at 34 weeks prompted induction of labor, and spontaneous vaginal delivery occurred. The normal twin weighed 1865 g at birth, and the acardiac twin weighed 785 g (Ash et al., 1990).

FETAL INTERVENTION

Many invasive procedures have been described with the goal of interrupting the umbilical circulation of the acardiac twin. There is a great deal of controversy in the literature concerning which cases are candidates for such procedures. It has been recommended that invasive procedures be performed only after heart failure has developed (Platt et al., 1983). Some have recommended surgical intervention only after medical therapy has failed (Ash et al., 1990). Others have suggested intervening before heart failure is present in the pump twin (Platt et al., 1983). Others consider the diagnosis of TRAP the indication for fetal intervention (Tsao et al., 2002).

Various percutaneous procedures have been described to interrupt the umbilical circulation in acardiac twins, including (1) insertion of a thrombogenic coil into the recipient twin's umbilical cord, (2) injection of silk soaked in alcohol into the cord, (3) injection of absolute alcohol into the cord, (4) fetoscopic ligation of the acardiac fetus's cord, (6) bipolar forceps cautery of the acardiac fetus's cord, (7) thermocoagulation of the aorta of the acradiac fetus, and (8) intrafetal radiofrequency thermablation (Porreco et al., 1991; Holzgreve et al., 1994; Quintero et al., 1994; Sepulveda et al., 1995;

Arias et al., 1998; Rodeck et al., 1998; Challis et al., 1999; Tsao et al., 2002; Livingston et al., 2007).

Injection of coils or slerosants is generally no longer performed because of the unreliability in achieveing complete occlusion. Fetoscopic cord ligation may be associated with a failure rate of 10% together with a 30% risk of preterm rupture of membranes (Challis et al., 1999). Laser and cautery options have the advantage of generally requiring one ccess port in the uterus and therefore may be associated with less morbidity. No comparative studies are available, however, to suggest one optimal method of selective termination in this setting.

Robie et al. (1989) reported a case of selective delivery by hysterotomy of an acardiac acephalic twin fetus at 22.5 weeks of gestation with the subsequent delivery of the normal twin at 33 weeks of gestation. Fries et al. (1992) subsequently reported 5 cases of selective delivery in 1992. In one case, placental abruption occurred shortly after the procedure, leading to fetal death. Two cases delivered at 35 weeks of gestation, and the remaining 2 delivered at 27 and 28 weeks.

Porreco et al. (1991) described the insertion of a helical metal coil under sonographic guidance to induce thrombosis in the umbilical artery of the acardiac twin at 24 weeks. The co-twin delivered at 39 weeks and had a normal course.

Quintero et al. (1994) described a percutaneous fetoscopic procedure that treated this condition at 19 weeks of gestation and was followed by the birth of a normal twin at 36 weeks of gestation. A further case was reported by McCurdy et al. (1993). A trial of maternal digoxin administration failed and was followed by a fetoscopic ligation of the acardiac twin's cord at 19 weeks. Ultrasound examination on the first postoperative day indicated death of the pump twin.

Holzgreve et al. (1994) injected multiple pieces of silk suture soaked in 96% alcohol into the umbilical cord of an acardiac twin at 21 weeks of gestation. This resulted in immediate interruption of flow in the cord and the ultimate delivery at term of a 2780-g healthy newborn. The advantage of this approach in comparison to umbilical cord ligation is the use of a much thinner needle. Less operative time is required, and there is no need for general anesthesia (Holzgreve et al., 1994).

Other methods of interrupting the circulation in the acardiac twin involve direct coagulation of the umbilical vessels or the aorta, using either laser photocoagulation or diathermy themocoaglulation. Laser photocoagulation of umbilical vessels using a neodymium yttrium aluminum garnet laser has been successfully reported, although this approach appears less likely to be successful when performed after 24 weeks' gestation (Arias et al., 1998). This may be because umbilical vessels are too large to adequately photocoagulate when the gestational age is greater than 24 weeks. Thermocoagulation of the aorta of the acardiac fetus using diathermy via a wire passed through an 18-gauge needle has been successfully reported in four cases at 24 weeks' gestation or less (Rodeck et al., 1998). The advantages of this latter approach include avoiding the need for microendoscopic instruments or skills, and avoiding the difficulties in identifying the target umbilical cord. Intrafetal radiofrequency ablation (RFA) has also been utilized in cases of TRAP. RFA causes thermal injury with high frequency radiowaves that denature proteins and initiate cell death through coagulative necrosis. In a series of 23 pregnancies complicated by TRAP and managed with RFA, there was a 91% survival rate with a mean gestational age of 35 weeks at delivery (Lee et al., 2004). Livingston et al. reported a 95% survival rate with an ultrasound-guided technique using a 17-gauge radiofrequency DePrest needle (Boston Scientific) with a mean gestational age at delivery of 36 weeks in a series of 26 patients. Survival rates of 85% have been reported with fetoscopic cord coagulation likely as a consequence of two ports being required (Lewi et al., 2006).

It has been suggested that successful interruption of the acardiac circulation after 24 weeks gestation may require a more invasive approach, such as fetoscopic ligation of the umbilical cord (McCurdy et al., 1993; Quintero et al., 1994; Arias et al., 1998). However, the series reported both by Tsao and Livingston included patients successfully treated after 24 weeks' gestation.

TREATMENT OF THE NEWBORN

A neonatologist should attend the delivery. In Moore et al.'s (1990) series, admission to a newborn intensive care unit was required in 41% of the pregnancies and 59% of those reaching viability. Five of 29 liveborn pump twins died during the newborn period. There is little information in the literature on the neonatal course of the pump twin. The main problems for the pump twin include complications of prematurity and congestive heart failure (Van Allen et al., 1983; Moore et al., 1990).

Other frequent neonatal findings include massive hepatosplenomegaly, ascites with hypoplasia of abdominal musculature, edema, and hypoalbuminemia due to inadequate liver synthesis of albumin (Van Allen et al., 1983).

Respiratory assistance as well as support of myocardial function with inotropic medication may be required. Early administration of surfactant therapy is indicated when premature delivery at less than 30 weeks of gestation is anticipated. Postnatal consultation with a pediatric cardiologist and echocardiography are recommended.

LONG-TERM OUTCOME

There is no information in the literature concerning long-term outcome for the pump twin. Considerations for the long-term prognosis must include the degree of prematurity, the severity of the neonatal course, and the degree of congestive heart failure.

GENETICS AND RECURRENCE RISK

Estimates of the recurrence risk of acardiac twin pregnancy are on the order of 1 in 10,000 (Van Allen et al., 1983). This recurrence risk is calculated from the recurrence risk for monoamniotic twinning, which is 1% (Myrianthopoulos, 1970), multiplied by the frequency of the occurrence of the TRAP sequence, which is approximately 1% of all monozygous twins (Gillim and Hendricks, 1953; Napolitani and Schreiber, 1960).

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121 CHAPTER

Conjoined Twins

Key Points

- Conjoined twins are rare, and they may be joined at a variety of sites. The nomenclature in use to describe conjoined twins is derived from the most prominent site of conjunction.
- The most common type of conjoined twins include thoracopagus, xiphagus or omphalopagus, pygopagus, ischiopagus, and craniopagus.
- Conjoined twins can be diagnosed with ultrasound examination, and suspicion should arise when a dividing membrane cannot be visualized.
- Congenital anomalies are common even in organs that are not shared.
- The antenatal natural history of conjoined twins is not well known due to the fact that cases are rare and many patients elect termination.
- Successful surgical separation is possible, and the prognosis for the surgery depends on the type of conjunction.

CONDITION

Although a rare event, the birth of conjoined twins has always fascinated both the physician and the layperson. The first well-documented case was reported in A.D. 1100 and described the Biddenden maids who were joined at the hips and shoulders. In 1134, when the maids had lived together for 34 years, Mary was suddenly taken ill and died. Eliza, her sister, died six hours later (Bondeson, 1992). The most famous conjoined twins were Eng and Chang Bunker, born in Siam in 1811. The inappropriate term "Siamese twins" was coined by P.T. Barnum, who promoted the exhibition of Chang and Eng Bunker. An early medical description of these most famous conjoined twins, who lived unseparated until they died at age 63, can be found in the works of Warren (1829). Many conjoined twins are stillborn. In one series 40% of conjoined twins were stillborn and an additional 35% survived only 1 day (Edmonds and Layde, 1982). Konig recorded the first successful separation of conjoined twins in 1689. These twins were joined at the umbilicus, and the division was accomplished by necrosing the band of tissue between the two children with a constricting ligature. Kiesewetter (1966) reviewed 24 surgical attempts at separation that appeared in the literature from 1689 to 1962. There are now over 100 reports of successful separations in the medical literature or lay press. Conjoined twins may be joined at a variety of anatomic sites,

and classifications have been developed to describe all the possibilities (Guttmacher and Nichols, 1967). The nomenclature in use clinically is derived from the most prominent site of conjunction. The common twin types include thoracopagus, xiphopagus or omphalopagus, pygopagus, ischiopagus, and craniopagus.

Thoracopagus is the most common type of conjoined twin and with omphalopagus (or xiphopagus) represents about 75% of cases reported (Malone and D'Alton, 2000). The two individuals lie face to face and share a common sternum, diaphragm, and upper abdominal wall from xiphoid to umbilicus. An extensive review of the anatomy of thoracopagus twins has been published by Nichols et al. (1967). In data from 32 cases, 75% have conjoined hearts. Because of the abnormal ventricular arrangements and associated anomalies of the great arteries and veins, successful surgical division is usually not possible. In about half of these cases, the intestinal tracts are also joined. Occasionally, the esophagus and stomach are single, but usually the union starts in the distal duodenum and ends in a pouch at the site of a Meckel diverticulum. The biliary tree is joined in 25% of cases.

Xiphopagus or omphalopagus twins usually considered a subgroup of thoracopagus, also face one another and usually have the least complicated union of all conjoined twins. They are joined at the anterior abdominal wall from xiphoid to umbilicus. The peritoneal cavity of one communicates with that of the other, but the upper intestinal tracts are usually separate. A bridge of liver connects the infants in the majority of cases. Evaluation of the single umbilical cord in twins joined at the umbilicus has revealed the presence of two to seven umbilical vessels. An omphalocele is often present at the umbilical cord insertion.

Pygopagus twins represent about 20% of cases. They are joined at the buttocks and perineum, and face away from each other. A significant length of sacrum may be fused, and as a result, the twins often share the sacral spinal canal. A single lower rectum and anus is common, and often the lower genital tract and external genitalia are fused.

Ischiopagus accounts for 5% of cases. These twins are united at a single bony pelvis. Four normal lower extremities (ischiopagus tetrapus) may be attached to the pelvis, but often two of the four lower extremities are fused into one malformed limb (ischiopagus tripus). The intestinal tracts usually join at the terminal ileum, which empties into a single colon.

Craniopagus is the least common type of conjoined twins and accounts for 2% of cases. There is always fusion of the skull, and often the twins share large dural sinuses and vascular structures. A classification into partial or total forms, having a junction at brow, vertex, or parietal bone, has been devised by O'Connell (1976). In the partial forms, the brains are separated by bone or dura and each brain has separate leptomeninges. In the total form, the brains of each twin are connected, or they are separated only by arachnoid. Separation of the total type is extremely difficult, and feasibility is often determined by the presence of a superior sagittal sinus for each brain that will provide adequate venous drainage.

INCIDENCE

The exact incidence of conjoined twins is not known, but estimates have varied from 1 in 25,000 to 1 in 80,000 births (Siegel, 1950; Freedman et al., 1962). Other reports on the frequency of conjoined twinning show the incidence to be from 1 in 2,800 to 1 in 200,000 (Hanson, 1975). Three conjoined twins over a 10-month period among residents of South Glamorgan with approximately 5400 deliveries a year is the highest reported incidence of conjoined twinning so far described (Rees et al., 1993). In Rudolph et al.'s (1967) review, about 70% of conjoined twins were female. Maternal age and parity do not appear to be factors that influence the occurrence of this type of twinning. However, use of assisted reproductive techniques may result in an increased risk for conjoined twins (Goldberg et al., 2000).

SONOGRAPHIC FINDINGS

The first report of conjoined twins diagnosed ultrasonographically was in 1977 (Fagan, 1977). Since then prenatal diagnosis has been reported many times and can be made in the first trimester (Figure 121-1) (Hill, 1997; Hubinot et al, 1997; Lam et al, 1998; Maymon et al, 1998). Three-dimensional ultrasound examination may be a valuable adjunct to two-dimensional ultrasound examination when diagnosing conjoined twins (Figure 121-2) (Johnson et al., 1997; Bega et al., 2000; MacKenzie et al., 2004). A suspicion of conjoined twins should arise when a dividing membrane cannot be visualized. van den Brand et al., (1994) have suggested nine sonographic

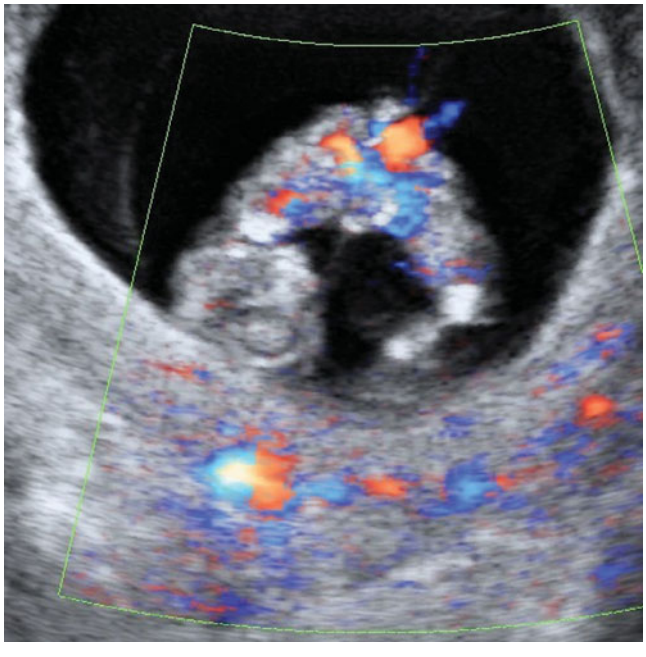

Figure 121-1 First trimester ultrasound demonstrating bifid appearance of the fetal pole consistent with a diagnosis of conjoined twins.

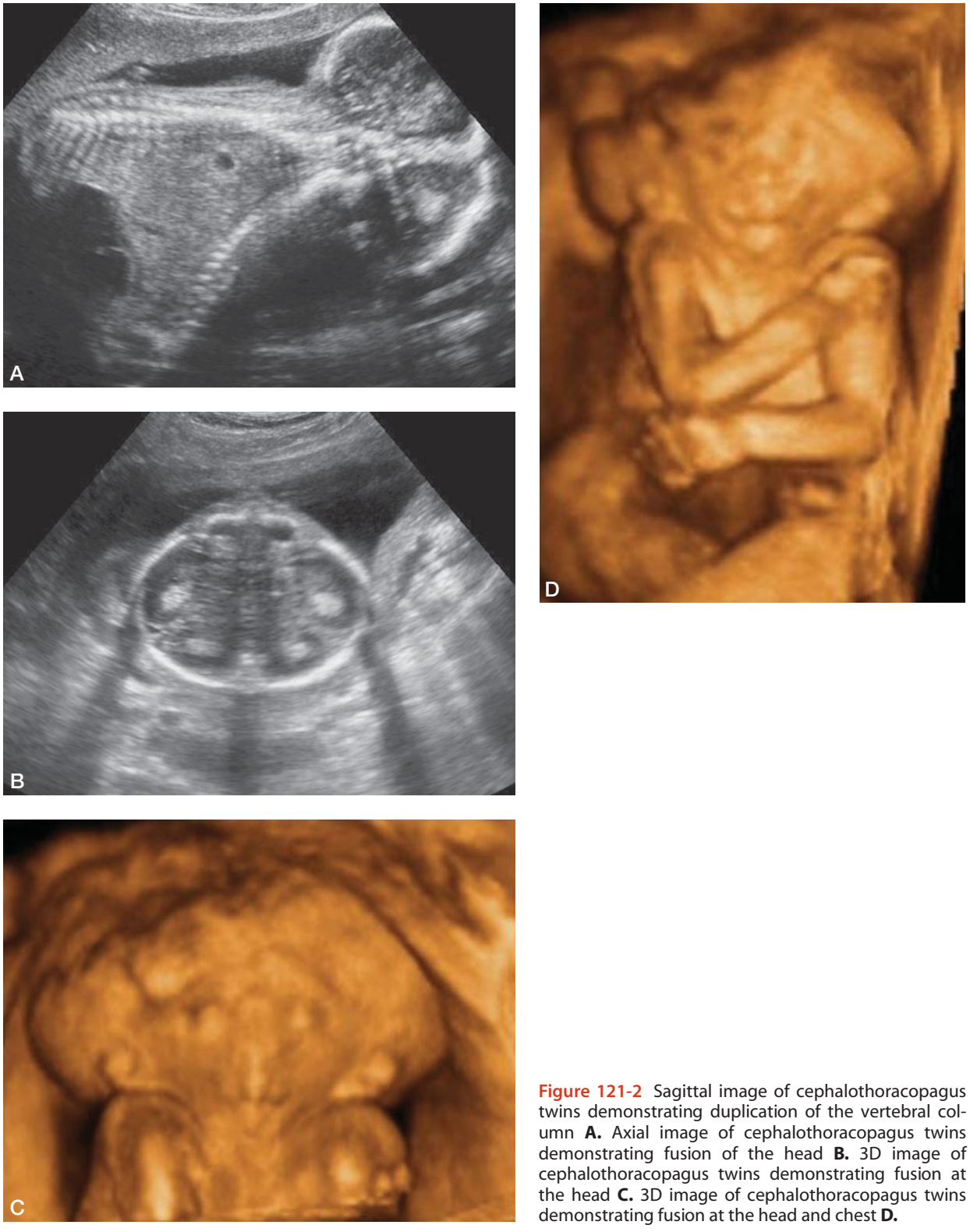

Figure 121-2 Sagittal image of cephalothoracopagus twins demonstrating duplication of the vertebral column **A.** Axial image of cephalothoracopagus twins demonstrating fusion of the head **B.** 3D image of cephalothoracopagus twins demonstrating fusion at the head **C.** 3D image of cephalothoracopagus twins demonstrating fusion at the head and chest **D.**

findings to diagnose conjoined twins (Table 121-1). Polyhydramnios is present in 75% of thoracopagus twins (Harper et al., 1980). Congenital anomalies are common in conjoined twins, even in the unshared organs. Congenital heart disease, renal and genitourinary abnormalities, intestinal duplication, and omphalocele have all been reported.

Ultrasound examination has been found useful in describing the extent of joining of the cardiovascular system in thoracoabdominally joined twins. Sanders et al. (1985) have reviewed their experience in four pairs of thoracoabdominally joined twins and demonstrated that prenatal echocardiography correctly diagnosed major cardiac anomalies, although

Table 121-1

Sonographic Findings used to Diagnose Conjoined Twins

Bifid appearance of the first trimester fetal pole
Lack of a separating membrane between the twins
Inability to separate the fetal bodies
Detection of fetal anomalies
More than three vessels in the umbilical cord
Heads at same level and body plane
Spines unusually extended
Extremities in unusual proximity
Fetuses do not change position relative to one another after movement or manipulation, or with passage of time

Source: van den Brand SFJJ, Nijhuis JG, van Dongen PWJ. Prenatal ultrasound diagnosis of conjoined twins. Obstet Gynecol Surv. *1994;49: 656-662.*

they missed certain important features because of their inability to detect abnormal pulmonary venous connections. In addition, the investigators concluded that conjoined twins were more easily and thoroughly examined in utero because more views could be obtained as compared with the postnatal examination, which is hampered by the conjunction and the associated omphalocele. With the use of ultrasound equipment it is always possible to detect whether bone tissue is interposed between the two brains. However, it is impossible to detect if the two cerebral hemispheres are joined or separated by either the dura or pia mater. Color flow mapping may be useful in craniopagus twins to determine vascular connections (Loverro et al., 1991).

DIFFERENTIAL DIAGNOSIS

There are several pitfalls for the sonographic diagnosis of conjoined twins. Caution should be exercised in making a definite diagnosis of conjoined twins at less than 10 weeks of gestation because false-positive diagnoses have been documented (Usta and Awwaad, 2000; Weiss and Devine, 2002) Three-dimensional ultrasonography may help with the diagnosis (Babinski et al., 1999). Later in gestation, inseparable fetal skin contours must be a persistent finding at the same anatomic level to avoid the false-positive diagnosis of conjoined twins (Barth et al., 1990). Even discordant presentation does not exclude the diagnosis, particularly in omphalopagus twins. The joining bridge may be sufficiently small to allow for rotation of the twins. Finally, with severe conjoining, twins may be melded into a conglomerative tissue mimicking a single pregnancy (Weingast et al., 1984). The diagnosis of conjoined twins does not exclude the presence of other problems unique to twinning. For example, many cases have been reported of conjoined twins coexisting in triplet pregnancies (Sanjaghsaz et al., 1998; Sepulveda et al., 2003).

ANTENATAL NATURAL HISTORY

Little is known about the antenatal natural history of conjoined twins. Polyhydramnios has been reported in 75% of thoracopagus twins (Harper et al., 1980). In the older obstetric literature on the subject, stillbirth occurred in approximately 20% to 40% of cases (Harper et al., 1980). In one recent series of 14 sets of prenatally diagnosed conjoined twin pregnancies from a single center, the combination of prenatal ultrasonography, echocardiography, and magnetic resonance imaging accurately defined the anatomy in all cases. In this series, 3 pregnancies were terminated, 1 resulted in intrauterine demise, and of the remaining 10 pregnancies delivered after viability, 5 individual fetuses survived (Mackenzie et al., 2002). Most of the contemporary literature has concentrated on the subject of surgical separation.

MANAGEMENT OF PREGNANCY

When the diagnosis of conjoined twins is made before viability, the option of pregnancy termination should be discussed with the parents. Since mortality and the ability to separate thoracopagus twins is directly related to the union of two hearts and associated cardiac abnormalities, echocardiography is recommended in all cases and may be of significant value to parents faced with the decision of whether to terminate the pregnancy. Although sonography is a standard technique for evaluation of fetal anatomy, its ability to characterize certain tissues is limited.

Three dimensional ultrasound and magnetic resonance imaging (MRI) improves soft-tissue definition and has been reported to be of additional use in the antenatal evaluation of conjoined twins (Figure 121-3). Zoppini et al. (1993) used MRI following fetal paralysis with pancuronium and identified bowel-to-bowel anastomosis. Prior to the MRI, a solution of gadolinium DTPA was also injected into the stomach of one twin to aid in the diagnosis of bowel-to-bowel anastomosis. Early prenatal diagnosis and precise character relation of conjoined twins are essential for optimal obstetric and postnatal management. Vaginal delivery may be possible for preterm conjoined twins for which postnatal survival is unlikely. Near term cesarean delivery is the delivery method of choice for conjoined twins to maximize survival and prevent birth trauma. Dystocia occurs frequently (Nichols et al., 1967), and in omphalopagus twins it has been reported in

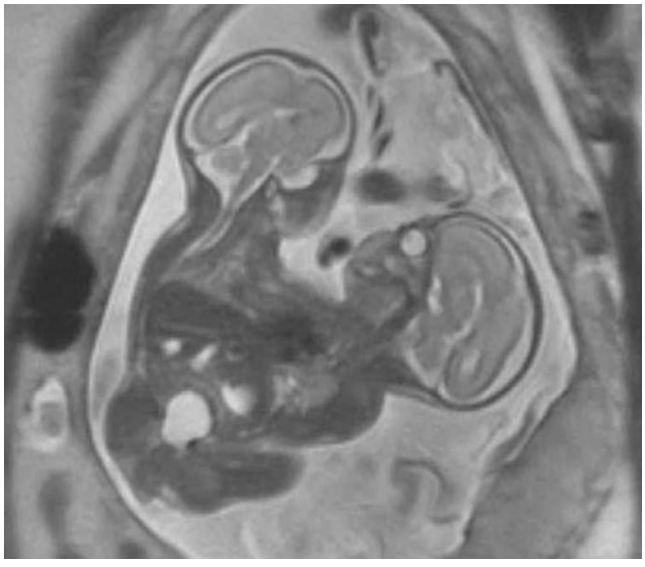

Figure 121-3 Prenatal MRI of thoracopagus twins joined at the chest and abdomen. Note the presence of a single heart, liver, and bladder.

36% of cases (Harper et al., 1980). Delivery at a tertiary care center is recommended for optimal neonatal intensive care and pediatric surgical support.

FETAL INTERVENTION

There are no fetal interventions for conjoined twins.

TREATMENT OF NEWBORN

Except for life threatening emergencies that must be treated by immediate separation of the twins, surgery should be delayed until an accurate assessment of shared structures is completed (Filler, 1986). Table 121-2 lists the important diagnostic studies, the structures that each study will best evaluate, and the type of twin that requires such a study. Comprehensive evaluation of the cardiovascular system is necessary in all thoracopagus twins (Figure 121-4). These studies should be obtained immediately after birth because of the high likelihood of an abnormality in one or both twins. One of the most important factors in prognosis is the degree of separation of the two hearts. Of the conjoined twins who are born alive, the

Table 121-2

Most Useful Diagnostic Studies for Evaluating Different Types of Twins

Test	Evaluation of	Type of Union in Twin
MRI	Nervous system	Cranial and thoracoabdominal
CT scan	Bony unions, kidneys, urinary tract, central nervous system	All types
Ultrasound	Liver, biliary system, pancreas	Thoracoabdominal
Plain films	Extremities	Ischiopagus
Radionuclide scans	Liver, spleen, biliary tract	Thoracoabdominal
Cystography, urethrography	Bladder, urethra	Abdominal and pelvic
Barium studies of gastrointestinal tract	Small bowel, colon	Abdominal and pelvic
Angiography	Heart and major blood vessels	Thoracoabdominal and cranial
Echocardiography*	Heart and great vessels	Thoracoabdominal
Electrocardiography		
Cardiac catheterization		

* *Prenatal test appears to be especially useful.*
Source: Filler RM. Conjoined twins and their separation. Semin Perinatol. *1986;10(1):82-91.*

Figure 121-4 Postnatal appearance of thoracopagus twins.

potential long-term survivors fall into two groups. The first group involves children who thrive despite being joined. Pygopagus, ischiopagus, and xiphopagus twins usually fall into this category. In this group there is sufficient time to evaluate organ sharing and to plan operative separation. Separation in these children should probably be delayed several months. The advantages of waiting are that the infants will be larger, important congenital anomalies not obvious at birth will have become apparent, and the risks of surgery and anesthesia should be less. In Filler's (1986) experience with four separations, delay was clearly beneficial. The second group involves twins whose lives are threatened because of the conjunction or coexistent congenital abnormalities. Emergency surgery with or without separation may be required before appropriate diagnostic studies can be completed. Urgent surgery is indicated in three clinical situations: (1) when the existence of one twin threatens the life of the other (Graivier and Jacoby, 1980); (2) when a potentially correctable life-threatening anomaly is present (e.g., severe congenital heart disease or intestinal obstruction); and (3) when surgical intervention is necessary for a traumatic injury to the bridge of tissue and underlying viscera joining the twins.

SURGICAL TREATMENT

Many descriptions of surgical procedures to separate different types of conjoined twins appear in the literature (Koop, 1961; Kiesewetter, 1966; DeVries, 1967; Gans et al., 1968; Kling et al., 1975; James et al., 1985; Kotrikova, 2004). It is beyond the scope of this review to describe the individual operations in detail. However, the surgeon is faced with two general considerations. First, the surgical team must try to separate the shared structures, leaving each child with functional residual organs and limbs whenever possible. Second, the skin, muscle, and bony defect at the site of conjunction must be closed after separation is completed. Closure of defects can be relatively simple when the defect is small, as in the case of omphalopagus twins. When the defect is large, closure can be extremely difficult. In cases of large defects, a flap of skin and muscle may be available for coverage. Silastic tissue expanders have been used to provide additional skin and muscle to aid closure in several cases (Filler, 1986). Teflon mesh and acrylic prostheses have also been described (Wilson, 1957; DeVries, 1967). It is essential to have a coordinated approach of the operating team, consisting of duplicate anesthesiologists, surgeons, and nursing personnel. The anesthesia team should be responsible for setting up methods of physiologic monitoring (Simpson et al., 1967; James et al., 1985). Existing operating tables may need to be modified as the standard tables are not properly designed for the separation of conjoined twins. The modifications required will depend on the type of separation (Savickis, 1984).

Significant ethical considerations arise in cases in which it is not possible to achieve separation without sacrificing the life or the quality of the life of one of the two twins (Pepper, 1967; Raffensperger, 1997; Annas, 2001).

LONG-TERM OUTCOME

The prognosis for surgery depends on the type of conjunction. The results for omphalopagus and xiphopagus twins are particularly good. Even over 30 years ago, in a review of 11 sets of omphalopagus twins, 19 of the 22 children survived (Nichols et al., 1967). When omphalocele is present in

this type of twinning, the prognosis appears to be somewhat worse. Votteler (1986) reviewed the results of separation in seven sets of omphalopagus twins with an associated omphalocele treated between 1963 and 1981. The omphalocele had ruptured in four sets. One twin in three of the four sets died, and one twin from two of the three sets with an intact omphalocele also died.

With the exception of a single case of a successful separation of a set of twins who shared a right atrium (Synhorst et al., 1979), thoracopagus twins sharing hearts have not survived. Survival is more frequent in those sharing a single pericardium (Edmonds and Layde, 1982). The most common causes of death in thoracopagus twins include cardiac abnormalities, infections, and respiratory failure. In many failures, closure of the chest wall has contributed to the poor outcome, either because of tight closure that restricts chest motion or a defect in the sternum that allows paradoxical respiratory motion (Filler, 1986). The outcome for craniopagus twins relates to whether the union is total or partial (Votteler, 1986; Bucholz et al., 1987). In a review of 21 cases of craniopagus, temporoparietal and occipital junctions had a worse outcome than frontal and parietal junctions (Bucholz et al., 1987). In the Votteler series, 50% had residual neurologic abnormalities, whereas in the Bucholz series only one of nine had severe neurologic deficit. The prognosis appears better when surgery is performed during the neonatal period and when craniopagus twins are separated in stages rather than in one procedure (Bucholz et al., 1987).

Successful separations of pygopagus twins have been reported by Koop (1961), Votteler (1982), Cloutier et al. (1979) and Fowler et al. (1999). The prognosis is usually good for pygopagus twins mainly because the joined structures are not essential for life. In most reported cases, both twins have survived (Filler, 1986).

The separation of ischiopagus twins is usually difficult because most of the abdominal viscera are joined. There is only one pelvis and often only three lower extremities. Votteler compiled a list of 12 ischiopagus separations from 1955 to 1981 in which one or both ischiopagus twins survived. Filler (1986), Ross et al. (1985), and Grantzow et al. (1985) have successfully separated four other sets. Albert et al. (1992) further reported on the orthopedic management of four cases treated at Children's Hospital in Philadelphia. Six of the eight infants survived. Significant postseparation orthopedic problems persisted in all of the successful separations. These included but were not limited to hip flexures, clubfoot, recurrent dislocated hip, one functional deformed foot, and quadriceps contractures. In addition to orthopedic problems, successfully separated ischiopagus twins require long-term rehabilitation because of gynecologic, urologic, and intestinal disabilities. In Filler's (1986) series of three cases of ischiopagus twins, one set at age 17 used a prosthesis for an absent lower extremity, and each had a colostomy. In a second set, at age 4 each child had a colostomy and an artificial limb. Because they shared a single set of male genitalia, one child is being raised as a boy and the other as a girl. In a further set reported at age 1.5 years, each had a colostomy, a suprapubic bladder catheter, and normal lower extremities (Filler, 1986).

It is interesting to note that while pregnancy is not recommended, it can occur in female survivors following successful separation. There are two case reports of separated conjoined twins having successful pregnancies themselves (Shan and Chazotte, 1994; Rosemeier et al., 2004). In one recent report, a 23-year-old primigravid woman who was a separated ischiopagus tetrapus twin delivered at 35 weeks of gestation by cesarean. The twins had been separated at 15 months of age but the co-twin died secondary to recurrent pneumonia (Rosemeier et al., 2004).

GENETICS AND RECURRENCE RISK

To our knowledge, the recurrence risk is not increased above background for conjoined twins.

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Monoamniotic Twins

122 CHAPTER

Key Points

- Monoamniotic twinning is a rare form of twinning where both twins occupy a single amniotic sac.
- This form of twinning occurs when a single embryo splits during postovulation days 8 to 10.
- The most common way to diagnose monoamniotic twins antenatally is failure to visualize a dividing membrane in the presence of a single placental mass and like-gender twins. During the first trimester, the presence of two embryos in a single sac, but with only one yolk sac, is highly suggestive of monoamnionicity.
- These pregnancies are at risk for significant perinatal morbidity and mortality. This has been attributed to preterm delivery, intrauterine growth restriction, congenital anomalies, vascular anastomoses between twins, and umbilical cord entanglement or cord accidents.
- Intense antenatal surveillance and timed delivery has been shown to improve outcomes. This typically takes the form of elective hospitalization with daily nonstress testing at 24 to 26 weeks' gestation, and increased frequency of testing if variable decelerations are noted.
- Elective delivery at 32 to 34 weeks' gestation is recommended if fetal testing remains reassuring and cesarean delivery is most commonly recommended.

CONDITION

Monoamniotic twinning is an unusual form of twinning in which both twins occupy a single amniotic sac. Monoamniotic twins account for 1% of all monozygotic twin pregnancies (Benirschke and Kim, 1973). This form of monozygotic twinning typically occurs when a single embryo splits between the ninth and twelfth day after fertilization. Splitting before this time gives rise to either dichorionic diamniotic twins (split between the first and third day after fertilization) or to monochorionic diamniotic twins (split between the third and eighth day after fertilization). Splitting later in embryogenesis (after the twelfth day postfertilization) gives rise to conjoined twins (Benirschke, 1998).

Although a rare event, monoamniotic twinning is important because of the high perinatal mortality rate associated with these pregnancies. The first comprehensive review of the world literature was performed in 1935 by Quigley, who found an overall mortality rate of 68% in 94 pregnancies. His opinion was that the poor prognosis was due mainly to twisting and knotting of the umbilical cords with subsequent occlusion of the blood supply to one or both twins. A subsequent review in 1959 added 35 new cases to the world literature and reported a high fetal mortality rate of 30% (Salerno, 1959). More recent series and reviews of prenatally diagnosed cases suggest mortality rates ranging from 10% to 32% (Rodis et al., 1997; Allen et al., 2001; Roque et al., 2003; Demaria et al., 2004; Heyborne et al., 2005). This decrease in perinatal mortality is likely secondary to increased rates of prenatal diagnosis, antenatal steroids, intense fetal surveillance, and timed delivery.

INCIDENCE

It is difficult to ascertain the exact incidence of monoamniotic twins. The incidence has ranged in various studies from 1 in 1650 to 1 in 93,734 livebirths (Simonsen, 1966; Colburn and Pasquale, 1982). Monoamniotic triplets are even more rare (Giannopoulos et al., 2001). Use of in vitro fertilization and embryo transfer may increase the risk for both monochorionic diamniotic twins and for monoamniotic twins (Alikani et al., 2003).

There may be a preponderance of female twins among monoamniotic twin pairs (Derom and Vlietinck, 1988). In

a study of 26 sets of monoamniotic twins, 20 (77%) were female pairs. However, this difference has not been as evident in more recent studies (Carr et al., 1990; Allen et al., 2001). Carr et al.'s (1990) series of 24 sets included 11 (46%) sets of females and 13 (54%) sets of males. Allen et al.'s (2001) series of 25 sets included 12 (48%) sets of females and 13 (52%) sets of males.

SONOGRAPHIC FINDINGS

Prenatal diagnosis is established when a dividing membrane cannot be identified by an experienced sonographer in a twin gestation with a single placental mass and like-gender twins. The diagnosis is confirmed after sonographic identification of entangled umbilical cords using Color flow Doppler (Belfort et al., 1993; Aisenbrey et al., 1995) (Figure 122-1). This feature has been reported in 70% to 100% of cases (Lee, 1992; Rodis et al., 1997). Cord entanglement has been diagnosed using Color Doppler ultrasonography as early as 10 weeks' gestation (Arabin et al., 1999; Sebire et al., 2000; Sherer et al., 2002).

Monoamnionicity may be suspected early in the first trimester. Between the sixth and tenth week, counting the number of gestational sacs is an accurate method of determining chorionicity. Amnionicity can be determined by counting the number of embryonic heartbeats in each gestational sac. A single gestational sac with two embryonic heartbeats can be either monochorionic diamniotic or monochorionic monoamniotic. Two yolk sacs indicate that the pregnancy is diamniotic. One gestational sac with one yolk sac and two embryonic heartbeats suggests monoamnionicity. If monoamnionicity is suspected in the first trimester, a follow-up ultrasound is suggested in the second trimester to reconfirm the diagnosis (Bromly and Benacerraf, 1995). Three-dimensional ultrasound has also been used to visualize monoamniotic fetuses lying in a single amniotic cavity (Su, 2002).

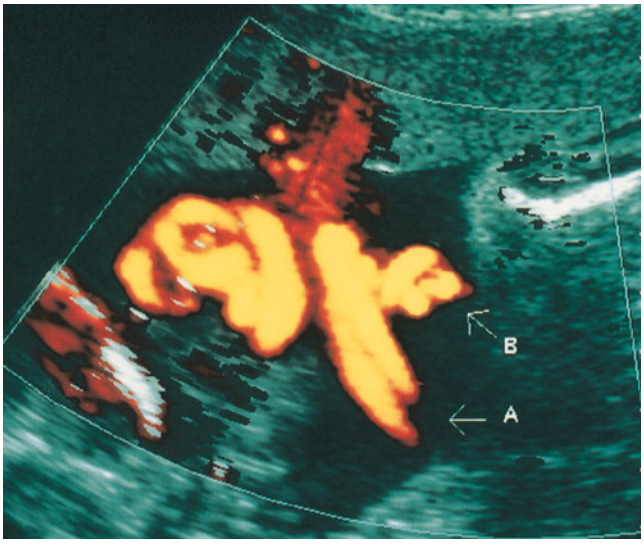

Figure 122-1 Power Doppler imaging of entangled umbilical cords in a case of monoamniotic twins.

It is important to remember that failure to visualize a dividing membrane does not ensure that the pregnancy is monoamniotic (Malone and D'Alton, 2000). Such a membrane may be missed even with well-performed sonography (Blane et al., 1987). As a result, other techniques have been utilized to confirm the diagnosis of monoamnionicity. Ultrasound-guided injection of indigo carmine dye mixed with air into the amniotic sac during genetic amniocentesis has been said to enhance the diagnosis of monoamniotic twins (Tabsh, 1990). If microbubbles are seen around both fetuses, the diagnosis of monoamniotic twinning is made with accuracy. Amniography is another technique, which may increase the accuracy of diagnosis (Lavery and Gadwood, 1990). In this report, 30 mL of 61% iopamidol (Isovue-M 300, Squibb) was injected into the amniotic fluid. Maternal abdominal x-ray films taken 24 hours after the injection revealed that both fetuses had swallowed contrast medium injected into a shared single amniotic sac. Computed tomography following intraamniotic injection of Renografin has also been suggested to confirm the diagnosis of monoamniotic twinning (Carlan et al., 1990; Perkins and Terry, 1992). Such invasive radiological procedures are now mostly of academic interest, and are rarely if ever performed in contemporary clinical practice.

DIFFERENTIAL DIAGNOSIS

A major consideration in differential diagnosis of monoamnionicity is the intrauterine rupture of a diamniotic twin membrane, which can mimic the sonographic appearance of true monoamniotic twins. Actual differential diagnosis between these two conditions is probably not necessary, as intrauterine membrane rupture has a perinatal mortality rate consistent with that of true monoamniotic gestations (Gilbert et al., 1991). This clinical scenario should be suspected when there is failure to visualize a dividing membrane following previous sonographic confirmation of a membrane. Possible causes for intrauterine rupture include trauma during amniocentesis, infection, and developmental disturbances of the membranes (Gilbert et al., 1991).

ANTENATAL NATURAL HISTORY

High intrauterine morbidity and mortality rates have been associated with monoamniotic twins (Quigley, 1935; Salerno, 1959; Raphael, 1961; Simonsen, 1966; Carr et al., 1990; D'Alton and Simpson, 1995). These high rates have been attributed to premature delivery, growth restriction, congenital anomalies, vascular anastomoses between twins, and umbilical cord entanglement and cord accidents. Discordant anatomical abnormalities are common. In a recent series of 25 monoamniotic twin pairs by Allen et al., 28% of the pregnancies had been complicated by fetal structural anatomical abnormalities including two cases of acardiac twinning (Allen at al., 2001). The twin–twin transfusion syndrome (TTTS) is

thought to be rare in monoamniotic twins as the placentas of monoamniotic twins have significantly greater numbers of both superficial and deep anastomoses than uncomplicated monochorionic twins which may be protective against TTTS (Bajoria, 1998; Umur et al., 2003). Cord accidents seem to be the greatest contributor to these high intrauterine mortality rates. In one of the earliest series of monoamniotic twins it was stated that double survival of such twins is a rare event (Quigley, 1935). However, more recent series and reviews of prenatally diagnosed cases suggest mortality rates range from 10% to 32% (Rodis et al., 1997; Allen et al., 2001; Demaria et al., 2004).

Because umbilical cord accidents seem to be the primary cause of fetal death, most management protocols emphasize intense fetal surveillance. Such fetal surveillance should occur from the time of fetal viability because intrauterine fetal demise has been documented in monoamniotic twins throughout gestation (Rodis et al., 1997; Arabin et al., 1999; Beasley et al., 1999). Additionally, surveillance must be repeated frequently because fetal compromise and death have been documented despite frequent testing (Beasley et al., 1999; Rodis et al., 1997).

Many of the older reports on monoamniotic twins are not optimal for guiding contemporary practice because of the fact that in almost all cases the diagnosis of monoamnionicity was only made postnatally. Nonetheless, there have been several recent series of prenatally diagnosed monoamniotic twins, which are helpful for contemporary patient counseling. Rodis et al. (1997) reviewed 13 cases of monoamnionicity at one tertiary care center over a ten-year period. All patients underwent serial ultrasounds and antenatal fetal surveillance 2 to 7 times per week starting at 24 to 26 weeks' gestation. The average gestational age at diagnosis was 16.3 weeks' gestation. All patients received antenatal steroids for fetal lung maturity. The mean gestational age at delivery was 32.9 weeks' gestation with a mean birth weight of 1,669 grams. One hundred percent of the pregnancies exhibited cord entanglement at the time of delivery, with 62% having knotted cords. Sixty-two percent of the pregnancies were delivered for abnormal fetal testing. All sets were delivered by cesarean section by 35 weeks' gestation. There were no fetal deaths. Two neonates died during the perinatal period: one due to a congenital heart defect and the other due to asphyxia and sepsis. The one case of demise secondary to asphyxia received antenatal testing less than two times per week. Perinatal survival was 92% in this series. These 13 cases were compared to 77 sets from the literature that had not been diagnosed prenatally. A 71% reduction in the relative risk of perinatal mortality was observed following prenatal diagnosis and fetal surveillance. Rodis et al., concluded that accurate prenatal diagnosis, intensive surveillance, and appropriately timed delivery all result in improved perinatal survival for monoamniotic twins (Rodis et al., 1997).

In a study by House et al., 22 patients with prenatally diagnosed monoamnionic twins were managed at one tertiary care center over a ten-year period (House et al., 2001). Management included close fetal surveillance with daily nonstress tests commencing at 24 to 26 weeks' gestation. Patients underwent prolonged monitoring if the daily nonstress test demonstrated variable decelerations or any other signs of potential fetal compromise. Frequent growth scans were performed. Management also included steroid administration and elective delivery at 34 to 35 weeks' gestation, provided that the testing was reassuring. Decision to deliver a patient prior to 34 to 35 weeks' gestation took into consideration the patient's gestational age and the frequency and severity of variable decelerations. Nonreassuring fetal status always resulted in emergent delivery. There were no fetal mortalities in this group of patients. While overall outcomes were favorable, monoamniotic twins were more likely to deliver prematurely and had more respiratory problems compared to monochorionic diamniotic and dichorionic diamniotic pregnancies (House et al., 2001).

MANAGEMENT OF PREGNANCY

The optimal management of monoamniontic twins with regards to frequency of fetal surveillance and the optimal timing of delivery is controversial because of the paucity of prospective data. As a result, recommendations are based on case reports, case series, and expert opinion. We acknowledge that the excellent outcomes described in the studies by Rodis et al., and House et al., could be optimistic. Cord accidents may occur without warning, and these studies could have been biased secondary to small patient numbers. Despite these limitations, we recommend that monoamniotic twins be managed with intensive fetal surveillance similar to the above studies. The objective of antenatal testing is to determine the presence and frequency of variable decelerations, as these changes may precede intrauterine fetal death. Further management takes into consideration gestational age, whether or not the patient received antenatal steroids, and overall fetal status.

Daily antenatal testing in the form of the nonstress test is recommended starting between 24 and 26 weeks' gestation. The decision as to whether or not to hospitalize the patient for this daily testing is individualized to the patient. Hospital admission and continuous fetal heart rate monitoring of both twins is recommended if variable decelerations increase in frequency or severity. Delivery may become necessary if fetal heart rate testing becomes nonreassuring. Because biophysical profile testing cannot predict variable decelerations, it is reserved for the evaluation of nonreactive nonstress tests and abnormal fetal growth. Doppler studies of umbilical artery waveforms may be useful in the management of monoamniotic twin pregnancies (Abuhamad et al., 1995). Narrowing of the umbilical vesels secondary to cord entanglement may result in hemodynamic alterations in the fetoplacental circulation and may be manifested as a notch in the umbilical artery waveform (Figure 122-2). Serial ultrasound examinations approximately every 2 to 3 weeks are performed to evaluate fetal growth and to assess amniotic fluid volume.

Antenatal corticosteroid therapy is used to enhance fetal pulmonary maturity because of the high incidence of

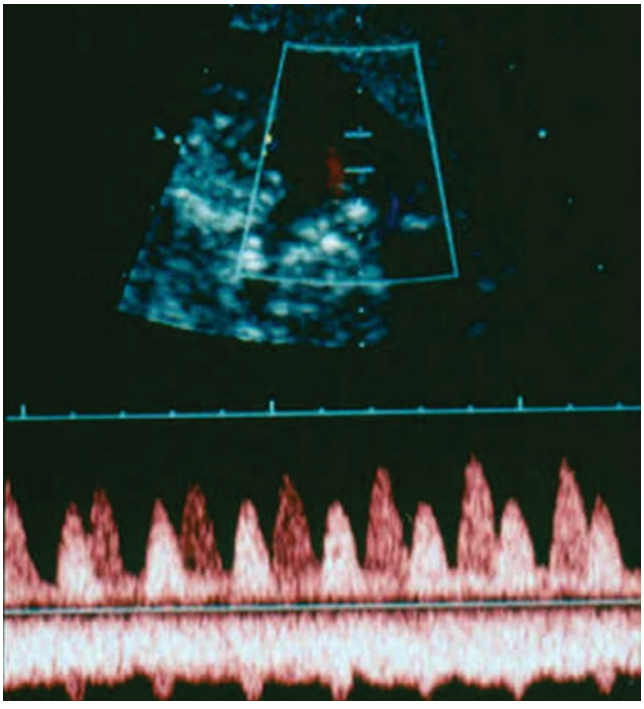

Figure 122-2 Doppler studies in monoamniotic twins. (*Courtesy of Alfred Abuhamad.*)

premature delivery in monoamniotic twins and also because of the significant risk for urgent delivery, secondary to variable decelerations. In general, the delivery of monoamniotic twins requires a tertiary care center setting. However, after 32 weeks of gestation, delivery may be accomplished in a community hospital with appropriate nursery capabilities.

In the absence of nonreassuring fetal testing, the timing of delivery is not well established as the optimal time to deliver monoamniotic twins is unknown (Su, 2002). Some authors have advocated delivery of all monoamniotic twin pregnancies immediately once fetal lung maturity has been demonstrated (Kassam and Tompkins, 1980). Others have recommended elective delivery at 32 weeks of gestation because of a presumed increased risk of cord accidents as the pregnancy progresses (Beasley et al., 1999). Other studies suggest it is unnecessary to deliver monoamniotic twins prematurely. One study by Carr et al., was a retrospective evaluation of 24 sets of mostly postnatally confirmed monoamniotic twin pregnancies (Carr et al., 1990). There were no perinatal deaths after 30 weeks of gestation. As a result, the authors saw no advantage in elective premature delivery. In their series, however, the diagnosis of monoamniotic twins was made prenatally in only 21% of cases, and the diagnosis of twins was known prenatally in only 29% of cases. In a second study by Tessen and Zlatnick, 20 monoamniotic twin pregnancies at the University of Iowa from 1961 to 1989 were reviewed (Tessen and Zlatnik, 1991). In this retrospective series no perinatal death occurred after 32 weeks of gestation. These authors suggested that prophylactic premature delivery might not be indicated. However, in an addendum to the original paper the authors report a double fetal death of 35-week monoamniotic twins just after completion of their study, again demonstrating that the safety of expectant management of monoamniotic twin pregnancies is unproven beyond 34 weeks' gestation.

Provided that the fetal status is reassuring, it is our practice to perform elective delivery following antenatal corticosteroid therapy at 34 weeks' gestation. Delivery at this time carries with it a low risk of neonatal morbidity when weighed against the uncertain risk of continuing the pregnancy. Although some series have questioned the need for early delivery, the double death referred to in the addendum to Tessen's report is particularly troubling (Carr et al., 1990; Tessen and Zlatnik, 1991). In addition, at present we do not have the technology to continuously trace both fetal hearts for a prolonged time. Consequently, it is our preference to perform elective delivery at 34 weeks of gestation. However, it is not unreasonable to manage selected cases of monoamniotic twins expectantly beyond 34 weeks of gestation, with careful fetal surveillance, and to decide on the timing of delivery based on fetal lung maturity.

The optimal mode of delivery of monoamniotic twins also remains uncertain. Cesarean delivery has been recommended by some authors to eliminate the risk of intrapartum cord accidents (Rodis et al., 1987). However, vaginal delivery of monoamniotic twins is not contraindicated. In one series, no fetal deaths and only one case of nonreassuring fetal testing requiring emergency cesarean delivery occurred during labor in 15 monoamniotic twin pregnancies delivered vaginally (Tessen and Zlatnik, 1991). In another series of 24 cases, vaginal delivery was accomplished in 75% of individual neonates and in 48% of liveborn infants, although the antenatal diagnosis of monoamniotic twins was unknown in most cases and could not have influenced management (Carr et al., 1990). Nonetheless, there are data suggesting potential difficulties with vaginal delivery of monoamniotic twins. In one case, a nuchal cord affecting the first twin was cut to facilitate delivery, and on delivery of this twin's body it was noted that the cut cord was actually that of the second twin (McLeod and McCoy, 1981; Kantanka and Buchman, 2001). Given these issues and the high incidence of nonreassuring fetal testing, all monoamniotic twin pregnancies have generally been delivered by elective cesarean delivery.

FETAL INTERVENTION

The only intervention described to reduce the incidence of cord accidents in monoamniotic twins is medical amnioreduction. In one small series, the prostaglandin inhibitor sulindac, 200 mg orally twice daily, was administered to three patients diagnosed with monoamniotic twins, beginning at 24 to 29 weeks of gestation (Peek et al., 1997). In two of the three cases, dose-related reduction in amniotic fluid volume was noted, and in all three cases fetal lie was stabilized. All fetal heart rate tracings remained normal, and all six infants survived. Although this was a very limited study, the authors

pointed out the difficulty of performing a randomized controlled trial given the rarity of the condition. Administration of a medication to deliberately reduce amniotic fluid volume in such pregnancies should therefore be considered experimental and generally not performed.

TREATMENT OF THE NEWBORN

Prematurity is the most important concern, together with growth restriction. Following delivery, a detailed examination should be performed because of the higher incidence of congenital anomalies in monoamniotic twins. No other specific neonatal intervention is required. Placental pathologic tests should be performed in all cases to confirm the prenatal diagnosis.

SURGICAL TREATMENT

No surgical treatments have been described.

LONG-TERM OUTCOME

There are no data available for long-term outcome.

GENETICS AND RECURRENCE RISK

There are no genetics and recurrence risks described in the literature.

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Intrauterine Growth Restriction

123
CHAPTER

Key Points

- Intrauterine growth restriction (IUGR) is commonly defined as a birth weight less than the 10th percentile at a given gestational age. It has also been defined as a fetus that has not reached its growth potential at a given gestational age.
- Small for gestational age (SGA) describes a population of fetuses with a weight below the 10th percentile without reference to the cause.
- Prenatal ultrasonography is the imaging method of choice for diagnosing and evaluating possible cases of IUGR. The typical finding is a significant discrepancy in some or all of the fetal biometric parameters as compared with measurements expected based on gestational age alone.
- Because sonographic prediction of fetal weight may vary by up to 20% from actual fetal weight, diagnosis and management of IUGR is generally guided by serial sonographic assessments of the fetus.
- Pregnancy management depends on the gestational age, the etiology of the IUGR, and the results of fetal surveillance. Fetal testing including Doppler studies and serial growth scans are important for determining whether a pregnancy can be continued expectantly.
- Detailed Doppler assessment including umbilical arterial, middle cerebral arterial, ductus venosus, and umbilical venous assessments are used to evaluate fetal status, and may be used to optimize timing of delivery.
- Gestational age at delivery is a strong predictor of neonatal outcome in IUGR cases.
- Elective delivery is recommended for all cases of IUGR reaching 37 weeks of gestation, while expectant management with close fetal surveillance is recommended for cases less than 34 weeks of gestation. For cases between 34 and 37 weeks of gestation, management is individualized depending on overall fetal status.
- A previous pregnancy complicated by IUGR is considered a risk factor for developing IUGR in a subsequent pregnancy. Such cases of recurrent IUGR usually reflect an underlying maternal medical problem, such as chronic hypertension or antiphospholipid antibody syndrome.

CONDITION

Intrauterine growth restriction (IUGR) is commonly defined as a birth weight less than the 10th percentile at a given gestational age (Table 123-1). It has also been defined as a fetus that has not reached its growth potential at a given gestational age, because of one or more causative factors (Lin and Santolaya-Forgas, 1998). The population from which expected fetal growth standards are derived to define the 10th percentile is of major importance. A review of all publications

Table 123-1

Tenth Percentile Birth Weight Cutoffs, in Grams, by Gestational Age and Fetal Gender, from 1991 National United States Population Data

Gestational Age (weeks)	Male	Female
20	270	256
21	328	310
22	388	368
23	446	426
24	504	480
25	570	535
26	644	592
27	728	662
28	828	760
29	956	889
30	1117	1047
31	1308	1234
32	1521	1447
33	1751	1675
34	1985	1901
35	2205	2109
36	2407	2300
37	2596	2484
38	2769	2657
39	2908	2796
40	2986	2872
41	3007	2891
42	2998	2884
43	2977	2868
44	2963	2853

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in the English language literature since 1963 that presented values for the 10th percentile of birth weight for gestational age has been published (Goldenberg et al., 1989). It was found that studies differed in how gestational age was determined, types of infants excluded, populations studied, and whether they were controlled for the sex of the infant as well as the race and parity of the mother. The 10th percentile birth weights at each gestational age from these various published standards differed substantially.

Different standards for fetal growth throughout gestation have been reported. These standards set the normal range of fetal growth as being between 2 SD of the mean (2.5th to 97.5th percentile) or between the 10th and 90th percentiles for gestational age. Fetal growth curves plotting fetal biometric values against gestational age have been published from a variety of populations. One of the earliest set of growth curves was derived from a population in Denver, Colorado (Lubchenco et al., 1966). These Denver curves soon became the standard fetal growth curves used throughout North America. However, these curves underestimate the incidence of small for gestational age (SGA) infants at sea level, especially during the third trimester, and also do not take into account the increase in birth weight noted during the past 30 years. Although many centers report the continued use of the Denver curves, more contemporary standards are available. These include growth standards from the state of California, based on data from more than 2 million singleton births occurring between 1970 and 1976, and also growth standards from Canada, based on data from more than 1 million singleton births and more than 10,000 twin births occurring between 1986 and 1988, as well as from national US standards, based on data from more than 3 million births in 1991 (Williams et al., 1982; Arbuckle et al., 1993; Alexander et al., 1996). Commonly used cutoffs for defining IUGR in male and female fetuses at various gestational ages are shown in Table 123-1. A further problem with the use of such cutoff values for diagnosing IUGR is that they cannot identify a fetus that has failed to reach its own growth potential, but whose weight is not yet below the usual cutoff value, such as the 10th percentile. Such a fetus may be identified through serial sonography, in which sequential weight estimates are associated with decreasing percentile values for gestational age.

The term intrauterine growth restriction is frequently and erroneously used as a substitute for the original term small for gestational age. SGA describes a population of fetuses with a weight below the 10th percentile without reference to the cause. Most SGA fetuses are normal except the small fetuses that simply reflect the normal weight distribution within a population. The use of a particular cutoff value such as the 10th percentile is clearly arbitrary, and will inevitably include a large number of fetuses that are constitutionally small, without any evidence of pathology. Up to 70% of SGA infants are small because of such constitutional reasons as maternal ethnicity, parity, or body mass index (Lin and Santolaya-Forgas, 1998). IUGR describes a subset of these SGA fetuses whose weight is below the 10th percentile as a result of a pathologic process that is due to a diverse group of disorders. The term intrauterine growth restriction is preferred to intrauterine growth retardation, as the word retardation has a tremendously negative influence on patients.

IUGR has classically been subdivided into two patterns: asymmetric and symmetric IUGR. This provides further information on fetal body size and length, rather than a simple reliance on fetal weight. With symmetric IUGR, both the head and abdomen are decreased proportionately, while asymmetric IUGR refers to a greater decrease in abdominal size, which is also referred to as the head-sparing effect (Lin and Santolaya-Forgas, 1998). Approximately 70% to 80% of cases of IUGR are asymmetric, with the remaining 20% to 30% being symmetric. It was commonly believed that asymmetric IUGR represented placental insufficiency, while symmetric

Table 123-2

Risk Factors for Intrauterine Growth Restriction

Fetal Factors	Placental Factors	Maternal Factors
Chromosomal abnormalities:	Abnormal trophoblast invasion	Constitutional factors:
Trisomies 21, 18, 13	Placental infarction	Race
Turner syndrome	Abruption	Height/weight
Chromosomal deletions	Vascular malformations	Nutritional factors:
Uniparental disomy	Velamentous cord insertion	Poor pregnancy weight gain
Confined placental mosaicism	Placenta previa	Low prepregnancy weight
Structural malformations:	Circumvallate placenta	Inflammatory bowel disease
Anencephaly	Chorioangioma	Chronic pancreatitis
Omphalocele/gastroschisis		Gastrointestinal surgeries
Diaphragmatic hernia		Hypoxic conditions:
Renal agenesis/dysplasia		Severe lung disease
Cardiac malformations		Cyanotic heart disease
Multiple malformations		Sickle cell anemia
Multiple pregnancies:		Vascular problems:
Monochorionic gestation		Chronic hypertension
Single anomalous fetus		Preeclampsia
Twin-to-twin transfusion		Collagen vascular disease
Fetal infections:		Insulin-dependent diabetes
Rubella		Antiphospholipid antibodies
Cytomegalovirus		Renal disease:
Varicella-zoster		Glomerulonephritis
		Renal transplantation
		Chronic renal failure
		Environmental factors:
		High altitude
		Cigarette smoking
		Substance abuse
		Medications
		Past obstetric history:
		Previous stillbirth
		Previous IUGR
		Previous preterm birth

Adapted from Lin CC, Santolaya-Forgas J: Current concepts of fetal growth restriction: part I. Causes, classification, and pathophysiology. Obstet Gynecol. *92:1044-55 1998. Reprinted, with permission, from the American College of Obstetricians and Gynecologists.*

IUGR was more likely to be associated with constitutional problems, such as aneuploidy. However, it is now recognized that the timing of the pathologic insult is of more importance than the actual nature of the underlying pathology in determining the pattern of IUGR, thereby calling into question the clinical utility of subdividing IUGR into such patterns (Lin and Santolaya-Forgas, 1998). Symmetric IUGR can be caused by placental insufficiency occurring early in gestation, so that by the time the fetus is examined it has evolved from an initial asymmetric pattern to a pattern of symmetric IUGR. Overall infant body proportions can be described also by using the ponderal index, which is the birth weight in grams divided by the crown-to-heel length in cubic centimeters.

The list of possible causes of IUGR is extensive and is summarized in Table 123-2. These causes can be conveniently divided into fetal, placental, and maternal factors (Lin and Santolaya-Forgas, 1998). The most common fetal factors associated with IUGR include fetal chromosomal abnormalities, structural fetal malformations, fetal infections, and complications related to multiple gestations (Figure 123-1). Chromosomal abnormalities are a major cause of IUGR (ACOG, 2000). Confined placental mosaicism is three times more common in placentas of IUGR fetuses compared with those from appropriately grown fetuses (Wilkins-Haug et al., 1995). Up to one-fourth of all infants with congenital structural malformations will have IUGR, and the incidence of

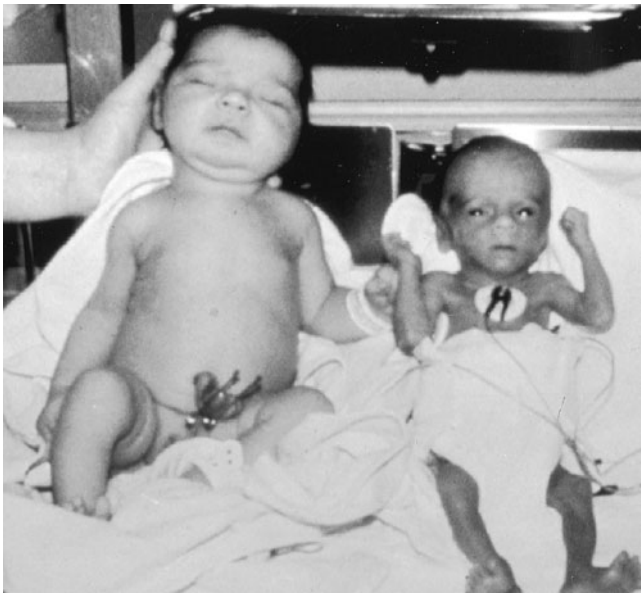

Figure 123-1 Monozygotic twins in which the twin on the right is severely growth restricted compared to its co-twin.

growth restriction increases significantly as the number of different malformations per infant increases (Khoury et al., 1988). The number of infectious agents proven to cause IUGR is limited; they include rubella and cytomegalovirus, although no known bacterial infections have been linked to IUGR. The importance of defining a subpopulation of fetuses with IUGR lies in its association with adverse pregnancy outcome. The likelihood of perinatal morbidity and perinatal mortality increases significantly as the birth weight percentile decreases, so that once below the third to fifth percentiles, the chances of fetal death increase by as much as 20-fold (Scott and Usher, 1966). For infants weighing less than 1500 grams at term, the perinatal mortality rate is increased at least 70-fold as compared with appropriately grown term infants (Williams et al., 1982). Much of the increased perinatal morbidity and mortality in IUGR fetuses is due to the strong association between aneuploidy and structural fetal malformations with IUGR (Scott and Usher, 1966).

INCIDENCE

The incidence of IUGR varies depending on the population examined and the standard growth curves used to make the diagnosis (Goldenberg et al., 1989). Using the commonly quoted cutoff of the 10th percentile for defining pregnancies at risk for IUGR implies that at least 10% of the entire obstetric population will be labeled as being IUGR. In Europe, the commonly used cutoff for defining IUGR of 2 SD below the mean will include 5% of the total population. Approximately one third of all infants weighing less than 2500 grams at birth are not just small for gestational age, but have sustained IUGR (Lin and Santolaya-Forgas, 1998). Approximately 4% to 7% of all infants born in developed countries and 6% to 30% in developing countries are classified as growth-restricted (Scott and Usher, 1966; Lugo and Cassady, 1971; Galbraith et al., 1979).

SONOGRAPHIC FINDINGS

Prenatal ultrasonography is the imaging method of choice for diagnosing and evaluating possible cases of IUGR. The typical finding is a significant discrepancy in some or all of the fetal biometric parameters as compared with measurements expected based on gestational age alone. The most common biometric parameters evaluated are the biparietal diameter, head circumference, abdominal circumference, and femur length. These measurements can then be used in a variety of formulas to provide an estimate of fetal weight (Hadlock et al., 1984; Shepard et al., 1982). However, it should be noted that sonographic prediction of fetal weight using such formulas may vary by up to 20% from actual fetal weight, thereby calling into question the accuracy of prenatal sonographic diagnosis of IUGR. For this reason, diagnosis and management of IUGR is generally guided by serial sonographic assessments of the fetus.

In cases of symmetric IUGR, measurements of the fetal head, abdomen, and femur should all be below the expected values for a given gestational age. By contrast, with asymmetric IUGR, measurements of the fetal abdomen will be less than expected, while fetal head and femur measurements will be appropriate for gestational age. While it is generally considered that symmetric IUGR represents an intrinsic insult to the fetus (chromosomal abnormality, fetal infection) and asymmetric IUGR represents an extrinsic insult (placental insufficiency), sonographic differentiation of these patterns may not be clinically relevant. Mixed patterns of fetal growth restriction are also possible, which further limits the clinical utility of subdividing IUGR into symmetric and asymmetric types.

Following the diagnosis of IUGR, a careful sonographic survey should be performed to search for some of the possible causes listed in Table 123-2. In cases of severe IUGR associated with placental problems, oligohydramnios is a frequent finding. In cases of severe IUGR but normal or increased amniotic fluid volume, fetal aneuploidy or structural malformation is likely.

Pulsed Doppler sonographic assessment of the umbilical artery may reveal abnormalities of flow in true cases of IUGR. As placental resistance increases, umbilical arterial flow toward the placenta during diastole will decrease, leading to an increase in the ratio of systolic to diastolic flow (SD ratio). The end-diastolic velocity decreases when approximately one-third of the fetal villous vessels are poorly perfused (Vergani et al., 2005). Eventually, umbilical arterial diastolic flow disappears and may even reverse direction toward the fetus, (absent end-diastolic flow and reversed end-diastolic flow). Absent end-diastolic flow is thought to occur when

60% to 70% of the villous vascular tree is damaged (Vergani et al., 2005). (Figures 123-1A to 123-1D) When these changes occur, the frequency of monitoring and the timing of delivery become important management issues. The risks and benefits of delivery versus expectant management must be balanced.

Doppler velocimetry has been used to detect signs of fetal compromise before more traditional tests such as the nonstress test and biophysical profile deteriorate. Doppler studies are thought to change in a consistent and temporal pattern; absent end-diastolic flow in the umbilical artery is present before changes in the fetal heart rate tracing. Compensatory increase in cerebral flow also occurs, which is seen as an increase in end-diastolic flow in the middle cerebral arteries. Changes in venous circulation usually occur just prior to development of an abnormal fetal heart rate tracing, although the reliability of this temporal sequence is still unclear. Such venous changes may be demonstrated by absent or reversed flow during the "a" wave in the ductus venosus (Figures 123-2A to 123-2C) or pulsatile umbilical venous flow.

DIFFERENTIAL DIAGNOSIS

The single most likely alternative cause of apparent IUGR following a single prenatal ultrasound examination is incorrect pregnancy dating. Also, because of the inherent inaccuracy of all forms of prenatal estimation of fetal weight, the differential diagnosis of IUGR should always include a normally grown fetus, which is just physiologically small. In addition, at least 70% of all cases of SGA infants are constitutionally small, and do not reflect a pathologic impairment of fetal growth (Lin and Santolaya-Forgas, 1998). Once a diagnosis of pathologic IUGR is considered likely, the differential diagnosis for the underlying cause is extensive and is listed in Table 123-2.

ANTENATAL NATURAL HISTORY

The antenatal natural history of IUGR is difficult to predict in individual cases. The antenatal natural history of fetuses with IUGR secondary to aneuploidy, structural malformation, or infection will be dictated to a large extent by the nature of the particular abnormality.

In cases of IUGR secondary to placental insufficiency, the typical in utero progression involves redistribution of fetal blood flow away from noncritical organs and maintaining cerebral blood flow (Baschat, 2004). This leads to reduced fetal renal blood flow, which often manifests as worsening oligohydramnios. In addition, further growth of the fetal abdominal dimensions is decreased and subcutaneous fat is no longer deposited. Doppler studies demonstrate decreased umbilical arterial diastolic flow, which may become absent or reversed as the IUGR worsens. In contrast, cerebral end-diastolic blood flow increases and, as the condition worsens, central cerebral vasodilation is lost (Arias, 1994).

Because of this apparent sequence in fetal deterioration with IUGR, many investigators have used intensive fetal surveillance in an effort to predict when a fetus with IUGR is sufficiently compromised that in utero death is likely. Unfortunately, the predictive value of such antenatal surveillance is imperfect. It has been suggested that, in fetuses with IUGR, the development of absent or reversed end-diastolic umbilical arterial flow heralds imminent fetal death, and therefore may warrant elective delivery (Reed et al., 1987). However, the time interval between development of such Doppler abnormalities and fetal heart rate tracing abnormalities and fetal death may be days or even weeks, and therefore abnormal Doppler findings alone cannot be relied on to dictate elective premature delivery of a fetus with IUGR (Lin and Santolaya-Forgas, 1999; Cosmi et al., 2005; Vergani et al., 2005).

The Growth Restriction Intervention Trial (GRIT) was carried out to compare immediate delivery of IUGR fetuses versus expectant management to decrease complications of prematurity (The GRIT Study Group, 2003). Patients (547 mothers and 587 babies) were included if IUGR was diagnosed between 24 and 36 weeks' gestation and the responsible physician was uncertain whether or not to deliver the pregnancy. Umbilical artery Doppler studies were recorded for all patients. Patients were randomized to "immediate delivery" after administration of antenatal steroids or "delay until the physician was no longer uncertain". The median time to delivery for the immediate delivery group was 0.9 days and was 4.9 days for the delayed delivery group. Total perinatal death rate was 10% in the immediate delivery group versus 9% in the delayed delivery group. Thus, there was no difference in the overall mortality rates between the two groups indicating that there was little evidence for choosing immediate delivery over delayed delivery and vice versa. There were however significantly more stillbirths in the delayed delivery group, although this was balanced by a similar increase in neonatal deaths in the immediate delivery group. This study suggests that obstetricians are currently delivering IUGR pregnancies at the correct time to minimize perinatal mortality. At two-year followup, however, the GRIT study group found an increased trend towards disability in the immediate delivery group but no overall difference in the Griffiths developmental quotient (GRIT, 2004). Most of the observed differences were in babies younger than 31 weeks' gestation at randomization. This study emphasizes the important contribution of gestational age at delivery for patients with IUGR.

MANAGEMENT OF PREGNANCY

When the prenatal diagnosis of IUGR is suspected, the patient should be referred to a maternal–fetal medicine physician for targeted ultrasound examination and counseling regarding further pregnancy management. The ultrasound examination should be repeated, with particular attention paid to all biometric parameters, amniotic fluid status, umbilical artery Doppler indices, and the presence of any structural

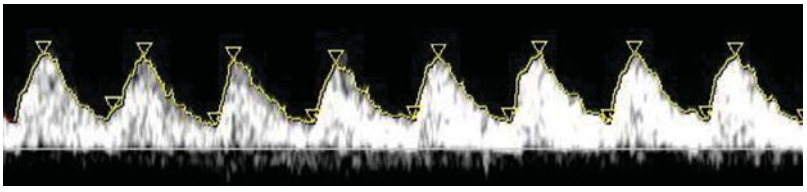

Figure 123-1A Umbilical artery Doppler studies demonstrating a normal SD ratio in a fetus at 28 weeks.

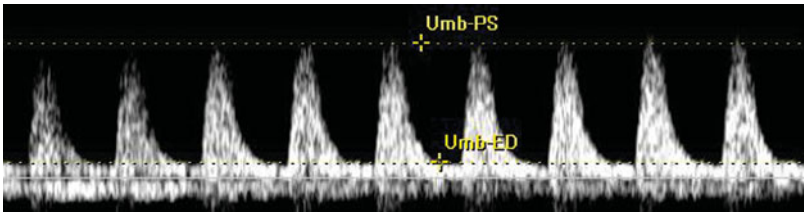

Figure 123-1B Umbilical artery Doppler studies demonstrating decreased diastolic blood flow and an increased SD ratio in a fetus at 28 weeks.

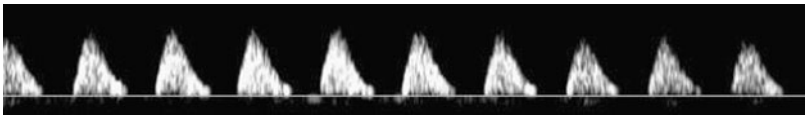

Figure 123-1C Umbilical artery Doppler study demonstrating absent end-diastolic flow.

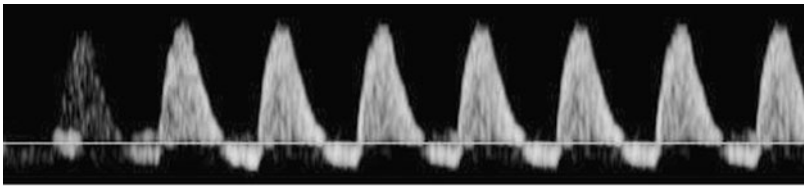

Figure 123-1D Umbilical artery Doppler study demonstrating reversed end-diastolic flow.

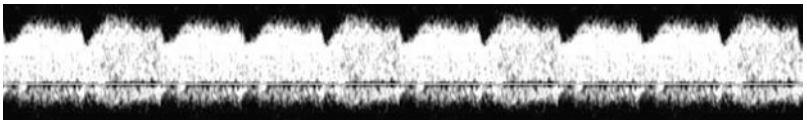

Figure 123-2A Ductus venosus Doppler demonstrating a normal waveform.

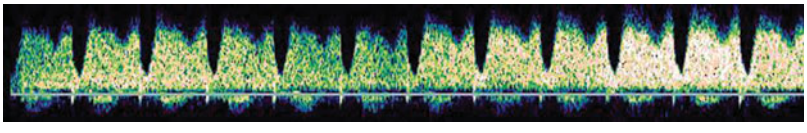

Figure 123-2B Ductus venosus waveform demonstrating decreased A-wave.

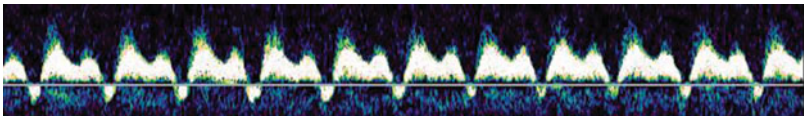

Figure 123-2C Ductus venosus waveform demonstrating reversal of the A-wave.

fetal malformations or stigmata of aneuploidy. Invasive testing for fetal karyotype should be considered (ACOG, 2000). Maternal evaluation should include careful obstetric, medical, family, and genetic histories to evaluate for possible causes of IUGR, as listed in Table 123-2. Maternal serum should be sent for rubella titers, and maternal urine should be evaluated with cytomegalovirus culture. Antiphospholipid antibody testing should be considered in a patient with a history suspicious for this syndrome (ACOG, 2000).

Further pregnancy management will depend on the gestational age and on the presence of additional malformations. If the pregnancy has already reached 37 weeks of gestation, delivery should be considered because of the extremely low risk of pulmonary immaturity. If the pregnancy is at less than 34 weeks of gestation and fetal testing is reassuring, expectant management is generally favored. The frequency of antenatal testing depends on the degree of IUGR, the amniotic fluid status, and umbilical artery Doppler indices (Harman and Baschat, 2003). Periodic fetal assessment using Doppler velocimetry, the fetal nonstress test, and the biophysical profile (traditional or modified) are all considered reasonable monitoring techniques (ACOG, 2000). Expectant management can continue as long as these tests remain reassuring. These tests should be supplemented by daily counting of fetal movements by the mother.

If umbilical artery Doppler indices are abnormal, especially in the presence of absent or reversed end-diastolic flow, more intense surveillance is suggested (Harman and Baschat, 2003). Venous Doppler studies are an independent predictor of adverse perinatal outcomes and should be added if the umbilical artery end-diastolic velocity is absent (Baschat, 2005). The addition of middle cerebral artery Doppler velocimetry also may be a useful predictor for fetuses at risk for neonatal mortality and morbidity (Vergani et al., 2005). Nonetheless, pregnancies may continue for days or weeks with reassuring fetal testing despite the presence of absent or reversed end-diastolic umbilical arterial flow (Lin and Santolaya-Forgas, 1999). Likewise, it is uncertain if delivery because of an abnormal venous Doppler improves outcomes (Hofstaetter et al., 2002; Bilardo et al., 2004). It is important to note that even in cases of IUGR neonatal outcomes are predominantly determined by gestational age at delivery (Cosmi et al., 2005). Thus, managing IUGR in a preterm infant can be a state of clinical equipoise requiring a delicate balance between continuing the pregnancy in a potentially hostile uterine environment versus delivering a neonate who will be confronted with the challenges of prematurity. Both expectant management and preterm delivery have the potential for long-term adverse consequences. Further studies are needed to determine the optimal management protocols for pregnancies complicated by IUGR.

For pregnancies between 34 and 37 weeks of gestation, further pregnancy management should be individualized and may be guided by fetal lung maturity indices. It is not unreasonable to manage all pregnancies with IUGR and reassuring fetal testing expectantly until 37 weeks of gestation, at which time elective delivery is arranged (Craigo et al., 1996). Using this management scheme, delivery before 37 weeks occurs only with nonreassuring fetal testing. If amniocentesis has documented fetal lung maturity during this 34- to 37-week gestational age range, delivery should be arranged promptly.

The mode of delivery for fetuses with IUGR should be based entirely on standard obstetric practices. There is no evidence to support a policy of routine cesarean delivery for all fetuses with IUGR (ACOG, 2000). That being said, it is quite common for IUGR pregnancies to demonstrate significant fetal heart rate changes during labor, most likely due to either oligohydramnios or diminished placental reserve. For this reason, decision on mode of delivery should be individualized depending on obstetric factors such as parity and cervical favorability. If an induction of labor is pursued for an individual fetus with IUGR, continuous electronic monitoring of the fetal heart rate should be conducted. The hospital location of delivery will depend on the gestational age and the presence of additional fetal abnormalities. In general, the optimal site for delivery of a fetus with severe IUGR will be a tertiary care facility with the immediate availability of a perinatologist and neonatologist to guide management.

FETAL INTERVENTION

Many fetal interventions have been evaluated in cases of IUGR to maximize neonatal outcome. These include treating any underlying problems, such as maternal hypertension. Behavior modification for the mother may include smoking cessation and modified bed rest (Lin and Santolaya-Forgas, 1999). More specific therapies for the fetus have included maternal low-dose aspirin therapy. In initial studies, there was a suggestion of increased fetal and placental weight associated with aspirin use (Trudinger et al., 1988). However, this potential benefit was subsequently refuted in a large randomized trial in which the administration of low-dose aspirin to the mother was shown to have no effect on the rate of IUGR or any other perinatal outcome measure (Caritis et al., 1998). Another possible fetal intervention is the antenatal administration to the mother of high-dose oxygen therapy, which in small studies has been shown to, at least transiently, improve umbilical arterial pH and oxygen content (Nicolaides et al., 1987). However, before this intervention can be recommended, larger, well-designed studies need to be completed.

TREATMENT OF THE NEWBORN

Because of their lack of placental reserve, infants with IUGR are more likely to require immediate resuscitation in the delivery room than appropriately grown infants. Problems that may be encountered include neonatal asphyxia, meconium aspiration, hypothermia, polycythemia, hypoglycemia, and other metabolic abnormalities. The infant should be examined carefully for any signs of structural malformation that may have been missed with prenatal ultrasonography,

for dysmorphic features suggestive of chromosomal abnormality, and for signs of perinatal infection with rubella, cytomegalovirus, varicella, syphilis, and toxoplasmosis (Alkalay et al., 1998). If any stigmata of perinatal infection or aneuploidy are present, appropriate serologic titers or karyotype should be obtained. A consultation with a clinical geneticist should also be obtained, if dysmorphic features are noted on examination.

SURGICAL TREATMENT

No surgical treatments have been described.

LONG-TERM OUTCOME

The long-term outcome of infants with IUGR will depend on the underlying cause and on the presence of additional malformations. Considerable data have now accumulated linking IUGR with poor cognitive function and adverse neurologic outcome in later childhood. In one study of 171 children with spastic cerebral palsy, it was found that up to 22% of cases could be attributed to IUGR, although a causal relationship could not be established (Blair and Stanley, 1990). In another study of 218 newborns at high risk, including 77 with IUGR, evaluation of cognitive skills at ages 9 to 11 revealed a significant learning deficit for infants with IUGR (Low et al., 1992). Data also suggest that IUGR infants can be expected to have higher rates of impaired gross motor development, lower intelligence quotient, and speech or reading disabilities (Gembruch and Gortner, 1998).

In a review of the many studies of long-term outcome of infants with IUGR, however, it was shown that after correcting for the effects of prematurity, most of the adverse cognitive outcomes could be diluted by socioenvironmental conditions (Hack, 1998). Therefore, it was suggested that fetal IUGR per se may not have a significant impact on final cognitive outcome in adulthood. Nonetheless, long-term followup has suggested that a history of IUGR may place these patients at risk for adult-onset hypertension and cardiovascular complications (Barker et al., 1989).

GENETICS AND RECURRENCE RISK

As described in Table 123-2, there are many genetic influences that can be associated with IUGR, ranging from genetic abnormalities such as aneuploidy to constitutional factors such as maternal height and weight. A previous pregnancy complicated by IUGR is considered a risk factor for developing IUGR in a subsequent pregnancy. Such cases of recurrent IUGR usually reflect an underlying maternal medical problem, such as chronic hypertension or antiphospholipid antibody syndrome. In the future, routine assessment of first trimester uterine artery Doppler studies might be useful to predict pregnancies at risk for IUGR and perhaps to modify pregnancy management (Dugoff et al., 2005).

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124 Overgrowth Syndromes

CHAPTER

Key Points

- Group of conditions characterized by generalized excessive growth for gestational age.
- Incidence between 1 in 10,000 and 1 in 15,000.
- Sonographic findings include overgrowth, polyhydramnios, placentomegaly, and macroglossia.
- Differential diagnosis includes incorrect gestational dating, maternal gestational diabetes, Sotos syndrome, Weaver syndrome, Beckwith–Wiedemann syndrome, and Simpson–Golabi–Behmel syndrome, as well as chromosome abnormalities.
- Management of pregnancy should include level II sonographic examination, high-resolution karyotype, and molecular testing for *NSD1* and *GPC3* mutations. If these tests are negative, imprinting disorders of 11p15.5 should be tested.
- Newborn treatment should include medical genetics consultation, cardiac evaluation, and monitoring for hypoglycemia.
- Some of the overgrowth conditions are associated with a predisposition to childhood cancer.
- Several of the overgrowth conditions have Mendelian patterns of inheritance.

CONDITION

The overgrowth syndromes refer to a heterogeneous group of conditions characterized by generalized excessive growth for gestational age. Many overgrowth syndromes are associated with anomalies, developmental delay, and a propensity for tumor development. Diagnostic characterization has been difficult because of the overlapping clinical features in many of these syndromes (Cytrynbaum et al., 2005). Recent studies using high-resolution cytogenetic techniques, as well as

molecular analysis of several genes, have illustrated the fact that there is substantial clinical as well as molecular overlap amongst the overgrowth disorders (Baujat et al., 2005).

INCIDENCE

The overall incidence of fetal overgrowth is unknown but it is not rare. The incidence of Beckwith–Wiedemann syndrome is about 1 in 13,700 livebirths (Cytrynbaum et al., 2005).Beckwith–Wiedemann syndrome is more common in women who have undergone in vitro fertilization to conceive. It is estimated that Beckwith–Wiedemann syndrome occurs in 1 in 4000 deliveries to women who have used assisted reproductive technology. Another common condition associated with fetal overgrowth is Sotos syndrome, which has an incidence of 1 of 15,000 livebirths (Tatton-Brown and Rahman, 2007). The incidence of some of the other rare genetic conditions, such as Simpson–Golabi–Behmel syndrome (SGBS), is unknown.

SONOGRAPHIC FINDINGS

In the obstetric literature, there has been no prospective study performed to ascertain the outcome of fetuses documented to have overgrowth. There have, however, been reports of prenatal ultrasound findings in fetuses that were postnatally diagnosed as having a specific syndrome. For example, Reish et al. (2002) described three unrelated cases of Beckwith–Wiedemann syndrome and tabulated anomalies that were detected prenatally. The anomalies common to all of the fetuses included overgrowth, polyhydramnios, placentomegaly, macroglossia, and a distended abdomen. In addition, Le Caignec et al., (2004) described a case of Beckwith–Wiedemann syndrome in a 28-year-old *G3P1*-pregnant woman who underwent sonography at 28 weeks of gestation. The fetus was macrosomic, but also had bilateral enlarged echogenic kidneys with a loss of corticomedullary differentiation.

An increasingly appreciated cause of fetal overgrowth is Sotos syndrome. There has been one prenatal description of the findings of Sotos syndrome (Chen et al., 2002). This group described fetal findings at 31 weeks of gestation, which included macrocephaly, an abnormally shaped skull, polyhydramnios, and right hydronephrosis. A subsequent scan at 33 weeks demonstrated the presence of fetal overgrowth. Postnatally, this fetus underwent magnetic resonance imaging (MRI), which showed enlargement of the lateral ventricles, hypoplasia of the corpus callosum, a mega cisterna magna, and a persistent cavum septum pellucidum.

The prenatal sonographic findings in pregnancies affected with SGBS were summarized in Hughes-Benzie et al. (1994). These authors described a case of SGBS in which sonography was performed for an increased maternal serum alpha-fetoprotein measurement. The fetal findings included macrosomia, polyhydramnios, omphalocele, and enlarged or cystic kidneys. Cardiac anomalies are also common in SGBS (Lin et al., 1999), but there have been no prenatal reports of their detection in this condition.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for fetal overgrowth is shown in Table 124-1. The differential diagnosis is complicated by the fact that many of these conditions have substantial clinical overlap. The most common reason for fetal "overgrowth" is incorrect gestational dating. Once this has been ruled out, the second most common cause is hyperinsulinism due to maternal diabetes. Sustained maternal hyperglycemia results in beta cell hyperplasia and fetal hyperinsulinism, which in turn induces fetal macrosomia with a weight that is greater than length.

There are multiple syndromic causes of fetal overgrowth. Sotos syndrome, also known as cerebral gigantism, consists of macrosomia, macrocephaly, a typical postnatal facial appearance, mild developmental delay, and advanced dental maturation. Weaver syndrome is now considered to be allelic with Sotos syndrome. Patients with Weaver syndrome have prenatal overgrowth, advanced skeletal maturation, advanced bone age, a distinctive postnatal facial appearance that consists of micrognathia with a deep horizontal chin crease, deep set nails. Approximately 80% of patients with Weaver syndrome have developmental delay.

Beckwith–Weidemann syndrome is in the differential diagnosis for fetal overgrowth. Affected fetuses have macrosomia, macroglossia (Figures 124-1 and 124-2) (see Chapter 27), and sometimes, an abdominal wall defect. Patients who have Beckwith–Wiedemann syndrome have visceromegaly and ear anomalies (Figure 124-3) that are only detectable postnatally.

Simpson–Golabi–Behmel syndrome (SGBS) overlaps significantly with Beckwith–Wiedemann syndrome. Affected individuals have macroglossia, macrosomia (a characteristic facial appearance that resembles a bulldog), renal and cardiac malformations. Compared with the other overgrowth syndromes, patients with SGBS are more likely to have skeletal abnormalities that include brachydactyly, camptodactyly, clinodactyly, polydactyly, syndactyly, clubfeet, scoliosis and vertebral anomalies (DeBaun et al., 2001). As many as 50% of SGBS patients have cardiac anomalies, which typically include patent ductus arteriosus, atrial septal defect, and ventriculoseptal defect. The distinctive coarse facial features and the presence of cardiac anomalies (Lin et al., 1999) make this condition distinct from Beckwith–Wiedemann syndrome.

Although chromosome abnormalities are typically associated with intrauterine growth restriction or postnatal failure to thrive, increasingly it is being recognized that certain chromosome abnormalities are associated with overgrowth. Most notably, abnormalities of the short arm of

Table 124-1

Differential Diagnosis of Fetal Overgrowth

	Gene Involved	Inheritance Pattern
Incorrect gestational dating	N/A	N/A
Maternal diabetes	N/A	N/A
Sotos syndrome	*NSD1*	Sporadic/AD
Weaver syndrome	*NSD1*	Sporadic/AD
Beckwith–Wiedemann syndrome	Imprinted gene on 11p15	85% sporadic/15% AD
Simpson–Golabi–Behmel syndrome	*GPC3*	X-linked
Bannayan–Riley–Ruvalcaba syndrome	*PTEN*	AD
Chromosome abnormalities	N/A	N/A
Trisomy 4p16.3	N/A	N/A
Trisomy 5p	N/A	N/A
Trisomy 12p	N/A	N/A
Pallister–Killian syndrome (mosaic tetrasomy 12p)	N/A	N/A
Trisomy 15q25	N/A	N/A
Deletion (monosomy) 22q13	N/A	N/A

N/A, not applicable; AD, autosomal dominant.

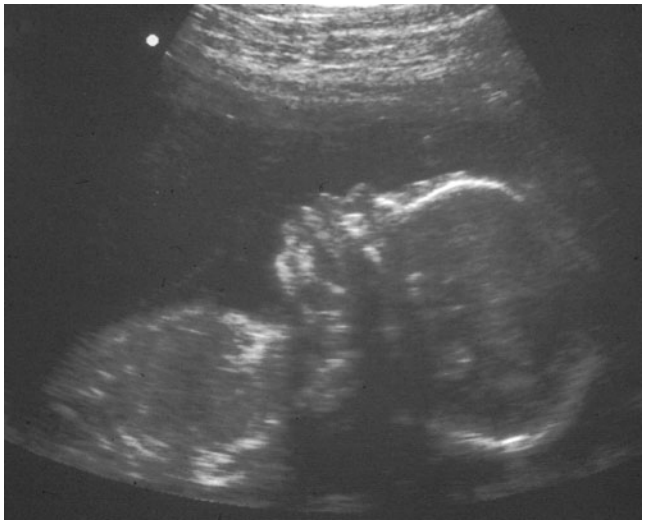

Figure 124-1 Prenatal sonographic image showing mild macroglossia in a fetus subsequently shown to have Beckwith–Wiedemann syndrome. *Image courtesy of Sabrina Craigo, MD.*

chromosome 12, including trisomy 12p and Pallister–Killian syndrome (mosaic tetrasomy 12p), are associated with fetal overgrowth disorders (see Chapter 138). Other chromosome abnormalities associated with overgrowth include trisomy 4p16.3, trisomy 5p, trisomy 11p15.5, and trisomy 15q25. It is also recognized that deletion, or monosomy, of 22q13 leads to overgrowth. There are a number of other rare conditions that are associated with fetal overgrowth, including syndromes such as Perlman, Marshall–Smith, Elejalde, and Bannayan–Riley–Ruvalcaba syndrome. There is no information available on the prenatal clinical manifestations of these conditions.

ANTENATAL NATURAL HISTORY

Little is known about the antenatal natural history of the overgrowth syndromes. Of note, however, is that SGBS has two clinical presentations. The more common presentation is the milder form, which is discussed in the "Genetics and

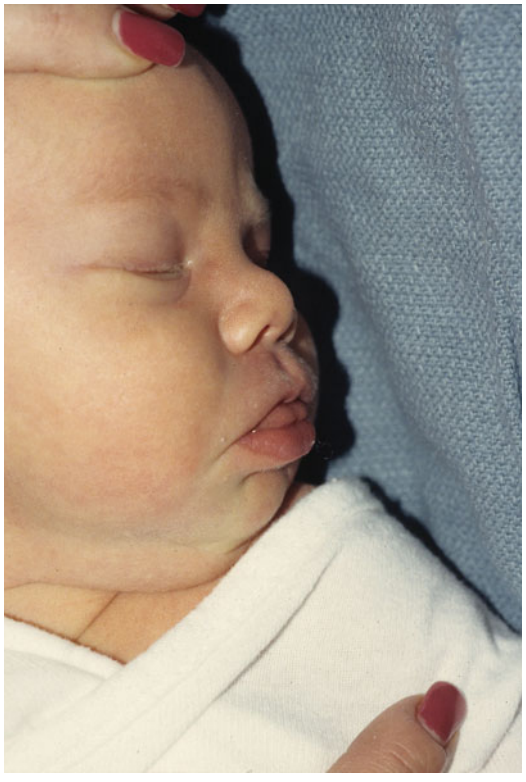

Figure 124-2 Postnatal image of the same infant as in Figure 124-1, showing mildly prominent tongue.

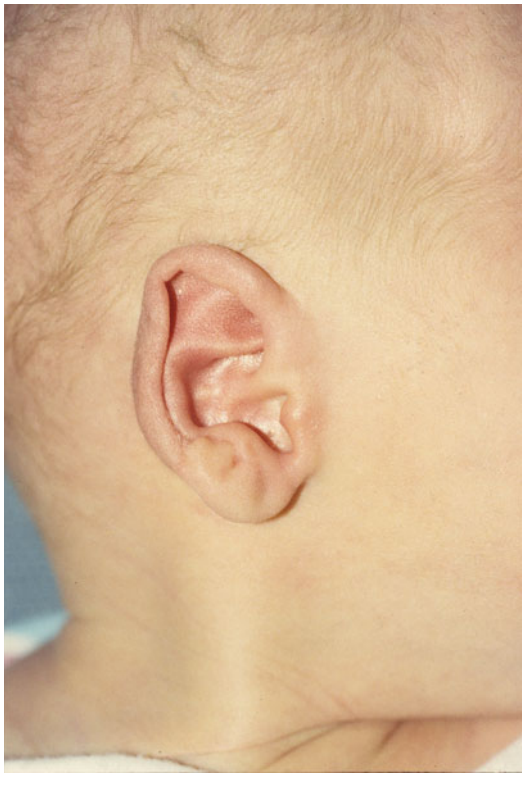

Figure 124-3 Postnatal image of the same infant with Beckwith–Wiedemann syndrome, showing the mild ear anomalies that are generally not observed by prenatal sonogram. These include a prominent antihelix and vertical creases in the lobe.

Recurrence Risks" section below. It is now appreciated that there is a more severe variant of this condition that is associated with severe neurologic impairment and neonatal death due to pneumonia and sepsis (Terespolsky et al., 1995). This more severe form could potentially be associated with antenatal demise.

MANAGEMENT OF PREGNANCY

When a fetus is demonstrated as being larger than expected for gestational age, the first step is to confirm the gestational dating. Subsequently, maternal diabetes should be ruled out. Assuming the mother does not have diabetes and that the pregnancy is dated correctly, the next step would be to perform a level II sonographic examination, specifically looking for the presence of associated renal or cardiac malformations. For the fetal overgrowth syndromes, we recommend obtaining a karyotype because of the increasingly recognized number of chromosome abnormalities associated with this finding (Faivre et al., 2004). There have been no prospective studies performed to assess the underlying etiology for fetal overgrowth. Based on postnatal studies, such as Baujat et al. (2005), we recommend the following molecular testing. Since amniocentesis would be performed to obtain the karyotype, cells should be grown for subsequent molecular testing including *NSD1* and *GPC3* mutation analysis. *NSD1* is the underlying gene that is responsible for the phenotype of most cases of Sotos syndrome and about half of the cases of Weaver syndrome. *GPC3* (glypican-3) is the gene that is the cause of SGBS. Molecular testing is commercially available for both *NSD1* and *GPC3* mutations. Detection of a mutation in either *NSD1* or *GPC3* is diagnostic and allows accurate genetic counseling regarding prognosis. Beckwith-Wiedemann syndrome is a genetically complex disorder with many underlying etiologies. Karyotype analysis should pay careful attention to the region of 11p15, which is the area involved in its pathogenesis. Beckwith–Wiedemann syndrome is a multigenic disorder that is caused by dysregulation of imprinted genes within the 11p15.5 region. Current molecular testing consists of determining whether uniparental disomy is present or whether there is abnormal methylation of the genes, *H19* or *KVDMR1*. In addition, mutation analysis can be performed in *P*57 or *CDKN1C*. Loss of function due to mutations in these genes will result in Beckwith–Wiedemann syndrome.

Using this strategy of molecular and cytogenetic testing in a postnatal setting, over half of the patients with a clinically diagnosed overgrowth syndrome were given a confirmatory molecular diagnosis (Baujat et al., 2005).

TREATMENT OF THE NEWBORN

There are many similarities in the postnatal presentation of newborns with overgrowth. All newborns should be observed

and tested for the presence of hypoglycemia. A postnatal cardiac evaluation should be performed, including cardiac consultation, echocardiogram, and electrocardiogram (Lin et al., 1999). Although Beckwith–Wiedemann syndrome is rarely associated with cardiac abnormalities, SGBS has a 50% incidence of associated cardiovascular problems. Therefore, a cardiac workup will help to distinguish between these two conditions. In addition, an abdominal ultrasound examination should be performed to look for the presence for underlying renal anomalies as well as vesicoureteric reflux. A medical genetics consultation may be helpful given the differing facial appearances in these overgrowth conditions.

SURGICAL TREATMENT

There is no specific surgical treatment recommended for overgrowth.

LONG-TERM OUTCOME

In general, the overgrowth syndromes are associated with normal intelligence, although in each of the conditions there has been significant variability described. For example, in Sotos syndrome there is a mild-to-moderate learning disability (Tatton-Brown and Rahman, 2007). In Sotos syndrome, interestingly, there is a genotype–phenotype correlation. If a microdeletion is detected in chromosome 5q35, there is a more severe learning disability and less pronounced overgrowth (Tatton-Brown et al., 2005). Childhood follow-up recommendations include screening for renal or cardiac abnormalities, and to check the spine for development of scoliosis.

For Beckwith–Wiedemann syndrome and SGBS, the biggest long-term issue is the increased risk of childhood cancer. Both conditions are associated with an increased risk of Wilms tumor and hepatoblastoma. The recommendations for Wilms tumor screening include ultrasound examinations every four months until the age of 7 to 8, and consideration of blood α-fetoprotein screening to look for hepatocellular carcinoma every 6 to 12 weeks during the first three years of life. SGBS has also been associated with neuroblastoma and testicular gonadoblastoma. Of all of the overgrowth conditions, Sotos syndrome is the least predisposed to neoplasia.

GENETICS AND RECURRENCE RISK

Most individuals with Sotos syndrome are the result of de novo mutations. Affected adults, however, have a 50% risk of having affected offspring. In 2002, haploinsufficiency of the gene *NSD1* was identified as a cause of Sotos syndrome (Kurotaki et al., 2002). Following this report, more than 100 distinct intragenic mutations have been identified (Tatton-Brown et al., 2005). There is also an ethnic difference in the type of mutation. For example, in the Japanese population, microdeletions of 5q35 (a 2.2 megabase sequence) are the most common cause of Sotos syndrome, observed in 50% of patients (Visser and Matsumoto, 2003). In contract, the Caucasian population has intragenic mutations. In both groups the deletions are derived from the paternal copy of chromosome 5 (Miyake et al., 2003). Overall, defects of the *NSD1* gene are present in 80% of individuals with Sotos syndrome (Waggoner et al., 2005). Although *NSD1* was originally associated with Sotos syndrome, subsequent studies have identified that about half of the patients with Weaver syndrome also have *NSD1* mutations, and occasionally patients that were previously classified as having Beckwith–Wiedemann syndrome also have *NSD1* mutations (Rio et al., 2003). *NSD1* is thought to act as a factor that positively and negatively influences transcription.

Simpson–Golabi–Behmel syndrome (SGBS) results from a deletion or point mutation that causes a loss of function in the glypican-3 *(GCP3)* gene on chomosome Xq26 (Pilia et al., 1996). Glypicans modify cellular responses to growth factors and morphogens. Glypican-3 interacts with *IGF2* and forms a complex that modulates *IGF2* action. A defect in *GPC3* results in higher circulating levels of *IGF2*. The condition is X-linked. Female carriers have a milder phenotype.

Of all of the overgrowth disorders, the underlying genetics of Beckwith–Wiedemann syndrome are the most complex. Most cases of Beckwith–Wiedemann syndrome are sporadic and are associated with a normal karyotype (Reish et al., 2002). Twenty percent of cases have paternal uniparental disomy of 11p15. One to two percent of cases have a recognized cytogenetic abnormality at 11p15. A few patients have loss of function mutations in *p*57 or *CDKN1C* genes. There have also been disorders of the maternal imprinting center near the *IGF2* gene associated with Beckwith–Wiedemann syndrome. Also, abnormal methylation of *H19* (Le Caignec et al., 2004) or *KVDMR1* has been proposed as a potential basis for Beckwith–Wiedemann syndrome. The inheritance patterns of these overgrowth conditions are outlined in Table 124-1. Recurrence risk will depend on the diagnosis of the affected proband. Should a cytogenetic abnormality or a molecular abnormality be documented in the affected fetus or newborn, similar testing could be performed by CVS or amniocentesis in a subsequent pregnancy.

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125 Oligohydramnios

CHAPTER

Key Points

- Oligohydramnios is a decrease in the volume of amniotic fluid, with the diagnosis usually being made using ultrasound.
- Causes of oligohydramnios include ruptured membranes, placental insufficiency, fetal anomalies, maternal injestion of medications, complications of a multiple gestation, chromosomal abnormalities, and idiopathic.
- Significant oligohydramnios occurring prior to 22 weeks of gestation is associated with a poor prognosis because of a high likelihood of pulmonary hypoplasia and associated malformations.
- Once oligohydramnios is diagnosed, a careful maternal history should be obtained and a physical examination should be performed to evaluate for preterm premature rupture of membranes.
- Whenever a diagnosis of oligohydramnios is made, a careful sonographic anatomical survey should be performed to evaluate for fetal anomalies such as features of urinary tract obstruction or renal malformation.
- Amnioinfusion may assist sonographic visualization of the fetus when severe oligohydramnios is diagnosed in the midtrimester.
- Management of oligohydramnios secondary to preterm premature rupture of membranes depends on the gestational age and on the fetal and maternal status.
- Long-term outcome will depend on gestational age at diagnosis, etiology of the problem, and gestational age at delivery.

CONDITION

Oligohydramnios is a decrease in the volume of amniotic fluid. The diagnosis of oligohydramnios is most frequently made by ultrasound examination. Oligohydramnios was initially defined as a subjective decrease in amniotic fluid volume resulting in fetal crowding as compared with normal values (Crowley et al., 1984). Objective sonographic estimation of amniotic fluid volume involves measuring different dimensions of amniotic fluid pockets. Various definitions of oligohydramnios exist. Oligohydramnios has been defined as a maximal vertical pocket (MVP) of less than 1 cm, but has also been defined as a MVP of less than 2 cm (Manning et al., 1981; Chamberlain et al., 1984). A semiquantitative four-quadrant technique, known as the amniotic fluid index (AFI), is also widely used. Oligohydramnios can be defined as an AFI of less than 5 cm, but has also been defined as an AFI of less than 8 cm (Phelan et al., 1987; Moore, 1993).

Amniotic fluid volume is the result of a balance between inflow and outflow to and from the amniotic cavity. In the first half of pregnancy, the majority of amniotic fluid is a result of active transport of sodium and chloride across the amniotic membrane and fetal skin, with water moving

passively in response (Brace and Resnik, 1999). In the second half of pregnancy, the majority of amniotic fluid is a result of fetal micturition (Underwood et al., 2005). Another major source of amniotic fluid is secretion from the respiratory tract. The average amniotic fluid volume is 30 mL at 10 weeks of gestation, rising to 780 mL at 32 to 35 weeks, after which time a natural decrease in volume occurs (Brace and Resnik, 1999). The amniotic fluid volume is not stagnant, but is completely turned over at least once daily. Fetal urine first appears at 8 to 10 weeks of gestation and reaches a production rate of 700 to 900 mL/d near term (Brace and Resnik, 1999).

Oligohydramnios can occur as a result of decreased urinary production or excretion, or can be a result of fluid loss, such as with premature rupture of membranes. Causes of oligohydramnios include ruptured membranes, placental insufficiency, fetal anomalies, medication use by the mother, abnormalities associated with multiple gestations, chromosomal abnormalities, and idiopathic (Garmel et al., 1997). In the second trimester, premature rupture of membranes accounts for 50% of all cases of oligohydramnios; fetal anomalies, 15%; abruption, 7%; abnormalities associated with multiple gestations, 5%; intrauterine growth restriction, 18%; and idiopathic causes, 5% (Shenker et al., 1991). The presence of oligohydramnios in a twin gestation may be due to twin-to-twin transfusion syndrome, intrauterine growth restriction of one twin, or intrauterine fetal death.

Premature rupture of membranes may be suggested with the sonographic appearance of oligohydramnios and an appropriately grown, structurally normal fetus. A sterile speculum examination demonstrating the absence of pooling following a negative phenaphthazine (nitrazine) test will usually rule out rupture of membranes. Occult rupture of membranes may occur, and amniocentesis with indigocarmine dye infusion may be necessary in some cases to rule out membrane rupture as a causative factor of oligohydramnios. Significant oligohydramnios occurring prior to 22 weeks of gestation is associated with a poor prognosis, most likely because of a high likelihood of pulmonary hypoplasia and also because of a high incidence of associated congenital malformations.

Medication use by the mother, such as prostaglandin synthetase inhibitors and angiotensin-converting enzyme inhibitors, has been reported to cause oligohydramnios. Indomethacin is used to treat preterm labor and can result in oligohydramnios, although this is usually reversible following discontinuation of the drug (Kirshon et al., 1991). Oligohydramnios, prolonged neonatal anuria, and ossification defects in the neonatal skull have been reported with in utero exposure to angiotensin-converting enzyme inhibitors (Cunniff et al., 1990; Barr and Cohen, 1991). The use of angiotensin-converting enzyme inhibitors is absolutely contraindicated during pregnancy. It is interesting to note that oligohydramnios is diagnosed more frequently in pregnancies delivered in the summer months suggesting that maternal dehydration may contribute to this finding (Varner et al., 2005).

INCIDENCE

Because of differing definitions, the reported incidence of oligohydramnios varies from 0.5% to 8% of all pregnancies (McCurdy and Seeds, 1993; Phelan et al., 1987). When an MVP of less than 2 cm is used as a cutoff, the incidence of oligohydramnios is 3% of all pregnancies (Chamberlain et al., 1984). When an AFI of less than 5 cm is used, the incidence of oligohydramnios is 8% (Phelan et al., 1987). Norms for amniotic fluid volume across gestation were established in one report of sonographic amniotic fluid measurements in 791 patients (Moore and Cayle, 1990). The 5th centile for AFI at term was approximately 7 cm. Interobserver variability may account for some of the variations in quoted incidences of oligohydramnios; however, interobserver and intraobserver variability have been reported as reliable and reproducible (Halperin et al., 1985; Moore and Cayle, 1990).

SONOGRAPHIC FINDINGS

A diagnosis of oligohydramnios is almost always made on the basis of sonographic findings. Several methods of sonographic amniotic fluid assessment have been described. The subjective assessment of amniotic fluid volume with ultrasound examination was the earliest technique described (Crowley et al., 1984). This method involved the assessment of the relative amount of amniotic fluid present by comparing the amount of echo-free fluid areas in the uterus with the space occupied by the fetus. Disadvantages of this method include the requirement of a trained observer and the lack of a numerical result that can be used to follow a trend in amniotic fluid volume. Studies of interobserver variability for subjective sonographic assessment of amniotic fluid volume found that among experienced observers subjective estimates had good agreement rates and that this was not improved by the use of an arbitrary amniotic fluid volume classification such as vertical pocket depth (Halperin et al., 1985; Goldstein and Filly, 1988).

However, most clinicians today use some form of objective semiquantitative estimate of amniotic fluid volume, based on the MVP or the AFI. The MVP involves surveying the entire uterus and measuring the depth of the deepest pocket of amniotic fluid in centimeters. Only amniotic fluid pockets free of fetal parts and umbilical cord are measured. The criteria for defining oligohydramnios vary, with some suggesting an MVP of less than 1 cm as an appropriate cutoff for oligohydramnios, while others use a cutoff of less than 2 cm to diagnose oligohydramnios (Manning et al., 1981; Chamberlain et al., 1984).

The AFI involves summing the maximum vertical pockets from each of the four quadrants of the uterus. In a report of sonographic AFI measurements in 197 patients, the mean AFI rose from 7 cm at 12 weeks of gestation to 20 cm at 26 weeks gestation, and then plateaued for the remainder of

gestation at approximately 16 cm (Phelan et al., 1987). In a cross-sectional study of 791 pregnancies with AFI measurements, an AFI of 7 cm was at the 5th centile at term, and only 1% of all pregnancies had an AFI of less than 5 cm at term (Moore and Cayle, 1990).

It is important to measure the AFI with the patient supine, to orient the transducer in the maternal sagittal plane, to measure the sonographic planes perpendicular to the floor, to measure fluid pockets free from umbilical cord or fetal extremities, and to use the umbilicus and linea nigra as landmarks for dividing the uterus into four quadrants (Phelan et al., 1987).

There is no agreement in the obstetric literature as to which method of sonographic measurement of amniotic fluid volume is best. In one study comparing MVP with AFI, the correlation coefficient was 0.51, and the MVP was associated with a lower sensitivity (Moore, 1990). Others have found good correlation between the MVP and AFI methods, with the MVP being better (Magann et al., 1994). Both MVP and AFI should therefore be considered reasonable methods for quantifying the amniotic fluid volume.

Whenever a diagnosis of oligohydramnios is made, a careful sonographic fetal anatomy survey should be performed to evaluate for fetal abnormalities, such as features of urinary tract obstruction or malformation. Absence of bladder filling following a 1-hour period of observation suggests a urinary tract abnormality. Fetal renal anomalies including renal agenesis (see Chapter 86), urethral obstruction (see Chapter 82), and multicystic kidneys (see Chapter 78) account for 11% of cases of oligohydramnios discovered during the second trimester (Shenker et al., 1991).

If severe oligohydramnios is present at less than 24 weeks of gestation, the possibility of pulmonary hypoplasia should be considered. Numerous sonographic criteria to predict pulmonary hypoplasia have been described. Measurements of chest circumference are highly predictive of pulmonary hypoplasia in patients with either severe oligohydramnios or prolonged premature rupture of membranes (D'Alton et al., 1992). Normal values for fetal thoracic circumference and for the ratio of thoracic circumference to abdominal circumference have been established, and this ratio has been found to remain constant throughout pregnancy (D'Alton et al., 1992). A thoracic to abdominal circumference ratio of less than 0.80 in the setting of severe oligohydramnios in the second trimester is suspicious for pulmonary hypoplasia. Fetal compression, including dolicocephaly and clubfeet, may be apparent (Figure 125-1).

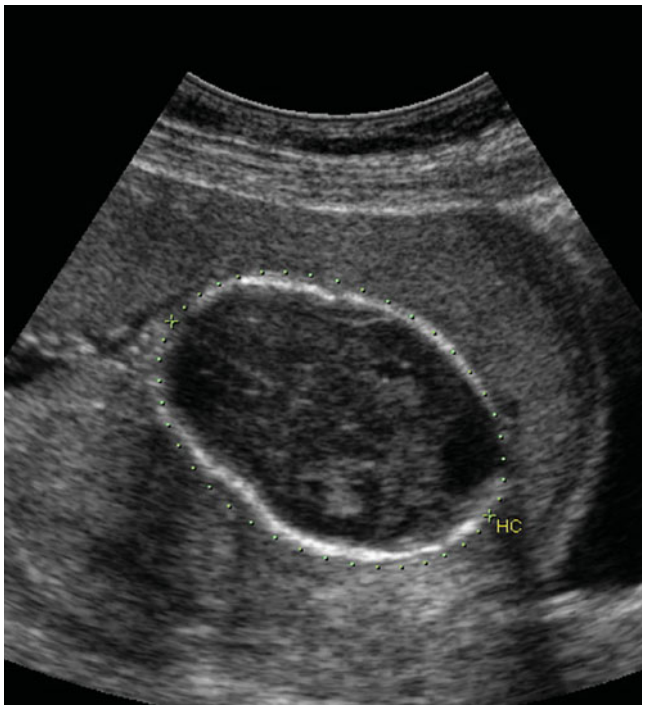

Figure 125-1 Prenatal ultrasound image at 20 weeks from pregnancy with severe oligohydramnios demonstrating fetal dolicocephaly. *(Courtesy of Prenatal Diagnosis Center, Women and Infants' Hospital.)*

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for oligohydramnios includes normal pregnancy during the late third trimester, postmaturity, intrauterine growth restriction, premature rupture of membranes, fetal death, fetal renal anomalies (bilateral multicystic dysplastic kidneys, bilateral renal agenesis, bilateral ureteral obstruction, posterior urethral valves, infantile polycystic kidney disease), neural tube defect, chromosomal abnormality, stuck twin, and medication use (such as indomethacin) by the mother.

ANTENATAL NATURAL HISTORY

The antenatal natural history of oligohydramnios depends on the gestational age at diagnosis and the cause of the oligohydramnios. Oligohydramnios accompanies a variety of serious fetal malformations, the most common being fetal renal abnormalities, and the underlying anomaly will dictate the natural history. Cardiac, skeletal, and neurologic malformations, in addition to aneuploidy and a variety of syndromic abnormalities, often coexist with the primary renal abnormality (McCurdy and Seeds, 1993). Bilateral renal agenesis (Potter syndrome) is uniformly lethal because of associated pulmonary hypoplasia and renal failure (Figure 125-2) (see Chapter 86).

The finding of significant oligohydramnios in the second trimester is associated with very high perinatal mortality (Barss et al., 1984; Bhutani et al., 1986; D'Alton et al., 1992). The combination of second trimester oligohydramnios and elevated maternal serum α-fetoprotein (MSAFP) has an extremely poor prognosis. In one report of 21 patients with

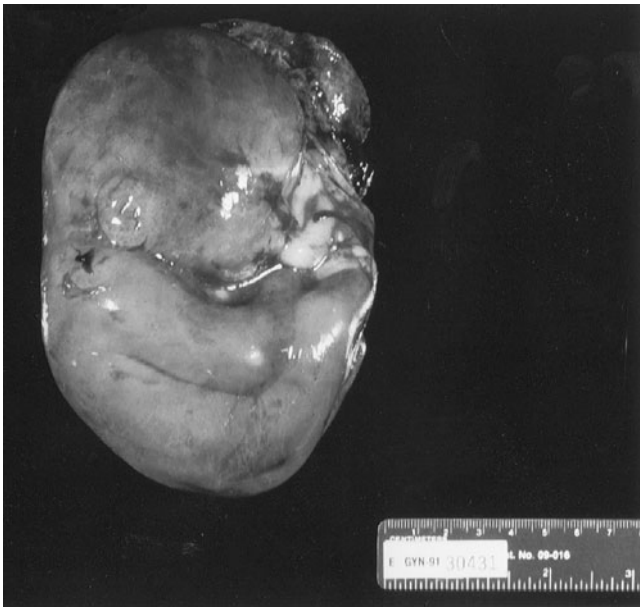

Figure 125-2 Severely constricted fetus with oligohydramnios due to bladder agenesis and a single dysplastic kidney. *(Courtesy of Dr. Joseph Semple.)*

midtrimester oligohydramnios and elevated MSAFP, only one infant survived (Dyer et al., 1987). Causes of perinatal loss in the setting of second trimester oligohydramnios include lethal congenital abnormalities, pulmonary hypoplasia, severe prematurity, and neonatal sepsis. Oligohydramnios in cases of chronic abruption appears to be an end-stage manifestation of severe uteroplacental insufficiency and is associated with a high incidence of intrauterine fetal death (Shenker et al., 1991).

Second trimester oligohydramnios following preterm premature rupture of membranes (PPROM) carries a poor prognosis, with up to a 60% fetal loss rate, due mostly to pulmonary hypoplasia (Bhutani et al., 1986; D'Alton et al., 1992). Sequelae of PPROM that contribute to the poor outcome include chorioamnionitis, amnion nodosum (Figure 125-3), neonatal sepsis, neonatal pneumonia, placental abruption, and cord prolapse (Gonen et al., 1989). Neonatal outcome following PPROM can be improved by the routine administration of antibiotics, such as ampicillin and erythromycin (Mercer et al., 1997).

The combination of oligohydramnios and fetal growth restriction is associated with significantly increased perinatal morbidity and mortality rates (Hill et al., 1983; Chamberlain et al., 1984; Seeds, 1984). The perinatal mortality rate ranges from 10% to 19% in these situations (Chamberlain et al., 1984). Close fetal surveillance is indicated to avoid antenatal deterioration of fetal status, and elective premature delivery may be needed.

Postmature pregnancies have increased rates of perinatal morbidity and mortality (Beischer et al., 1969). The finding of oligohydramnios in a pregnancy beyond 41 weeks of gestation identifies a subset of patients who are at significantly increased risk for adverse outcomes. There is a significantly higher risk of abnormal fetal testing, presence of fetal heart rate decelerations during labor, meconium staining, cesarean delivery for nonreassuring fetal testing, and depressed 1- and 5-minute Apgar scores (Rutherford et al., 1987; Sarno et al., 1990; Robson et al., 1992).

Little information exists on the antenatal natural history of oligohydramnios prior to 37 weeks of gestation in the absence of intrauterine growth restriction, PPROM, or fetal anomalies. In one case–control study of pregnancies with unexplained oligohydramnios, there was a significantly higher incidence of premature delivery but no difference in overall neonatal outcomes (Garmel et al., 1997). Oligohydramnios associated with maternal hypovolemia is associated with a good perinatal outcome and is generally reversible with hydration (Sherer et al., 1990).

MANAGEMENT OF PREGNANCY

Following a diagnosis of oligohydramnios, a careful maternal history should be obtained to evaluate for illnesses such as hypertension or chronic renal disease and to assess for use of medications such as prostaglandin synthetase inhibitors. Physical examination should include a sterile speculum examination to evaluate for pooling of amniotic fluid in the vaginal vault, phenaphthazine (nitrazine) paper analysis, and microscopic examination of a vaginal smear on a slide for the presence of ferning. The presence of oligohydramnios should prompt a thorough sonographic survey of the fetal anatomy. Visualization of the fetal anatomy may be extremely difficult in cases of severe oligohydramnios. Administration of furosemide to the mother has been advocated to improve detection of bilateral renal agenesis (Kurjak et al., 1981). Other authors have suggested that fetuses with severe growth restriction may not respond to furosemide administration secondary to decreased renal perfusion and decreased glomerular filtration rate, and therefore extreme caution should be used with this approach (Goldenberg et al., 1984).

Amnioinfusion may assist sonographic visualization of the fetus in pregnancies complicated by severe oligohydramnios. In one report of 13 pregnancies complicated by severe oligohydramnios, amnioinfusion of warmed normal saline was successfully performed in all patients and fluid for karyotype analysis was successfully obtained in 8 patients (Quetel et al., 1992). The use of amnioinfusion, together with indigocarmine dye instillation, allowed subsequent adequate ultrasound examination in 12 of 13 patients, a correct diagnosis of ruptured membranes in 6 patients, and an antenatal diagnosis of Meckel–Gruber syndrome in one case (Quetel et al., 1992). If a structural fetal anomaly is identified, karyotyping should be performed. In cases of severe oligohydramnios prior to 24 weeks of gestation, termination of pregnancy may be discussed with the patient.

The management of pregnancies with oligohydramnios secondary to PPROM depends on the gestational age at presentation. Ruptured membranes beyond 34 weeks of

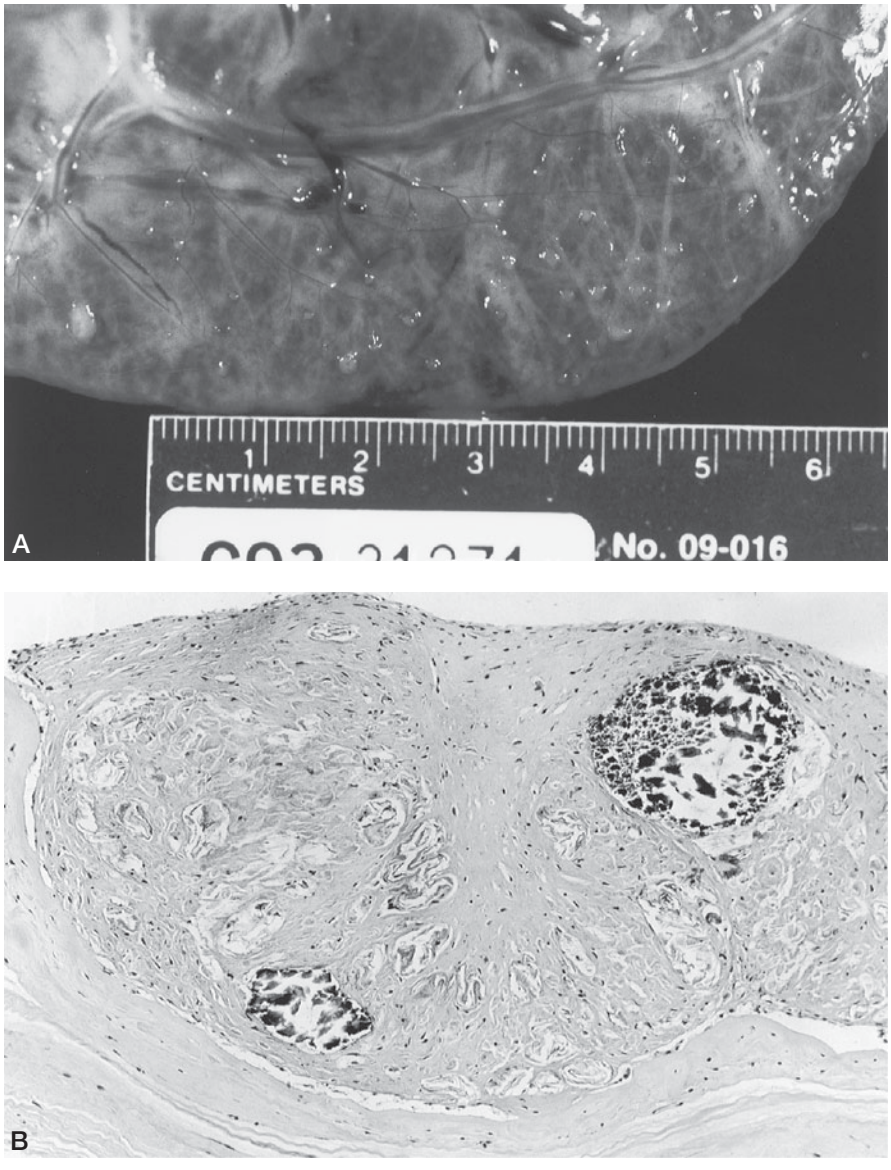

Figure 125-3 Gross (panel **A**) and microscopic (panel **B**) appearances of amnion nodosum in a fetus with oligohydramnios. *(Courtesy of Dr. Joseph Semple.)*

gestation should be managed by prompt induction of labor to minimize infectious maternal and fetal morbidity. In cases of PPROM at less than 34 weeks of gestation, expectant management is reasonable, provided there is no evidence of intrauterine infection, fetal compromise, or preterm labor. Frequent assessment in the form of daily fetal heart rate monitoring is recommended. Administration of betamethasone to the mother is advocated with PPROM prior to 32 to 34 weeks of gestation to reduce complications of prematurity. Although the evidence for improving neonatal outcome is less clear than with the use of corticosteroids in patients with intact membranes, there is an additional benefit in reduction of the incidence of intraventricular hemorrhage (National Institutes of Health, 1995). In cases of PPROM prior to 34 weeks of gestation, administration of antibiotics to the mother, typically ampicillin and erythromycin for 7 days, has been shown to increase the latency period prior to delivery and improves overall neonatal outcome (Mercer et al., 1997). There is no conclusive evidence to support or exclude a benefit from tocolysis in the setting of PPROM. Expectant inpatient management of PPROM is recommended from 24 to 32 weeks of gestation, provided there is reassuring maternal and fetal testing on a daily basis. In cases of PPROM from 32 to 34 weeks of gestation, evaluation of fetal lung maturity may help decide between expectant management and induction of labor.

In cases of fetal growth restriction with oligohydramnios at less than 36 to 37 weeks of gestation, careful fetal assessment is suggested, consisting of nonstress and biophysical testing at least twice weekly. If there is absent end-diastolic flow in the fetal umbilical artery, daily fetal testing is recommended. Delivery is indicated once a gestational age of 36 to 37 weeks is reached or if fetal testing becomes nonreassuring. In cases of oligohydramnios in the presence of an appropriately grown fetus, delivery should be considered once a gestational age of 37 weeks is reached.

The location of delivery will depend on the cause of the oligohydramnios and the gestational age at diagnosis. If a

congenital abnormality is present, delivery at a tertiary care center where appropriately trained personnel are available is recommended. In patients with PPROM, delivery location will depend on the gestational age. For patients at less than 32 weeks of gestation, delivery should occur in a tertiary care center with a neonatal intensive care unit. The mode of delivery should be based on usual obstetric practices; there is no indication to alter the mode of delivery based solely on the presence of oligohydramnios or PPROM. However, there is an increased incidence of cesarean delivery in pregnancies complicated by oligohydramnios, regardless of cause. For this reason, elective cesarean delivery may be reasonable in the setting of significant oligohydramnios with an unfavorable cervix. The significance of oligohydramnios as an isolated finding in the management of labor is difficult to ascertain. In one retrospective case–control study, the frequency of nonreassuring fetal testing, meconium staining, cesarean delivery, and admission to the neonatal intensive care unit were not significantly different when 65 women with oligohydramnios in the absence of IUGR, PPROM, or fetal anomalies were compared with 122 controls matched by indication for sonography (Garmel et al., 1997).

The management of pregnancy complicated by oligohydramnios secondary to PPROM at previable gestational ages (less than 24 weeks) should be individualized. The option of pregnancy termination should be discussed because of the risks of maternal infectious morbidity and the high likelihood of poor perinatal outcome. When expectant management is selected in such cases, inpatient hospitalization is generally not recommended after the initial evaluation, as active fetal intervention is not generally an option. Expectant management should include bed rest at home, daily monitoring of maternal temperature, and observation for the development of regular contractions. In 10% of such patients, leakage of amniotic fluid stops because of membrane resealing, amniotic fluid reaccumulates, and perinatal outcome is significantly improved (Johnson et al., 1990).

FETAL INTERVENTION

Amnioinfusion has been described to reduce the incidence of pulmonary hypoplasia in patients with severe oligohydramnios who are remote from term (Nakayama et al., 1983; Hansmann et al., 1991). However, this treatment remains experimental. The instillation of an isotonic antibiotic solution via the cervix has been used for treating patients with PPROM, but should also be considered experimental (Ogita et al., 1984). Amnioinfusion has also been described for patients with PPROM (Garzetti et al., 1997; Locatelli et al., 2000, Tranquilli et al., 2005). Because of the invasive nature of such approaches and the possibility for adverse maternal and perinatal outcomes, appropriately controlled clinical trials are necessary before these techniques can be recommended.

Another potential intervention for midtrimester PPROM is attempting to correct the defect. It is hoped that this treatment can increase the latency time to delivery, restore amniotic fluid volume to decrease the risk for lung hypoplasia as well as limb and muscular contracture defects, and decrease infectious morbidity.

Amniotic membrane patching has been suggested in carefully selected patients without evidence of intramniotic infection and confirmed PPROM. Transabdominal intraamniotic injection of platelets and cryoprecipitate has been used as a therapy for midtrimester PPROM. In a preliminary study, Quintero et al. treated 7 patients with iatrogenic PPROM (all cases of PPROM occurred following an invasive procedure such as amniocentesis or fetoscopy) diagnosed between 16 and 24 weeks of gestation with an amniopatch (Quintero et al., 1999). For the amniopatch, an amniocentesis was performed with a 22-gauge needle and platelets were administered followed by cryoprecipitate. Two mililiters of indigo carmine was then instilled to aid in documentation of amniotic fluid leakage. Intravenous antibiotics were then given for one week. Three pregnancies progressed well. The amniotic fluid re-accumulated and there was no further leakage. Two patients had unexplained intrauterine fetal demise despite resealing. One patient resealed but continued to have oligohydramnios secondary to fetal bladder outlet obstruction, and one patient had a miscarriage secondary to twin-to-twin transfusion syndrome despite resealing. This study demonstrates that, although experimental, an amniopatch with platelets and cryoprecipitate might be a promising therapy for iatrogenic cases of PPROM.

Administration of a cervical plug to retard the loss of fluid from the amniotic cavity is another potential treatment of midtrimester PPROM. In one study, 15 women with PPROM (either iatrogenic or spontaneous) had a gelatin sponge placed within the uterine cavity (O'Brien et al., 2002). The research protocol included hospital admission, amnioinfusion, cerclage placement, antibiotic administration, and perioperative tocolysis. Eight pregnancies (53%) delivered after 24 weeks of gestation, 6 of whom (30%) survived until hospital discharge. There were two intrauterine fetal deaths. The mean gestational age at delivery was 31.8 weeks (range 25–36 weeks). No adverse sequelae were attributed to the gelatin sponge. However, several anatomic abnormalities were diagnosed that were likely to be secondary to decreased amniotic fluid volume. This aggressive interventional protocol may improve outcomes in patients with previable PPROM by reducing the incidence of lethal pulmonary hypoplasia. However, further study is needed, before this approach could be considered mainstream. Several issues must be addressed such as route of applications (transvaginal versus transcervical), whether combinations of plugging agents are more efficacious, which fetuses are likely to benefit, and whether or not maternal complications are associated with this intervention.

Prophylactic amnioinfusion during labor to correct abnormal fluid volumes has not been found to be beneficial unless associated with recurrent variable decelerations.

Fetal intervention by means of vesicoamniotic shunting may be considered in selected fetuses with severe

oligohydramnios secondary to bladder outlet obstruction. Benefits of shunting may include a decreased incidence of pulmonary hypoplasia. Prognosis in these cases is related to the duration of exposure of the developing fetal lung to severe oligohydramnios and to the severity of the underlying renal condition. The option of vesicoamniotic shunting in such cases is described in more detail in Chapter 82.

TREATMENT OF THE NEWBORN

The extent of newborn intervention in cases of oligohydramnios will depend on the gestational age at diagnosis, the gestational age at delivery, and the cause of the oligohydramnios. If a sonographic diagnosis of renal agenesis is certain, no resuscitation of the newborn is indicated. However, if doubt exists about the diagnosis, a neonatologist should be present at delivery to evaluate for features of Potter syndrome and pulmonary hypoplasia. Intubation and mechanical ventilation of the newborn may be considered appropriate until a more definitive diagnosis for severe oligohydramnios is made. Pulmonary air leak may develop secondary to positive pressure ventilation in the setting of pulmonary hypoplasia, which may require the placement of chest tubes.

SURGICAL TREATMENT

No surgical treatments have been described.

LONG-TERM OUTCOME

The long-term outcome will depend on the gestational age at diagnosis, the gestational age at delivery, and the underlying cause of the oligohydramnios. The longest duration of survival reported with a diagnosis of bilateral renal agenesis is 39 days. Severe oligohydramnios may result in the development of arthrogryposis (see Chapter 101). Contractures of previously normal joints may also occur in cases of severe oligohydramnios of long duration. The feet are most commonly involved, typically resulting in positional clubfoot. Compression of the fetus against the uterine wall in the setting of severe oligohydramnios can produce a spectrum of abnormalities. Potter syndrome is characterized by low-set ears, hypertelorism, receding chin, flattened nose, wrinkled skin, and joint contractures.

GENETICS AND RECURRENCE RISK

The recurrence risk of oligohydramnios will depend on the underlying cause. The cause of bilateral renal agenesis is multifactorial. The recurrence risk following delivery of an infant with bilateral renal agenesis and a negative family history is approximately 3% to 4%. In a study of 41 index patients with bilateral renal agenesis, bilateral severe renal dysgenesis, or agenesis of one kidney with dysgenesis of the other, 10 of 111 first-degree relatives were found to have clinically unsuspected renal malformations (Roodhooft et al., 1984). Parents of fetuses with oligohydramnios due to renal anomalies should therefore be evaluated by ultrasound examination for renal anomalies.

The recurrence risk for premature rupture of membranes occurring in a future pregnancy is uncertain, but may be as high as 32% (Asrat et al., 1991). Such patients should therefore be considered at high risk for this complication in all future pregnancies.

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126 CHAPTER

Polyhydramnios

Key Points

- Polyhydramnios is an increase in the volume of amniotic fluid, the diagnosis of which is usually made using ultrasound.
- Causes of polyhydramnios include fetal congenital malformations, fetal neurological anomalies, fetal genetic abnormalities, and maternal issues, although the majority of cases are idiopathic.
- Sonographic assessment of polyhydramnios should include a careful survey of the fetal anatomy to rule out the presence of structural abnormalities or fetal growth restriction, and karyotyping should be considered if these are present.
- Polyhydramnios has been associated with an increased risk for preterm contractions and preterm delivery, in which case-reduction amniocentesis may be considered.
- Delivery at 39 weeks may be reasonable to relieve maternal symptoms as well as to reduce the risk of cord prolapse, should spontaneous rupture of membranes occur.
- Pregnancies complicated by polyhydramnios have a higher incidence of inefficient uterine activity leading to prolonged labor, postpartum uterine atony, and postpartum hemorrhage; cesarean delivery should be reserved for standard obstetric indications.
- Neonates should be evaluated carefully to assess for anatomical abnormalities that may have caused polyhydramnios.
- The long-term outcome for infants following a prenatal diagnosis of polyhydramnios depends on the gestational age at delivery and the presence of associated structural malformations.

CONDITION

Polyhydramnios, also known simply as hydramnios, is an increase in the volume of amniotic fluid. The diagnosis of polyhydramnios is most frequently made by ultrasound examination, but is often suspected by clinical examination revealing a fundal height greater than that expected for gestational age. Before the advent of prenatal sonography, polyhydramnios was defined as an amniotic fluid volume of more than 2 L. Sonographic diagnosis of polyhydramnios relies on the finding of a maximum vertical pocket of more than 8 cm (Figure 126-1) (Chamberlain et al., 1984). However, due to the asymmetric location of the fetus within the uterus, the use of this maximum vertical pocket (MVP) technique may lead to an overestimation of the amniotic fluid volume.

The amniotic fluid index (AFI) has been described as a more reliable means of quantifying amniotic fluid volume (Phelan et al., 1987). The AFI involves the summing of the largest vertical pockets from each of the four quadrants of the uterus. A normal amniotic fluid volume is defined as an AFI of between 8 and 18 cm, while polyhydramnios is defined as an AFI of greater than 24 cm. Normal values for the AFI throughout gestation have been described based on sonographic measurements of amniotic fluid volume in 791 uncomplicated pregnancies between 16 and 42 weeks of gestation (Moore and Cayle, 1990). These values are listed in Table 126-1. A reasonable working definition of polyhydramnios using current sonographic criteria is an AFI greater than the 95th percentile for the corresponding gestational age.

Amniotic fluid volume is the result of a balance between flow into and out of the amniotic cavity. In the first half of pregnancy, the majority of amniotic fluid is a result of active transport of sodium and chloride across the amniotic membrane and fetal skin, with water moving passively in response (Brace and Resnik, 1999). In the second half of pregnancy, the majority of amniotic fluid is a result of fetal micturition. Another major source of amniotic fluid is secretion from the

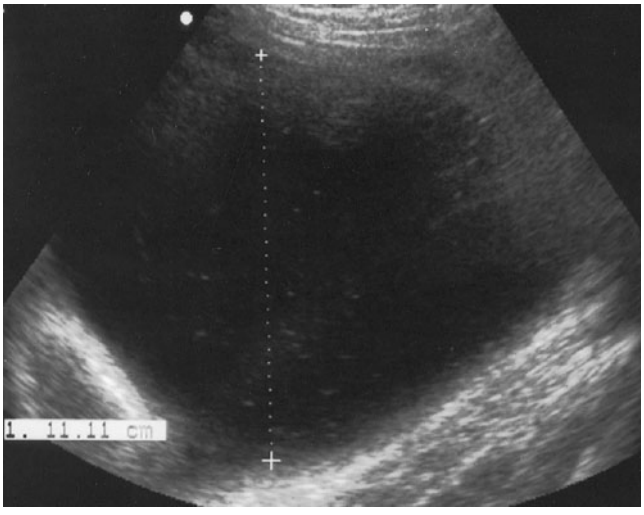

Figure 126-1 Prenatal sonographic image demonstrating a maximal vertical pocket of 11.11 cm of amniotic fluid.

fetal respiratory tract. The average amniotic fluid volume is 30 mL at 10 weeks, rising to 780 mL at 32 to 35 weeks, following which time a natural decrease in volume occurs (Brace and Resnik, 1999). The amniotic fluid volume is not stagnant, but is completely turned over at least once daily. Fetal urine first appears at 8 to 10 weeks of gestation, and reaches a production rate of 700 to 900 mL per day near term (Brace and Resnik, 1999).

Polyhydramnios can occur because of increased production of fluid by the fetus, as in the case of hydrops, or it can be due to an obstruction to fetal swallowing, as in the case of congenital gastrointestinal obstruction. Polyhydramnios is idiopathic in greater than 50% of cases (Mann et al., 2006). Maternal diabetes mellitus accounts for 15% of cases, fetal malformations for 13%, multiple gestations for 5%, and other causes for 1% (Hill and Breckle, 1987). However, the proportion of cases of polyhydramnios secondary to fetal malformation increases significantly as the severity of polyhydramnios increases. As the definition of polyhydramnios varies, so too does the reported incidence of associated fetal malformations. Two recent series have reported a 58% to 63% incidence of structural fetal malformations in pregnancies complicated by polyhydramnios (Damato et al., 1993; Many et al., 1996).

Fetal malformations associated with polyhydramnios include neural tube defects (such as anencephaly, Chapter 7), holoprosencephaly (see Chapter 14), cardiac anomalies (such as truncus arteriosus, Chapter 54), gastrointestinal atresias or stenoses (see Chapters 71–73), chest or abdominal masses such as cystic adenomatoid malformation (see Chapter 35) or diaphragmatic hernia (see Chapter 37), skeletal dysplasias, neuromuscular disorders (such as myotonic dystrophy), infections (such as parvovirus), metabolic disorders (such as Gaucher disease), chromosomal abnormalities (such as trisomy 18, Chapter 130), tumors (such as sacrococcygeal teratoma, Chapter 115), and genetic syndromes (such as Beckwith–Wiedemann syndrome).

Table 126-1

Amniotic Fluid Index Values in Normal Pregnancy

Week	No. of Patients	Amniotic Fluid Index Percentile Values				
		2.5th	5th	50th	95th	97.5th
16	32	73	79	121	185	201
17	26	77	83	127	194	211
18	17	80	87	133	202	220
19	14	83	90	137	207	225
20	25	86	93	141	212	230
21	14	88	95	143	214	233
22	14	89	97	145	216	235
23	14	90	98	146	218	237
24	23	90	98	147	219	238
25	12	89	97	147	221	240
26	11	89	97	147	223	242
27	17	85	95	146	226	245
28	25	86	94	146	228	249
29	12	84	92	145	231	254
30	17	82	90	145	234	258
31	26	79	88	144	238	263
32	25	77	86	144	242	269
33	30	74	83	143	245	274
34	31	72	81	142	248	278
35	27	70	79	140	249	279
36	39	68	77	138	249	279
37	36	66	75	135	244	275
38	27	65	73	132	239	269
39	12	64	72	127	226	255
40	64	63	71	123	214	240
41	162	63	70	116	194	216
42	30	63	69	110	175	192

Reproduced, with permission, from Moore TR, Cayle JE. The amniotic fluid index in normal human pregnancy. Am J Obstet Gynecol 1990;162:1168-1173.

INCIDENCE

The reported incidence of polyhydramnios varies, reflecting differences in definition. Polyhydramnios is reported in 0.1% to 3% of pregnancies when clinical methods are used to make the diagnosis (Kramer, 1966). In one series of 9,189 patients who had sonographic assessment of amniotic fluid volume by measuring the MVP, the overall incidence of polyhydramnios was 0.9% (Hill and Breckle, 1987). In this study, mild polyhydramnios was diagnosed when the MVP measured between 8 cm and 11 cm, moderate polyhydramnios was defined as an MVP of 12 cm to 15 cm, and severe polyhydramnios was diagnosed when the MVP exceeded 16 cm. Mild

polyhydramnios accounted for 79% of cases, moderate polyhydramnios 16%, and severe polyhydramnios accounted for 5% (Hill and Breckle, 1987). In another series, using an AFI cutoff of greater than 24 cm, mild polyhydramnios was diagnosed in 8% of patients (Smith et al., 1992).

SONOGRAPHIC FINDINGS

Most diagnoses of polyhydramnios are now based on sonographic findings. The two most common methods of objectively measuring the amniotic fluid volume are the maximum vertical pocket (MVP) and the amniotic fluid index (AFI). The MVP involves surveying the entire uterus and measuring the depth of the deepest pocket of amniotic fluid in centimeters. Only amniotic fluid pockets free of fetal parts and umbilical cord are measured. The most commonly used cutoff for polyhydramnios using the MVP technique is a depth greater than 8 cm. The AFI involves summing the MVPs from each of the four quadrants of the uterus. In a report of sonographic AFI measurements in 197 patients, the mean AFI rose from 7 cm at 12 weeks' gestation to 20 cm at 26 weeks' gestation, and then plateaued for the remainder of gestation at approximately 16 cm (Phelan et al., 1987). The 95th percentile value for AFI at 37 weeks is 24 cm, but decreases to 19 cm at 41 weeks, reflecting the normal decrease in amniotic fluid production at term (Moore and Cayle, 1990). It is important to measure the AFI with the patient supine, to orient the transducer in the maternal sagittal plane, to measure the sonographic planes perpendicular to the floor, to measure fluid pockets free from umbilical cord or fetal extremity, and to use the umbilicus and linea nigra as landmarks for dividing the uterus into four quadrants (Phelan et al., 1987).

There is no agreement in the obstetric literature as to which method of sonographic measurement of amniotic fluid volume is best. In one study comparing MVP with AFI, the correlation coefficient was 0.51, and the MVP was associated with a lower sensitivity (Moore, 1990). Others have found good correlation between the MVP and AFI methods, with the MVP being better (Magann et al., 1994). In another study comparing 13 different sonographic methods of amniotic fluid volume assessment with a dye dilution technique, the AFI underestimated the actual amniotic fluid volume by as much as 52% in cases of polyhydramnios (Dildy et al., 1992). When compared with the AFI, several of the other 12 methods of ultrasound prediction of amniotic fluid volume produced lower mean errors as compared with true amniotic fluid volume. However, the investigators concluded that the minimal improvement in accuracy offered by other ultrasound measurements was not sufficient to warrant replacement of the AFI (Dildy et al., 1992).

Sonographic assessment of polyhydramnios should include a careful survey of the fetal anatomy to rule out the presence of structural malformations. Because of the possibility of underlying fetal neuromuscular disorders, fetal swallowing, muscle tone, and fetal movement should be observed. In a study of 41 fetuses with a diagnosis of idiopathic polyhydramnios who were tested for the presence of a myotonic dystrophy mutation, 4 (9.7%) were shown to be affected. Three of the four fetuses had a positive family history of myotonic dystrophy (Esplin et al., 1998).

DIFFERENTIAL DIAGNOSIS

The causes of polyhydramnios are diverse, involving many maternal and fetal conditions, including those associated with immune and nonimmune hydrops fetalis (see Chapters 127 and 128). Maternal abnormalities should be considered, such as diabetes mellitus, rhesus isoimmunization, and preeclampsia resulting in the "mirror syndrome" (Ballantyne syndrome). If a multiple gestation is present, the possibility of twin–twin transfusion syndrome should be considered (see Chapter 119), especially if one fetus has severe oligohydramnios (stuck twin). Fetal infections associated with polyhydramnios include parvovirus, cytomegalovirus, toxoplasmosis, and syphilis. Polyhydramnios can also be seen with inborn errors of metabolism such as Gaucher disease, gangliosidoses, and mucopolysaccharidoses. Chromosomal abnormalities should also be considered, such as trisomy 18 (see Chapter 130), trisomy 21 (see Chapter 131), Turner syndrome (see Chapter 134), and 4p– (Wolf–Hirschhorn) syndrome.

Fetal neurologic malformations associated with polyhydramnios include anencephaly, encephalocele, meningomyelocele, holoprosencephaly, Dandy–Walker malformation, lissencephaly, and agenesis of the corpus callosum. Fetal cardiac abnormalities associated with polyhydramnios include cardiac arrhythmias, truncus arteriosus, aortic coarctation, and aortic arch interruption. Fetal thoracic abnormalities associated with polyhydramnios include congenital cystic adenomatoid malformation (CCAM), bronchopulmonary sequestration (BPS), diaphragmatic hernia, chylothorax, and tracheal atresia. Fetal gastrointestinal malformations associated with polyhydramnios include cleft lip and palate, tracheoesophageal fistula, esophageal or intestinal atresia, omphalocele, gastroschisis, and annular pancreas. Fetal skeletal abnormalities associated with polyhydramnios include achondroplasia, osteogenesis imperfecta, hypophosphatasia, campomelic dysplasia, and thanatophoric dysplasia. Fetal neuromuscular abnormalities associated with polyhydramnios include myotonic dystrophy and arthrogryposis multiplex congenita (Bianchi and Van Marter, 1994; Esplin et al., 1998). Other fetal abnormalities associated with polyhydramnios include cystic hygroma, neck masses such as cervical teratoma or goiter, sacrococcygeal teratoma, or lethal multiple pterygium syndrome.

ANTENATAL NATURAL HISTORY

The antenatal natural history of pregnancies complicated by polyhydramnios is largely determined by the underlying

cause of the polyhydramnios. In addition, different clinical forms of polyhydramnios are described. Polyhydramnios is described as being acute when there is a rapid accumulation of excessive amniotic fluid within 1 week associated with severe abdominal pain and respiratory distress, subacute when it develops over a period of 2 weeks with less severe symptoms, and chronic when there is gradual accumulation of amniotic fluid with less maternal discomfort (Desmedt et al., 1990). The most common form of polyhydramnios is a gradual progression with minimal maternal symptoms, and the vast majority of pregnancies complicated by polyhydramnios are diagnosed during the third trimester.

Adverse maternal and perinatal outcomes have been associated with polyhydramnios (Desmedt et al., 1990). The overall perinatal mortality in one series of 243 patients with polyhydramnios was 33 per 1000 births (Chamberlain et al., 1984). One of the eight perinatal deaths occurred in a structurally normal fetus, while the remaining seven perinatal deaths were related to major fetal malformations. The corrected perinatal mortality rate for normal fetuses with polyhydramnios was 4 per 1000 births. Both the overall and the corrected perinatal mortality rates in this series were significantly greater than that observed in patients with normal amniotic fluid volume (Chamberlain et al., 1984).

Polyhydramnios has been associated with a higher frequency of prematurity. The presence of an overdistended uterus appears to be significantly associated with preterm contractions and premature delivery (Queenan and Gadow, 1970). The frequency of preterm delivery in pregnancies complicated by polyhydramnios ranges from 11% to 29% (Phelan et al., 1990). The incidence of preterm delivery appears to be significantly greater for subgroups with insulin-dependent diabetes mellitus and structural fetal malformations as compared with patients with idiopathic polyhydramnios (Many et al., 1996). The incidence of preterm delivery in patients with gestational diabetes was no greater than in the general population. The higher incidence of preterm delivery in insulin-dependent diabetes is because of the higher rate of pregnancy-induced hypertension, nonreassuring fetal testing, and elective delivery (Greene et al., 1989). It would therefore appear that the underlying cause of polyhydramnios is the major determining factor in predicting the risk of preterm delivery. In patients with polyhydramnios of undetermined cause, the frequency of preterm delivery appears to be no different than in the general population (Hill and Breckle, 1987).

The clinical implications of polyhydramnios that resolve spontaneously prior to delivery are uncertain. In one series of 41 cases of resolving polyhydramnios in nondiabetic patients, there was no increase in the rate of congenital anomalies but there was significantly higher mean birth weight and glucose intolerance as compared with controls with normal amniotic fluid volume (Hill et al., 1995).

MANAGEMENT OF PREGNANCY

Following the diagnosis of polyhydramnios, a careful maternal history should be performed to evaluate for possible underlying causes, such as diabetes mellitus. If a screening test for maternal diabetes has not yet been performed, one should be performed as soon as possible. A careful sonographic survey of fetal anatomy should be performed to exclude the presence of associated structural fetal malformations. Serial sonographic examinations are recommended to follow the degree of polyhydramnios.

The need for karyotyping in a fetus with polyhydramnios and no identifiable structural abnormalities is controversial. In one series of idiopathic polyhydramnios, the incidence of aneuploidy was 3.2%, which included two cases of trisomy 21 and one case of trisomy 18 (Brady et al., 1992). In another series of 59 cases of polyhydramnios, there was one case (1.7%) of aneuploidy (Landy et al., 1987). In a series of 49 patients with an AFI of 24 cm or greater, 27 patients had unexplained polyhydramnios, and there were no chromosomal abnormalities (Carlson et al., 1990). In a further series of 131 pregnancies complicated by polyhydramnios prior to 26 weeks' gestation, all 7 cases of chromosomal abnormalities were associated with abnormal sonographic findings (Hendricks et al., 1991). Our policy is to offer amniocentesis when there are associated sonographic abnormalities, when there is intrauterine growth restriction, or when there is imperfect sonographic visualization of fetal anatomy. Although general visualization of fetal anatomy is enhanced when there is a mild increase in amniotic fluid volume, there may be great difficulty in imaging due to fetal depth in cases of extreme polyhydramnios.

If fetal sonographic imaging demonstrates the presence of polyhydramnios and abnormal posturing of the extremities, consideration should be given to prenatal DNA testing for the myotonic dystrophy mutation (Esplin et al., 1998).

Treatment of polyhydramnios should focus on the underlying cause. Intervention to reduce the amount of amniotic fluid with the goal of decreasing contractions and avoiding preterm delivery has been advocated. Such temporizing measures include the administration of indomethacin and serial reduction amniocentesis. Most of the experience with the use of serial reduction amniocentesis has been associated with treatment of the twin–twin transfusion syndrome (see Chapter 119).

Delivery should occur at a tertiary care center if there are associated structural malformations, twin–twin transfusion syndrome, or hydrops fetalis, or if a congenital neuromuscular disorder is suspected. While elective preterm delivery is not indicated in cases of severe polyhydramnios, consideration should be given to delivery at 39 weeks' gestation because of maternal discomfort and also because of the risk of umbilical cord prolapse, should rupture of membranes occur. If artificial rupture of membranes is carried out, the procedure should be performed in or near a delivery room, with the capability of performing a cesarean delivery if there is a cord prolapse or placental abruption. Amniotic fluid should be allowed to drain slowly through a needle puncture. Pregnancies complicated by polyhydramnios have a higher incidence of inefficient uterine action, prolonged labor, postpartum uterine atony, and postpartum hemorrhage. Cesarean delivery is reserved for usual obstetric indications.

FETAL INTERVENTION

Fetal therapy is possible for some causes of polyhydramnios. In cases of polyhydramnios associated with hydrops fetalis, the possibility of direct fetal intravascular transfusion may exist (see Chapter 127). Polyhydramnios and hydrops fetalis secondary to supraventricular tachyarrhythmia may be amenable to digoxin therapy (Simpson and Marx, 1994). As discussed in Chapetr 119, polyhydramnios in the setting of severe twin–twin transfusion syndrome has been successfully treated with serial reduction amniocentesis and with laser ablation of placental surface anastomotic vessels.

Several investigators have reported the successful use of indomethacin therapy for idiopathic polyhydramnios (Cabrol et al., 1987; Lange et al., 1989; Ash et al., 1990; Kirshon et al., 1990b; Mamopoulos et al., 1990; Rosen et al., 1990; Gerson et al., 1991; Malas and Hamlett, 1991). Mechanisms proposed for the therapeutic effect of indomethacin in cases of polyhydramnios include decreased fetal urine production and enhanced fluid absorption in the lungs, secondary to increased fetal breathing. Reports involving a total of 44 patients have described use of indomethacin varying from an upper dose of 2 to 3 mg per kilogram of body weight per day in the form of oral tablets or rectal suppositories, to a lower dose of 25 mg orally every 6 hours. Maternal complications of indomethacin therapy include gastrointestinal disturbance, transient cholestatic jaundice, transient renal insufficiency, and pulmonary edema (Moise, 1993b). Fetal complications include oligohydramnios and ductal constriction (Kirshon et al., 1990a; Mamopoulos et al., 1990). Neonatal complications include renal insufficiency, persistent fetal circulation, ileal perforation, and necrotizing enterocolitis (Csaba et al., 1978; Cantor et al., 1980; Mogilner et al., 1982; Vanhaesebrouck et al., 1988; Gerson et al., 1991). If indomethacin is to be used for the treatment of polyhydramnios, weekly assessment of amniotic fluid volume should be performed and the medication should be discontinued when the amniotic fluid volume reduction exceeds two-thirds of the initial volume. Fetal echocardiography should be performed within the first 24 hours after the initiation of indomethacin to evaluate for ductal constriction and should then be repeated weekly (Moise, 1993a). If mild ductal constriction is noted, the indomethacin dose should be reduced, and if tricuspid regurgitation is noted the medication should be discontinued completely.

At our center, indomethacin has not been used for the treatment of polyhydramnios because of the potential for significant fetal complications. Although indomethacin has been shown to be effective as defined by normalization of amniotic fluid volume, we have not found evidence that this resulted in any change in overall perinatal outcome. Given the risks associated with indomethacin, our approach has been to educate patients about the signs and symptoms of premature labor and to evaluate them if they are symptomatic. Amniocentesis is reserved for cases of polyhydramnios associated with significant maternal discomfort and likely impending preterm labor.

TREATMENT OF THE NEWBORN

A detailed newborn physical examination is recommended because a structural malformation may be present despite a thorough prenatal ultrasound examination. In one series of 59 cases of polyhydramnios a false-negative ultrasound survey was reported in 8 cases (Hendricks et al., 1991). Particular attention should be paid in the newborn nursery to the infant's suck-and-swallow coordination and to the passage of meconium. If bilious vomiting or abdominal distention occurs, a plain abdominal radiograph should be obtained immediately. In cases of polyhydramnios secondary to maternal diabetes, a delivery room neonatal glucose measurement should be obtained because of the possibility of profound neonatal hypoglycemia.

SURGICAL TREATMENT

No specific surgical treatment of the newborn is described for idiopathic polyhydramnios. However, surgical treatment may be necessary if associated structural malformations such as tracheoesophageal fistula or intestinal atresias are present.

LONG-TERM OUTCOME

Long-term outcome for infants following a prenatal diagnosis of polyhydramnios depends on the gestational age at delivery and on the presence of associated structural malformations. In cases of additional malformations, the long-term outcome will primarily be dictated by the nature of the abnormality rather than by the existence of polyhydramnios.

GENETICS AND RECURRENCE RISK

Recurrence of idiopathic polyhydramnios is uncommon, although case reports documenting such recurrences do exist (Sieck and Ohlsson, 1984; Weissman and Zimmer, 1987; Shimizu et al., 1988). In one series of 780 cases of polyhydramnios, there were 36 cases (4.6%) of recurrent polyhydramnios (Beischer et al., 1993). The risks associated with recurrent polyhydramnios include the risk of fetal malformation and premature delivery (Beischer et al., 1993). Polyhydramnios attributable to a specific genetic diagnosis may recur based on the pattern of inheritance of the condition.

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Immune Hydrops

127
CHAPTER

Key Points

- Immune hydrops is a serious condition in which abnormal fluid collections accumulate in at least two different fetal compartments, and in which circulating antibodies against red cell antigens are detected in the mother.
- If a first-time mother is Rh negative and her fetus is Rh positive, there is a 16% risk that the fetal Rh antigen will stimulate the maternal immune system to produce anti-D antibody.
- Isoimmunization due to non-Rh(D) and non-ABO incompatibility usually occurs as a result of blood transfusions, and atypical antibodies develop in approximately 1% to 2% of recipients.
- Fetal anemia secondary to Kell isoimmunization differs from that due to Rh(D) isoimmunization because the mechanism for the anemia is most likely erythroid suppression rather than hemolysis.
- Immune and nonimmune hydrops can be differentiated by maternal indirect Coombs test to screen for antibodies associated with blood group incompatibility.
- Immune hydrops should be considered an emergency, and arrangements should be made to promptly perform percutaneous umbilical blood sampling (PUBS) and possibly fetal blood transfusion or immediate delivery depending on gestational age.
- Blood for PUBS should be group O red cells, packed to a hematocrit of approximately 80%, less than 4 days old, irradiated, anti-cytomegalovirus negative, negative for the antigen to which the mother is immunized, and Kell negative.
- It is generally not a good idea to transfuse a hydropic fetus to a final hematocrit that is greater than 25% or greater than four times the initial hematocrit, as this has been associated with fluid overload and sudden intrauterine fetal death.
- The optimal mode of delivery for the hydropic fetus is uncertain, although cesarean delivery is usually considered safer to decrease the risk of soft-tissue trauma.
- Minimal data are available regarding the long-term outcome of surviving fetuses that had immune hydrops.
- The recurrence risk for immune hydrops is significant. In general, the more severe the obstetric history of rh isoimmunization, the more likely the recurrence risk for severe disease in the future.

CONDITION

Immune hydrops fetalis is a serious fetal condition in which abnormal fluid collections accumulate in at least two different fetal compartments, and in which circulating antibodies against red cell antigens are detected in the mother. Hydrops fetalis is associated with a pathologic increase in interstitial and total fetal body water, usually appearing in fetal soft tissues and serous cavities. The cause may be either immunologic or nonimmunologic, depending on the presence or absence of maternal antibodies against fetal red cell antigens. While previously it was considered that the majority of cases of hydrops fetalis were secondary to maternal–fetal blood group incompatibilities, it is now estimated that the causes are nonimmunologic in more than 90% of cases (see Chapter 128) (Santolaya et al., 1992).

Immune hydrops is most likely a result of maternal–fetal Rhesus (Rh) blood group incompatibility, in which maternal antibodies to certain fetal blood group antigens cross the placenta, causing hemolysis of fetal blood and profound fetal anemia. This process is also referred to as Rh isoimmunization. An in-depth discussion of the pathogenesis of Rh blood group incompatibility is beyond the scope of this textbook. Briefly, the five antigens that make up the Rh system are D, C, c, E, and e. The presence of the D antigen confers Rh blood group positivity, while its absence indicates Rh negativity. Approximately 15% of Caucasians are Rh negative, while 30% of Basques are Rh negative, and 4% to 8% of blacks are Rh negative (Bowman, 1999). A total of 45% of Rh-positive individuals are homozygous, so all their offspring will be Rh positive. By contrast, 55% of Rh-positive individuals are heterozygous, so there is a 50/50 chance that their offspring will be Rh positive. If a first-time mother is Rh negative and her fetus is Rh positive, there is a 16% risk that fetal Rh antigen will stimulate the maternal immune system to produce anti-D antibody (Bowman, 1999). This first immune response generally consists of anti-D IgM antibody, which cannot cross the placenta to cause fetal hemolysis. In a subsequent pregnancy, if the fetus is again Rh positive, a more rapid immune response occurs, consisting of high titers of anti-D IgG antibody, which rapidly crosses the placenta to produce fetal hemolysis and profound fetal anemia.

The mechanism by which maternal–fetal Rh incompatibility produces immune hydrops fetalis is complex and the exact pathophysiologic process has not yet been elucidated. It is known that maternal anti-D IgG antibody attaches itself to the Rh antigen present on fetal red cells. This results in chemotaxis of phagocytes in the fetal spleen, which leads to destruction and hemolysis of fetal red cells. In response, the fetus produces more erythropoietin, which stimulates the fetal bone marrow to increase red cell production. Eventually, marrow capacity is reached, and extramedullary erythropoiesis occurs, with fetal red cell production in the fetal liver, spleen, kidney, adrenal glands, and intestine. Fetal hepatosplenomegaly is, therefore, common. Red cells produced at these sites are often immature, are nucleated, and appear in the circulation as erythroblasts. Hence, the synonym erythroblastosis fetalis for immune hydrops.

The majority of cases of Rh isoimmunization lead to mild or moderate fetal or neonatal hemolytic disease. However, approximately 20% to 25% of cases result in severe hemolytic disease, with immune hydrops developing in utero (Bowman, 1999). Hydrops develops in approximately half of these fetuses between 18 and 34 weeks of gestation, with hydrops developing in the remaining fetuses between 34 weeks and term. The pathophysiology of fetal hydrops is unclear. Several hypotheses have been suggested. One thought is that simple congestive heart failure secondary to fetal anemia leads to hydrops. Another more complicated hypothesis is that severe fetal anemia leads to extensive extramedullary erythropoiesis, with associated hepatosplenomegaly and distortion of intrahepatic architecture. This distortion results in portal and umbilical venous distortion, portal hypertension, placental edema, and placental hypoperfusion (Bowman, 1999). With deteriorating hepatic synthesis, progressive hypoalbuminemia occurs, adding to the generalized edema, anasarca, and pleural and pericardial effusions. However, a recent study calls into question whether or not hypoalbuminemia is the cause of immune hydrops (Pasman et al., 2006). Pasman et al. evaluated fetal blood samples taken at the first fetal blood transfusion in 244 Rh-D alloimmunized pregnancies. Hemoglobin concentration, albumin concentration, and severity of hydrops were assessed. Most fetuses (71%) with immune hydrops had an albumin concentration within the normal range suggesting that decreased albumin is unlikely to cause hydrops. Nonetheless, there was a negative correlation between the degree of fetal hydrops and the fetal serum albumin level suggesting that hypoalbuminemia occurs as a secondary effect in hydrops. The authors suggest that cardiac failure and lymphatic flow obstruction may be more important causative factors of hydrops.

Effective prevention programs to reduce the incidence of Rh(D) isoimmunization, using passive maternal immunization with Rh immunoglobulin, have significantly decreased the numbers of fetuses with immune hydrops. Because of the efficacy of these programs, non-Rh(D) blood group isoimmunization is becoming proportionately more frequent as a cause of immune hydrops. Immune hydrops secondary to ABO blood group incompatibility is extremely rare, as the resulting hemolytic disease is almost always mild in nature (Gilja and Shah, 1988; Bowman, 1999). Isoimmunization due to non-Rh(D) and non-ABO incompatibility usually occurs as a result of blood transfusions, with such atypical antibodies developing in 1% to 2% of recipients (Bowman, 1999). At least 60 such atypical antibodies have been identified as potentially causing hemolytic disease of the fetus or newborn, with anti-c, anti-E, and anti-Kell antibodies being the most important causes of severe disease, including hydrops (Bowman, 1990). Fetal anemia secondary to Kell isoimmunization differs from that due to Rh(D) isoimmunization, as the mechanism for anemia is most likely

erythroid suppression rather than hemolysis (Vaughan et al., 1994).

INCIDENCE

The risk of immune hydrops in a first Rh-sensitized pregnancy is approximately 8% to 10% (Bowman, 1999). The incidence of immune hydrops has decreased significantly with the widespread use of passive immunization using Rh immunoglobulin for Rh-negative mothers at 28 weeks of gestation, following suspected fetomaternal hemorrhage, and postpartum following the delivery of an Rh-positive infant. The efficacy of this prevention program has been demonstrated by a decline in the incidence of Rh hemolytic disease of the fetus or newborn, from 65 in 10,000 births in the United States in 1960 to 10.6 in 10,000 births in 1990 (Chavez et al., 1991). The relative proportion of cases of immune hydrops secondary to non-Rh(D) atypical antibodies is increasing, as the use of Rh immunoglobulin has become widespread, with Kell isoimmunization now affecting 0.1% of all pregnancies (Caine and Mueller-Heubach, 1986).

SONOGRAPHIC FINDINGS

The diagnosis of hydrops is made following the detection of abnormal or increased fluid accumulation in at least two distinct fetal body cavities. Examples include pericardial effusion, pleural effusion, ascites, subcutaneous edema, cystic hygroma, polyhydramnios, and placental thickening (Figures 127-1 to 127-3). In general, skin thickness of at least 5 mm is required to diagnose subcutaneous edema, and a placental thickness of at least 6 cm is required to diagnose placentamegaly (Romero et al., 1988). These features do not necessarily indicate hydrops; it should be noted that skin thickening of at least 5 mm may be commonly seen in macrosomic fetuses. If abnormal fluid accumulation is confined to only one

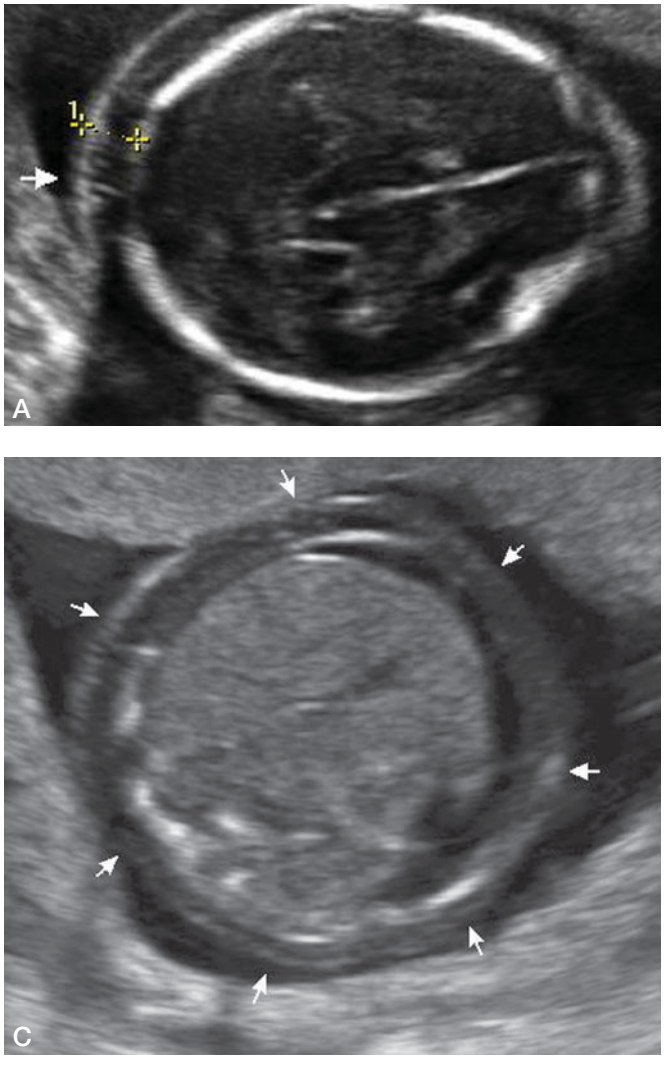

Figure 127-1 **A.** Axial image of a fetus demonstrating scalp edema due to immune hydrops. **B.** Sagittal image demonstrating edema of the scalp and face in a fetus with immune hydrops. **C.** Axial image demonstrating abdominal ascities and edema of the abdominal wall in a fetus with immune hydrops.

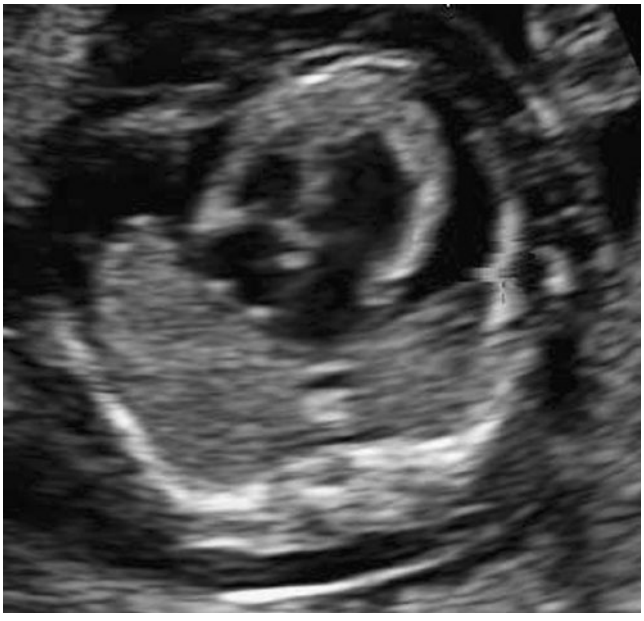

Figure 127-2 Axial image demonstrating a pericardial effusion in a fetus with immune hydrops.

site, then the diagnosis of hydrops should not be used, and the case should be described simply in terms of the involved site, such as isolated ascites or isolated pleural effusion.

Fetal ascites is diagnosed sonographically by the visualization of an echolucent rim encompassing the entire fetal abdomen in a transverse view. Loops of bowel and the outline of the fetal liver, spleen, bladder, and diaphragm are generally more easily seen in the presence of ascites. Pericardial effusion

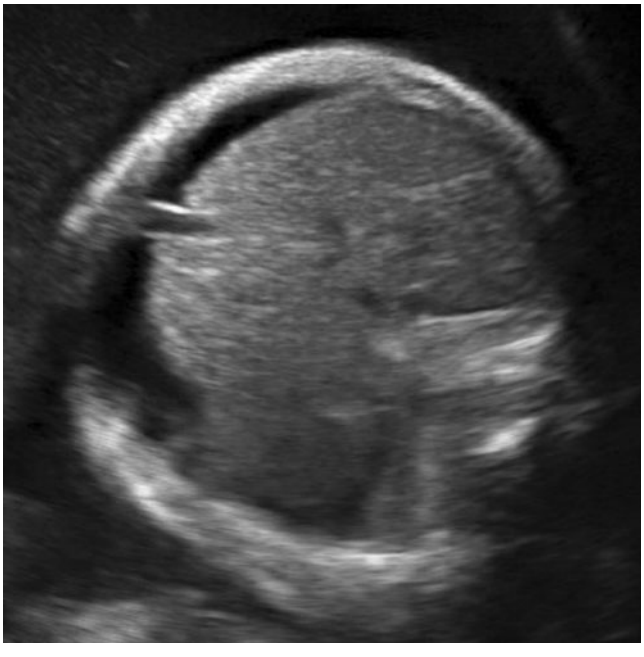

Figure 127-3 Axial image demonstrating abdominal ascites in a fetus with immune hydrops.

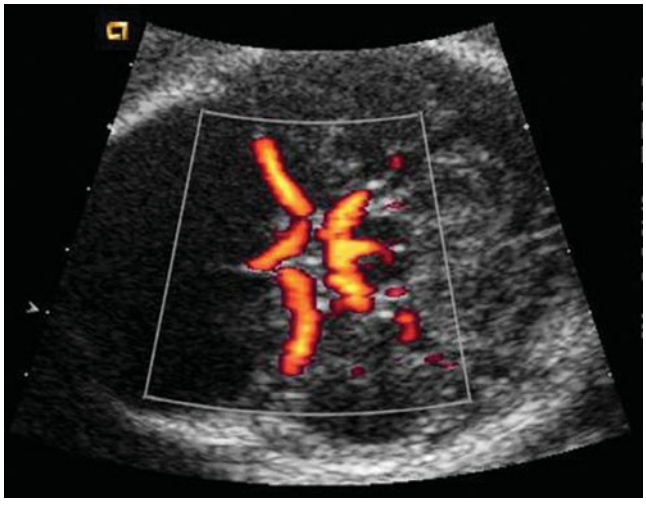

Figure 127-4 Axial section through the fetal head using power Doppler to identify the middle cerebral artery arising from the Circle of Willis.

is diagnosed by the appearance of an echolucent rim at least 1 to 3 mm thick around both cardiac ventricles.

In general, fetal hydrops is not seen sonographically until the fetal hematocrit has fallen to below one-third of its normal range. However, there is no direct relationship between actual fetal hemoglobin level and sonographic appearance or severity of hydrops. The correlation between various sonographic findings and the degree of fetal anemia has been evaluated. No correlation has been found between the degree of fetal anemia and placental thickness or umbilical vein diameter, and poor correlation has been found between fetal liver and spleen dimensions and the degree of anemia (Nicolaides et al., 1988; Roberts et al., 1989; Oepkes et al., 1993). The use of Doppler sonography to predict fetal anemia has been more successful (Mari et al., 1995). An elevated peak systolic velocity (PSV) measured in the middle cerebral artery (MCA) is associated with an increased likelihood of fetal anemia (Figures 127-4 and 127-5). Mari et al. measured hemoglobin concentration from cordocentesis and PSV of blood flow in the MCA by Doppler velocimetry in 111 fetuses at risk for anemia due to maternal red cell alloimmunization (Mari et al., 2000). Hemoglobin values were compared to 265 normal fetuses. Forty-one fetuses did not have anemia, 35 had mild anemia, 4 had moderate anemia, and 31 had severe anemia (12 of which had hydrops). The sensitivity of an increased PSV of blood flow in the MCA for the prediction of moderate or severe anemia was 100%, including all cases of hydrops. The false-positive rate of PSV in an MCA of 1.5 MoM was 12%. The authors concluded that moderate-to-severe fetal anemia can, therefore, be reliably detected noninvasively. Several studies have suggested that Doppler ultraonography can replace invasive testing (measurement of Dela OD450) in the management of Rh-alloimmunized pregnancies (Zimmerman et al., 2002; Pereira et al., 2003; Bullock et al., 2005; Oepkes et al., 2006). Such Doppler measurements may be useful for surveillance following intrauterine transfusions

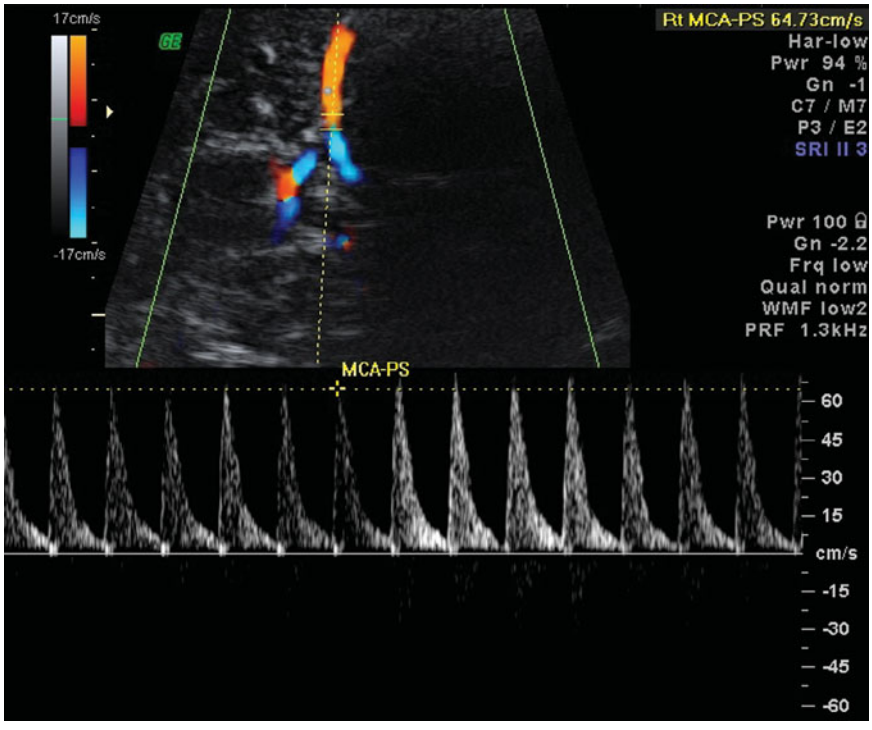

Figure 127-5 Elevated peak systolic velocity measured in the middle cerebral artery suggestive of fetal anemia in a pregnancy complicated by Rh alloimmunization.

to aid in the timing of repeat fetal blood sampling or transfusion (Mari et al., 2005). PSV in an MCA is also useful in detecting fetal anemia secondary to Kell alloimmunization (van Dongen et al., 2005).

DIFFERENTIAL DIAGNOSIS

Following the sonographic diagnosis of hydrops, the first step is to differentiate between immune and nonimmune causes. This is easily accomplished by the performance of a maternal indirect Coombs test to screen for antibodies associated with blood group incompatibility. Even if a maternal antibody that can be implicated in immune hydrops is detected, consideration should still be given in the differential diagnosis to the possibility of nonimmune hydrops. A detailed fetal sonographic survey of anatomy should be performed to exclude the presence of structural malformations that may also be associated with hydrops (see Chapter 128).

ANTENATAL NATURAL HISTORY

No data are available on the antenatal natural history of immune hydrops managed expectantly. In general, the finding of fetal hydrops in a pregnancy complicated by Rh isoimmunization or other atypical antibodies is ominous. If left untreated, the fetus will rapidly become moribund and will most likely die in utero. Therefore, the finding of fetal hydrops in such at-risk pregnancies should be considered an emergency, and arrangements should be made promptly to either perform percutaneous umbilical blood sampling (PUBS) and possibly fetal transfusion, or immediate delivery, depending on the gestational age.

PUBS is associated with high rates of fetal survival in fetuses with hydrops (78%–88.9%) (van Kamp et al., 2004; Craparo et al., 2005; Mesogitis et al., 2005). Mesogitis et al. reported on 18 patients diagnosed with fetal hydrops secondary to Rh disease (Mesogitis et al., 2005). All cases were managed with serial intravascular fetal transfusions. There were 11 mildly, and 7 severely, hydropic fetuses. Two fetuses with severe hydrops died in utero. The remaining cases delivered after 32 weeks of gestation. Hydrops reversed in utero in 90.9% of the mild cases and in 57.1% of the severe cases.

MANAGEMENT OF PREGNANCY

Following the diagnosis of immune hydrops, the patient should be immediately referred to a tertiary care center, with trained perinatologists to perform intrauterine transfusions and neonatologists to counsel parents and direct treatment of the newborn. A detailed sonographic fetal anatomy survey should be performed to quantify the severity of the hydrops and to rule out the presence of any additional structural malformations. In general, once immune hydrops has been diagnosed, the prognosis for the fetus is guarded, and arrangements to perform PUBS and possible intrauterine fetal transfusion should be expedited as rapidly as possible. It should be noted, however, that this requires the assembly of an experienced multidisciplinary team, including perinatologists, sonographers, blood bank personnel, hematology laboratory personnel, and nursing staff. The assembly of appropriate personnel can take time and is best expedited at

a tertiary care facility that has significant experience in performing fetal transfusions. If the gestational age is between 24 and 34 weeks, intramuscular betamethasone should be given to the mother to reduce the complications of prematurity in such high-risk pregnancies. If the gestational age is less than 24 weeks, the option of elective termination of the pregnancy should be discussed with the parents.

A maternal blood sample should be obtained immediately and sent to a blood bank for typing, antibody determination, and preparation of blood appropriate for fetal transfusion. The details of fetal transfusion for immune hydrops are described in the section on "Fetal Intervention." Following intrauterine transfusion, careful sonographic surveillance should be instituted, depending on the gestational age. Daily fetal testing with nonstress tests or biophysical profiles is reasonable for all potentially viable fetuses. Once there is sonographic evidence of resolution of hydrops, testing can be decreased to twice weekly. Sonographic surveillance for appropriate fetal growth should continue every 2 weeks.

Timing of delivery is variable with immune hydrops. If the fetus responds well to an initial intrauterine transfusion, repeat PUBS procedures should be scheduled at 1- to 3-week intervals, with repeat transfusions depending on changes in fetal hematocrit and the sonographic appearance of hydrops. The final PUBS is generally scheduled at 34 to 35 weeks of gestation; fetal lung maturity guides the timing of delivery. Such pregnancies should not be allowed progress beyond 37 to 38 weeks of gestation. If hydrops does not improve, or if fetal testing becomes nonreassuring despite correction of fetal anemia, premature delivery may be indicated, depending on the gestational age. It is possible that mature lecithin/sphingomyelin ratios may be obtained less frequently near term in fetuses with hydrops as compared with nonhydropic fetuses (Romero et al., 1988).

The optimal mode of delivery for the hydropic fetus is uncertain. Because of the risk of soft-tissue dystocia associated with hydrops, it is often considered safer to deliver all potentially viable fetuses with immune hydrops by cesarean. This should minimize the chances of maternal and fetal trauma. However, there are no data to support routine cesarean delivery for immune hydrops as compared with cesarean delivery based on standard obstetric indications. A trial of labor may be reasonable in cases in which the fetal anemia has been adequately corrected, and in which the hydropic features improve. In carefully selected and monitored cases, up to 80% of fetuses with immune hydrops may successfully deliver vaginally (Bowman, 1999). The optimal location of delivery should be a tertiary care center, with the immediate availability of skilled neonatologists and other appropriate pediatric subspecialists.

FETAL INTERVENTION

Immune hydrops is one of the few fetal abnormalities in which a well-established program of fetal intervention has been described. The ability to perform intrauterine fetal transfusions has revolutionized the management of Rh isoimmunization and has resulted in the survival of many fetuses that would otherwise have died from hydrops. The first step in fetal intervention for immune hydrops is to urgently schedule a PUBS procedure to document the fetal hematocrit and to perform potentially lifesaving therapy.

In all cases of immune hydrops, appropriate blood for fetal transfusion should be available at the time of a scheduled PUBS procedure. The blood should be group O red cells, packed to a hematocrit of approximately 80%, less than 4 days old, irradiated, anti-cytomegalovirus negative, negative for the antigen to which the mother is immunized, and Kell negative. If a previous PUBS has been performed, so that the fetal ABO blood group is known, and there is no maternal–fetal ABO incompatibility, red cells of the same ABO status as the fetus can be transfused (Bowman, 1999). When the initial PUBS procedure is scheduled, appropriate blood should be immediately available. This will allow for immediate transfusion as soon as the initial fetal blood sample has been obtained, without the need to replace the needle.

The appropriate target for fetal intravascular transfusion will depend on the gestational age and fetal position. In general, the preferred target is the umbilical vein, at its placental insertion site. Sterile technique is used throughout. The mother is generally premedicated with a sedative and some centers also use a prophylactic antibiotic, such as dicloxacillin. A 20-gauge spinal needle, of sufficient length to reach the target, is used to cannulate the umbilical vein under direct ultrasound guidance. The free return of blood confirms entry into the vein following removal of the needle stylet. A sample is drawn into a heparinized tuberculin syringe and sent to the hematology laboratory, which should be on standby to receive all such samples. The presence of fetal, as opposed to maternal, blood is confirmed by noting an elevated mean corpuscular volume, generally greater than 120 fL, or by alkaline denaturation. Fetal blood should also be measured for hematocrit, hemoglobin, platelet count, total bilirubin, blood type, and antibody screen. Fetal paralysis with pancuronium or vecuronium is generally not required in cases of hydrops, as fetal activity is often minimal. However, if fetal movement significant enough to dislodge needle's access to the umbilical vein occurs, pancuronium or vecuronium can be injected directly into the fetal circulation.

Since the fetal hematocrit will invariably be less than 30% in cases of immune hydrops, the fetal transfusion can be started as soon as the initial fetal sample is obtained, while awaiting results of the hematocrit from the hematology laboratory. Once the initial fetal hematocrit result is available, a calculation can be performed to estimate the volume of transfused blood needed to correct the fetal anemia. The volume of packed red cells to be transfused is derived using formulas that take into account the starting hematocrit, the hematocrit of transfused blood, the target hematocrit, and a correction factor for the volume of blood in the placental circulation. A commonly used formula for the volume of blood to be

transfused is

$$V_T = \frac{(\text{desired final hematocrit} - \text{initial fetal hematocrit})}{(\text{donor blood hematocrit})} \times (150) \times (\text{EFW}),$$

where V_T is volume of blood transfused, 150 is a placental correction factor, and EFW is estimated fetal weight in kilograms (Kaufman and Paidas, 1994).

It is generally not advised to transfuse a hydropic fetus to a final hematocrit that is either greater than 25% or greater than four times the initial hematocrit (Radunovic et al., 1992). This has been associated with fluid overload and sudden intrauterine fetal death. In cases of hydrops secondary to fetal anemia, the goal of the first intrauterine transfusion should be a hematocrit of 20% to 25%, and the transfusion should then be repeated in 48 to 72 hours to bring the final hematocrit to a level of 45% to 50%. Repeat procedures are then performed at 2- to 3-week intervals, with the last procedure being performed at 34 to 35 weeks of gestation.

Another therapeutic option for fetuses with immune hydrops is to perform a combined intravascular and intraperitoneal transfusion, with the intravascular aliquot of blood designed to provide an acute increase in fetal hematocrit and the intraperitoneal aliquot designed to provide a slower sustained increase in hematocrit. Intraperitoneal transfusion should rarely be considered an option for the hydropic fetus. If the fetus is moribund, and there is no evidence of fetal breathing, red cells placed in the intraperitoneal cavity will not be absorbed and will result in no benefit to the fetus. However, if an umbilical vessel cannot be cannulated for technical reasons, the option of intraperitoneal transfusion can be considered. If ascites is present, up to 150 mL of ascitic fluid should be drained prior to performing an intraperitoneal transfusion (Bowman, 1999). This will minimize the chance of increasing the intraperitoneal pressure to a level greater than umbilical venous pressure. To do so would result in impaired return of blood to the fetal heart and subsequent fetal death. Another alternative for fetal transfusion in cases of hydrops, if an umbilical vessel cannot be cannulated, is to perform a direct fetal cardiac transfusion. However, this should be considered a method of last resort as it is associated with a significant risk of fetal death (Westgren et al., 1988).

TREATMENT OF THE NEWBORN

Infants with hydrops should be delivered in a tertiary care center, with immediate availability of a multidisciplinary neonatal resuscitation team. Most fetuses with immune hydrops should improve with successful intrauterine transfusions, so the degree of neonatal hydrops and anemia should also be improved. However, if hydrops fails to resolve with appropriate intrauterine therapy, the neonatal team should be prepared for a complex resuscitative effort. Immediate neonatal endotracheal intubation may be needed, and such intubations can be technically difficult (Carlton et al., 1989). A high-frequency ventilator and high airway pressure settings may be needed to achieve adequate gas exchange. Paracentesis and thoracentesis, with placement of bilateral chest tubes, may also be needed to allow adequate ventilation and effective gas exchange. Placement of umbilical artery and umbilical vein lines may be needed to aid in the resuscitation (McMahan and Donovan, 1995). Use of blood products, albumin, and diuretics may be needed to effectively maintain adequate intravascular volume without significant fluid overload or soft-tissue edema. If the neonate can be stabilized in the delivery room, transport to a neonatal intensive care unit should be arranged promptly.

Approximately 50% of neonates will require "top-up" transfusions in the neonatal intensive care unit (Saade et al., 1993). Infants should therefore be followed with weekly hematocrit and reticulocyte determinations for 4 to 6 weeks. This requirement for future transfusions may reflect persistent hypoplasia of the neonatal bone marrow as well as the persistence of passively acquired IgG antibodies from the mother.

SURGICAL TREATMENT

No surgical treatments have been described.

LONG-TERM OUTCOME

Minimal data are available on the long-term follow-up of fetuses with immune hydrops. With advances in intrauterine therapy, more moribund fetuses are being rescued, and this has led to concerns regarding the long-term neurologic outcome for such infants. In one series of 38 fetuses who received intravascular transfusions for Rh isoimmunization, 35 (92%) were normal at 2 years of follow-up and 3 had cerebral palsy, which was thought to be a result of prematurity (Doyle et al., 1993).

GENETICS AND RECURRENCE RISK

The recurrence risk for immune hydrops is significant. In general, the more severe the obstetric history of Rh isoimmunization, the more likely the recurrence of severe disease in a future pregnancy. For an Rh-negative mother, if the father is homozygous for the Rh(D) allele, all of the offspring will be Rh positive and will, therefore, be at risk for severe hemolytic disease. If the father is heterozygous Rh positive, then there is a 50/50 chance that the fetus will be Rh positive. If the fetus is Rh negative, the risk of hemolytic disease is zero. Preimplantation genetic diagnosis with biopsy of the eight-cell embryo is now available in cases of a heterozygous father, to predict the Rh status of a future fetus (Van den Veyver et al., 1995). However, this approach would obviously require the performance of in vitro fertilization in future pregnancies.

Previously, another prenatal diagnosis option was to perform a chorionic villus sampling (CVS) or amniocentesis in future pregnancies with a heterozygous father, which would allow early prenatal diagnosis of fetal Rh and Kell status (Bennett et al., 1993). However, this should be avoided if possible as there is a risk of stimulating a significant antibody/antigen response in that pregnancy, especially with a CVS procedure. In Europe, such invasive testing methods using CVS or amniocentesis have been abandoned due to the easy availability of fetal Rh(D) status identification using PCR amplification of fetal DNA from a maternal blood sample. This can be performed as early as 14 weeks of gestation in a subsequent pregnancy and accurately determines whether the fetus is Rh(D) positive or negative.

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Nonimmune Hydrops Fetalis

128 CHAPTER

Key Points

- Nonimmune hydrops fetalis is a serious fetal condition in which abnormal fluid accumulates in at least two different fetal compartments, and in which circulating antibodies against red-cell antigens are absent in the mother.
- Nonimmune hydrops fetalis is a heterogeneous disorder, caused by a large number of underlying pathologic processes. While the majority of cases appear to be idiopathic, the most common recognizable cause is cardiovascular pathology.
- Following the sonographic detection of hydrops, the most important step is to differentiate between immune and nonimmune causes. Once immune causes are excluded, a detailed anatomical survey is needed to rule out congenital abnormalities, which could be the cause of the hydrops.
- Nonimmune hydrops can occur secondary to fetal anatomical abnormalities (cardiac, thoracic, gastrointestinal, neurologic, genitourinary, vascular, or skeletal), placental/cord abnormalities, fetal hematologic, neoplastic or metabolic disorders, infection, fetal genetic anomalies, and maternal abnormalities.
- Maternal blood tests should include an indirect Coombs antibody screen, maternal blood type, Kleihauer–Betke stain, complete blood count with differential and erythrocyte indices, hemoglobin electrophoresis, and glucose-6-phosphate dehydrogenase deficiency screen. Additional maternal blood work should include TORCH titers, syphilis screen, and parvovirus B19 IgG and IgM titers.
- Fetal echocardiography and invasive testing for fetal karyotype should be offered.
- While the optimal mode of delivery is uncertain, cesarean section is advised for all potentially viable fetuses due to the risk for soft-tissue dystocia.
- Fetal therapy may be possible, including PUBS with transfusion, maternal administration of cardiac medications, and fetal shunt placement.
- The long-term prognosis will depend on the nature of the underlying abnormality.
- The recurrence risk will depend on the underlying etiology of the nonimmune hydrops.

CONDITION

Nonimmune hydrops fetalis (NIHF) is a serious fetal condition in which abnormal fluid accumulates in at least two different fetal compartments, and in which circulating antibodies against red cell antigens are absent in the mother. Hydrops fetalis is associated with a pathologic increase in interstitial and total fetal body water, usually appearing in fetal soft tissues and serous cavities. It may be either immunologic or nonimmunologic, depending on the presence or absence of maternal antibodies against fetal red cell antigens. While it was previously thought that the majority of cases of hydrops fetalis were secondary to maternal–fetal blood group incompatibilities, it is now estimated that over 90% of cases are nonimmunologic (Santolaya et al., 1992).

NIHF is a heterogeneous disorder, caused by a large number of underlying pathologic processes. The majority of cases appear to be idiopathic, although some investigators have stated that with thorough investigation an underlying cause can be identified in as many as 84% of cases (Holzgreve et al., 1984; Norton, 1994; Wilkins, 1999). When prenatally diagnosed cases of NIHF and cases of intrauterine fetal death are included, the success rate in discovering an underling cause for NIHF may be as low as 40% (Norton, 1994). The literature on NIHF consists almost entirely of case reports or small case series, together with reviews of these case series. A review of these reports suggests that the most common recognizable

cause of NIHF is cardiovascular pathology (accounting for 17% to 35% of cases), followed by chromosomal abnormalities (accounting for 14% to 16% of cases), and hematologic disorders (accounting for 4% to 12% of cases) (Norton, 1994). The remainder of causes of NIHF are rare conditions, many of which are difficult to diagnose prenatally. The range of possible underlying causes for NIHF is summarized in Table 128-1, listed in order of expected incidence.

Other than idiopathic cases, cardiac malformations account for the majority of cases of NIHF (Knilans, 1995). There is no particular form of cardiac abnormality that always results in hydrops, although the more severe the malformation the greater the likelihood of hydrops developing. The common mechanism of NIHF in cases of cardiac malformation or arrhythmia is the development of congestive heart failure, with increasing generalized fluid overload. The prognosis for fetuses with structural cardiac malformations and hydrops is extremely poor, with a mortality rate approaching 100% in some series (Crawford et al., 1988).

Chromosomal causes of NIHF are common; the most frequent is Turner syndrome, with its typical sonographic finding of cystic hygroma. A wide range of other genetic syndromes is also associated with NIHF, such as arthrogryposis, tuberous sclerosis, Pena–Shokeir syndrome, and Noonan syndrome (Jauniaux et al., 1990).

The underlying mechanism for the association of NIHF with hematologic abnormalities is most likely severe fetal anemia leading to high-output cardiac failure (Arcasoy and Gallagher, 1995). Fetal anemia can result from failure to manufacture normal hemoglobin (such as α-thalassemia), fetal hemorrhage (such as intracranial bleeding), hemolysis, (such as glucose-6-phosphate dehydrogenase deficiency), or failure to form erythrocytes because of marrow destruction (such as parvovirus B19 infection).

Congenital cystic adenomatoid malformation (CCAM) is the most common thoracic lesion associated with hydrops. Other thoracic causes of hydrops include bronchopulmonary sequestration, thoracic masses, and diaphragmatic hernia. The underlying mechanism for the association of hydrops with these thoracic conditions is most likely obstruction to venous return because of increased intrathoracic pressure.

Congenital infection with a wide variety of organisms is a well-recognized cause of hydrops (Barron and Pass, 1995). Causative organisms include syphilis, cytomegalovirus, parvovirus B19, toxoplasmosis, herpes simplex, rubella, and coxsackievirus. Possible mechanisms for the association of congenital infection with hydrops include fetal anemia from suppression of erythrocyte production, fetal myocarditis, or fetal hepatitis. In some cases of congenital infection, such as syphilis, the presence of hydrops is associated with a very poor prognosis. In other cases, hydrops from congenital infection may be self-limited and may resolve spontaneously. Fetal parvovirus B19 infection results in an aplastic crisis, which leads to profound anemia, and hydrops, the outcome of which may be either fetal death or spontaneous resolution without long-term morbidity (Morey et al., 1991; Levy et al., 1997).

A wide variety of structural fetal malformations has been associated with the development of NIHF. These include skeletal dysplasias, which may be associated with thoracic compression, impairment of venous return, and subsequent hydrops. The association of other structural malformations with NIHF, such as gastrointestinal, genitourinary, and neurologic abnormalities, may represent chance occurrences, as it is difficult to elucidate a plausible underlying mechanism for hydrops in many cases.

Some fetal conditions, such as Finnish nephrosis and hepatic fibrosis, result in profound hypoproteinemia or cirrhosis, which may subsequently lead to hydrops. The mechanism for the association between metabolic disorders and NIHF is unclear, but may be related to soft-tissue swelling and obstruction of venous return to the heart. Certain noncardiac fetal abnormalities may result in hydrops by causing high-output cardiac failure. Examples include sacrococcygeal teratoma, neuroblastoma, placental chorioangioma, and umbilical cord masses.

NIHF may very rarely occur in association with significant maternal medical illnesses, such as severe anemia, hypoproteinemia, or diabetes mellitus. The "mirror" syndrome, also known as Ballantyne syndrome, is the combination of fetal hydrops with generalized fluid overload and a preeclampsia-like state in the mother (Carbillon et al., 1997). In general, the maternal clinical features resolve only with delivery of the fetus and placenta.

INCIDENCE

The precise incidence of NIHF is difficult to elucidate, as many cases are not detected prior to intrauterine fetal death, and some cases may resolve spontaneously in utero. The generally reported incidence of NIHF is 1 in 1500 to 1 in 4000 deliveries (Romero et al., 1988; Wilkins, 1999).

SONOGRAPHIC FINDINGS

The diagnosis of hydrops is made following the detection of abnormal or increased fluid accumulation in at least two distinct fetal body cavities. Examples include pericardial effusion, pleural effusion, ascites, subcutaneous edema, cystic hygroma, polyhydramnios, and placental thickening (Figures 128-1 and 128-2). In general, skin thickness of at least 5 mm is required to diagnose subcutaneous edema, and a placental thickness of at least 6 cm is required to diagnose placentomegaly (Romero et al., 1988). These features do not necessarily indicate hydrops; it should be noted that skin thickening of at least 5 mm may be commonly seen in macrosomic fetuses. If abnormal fluid accumulation is confined to only one site, then the diagnosis of hydrops should not be used, and the case should be described simply in terms of the involved site, such as isolated ascites or isolated pleural effusion.

Table 128-1

Conditions Associated with Nonimmune Hydrops Fetalis

Idiopathic hydrops	Unknown cause
Cardiac malformation	Hypoplastic left ventricle; Atrioventricular canal defect; Atrial septal defect; Ventricular septal defect; Tetralogy of Fallot; Hypoplastic right ventricle; Ebstein's anomaly; Truncus arteriosus; Transposition of great vessels; Aortic stenosis or atresia; Pulmonary stenosis or atresia; Cardiomyopathy; Endocardial fibroelastosis; Premature closure of ductus arteriosus; Premature closure of foramen ovale; Rhabdomyoma; Intrapericardial teratoma
Cardiac arrhythmia	Supraventricular tachycardia; Atrial flutter; Heart block; Bradyarrhythmias; Wolff–Parkinson–White syndrome
Chromosomal abnormality	Trisomy 21; Trisomy 18; Trisomy 13; Turner syndrome; Triploidy; Tetraploidy; 18q+; 13q−; Others
Hematologic disorder	Alpha-thalassemia; Parvovirus B19 infection; Fetomaternal transfusion; In utero hemorrhage; Glucose-6-phosphate dehydrogenase deficiency; Fetal red cell enzyme deficiencies; Twin-to-twin transfusion syndrome
Thoracic abnormality	Congenital cystic adenomatoid malformation of lung; Bronchopulmonary sequestration; Diaphragmatic hernia; Chylothorax; Pulmonary lymphangiectasia; Intrathoracic mass (teratoma, leiomyosarcoma); Bronchogenic cyst
Genetic syndrome	Arthrogryposis; Multiple pterygium syndrome; Noonan syndrome; Pena–Shokeir syndrome; Cornelia de Lange syndrome; Tuberous sclerosis; Prune belly syndrome; Myotonic dystrophy; Neu–Laxova syndrome
Infectious disease	Cytomegalovirus; Parvovirus B19; Toxoplasmosis; Syphilis; Herpes simplex; Rubella; Coxsackievirus; Varicella; Respiratory syncytial virus
Skeletal dysplasia	Achondroplasia; Achondrogenesis; Osteogenesis imperfecta; Hypophosphatasia; Short rib polydactyly; Thanatophoric dwarfism; Asphyxiating thoracic dysplasia; Osteochondrodystrophy; Osteochondrodysplasia; Chondrodystrophy; Chondrodysplasia
Gastrointestinal disorder	Diaphragmatic hernia; Esophageal or intestinal atresia; Imperforate anus; Midgut volvulus; Meconium peritonitis; Duodenal diverticulum; Intestinal duplication; Malrotation
Genitourinary disorder	Congenital Finnish nephrosis; Hypoplastic kidney; Polycystic kidneys; Renal vein thrombosis; Bladder outlet obstruction; Dysplastic kidneys
Hepatic disorder	Hepatic fibrosis; Cholestasis; Polycystic liver disease; Biliary atresia; Hepatic calcification; Giant cell hepatitis; Cirrhosis with portal hypertension; Hepatic necrosis
Neoplastic disorder	Neuroblastoma; Teratoma; Congenital leukemia; Pulmonary leiomyosarcoma; Hemangioendothelioma of liver
Metabolic disorder	Gaucher disease; GM_1 gangliosidosis; Mucolipidoses; Mucopolysaccharidoses; Galactosialidosis; Carnitine deficiency; Pyruvate kinase deficiency
Neurologic disorder	Encephalocele; Fetal intracranial hemorrhage; Vein of Galen aneurysm; Porencephaly with absent corpus callosum
Vascular disorder	Arteriovenous malformation; Sacrococcygeal teratoma; Vena caval thrombosis; Hemangioendothelioma; Arterial calcification; Cerebral angioma
Placenta/cord abnormality	Chorioangioma; Chorionic vein thrombosis; Umbilical cord torsion; True knot of cord; Angiomyxoma of cord; Placental hemorrhagic endovasculitis
Maternal abnormalities	Mirror syndrome; Severe maternal anemia, diabetes mellitus or hypoproteinemia; Maternal indomethacin use

Adapted from:

Holzgreve W, Holzgreve B, Curry CJ: Nonimmune hydrops fetalis: diagnosis and management. Semin Perinatol 1985;9:52-57.

Romero R, Pilu G, Jeanty P, et al. Nonimmune hydrops fetalis. In Romero R, Pilu G, Jeanty P, Ghidini A, Hobbins JC (eds): Prenatal Diagnosis of Congenital Anomalies. Norwalk, Appleton And Lange, 1988;414-426.

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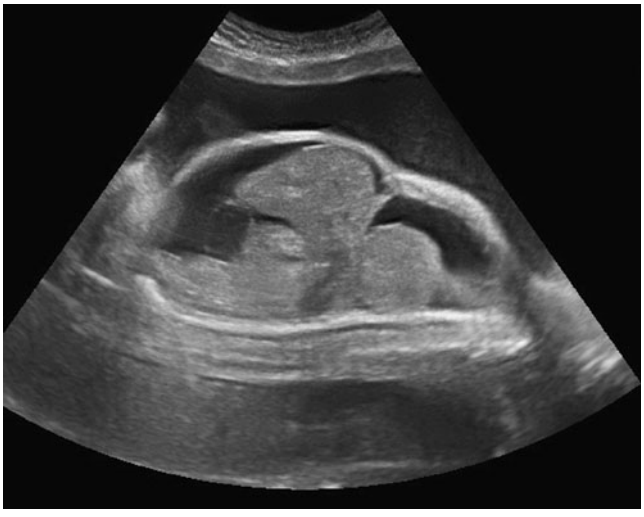

Figure 128-1 Prenatal ultrasound image of fetus at 26 weeks with nonimmune hydrops. Sagittal view demonstrates extensive ascites and pleural effusions.

NIHF may initially present with an isolated fluid accumulation in one site, such as pleural effusion with congenital cystic adenomatoid malformation, but as intrathoracic pressure increases and venous return decreases, generalized hydrops may present.

Fetal ascites is diagnosed sonographically by the visualization of an echolucent rim encompassing the entire fetal abdomen in a transverse view (see Figure 128-1). Loops of bowel and the outline of the fetal liver, spleen, bladder, and diaphragm are generally more easily seen in the presence of ascites. Pericardial effusion is diagnosed by the appearance of an echolucent rim of at least 1 to 3 mm thickness around both cardiac ventricles. Pleural effusion, which may be unilateral or bilateral, also presents as an echolucent space outlining the diaphragm.

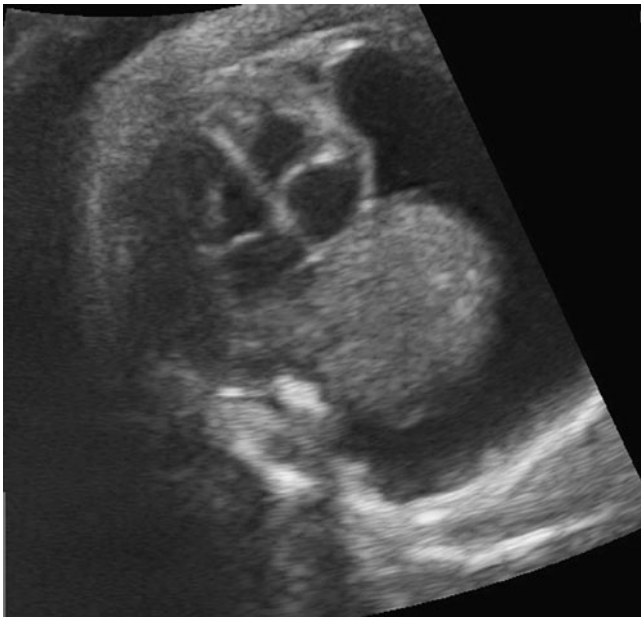

Figure 128-2 Prenatal ultrasound image of fetus at 30 weeks with nonimmune hydrops. Transverse view through fetal chest demonstrates extensive pleural effusion with deviation of cardiac axis to left.

Other sonographic features of NIHF will depend on the cause of the hydrops. A careful fetal anatomical survey, including fetal echocardiography, should be performed in all cases to detect any associated structural fetal malformations. Measurement of the middle cerebral artery peak systolic velocity using Doppler ultrasound can help identify cases of NIHF associated with fetal anemia (Hernandez-Andrade et al., 2004).

DIFFERENTIAL DIAGNOSIS

Following the sonographic diagnosis of hydrops the first step is to differentiate between immune and nonimmune causes. This is easily accomplished by the performance of a maternal indirect Coombs test to screen for antibodies associated with blood group incompatibility.

Following the exclusion of immune causes of hydrops, each condition listed in Table 128-1 should be considered when trying to determine the cause of NIHF. This is accomplished by a review of maternal and paternal histories, detailed fetal sonographic survey, and the use of appropriate diagnostic laboratory studies.

ANTENATAL NATURAL HISTORY

The precise antenatal natural history of NIHF depends entirely on the underlying cause. The natural history of hydrops is poorly understood, so little information is available regarding prognostic factors to predict in utero progression. In general, NIHF is associated with a 75% to 90% fetal mortality rate (Romero et al., 1988). The progression of fetal signs and development reflects the underlying cause. Cases of NIHF secondary to fetal parvovirus B19 infection, for example, may result in intrauterine fetal death or may result in spontaneous resolution. By contrast, cases of NIHF associated with structural cardiac malformation almost always result in intrauterine fetal death or early neonatal death. No series are available for review describing sufficient cases of NIHF caused by each individual underlying cause, to enable accurate prediction of antenatal natural history.

MANAGEMENT OF PREGNANCY

Following the sonographic detection of hydrops, the pregnant woman should be promptly referred to a tertiary care facility, with availability of a multidisciplinary team consisting of perinatologists, neonatologists, clinical geneticists,

and other pediatric subspecialists. Careful maternal and paternal histories should be obtained, to evaluate for possible health problems, family histories, or ethnic predisposition to any of the conditions listed in Table 128-1. Maternal blood work should include an indirect Coombs antibody screen, maternal blood type, Kleihauer–Betke stain, complete blood count with differential and erythrocyte indexes, hemoglobin electrophoresis, and glucose-6-phosphate dehydrogenase deficiency screen. Additional maternal blood work should include an evaluation for infectious diseases, including TORCH (toxoplasmosis, rubella, cytomegalovirus, and herpes simplex) titers, rapid plasma reagent test, and parvovirus B19 IgG and IgM titers.

A detailed fetal sonographic anatomy survey should be performed to evaluate for possible associated structural malformations. Because of the strong association between NIHF and cardiac malformations, fetal echocardiography should also be performed, with particular attention paid to possible fetal rhythm disturbances. Fetal heart rate monitoring for 12 to 24 hours should be considered to rule out an underlying fetal arrhythmia.

Invasive testing for fetal karyotype should also be offered. This can be performed by means of amniocentesis, with the use of fluorescence in situ hybridization or polymerase chain reaction (PCR), to facilitate a rapid diagnosis of the common aneuploidies. While previously the preferred invasive diagnostic procedure at late gestational age was a fetal percutaneous umbilical blood sample (PUBS), this is now rarely necessary. The previously cited advantage of a PUBS was that it allowed rapid determination of fetal karyotype, in addition to providing details of fetal hematocrit, platelet count, liver-function tests, hemoglobin electrophoresis, and fetal IgM specific to the various infectious causes of NIHF. In addition, it also allowed the opportunity to transfuse the fetus with packed red cells immediately if profound fetal anemia is diagnosed. However, given the precision of middle cerebral artery Doppler evaluation in predicting the anemic fetus, and the easy availability of either FISH or PCR for rapid chromosome evaluation, the need for PUBS continues to decrease. Amniotic fluid (obtained either at the same time as a PUBS or by amniocentesis) may be sent for α-fetoprotein level (increased in Finnish nephrosis and sacrococcygeal teratoma), and polymerase chain reaction (PCR) testing for infectious agents. Metabolic testing can also be performed on amniotic fluid when a specific disorder is suspected.

Following the laboratory and sonographic evaluation, a diagnosis of idiopathic NIHF, or NIHF secondary to a specific condition, will be made. If a specific underlying cause has been discovered, patient counseling will be dictated by the particular abnormality. In general, the presence of hydrops together with a structural malformation, such as cardiac abnormality, is associated with a very poor prognosis. Counseling should therefore also include the possibility of elective pregnancy termination, depending on the gestational age at presentation. Patients should be counseled by a multidisciplinary team that includes a perinatologist, neonatologist, geneticist, and appropriate additional pediatric subspecialists. Options for fetal intervention to treat the underlying problem and hydrops are available and are discussed in the following section.

If expectant management of the fetus with NIHF is chosen, careful sonographic surveillance should be performed, including biophysical profiles on a frequent basis. The precise timing of fetal surveillance testing is uncertain and depends on the gestational age at presentation. If the fetus is considered viable, it may be reasonable to admit the mother and perform daily fetal testing with nonstress tests or biophysical profiles. If the hydrops appears to be resolving it would be reasonable to decrease the frequency of testing, provided that fetal testing has been reassuring to date. Repeat sonographic fetal anatomy surveys should be performed every 2 weeks to confirm appropriate fetal growth and to improve the chances of detecting an underlying structural fetal malformation.

Timing of delivery is also uncertain with NIHF. Depending on the gestational age, premature delivery may be indicated if fetal testing becomes nonreassuring. Otherwise, the most common practice is to continue expectant management until 37 weeks of gestation, or until fetal lung maturity has been confirmed by amniocentesis. It is possible that mature lecithin:sphingomyelin ratios may be less frequently obtained near term in the fetus with hydrops, as compared with nonhydropic fetuses (Romero et al., 1988). Expectant management may also be complicated by preeclampsia in up to 50% of cases, and this may necessitate immediate preterm delivery. In addition, NIHF is frequently associated with polyhydramnios, which may precipitate preterm labor due to uterine overdistention. Periodic reduction amniocenteses may be required to relieve maternal discomfort from severe polyhydramnios.

The optimal mode of delivery for the hydropic fetus is uncertain, as the overall prognosis is poor regardless of the form of delivery. Because of the risk of soft-tissue dystocia associated with hydrops, it is generally advisable to deliver all potentially viable fetuses with NIHF by cesarean. This should minimize the chances of maternal and fetal trauma. In cases in which the fetus is not expected to survive, the option of therapeutic thoracentesis or paracentesis to optimize a vaginal delivery is also reasonable. However, patients should be made aware of the extremely small likelihood of neonatal survival. The optimal location of delivery should be a tertiary care center, with the immediate availability of skilled neonatologists and other appropriate pediatric subspecialists.

FETAL INTERVENTION

The option of fetal therapy in select cases of NIHF is possible. The underlying pathology that is most amenable to prenatal therapy is fetal anemia. When a diagnostic PUBS is undertaken for any fetus with NIHF, immediate transfusion of packed red cells, if profound fetal anemia is diagnosed, should be performed. Arrangements prior to performance of a PUBS

in such cases should include preparation of group O, irradiated, packed red blood cells that are anticytomegalovirus negative, $Rh_o(D)$ negative, Kell negative, and cross-matched compatible with maternal serum. The unit of red cells should be tightly packed with a hematocrit of at least 80%, and a blood transfusion setup should be primed as the diagnostic PUBS is performed. This will ensure that prompt intravascular fetal transfusion can be performed as soon as significant fetal anemia is diagnosed, and prior to withdrawal of the needle from the umbilical vein. Once a fetal hematocrit of less than 30% is detected, fetal intravascular transfusion should begin. Fetal paralysis with pancuronium or vecuronium is generally not required in cases of hydrops, as fetal activity is often minimal.

The volume of packed red cells to be transfused is derived using formulas that take into account the starting hematocrit, hematocrit of transfused blood, target hematocrit, and a correction factor for the volume of blood in the placental circulation. A commonly used formula for volume of blood to be transfused is

$$V_T = \frac{(\text{desired final hematocrit} - \text{initial fetal hematocrit})}{(\text{donor blood hematocrit})} \times (150) \times (\text{EFW})$$

where V_T is volume of blood transfused, 150 is a placental correction factor, and EFW is the estimated fetal weight in kilograms (Kaufman and Paidas, 1994). It is generally not advisable to transfuse a hydropic fetus to a final hematocrit that is either greater than 25% or greater than four times the initial hematocrit (Radunovic et al., 1992). This has been associated with fluid overload and sudden intrauterine fetal death. In cases of NIHF secondary to fetal anemia, the goal of the first intrauterine transfusion should be a hematocrit of 20% to 25%, and the transfusion should then be repeated in 48 to 72 hours to bring the final hematocrit to a level of 40% to 45%. For many fetuses with NIHF and anemia secondary to parvovirus B19 infection, this transfusion may be all that is needed to maintain a normal fetal hematocrit, as the initial insult to the fetal marrow is generally self-limiting. Another therapeutic option for fetuses with NIHF and anemia is to perform a combined intravascular and intraperitoneal transfusion, with the intravascular aliquot of blood designed to provide an acute increase in fetal hematocrit and the intraperitoneal aliquot designed to provide a slower sustained increase in hematocrit. To date there are no adequate series comparing these different approaches for the treatment of NIHF secondary to fetal anemia.

Other forms of fetal intervention for NIHF include medical therapy for the mother to correct fetal arrhythmias (see Chapters 42 and 54). Digoxin administration to pregnant women has been successful in the treatment of fetal arrhythmias, with resolution of hydrops in some cases (Knilans, 1995).

Surgical treatment for the fetus with NIHF is also possible. Fetal thoracentesis may be performed under sonographic guidance with resolution of pleural effusions (Jones, 1995). If repeat thoracenteses are needed, consideration should be given to placement of a thoracoamniotic shunt. Such procedures are likely to be beneficial only for cases of NIHF in which pleural effusions are secondary to intrinsic thoracic malformations. Other surgical procedures that can be considered for fetuses with NIHF and underlying structural malformations include open fetal surgical resection of thoracic masses or sacrococcygeal teratoma (Bullard and Harrison, 1995). However, few data are available confirming whether such invasive approaches have a significant impact on fetal or neonatal outcome.

TREATMENT OF THE NEWBORN

Infants with hydrops should be delivered in a tertiary care center with immediate availability of a multidisciplinary neonatal resuscitation team. Immediate neonatal endotracheal intubation will almost certainly be needed, and such intubations can be technically difficult (Carlton et al., 1989). A high-frequency ventilator and high airway-pressure settings may be needed to achieve adequate gas exchange. Paracentesis and thoracentesis, with placement of bilateral chest tubes, may also be needed to allow adequate ventilation and effective gas exchange. Placement of umbilical artery and umbilical vein lines may be needed to aid in the resuscitation (McMahan and Donovan, 1995). Use of blood products, albumin, and diuretics may be needed to effectively maintain adequate intravascular volume without significant fluid overload or soft-tissue edema.

If the neonate can be stabilized in the delivery room, transport to a neonatal intensive care unit should be arranged promptly. This should be followed by a thorough physical examination, with the aid of appropriate radiologic investigations and echocardiography, to confirm absence of significant structural malformation. If additional structural malformations are detected, specific therapy should be tailored to the individual abnormalities. Appropriate pediatric subspecialist consultation, including a clinical geneticist, should also be arranged.

SURGICAL TREATMENT

Possible surgical treatments for fetal hydrops include fetal thoracoamniotic shunt placement for cases of NIHF associated with thoracic masses or persistent pleural effusions. Open fetal surgical resection of thoracic masses, such as congenital cystic adenomatoid malformation (see Chapter 35) and bronchopulmonary sequestration (see Chapter 34), are also possible (Bullard and Harrison, 1995). Open surgical resection of fetal sacrococcygeal teratoma with associated hydrops is also possible, although there are so few cases that it is currently difficult to evaluate the role of such invasive procedures (see Chapter 115).

LONG-TERM OUTCOME

The prognosis for infants with hydrops depends entirely on the nature of any underlying abnormalities. The perinatal mortality rate ranges from 40% to 90%, depending on the cause, but may approach 100% in cases of NIHF associated with structural cardiac malformations (Romero et al., 1988; Wilkins, 1999; Jones, 1995). No long-term studies are available for counseling parents on the likely survival or morbidity if a successful neonatal resuscitation is achieved.

GENETICS AND RECURRENCE RISK

A postmortem examination is indicated in all cases of NIHF that result in fetal or neonatal death. This will maximize the number of cases in which a definite underlying cause is identified and will facilitate appropriate genetic counseling and prediction of recurrence risk (Steiner, 1995). Recurrence of idiopathic NIHF is rare, although case series of recurrences have been documented (Wilkins, 1999). In one case series, one mother had three consecutive pregnancies complicated by recurrent idiopathic NIHF and another had two consecutive pregnancies complicated by recurrent idiopathic NIHF (Onwude et al., 1992). Patients should therefore be made aware that, while idiopathic NIHF is extremely rare, recurrences can and do occur.

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PART

III

Management of Fetal Chromosome Abnormalities

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Trisomy 13

129 CHAPTER

Key Points

- Third most common liveborn autosomal aneuploidy. Incidence is approximately 1 in 5000 livebirths.
- Sonographic findings include holoprosencephaly, abnormal midface, congenital heart defects, polydactyly, and echogenic kidneys. First trimester findings include increased nuchal translucency measurement, fetal tachycardia, and early onset growth restriction.
- Differential diagnosis includes pseudotrisomy 13, Meckel–Gruber syndrome, Bardet–Biedl syndrome, and Smith–Lemli–Opitz syndrome.
- Associated with increased lethality in utero, and increased incidence of preeclampsia.
- 80% of patients have full trisomy 13; 20% have mosaicism or a translocation. If a translocation is demonstrated, parental chromosomes should be studied.
- Prognosis is uniformly poor. Median survival time is 7 to 10 days. Five to 10% of patients survive up to one year of age.

CONDITION

Trisomy 13 presents as constellation of congenital anomalies that result from the presence of an extra chromosome 13, either whole or translocated onto another chromosome. It is not known how the presence of the extra chromosome disrupts so many different systems during organogenesis.

Although the clinical findings of the condition were previously known, the association of the extra chromosome with the clinical syndrome was not described until 1960 (Patau et al., 1960). Synonyms for trisomy 13 include trisomy D or Patau syndrome.

INCIDENCE

Trisomy 13 is the third most common liveborn autosomal aneuploidy. The incidence of trisomy 13 has been variously reported as 1 in 2206 to 1 in 7602 livebirths (Taylor, 1968). Most authors give the approximate incidence figure of 1 in 5000 livebirths (Wladimiroff et al., 1989). The incidence of trisomy 13 is equal among all races. It is thought that there are equal numbers of conceptuses of both genders. However, a slight excess of females exists at birth presumably due to a survival advantage (Jacobs et al., 1987).

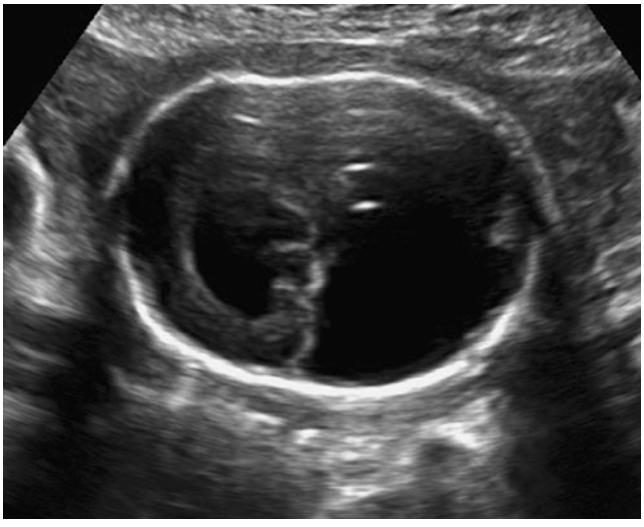

Figure 129-1 Transaxial view of fetal head indicating alobar holoprosencephaly in a fetus at 23 weeks with trisomy 13.

SONOGRAPHIC FINDINGS

Fetuses with trisomy 13 are more active in utero than comparable fetuses with trisomy 18. In addition, fetuses with trisomy 13 have a higher frequency of major congenital anomalies than fetuses with trisomy 21. The most common major abnormality seen in trisomy 13 is holoprosencephaly, which can be seen as early as 12 weeks of gestation (Figure 129-1). Other important findings associated with trisomy 13 include an abnormal midface with hypotelorism, cleft lip or palate, and even cyclopia (see Chapter 14) (Figure 129-2). Many studies have shown that there is a greatly increased incidence of congenital heart disease in fetuses affected with trisomy 13

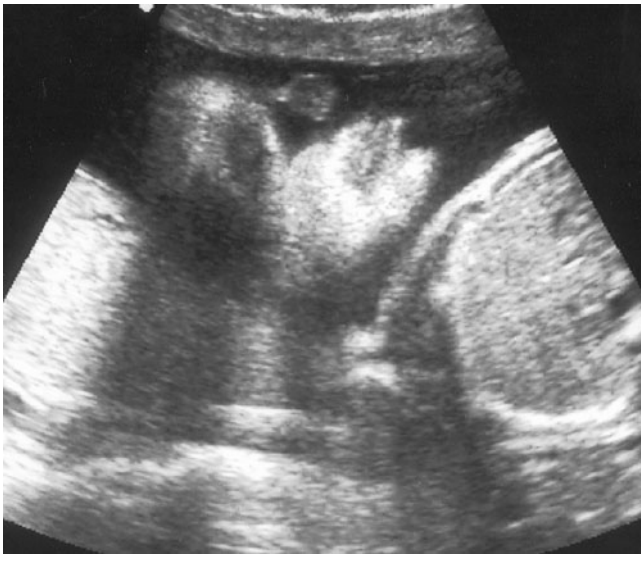

Figure 129-2 Sonographic profile of a fetus with trisomy 13 demonstrating severely abnormal midface with proboscis and absent orbit.

(Wladimiroff et al., 1995). The most common cardiac defects include ventricular septal defect (VSD), hypoplastic left ventricle, or double outlet right ventricle. Other common sonographic findings include ulnar/fibular polydactyly and echogenic or polycystic kidneys. In one study, all fetuses with trisomy 13 had one or more sonographic abnormalities or abnormal measurements present (Seoud et al., 1994).

Benacerraf et al. (1988, 1992, 1994) developed a sonographic scoring index to identify fetuses with aneuploidy. She and her co-authors gave 2 points for nuchal thickening of greater than 6 mm, 2 points for demonstration of a major structural defect, and 1 point each for a short femur, short humerus, and the presence of renal pyelectasis. This scoring system identified 2 of 2 fetuses with trisomy 13. In another report, Benacerraf et al. (1986) demonstrated that 6 of 6 affected fetuses with trisomy 13 had holoprosencephaly and a severely malformed face.

In the largest study of sonographic abnormalities in 33 consecutive fetuses with trisomy 13, Lehman et al. (1995) demonstrated that 91% of affected fetuses had one or more sonographically detectable abnormalities. In this study, 18 of the 33 fetuses described were at less than 20 weeks of gestation, and 15 of the affected fetuses were at greater than 20 weeks of gestation. The mean gestational age for the fetuses in the study was 20.7 weeks. Thirty of the 33 fetuses had structural abnormalities, as documented in Table 129-1. Only 3 of the fetuses had no sonographically detectable abnormalities. The most common abnormalities observed were holoprosencephaly, other central nervous system abnormalities, facial abnormalities, and cardiac defects (Table 129-1).

An increased nuchal translucency measurement for gestational age is also associated with trisomy 13 (Pandya et al., 1994). In the Pandya study, 80% of fetuses with trisomy 13, 18, or 21 had a nuchal translucency of at least 3 mm. Omphalocele is also somewhat frequent in fetuses with trisomy 13. In the presence of an omphalocele, the risk of trisomy of 13 or 18 is increased by 340-fold (Snijders et al., 1995).

First trimester sonographic findings in fetuses with trisomy 13 include increased nuchal translucency measurement, early onset fetal growth restriction, fetal tachycardia (2/3 of cases), holoprosencephaly, megacystis and omphalocele (Snijders et al., 1999; Nicolaides, 2004). Nonspecific sonographic markers seen in trisomy 13 include mild dilatation of the lateral cerebral ventricles, echogenic bowel, and echogenic intracardiac foci (EIF). The combination of EIF and a hypoplastic left heart is characteristic of trisomy 13 (Nyberg and Souter, 2001).

In summary, fetuses with holoprosencephaly, cardiac abnormalities, evidence of facial clefting or midface anomalies, and possibly polydactyly should strongly suggest a diagnosis of trisomy 13 (Twining and Zuccollo, 1993).

DIFFERENTIAL DIAGNOSIS

Since holoprosencephaly is one of the most commonly found malformations in trisomy 13, isolated holoprosencephaly

Table 129-1

Prenatal Ultrasound Findings in 33 Fetuses with Trisomy 13 Syndrome*

Sonographic Abnormality	Menstrual Age at Ultrasound Examination		
	12–20 wk (n = 18)	20–32 wk (n = 15)	Total (n = 33)
Intrauterine growth restriction†	4 (22)	12 (80)	16 (48)
Central nervous system and cranium			
Holoprosencephaly	4 (22)	9 (60)	13 (39)
Lateral ventricular dilation	2 (11)	1 (7)	3 (9)
Enlarged cisterna magna	2 (11)	3 (20)	5 (15)
Microcephaly†	0 (0)	4 (27)	4 (12)
Total	7 (39)	12 (80)	19 (58)
Face			
Cleft lip/palate*	3 (17)	9 (60)	12 (36)
Cyclopia	2 (11)	0 (0)	2 (6)
Hypoplastic face	3 (17)	7 (47)	10 (30)
Hypotelorism†	3 (17)	7 (47)	10 (30)
Total	6 (33)	10 (67)	16 (48)
Neck/hydrops†			
Nuchal thickening/cystic hygroma	6 (33)	1 (7)	7 (21)
Hydrops/lymphangiectasia	3 (17)	1 (7)	4 (12)
Total	6 (33)	2 (13)	8 (24)
Renal			
Echogenic kidneys	4 (22)	6 (40)	10 (30)
Enlarged kidneys†	2 (11)	6 (40)	8 (24)
Hydronephrosis	2 (11)	2 (13)	4 (12)
Total	4 (22)	7 (47)	11 (33)
Cardiac defects	8 (44)	8 (53)	16 (48)
Extremities†			
Polydactyly†	1 (6)	6 (40)	7 (21)
Club/rocker bottom feet	2 (11)	1 (7)	3 (9)
Clenched/overlapping digits†	0 (0)	5 (33)	5 (15)
Total	3 (17)	8 (53)	16 (48)
Abdomen			
Omphalocele	3 (17)	2 (13)	5 (15)
Bladder exstrophy	1 (6)	0 (0)	1 (3)
Echogenic bowel	2 (11)	0 (0)	2 (6)
Total	6 (33)	2 (13)	8 (24)
Other			
Echogenic chordae tendineae†	7 (39)	3 (20)	10 (30)
Single umbilical artery	1 (6)	7 (47)	8 (24)

**Numbers in parentheses are percentages.*

† Statistically significant difference (P = <0.05) between frequency of detection before and after 20 menstrual weeks.

Source: Lehman CD, Nyberg DA, Winter TC, Kapur RP, Resta RG, Luthy DA. Trisomy 13 syndrome: prenatal US findings in a review of 33 cases. Radiology. *1995;194:217-222.*

should be considered within the differential diagnosis (see Chapter 14). Trisomy 13 is a diagnosis that can be made definitively only by karyotyping. Prior to obtaining karyotype results, however, the following diagnoses should also be considered: pseudotrisomy 13 (Cohen–Gorlin syndrome), Smith–Lemli–Opitz syndrome, Meckel–Gruber syndrome, Bardet–Biedl syndrome, and Pallister–Hall syndrome.

Pseudotrisomy 13 syndrome has been described to encompass the triad of normal chromosomes, holoprosencephaly, and ulnar-fibular polydactyly (Seller et al., 1993). The phenotype has been expanded to include hypoplastic radii (Boles et al., 1992). The inheritance of this condition is autosomal recessive and carries a 25% risk of recurrence. Neither holoprosencephaly nor polydactyly is an obligatory manifestation of pseudotrisomy 13. Each of these anomalies is found only in 60% of affected siblings. The diagnostic criteria for this condition are a normal karyotype with either holoprosencephaly and ulnar-fibular polydactyly, or holoprosencephaly plus other major malformations without polydactyly, or ulnar-fibular polydactyly with other brain defects, such as microcephaly, hydrocephaly, or agenesis of the corpus callosum, with the presence of other malformations (Lurie and Wulfsberg, 1993). Other specific organ findings can distinguish trisomy 13 from pseudotrisomy 13 in the absence of karyotyping. For example, patients with trisomy 13 have a very characteristic type of renal cystic dysplasia, whereas patients with pseudotrisomy 13 have hypoplastic kidneys but no evidence of cysts. Patients with trisomy 13 have hydronephrosis and patients with pseudotrisomy 13 have horseshoe kidneys. Scalp defects (Figure 129-3) and a pathognomonic type of pancreatic fibrosis are present in patients with trisomy 13; neither of these findings is present in pseudotrisomy 13.

Another important consideration in the differential diagnosis is Meckel–Gruber syndrome. This condition was described in 1822 by Meckel and redefined by Gruber in 1934, who called the condition "dysencephalia splanchnocystica." In this condition, 100% of affected patients have polycystic kidneys, 80% have encephalocele, 70% have polydactyly, and 30% have cleft lip and palate. This condition is also inherited as an autosomal recessive (Miller, 1983). In a study of 38 affected siblings, the cystic renal dysplasia was invariably present. The other findings associated with the condition, however, were less common. For example, occipital meningocele was present in only 63% of siblings and polydactyly was present in only 55% of siblings (Miller, 1983). Meckel–Gruber syndrome is associated with increased levels of α-fetoprotein in the amniotic fluid.

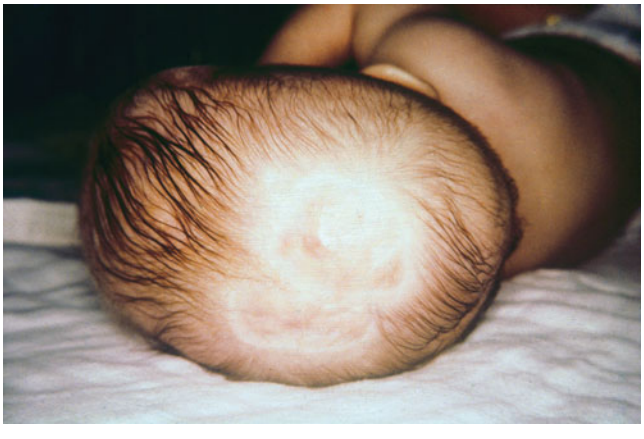

Figure 129-3 Scalp defects in an infant with trisomy 13.

ANTENATAL NATURAL HISTORY

Trisomy 13 is associated with increased lethality in utero. For every trisomy 13 patient born alive, approximately 50 are lost prenatally as a spontaneous abortion (Jacobs et al., 1987). In one study, Jacobs et al. (1987) described a series of 2922 spontaneous abortuses who were karyotyped. Of these, 62 had trisomy 13. Forty-six had 47 chromosomes, consistent with a full trisomy. Sixteen had translocation trisomy 13. A similar proportion of translocation cases to full trisomy cases were seen in this study as is seen in liveborn infants. Therefore, full trisomy 13 and translocation trisomy 13 are similar with respect to their effect on intrauterine mortality. In this spontaneous abortion study, trisomy 13 was shown to be the fourth most common trisomy (after trisomies 16, 21, and 22).

With regard to antenatal natural history, the mean gestational age of the fetuses with full trisomy 13 that spontaneously miscarried was 79.8 days and translocation trisomy 13, 82.6 days. These ages are significantly less than the fetuses with normal chromosomes that were miscarried. Only 5 of the trisomy 13 conceptuses in the study were older than 100 days of gestational age. This data suggests that specific stages in development exist in which trisomy 13 conceptuses are likely to die, but if they survive, they may survive until term.

MANAGEMENT OF PREGNANCY

Fetuses with sonographic evidence of either holoprosencephaly or congenital heart disease in addition to other structural abnormalities or intrauterine growth restriction should have karyotyping performed (Figure 129-4). Once the diagnosis of trisomy 13 has been made, the prospective parents should have the opportunity to speak with a medical geneticist regarding the implications of this diagnosis. The overall prognosis for extra uterine survival for an infant with trisomy 13 is extremely poor. In addition, there are complications for the mother when a diagnosis of trisomy 13 has been made. In particular, trisomy 13 is associated with increased risk of the mother developing preeclampsia. This was first noted by Boyd et al. (1987) who described five nulliparous women who had a fetus with trisomy 13; severe preeclampsia developed in all of the mothers. The medical records of these women were compared with four women whose first babies had

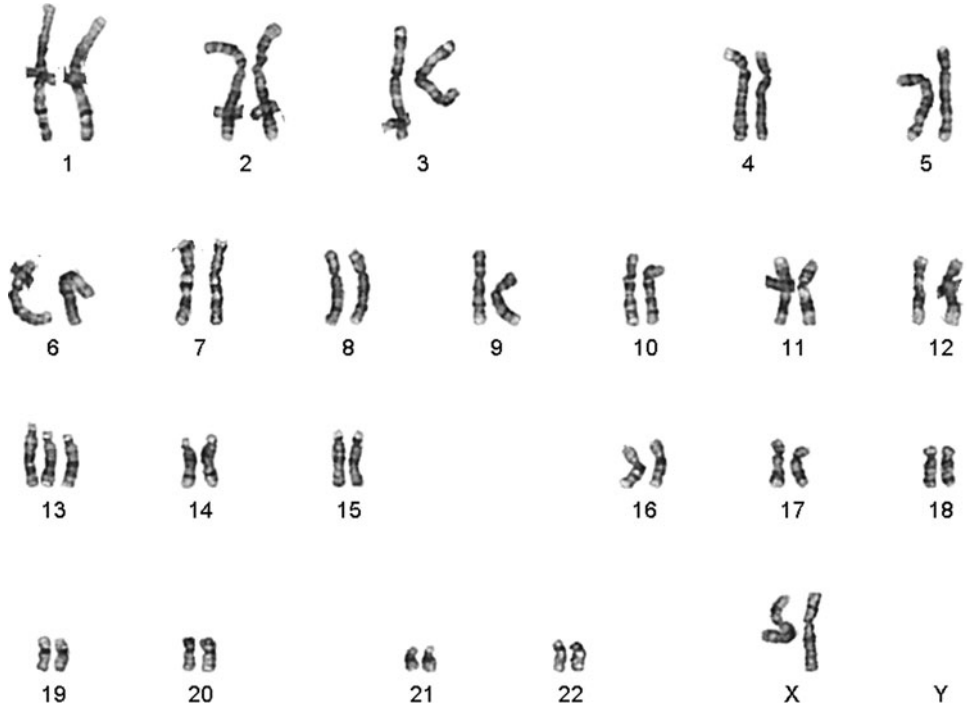

Figure 129-4 The karyotype in a female fetus with trisomy 13. (*Courtesy of Dr. Janet Cowan.*)

trisomy 18 and seven women whose first babies had trisomy 21; preeclampsia did not develop in any of these women. A similar finding was not seen in control patients. The association between trisomy 13 and preeclampsia was later extended in a study of 25 women who gave birth to an infant with trisomy 13. These investigators showed that the incidence of preeclampsia is significantly higher when the fetus has trisomy 13 as compared with pregnancies in which the fetus has trisomy 18 or a normal karyotype (Tuohy and James, 1992). Interestingly, pregnant women carrying a trisomy 13 fetus have excess circulating soluble fmslike tyrosine kinase-1 and decreased circulating placental growth factor (Bdolah et al., 2006). The gene for soluble fms-like tyrosine kinase-1 maps to chromosome 13q12, so it is hypothesized that the extra copy of this gene affects maternalcirculating angiogenic proteins, which may account for the increased incidence of preeclampsia in trisomy 13 pregnancies.

The current second trimester maternal quadruple serum screen (α-fetoprotein, human chorionic gonadotropin, unconjugated estriol, inhibin-A) does not detect fetuses with trisomy 13. A newer serum analyte, pregnancy-associated plasma protein A (PAPP-A) may be more useful in the first trimester detection of fetuses with trisomy 13. The median maternal serum PAPP-A levels are significantly lower in pregnancies that have a trisomy 13 fetus than in normal pregnancies. A level of less than 0.4 multiples of the median (MoM) detects 89% of fetuses with trisomy 13 at a calculated false-positive rate of 5% (Brizot et al., 1994). Maternal cell free fetal DNA levels are increased in archived second trimester serum samples of women carrying fetuses with trisomy 13 (Wataganara et al., 2003).

If the diagnosis of trisomy 13 is made before 24 weeks of gestation, the parents should be offered the opportunity to terminate the pregnancy. If a definite diagnosis of trisomy 13 is made after 24 weeks of gestation there is no need to deliver at a tertiary care center, provided that the community obstetrician and pediatrician are comfortable with providing supportive care for the affected infant. The experience of a couple's decision to continue an affected pregnancy and deliver their son has been published (Locock, 2005).

FETAL INTERVENTION

There are no fetal interventions for trisomy 13.

TREATMENT OF THE NEWBORN

Most infants with trisomy 13 deliver between 38 and 40 weeks of gestation, with an average birth weight of 2.48 kg (Warkany et al., 1966). The most common physical findings in liveborn infants with trisomy 13 include scalp defects, which are often confused with lacerations made by fetal scalp electrodes; microcephaly with a sloping forehead; microphthalmia; cleft lip and palate; congenital heart disease in 80% to 100% of patients; omphalocele; genital abnormalities, including cryptorchidism in all males, with micropenis in some males, and bicornuate uterus with ovarian abnormalities in most females; cystic kidneys; polydactyly, which is the most frequent external malformation of trisomy 13; and capillary

hemangiomata (Hodes et al., 1978). Laboratory findings include abnormalities in the complete blood count, manifested by an increased frequency of nuclear projections in polymorphonuclear leukocytes and persistence of fetal hemoglobin. Infants, who are delivered with a suspected diagnosis of trisomy 13, but without an antenatal confirmatory chromosome analysis, should have karyotyping performed. Peripheral blood leukocytes should give a definitive answer within 48 hours. If an affected infant has a life threatening anatomic obstruction requiring surgery, fluorescence in situ hybridization (FISH) can be performed using a chromosome 13-specific probe. This study will give a tentative diagnosis of trisomy 13 within a few hours of obtaining the blood sample.

Because the few infants who survive with trisomy 13 are severely retarded, usually only comfort measures are indicated. Early involvement of a medical genetics team is recommended to provide family support, to provide continuity of care if the infant is discharged to home, and to counsel about risk recurrence. Most infants with trisomy 13 die during the perinatal period.

Autopsy findings in 12 cases of trisomy 13 were described by Moerman et al. (1988). Of the 12 cases, 6 were liveborn, 1 was stillborn, 4 were terminated electively, and 1 died in utero. The longest survival postnatally was 6 days of age. Severe craniofacial, ocular, and cerebral malformations were noted in 10 of 12 patients (Figure 129-5). Eight of the 12 had holoprosencephaly. In all cases in which the eyes were examined, retinal dysplasia was present. The main cardiovascular anomalies were ventricular septal defect and abnormalities of the arterial valves. Four of 12 patients had complex cardiac disease, including tetralogy of Fallot or double outlet right ventricle. Interestingly, 11 of 12 patients had malformations of the gastrointestinal tract, specifically malrotation and unfixed mesentery. A pathognomonic microscopic pancreatic dysplasia was also present. Renal cystic disease was demonstrated in most patients. Renal cysts became more prominent in number and diameter as gestational age increased. Congenital malformations of the Müllerian duct system were present in 5 of 8 affected females. The ovaries were invariably small and demonstrated ovarian dysgenesis (Moerman et al., 1988).

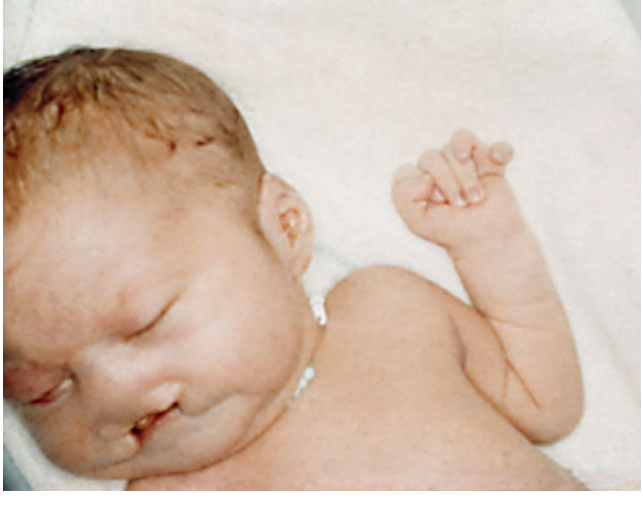

Figure 129-5 Infant with trisomy 13, showing severe midface abnormalities, including cleft lip and palate. The infant also has postaxial polydactyly of the left hand.

SURGICAL TREATMENT

Surgical treatment is indicated only as a temporizing measure to allow a potentially affected infant with trisomy 13 to survive long enough to make a definitive diagnosis. Surgical treatment does not improve or change the overall prognosis.

LONG-TERM OUTCOME

Rasmussen et al. (2003) used two population-based strategies to determine mortality in trisomy 13. The median survival time was 7 to 10 days. Five to 10% of patients survived to at least one year of age. Race and gender seemed to affect survival in that females and blacks had higher median ages at death. All infants who survive the perinatal period are severely retarded. Postnatal survival is inversely correlated with the severity of cardiac and brain anomalies.

Common medical problems for affected infants with trisomy 13 who survive beyond 1 month of age include feeding difficulties, gastroesophageal reflux, poor postnatal growth, apnea, seizures, hypertension, severe developmental delay, and scoliosis. Early puberty (at 8 ½ years) was described in a female with full trisomy 13 who survived until the age of 12 years, 2 months (Iliopoulos et al., 2006). A support organization exists for parents of long-term survivors with trisomies 13 and 18. The organization is known as S.O.F.T. (Support Organization for Trisomies 13 and 18). This organization recommends routine child care and anticipatory guidance, thorough cardiac evaluation, antibiotics prior to dental procedures if a cardiac abnormality is present, hearing evaluation, evaluation by an infant preschool intervention team, screening for scoliosis, and ongoing social support for families.

GENETICS AND RECURRENCE RISK

Eighty percent of affected individuals with trisomy 13 have the full trisomy due to meiotic or mitotic nondisjunction (47, XX, +13 or 47, XY +13). Twenty percent of patients have mosaicism or a translocation. The proportion of cases of translocation trisomy 13 (20% to 25%) is much higher than that seen in trisomy 21 (4%) (Jacobs et al., 1987). The mean maternal age is increased for the full trisomies but not for translocations, although the rate of increased risk with advanced maternal age does not increase as sharply as for trisomies 18 and 21 (Schreinemachers et al., 1982).

Hassold et al. (1987) used chromosome heteromorphisms and restriction fragment length polymorphisms

(RFLPs) to determine parental origin of the extra chromosome in 33 cases of trisomy 13. In 68% of cases, maternal meiosis I was the source of the error. This study demonstrated that pairing failure is not the primary cause of trisomy 13, as crossing over between the two nondisjoined chromosomes was detected in almost all of the cases studied. In the cases of mosaic trisomy 13, these authors demonstrated that conception began as a trisomic zygote. Subsequently, the paternal copy of chromosome 13 was lost in some cells with remaining maternal disomy due to a maternal meiosis type I error.

When the affected fetus or infant has been shown to have the full trisomy 13, the recurrence risk is 1% or the risk according to maternal age, whichever is higher. For the affected infant with a translocation, parental chromosomes should be studied. If the parents are both shown to be normal, there is less than a 1% risk of recurrence. If one parent has a balanced translocation involving chromosome 13, there is a 20% risk of a spontaneous abortion and a 5% risk of a liveborn infant with trisomy 13 in subsequent pregnancies. However, if one of the parents is demonstrated to have a robertsonian translocation (a translocation between two acrocentric chromosomes that results in the loss of ribosomal material in the short arm and fusion between the two centromeres) between both copies of chromosome 13, no normal offspring are possible, and gamete donation should be considered. For parents who have had a fetus or infant with trisomy 13, prenatal diagnosis in subsequent pregnancies can be achieved by obtaining a karyotype on chorionic villus material or on amniocytes obtained at midtrimester amniocentesis.

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130 CHAPTER Trisomy 18

Key Points

- Second most common autosomal trisomy in liveborn infants.
- Eighty to 85% of cases result from full trisomy, 10% are mosaics, and 5% are due to translocation.
- Incidence is about 1 in 3000 livebirths. Females are more likely to be born alive and survive longer.
- Most affected fetuses have more than one sonographic abnormality. Most common sonographic abnormalities include IUGR, cardiac structural anomalies, choroid plexus cysts, central nervous system anomalies, and overlapping fingers/clenched hands.
- Associated with low maternal serum screening levels of pregnancy-associated plasma protein A, estriol, α-fetoprotein, and β human chorionic gonadotropin.
- Median postnatal survival for males is 1 to 2 months, and for females it is 9 to 10 months. The presence of a heart defect (surprisingly) does not affect postnatal survival time. About 5% to 10% of infants survive until their first birthday.
- All long-term survivors are profoundly retarded. Despite this, there are increasing reports in the literature of aggressive postnatal treatment, including mechanical ventilation, cardiovascular drugs, parenteral nutrition, and surgical repair of congenital anomalies.
- Reports exist of adults with mosaic trisomy 18 who have normal intelligence.

CONDITION

Trisomy 18 is a chromosomal abnormality that results from the presence of an extra copy of chromosome 18. It is the second most common autosomal trisomy in liveborn infants. The clinical features associated with the abnormality were first described by Edwards in 1960. The condition is also known as Edwards syndrome or trisomy E. Of patients with trisomy 18, 80% to 85% have a full extra copy of chromosome 18 in all of their cells, 10% have mosaicism, with a normal cell line in some of their cells, and 5% have the long arm of chromosome 18 translocated onto another chromosome (Hill, 1996).

INCIDENCE

The incidence of trisomy 18 varies from approximately 1 in 3000 to 1 in 7000 livebirths. The specific incidence of trisomy 18 in Leicestershire, England, was studied during the years 1980 through 1985. At that time the incidence was noted to be 1 in 3086 livebirths (Young et al., 1986). A less frequent incidence of 1 in 6806 livebirths was noted during a 10-year period in Denmark (Goldstein and Nielsen, 1988). The incidence of trisomy 18 mosaicism is approximately 1 in 70,000 livebirths (Bass et al., 1982). Interestingly, the sex ratio of fetuses and livebirths with trisomy 18 differs. Sex ratios are defined as the number of males divided by the number of females. In prenatal normal controls, the ratio is 1.07. The sex ratio for fetal cases of trisomy 18 is 0.90 and for livebirths it is 0.63. Therefore, a clear-cut differential natural selection against males with trisomy 18 exists after 16 weeks of gestation (Huether et al., 1996). Females with trisomy 18 are more likely to be born alive and survive longer than males (Rasmussen et al., 2003; Lin et al., 2006; Niedrist et al., 2006).

SONOGRAPHIC FINDINGS

Nyberg et al. (1993) reviewed prenatal sonographic findings in 47 consecutive fetuses with trisomy 18. They documented that the type and frequency of sonographic abnormalities varies with gestational age (Table 130-1). Excluding choroid

Table 130-1

Frequency of Abnormalities Among 47 Fetuses with Trisomy 18 Examined with Prenatal Sonography by Menstrual Age at Detection

	Time of Sonographic Examination*		
Sonographic Abnormality	**14–24 Weeks ($n = 29$)**	**24–40 Weeks ($n = 18$)**	**Total Ultrasound Findings ($n = 47$)**
Cystic hygroma or nuchal thickening	9 (31%)†	0 (0%)	9 (19%)
Omphalocele	5 (17%)	5 (28%)	10 (21%)
Large cisterna magna	1 (3%)	8 (44%)	9 (19%)
Cardiac defects	4 (14%)	14 (78%)	18 (38%)
Clenched hands	5 (17%)	4 (22%)	9 (19%)
Clubfeet or rocker-bottom feet	6 (21%)	4 (22%)	10 (21%)
Single umbilical artery	3 (10%)	3 (17%)	6 (13%)
Meningomyelocele	4 (14%)	4 (22%)	8 (17%)
Renal anomaly	5 (17%)	2 (11%)	7 (15%)
Intrauterine growth restriction	8 (28%)	16 (89%)†	24 (51%)

** Numbers in parentheses are percentages.*
† Statistically significant difference ($P < 0.05$) between frequency of detection before 24 weeks versus after 24 weeks.
Source: Nyberg DA, Kramer D, Resta R, et al. Prenatal sonographic findings of trisomy 18: review of 47 cases. J Ultrasound Med. *1993;2:103-113.*

plexus cysts, one or more sonographic abnormalities were found in 39 of 47 (83%) of fetuses with trisomy 18, including 21 of 29 fetuses examined between 14 and 24 weeks of gestation and 100% of fetuses examined at greater than 24 weeks of gestation. Intrauterine growth restriction (IUGR) was the most common abnormality. It was observed in 51% of all fetuses with trisomy 18 and in 89% of fetuses after 24 weeks of gestation. The most common abnormalities seen before 24 weeks of gestation included cystic hygroma, nuchal thickening, and meningomyelocele. After 24 weeks of gestation, IUGR, cardiac defects, and enlarged cisterna magna were more commonly detected. In this study, choroid plexus cysts were seen in 25% of fetuses with trisomy 18 (Nyberg et al., 1993).

A variety of sonographic abnormalities are seen in fetuses with trisomy 18 (Table 130-2). IUGR occurs as early as the first trimester (Lynch and Berkowitz, 1989). The long bones of the extremities are significantly shortened in trisomy 18 (Droste et al., 1990). This affects the lower extremities more than the upper extremities and this begins before the 18th week of gestation. In addition, Droste et al. (1990) documented a poor correlation between fetal foot length and gestational age by menstrual dating. The results of this study imply a significant effect of this chromosomal abnormality on fetal bone growth. Two sonographic markers, the biparietal diameter (BPD) to femur length (FL) ratio and nuchal translucency measurement were found to be sensitive indicators for the prenatal detection of trisomy 18. A BPD:FL ratio of greater than 1.5 SD above the mean identified three of four fetuses with trisomy 18, whereas nuchal thickening identified two of four fetuses with trisomy 18 (Ginsberg et al., 1990). Combining these sonographic markers gave a positive predictive value of 1 in 47 for the detection of trisomy 18.

A variety of cranial abnormalities are seen in trisomy 18. There is an unusually shaped head with a wide occipitoparietal and narrow frontal diameter. This has been called the "strawberry sign" by Nicolaides et al. (1992). Nicolaides and colleagues hypothesized that the narrowed frontal cranium is due to hypoplasia of the face and underdevelopment of the frontal lobes. The presence of choroid plexus cysts has elicited much debate over the association between this finding and trisomy 18. Choroid plexus cysts are present in 50% of fetuses with trisomy 18, but these are never an isolated finding

Table 130-2

Sonographic Malformations Associated with Trisomy 18

- Craniofacial
  - "Strawberry" calvarium
  - Low-set, abnormally shaped ears
  - Micrognathia
  - Thickened nuchal fold or translucency
- Central nervous system
  - Choroid plexus cysts
  - Meningomyelocele
  - Enlarged cisterna magna
  - Cerebellar hypoplasia
  - Absence of the corpus callosum
  - Microcephaly
- Cardiovascular system
  - Atrial septal defect
  - Membranous ventricular septal defect
  - Double outlet right ventricle
  - Atrioventricular canal defect
  - Coarctation of the aorta
  - Dextroposition of the heart
  - Calcification of the chordae tendineae
  - Two-vessel umbilical cord
  - Pulsatile flow in umbilical vein
  - Abnormal blood flow during atrial contraction
- Gastrointestinal system
  - Omphalocele
  - Diaphragmatic hernia
  - Esophageal atresia with tracheoesophageal fistula
- Urogenital system
  - Horseshoe kidneys
  - Cystic renal dysplasia
  - Hydronephrosis
  - Unilateral renal agenesis
- Skeletal system
  - Overlapping fingers
  - Limb-reduction abnormalities
  - Clubfeet
  - Rocker-bottom feet
- Amniotic fluid volume
  - Polyhydramnios
- Intrauterine growth restriction
  - Small placenta
- Behavioral abnormalities

Source: Hill LM. The sonographic detection of trisomies 13, 18 and 21. Clin Obstet Gynecol. *1996;39:831-850.*

(Seoud et al., 1994; Snijders et al., 1994; Hill, 1996; DeVore, 2000; Yeo et al., 2003). Another cranial sonographic finding associated with trisomy 18 is the presence of an enlarged cisterna magna due to cerebellar hypoplasia. Thurmond et al. (1989) described five fetuses with enlarged cisterna magna, which prompted a search for additional fetal anomalies. These five fetuses had a predicted biparietal diameter less than the measured biparietal diameter, and all turned out to have trisomy 18 (Thurmond et al., 1989).

Although echogenic bowel is more characteristic of fetuses with trisomy 21, it has also been described in fetuses with trisomy 18 (Hamada et al., 1996). Hamada et al., described a normal-appearing fetus during the second trimester, but echogenic bowel developed during the third trimester. They hypothesized that the mechanisms for the echogenic bowel included decreased fetal swallowing, hypoperistalsis, and a hypercellular meconium. They also noted that this fetus was growth-restricted, which potentially caused redistribution of regional blood flow, further causing ischemia of the mesentery and the impairment of bowel motility. These abnormalities resulted in thickened echogenic meconium.

Cardiovascular abnormalities are present in 73% to 90% of fetuses with trisomy 18. Most commonly, these include large ventricular septal defects (VSD), atrial septal defects (ASD), tetralogy of Fallot, and left heart disease (Moyano et al., 2005). Diagnosis of heart malformations can be made reliably in the first trimester. One study suggested that male fetuses with trisomy 18 have more complex congenital heart disease than female fetuses (Chen, 2006). This may be the underlying basis for the increased mortality seen in affected males.

Wladimiroff et al. (1989) described the antenatal sonographic markers in 16 fetuses with trisomy 18. All fetuses had a cardiac abnormality. The majority of these were due to VSDs, double outlet right ventricle, or complete atrioventricular septal defect. The extracardiac structural pathology consisted of abnormal hands and feet, symmetrical IUGR, and polyhydramnios. It is thought that the increased nuchal translucency (see Chapter 2) seen in 90% of affected fetuses with trisomy 18 may be due to the cardiac abnormalities. The increased fluid collection at the back of the neck may be an early sign of congestive heart failure.

A variety of limb abnormalities are also a characteristic of trisomy 18, including the typical overlapping flexed fingers, positional abnormalities of the wrist or fingers, and rocker-bottom feet. Overlapping of the fingers occurs sometime between 12 and 14 weeks (Quintero et al., 1999). The prenatal detection of preaxial upper limb reduction facilitated the diagnosis of trisomy 18 in three cases (Sepulveda et al., 1995). In a report of 7 cases of fetal radial ray reduction malformations, three fetuses had trisomy 18 (Brons et al., 1990).

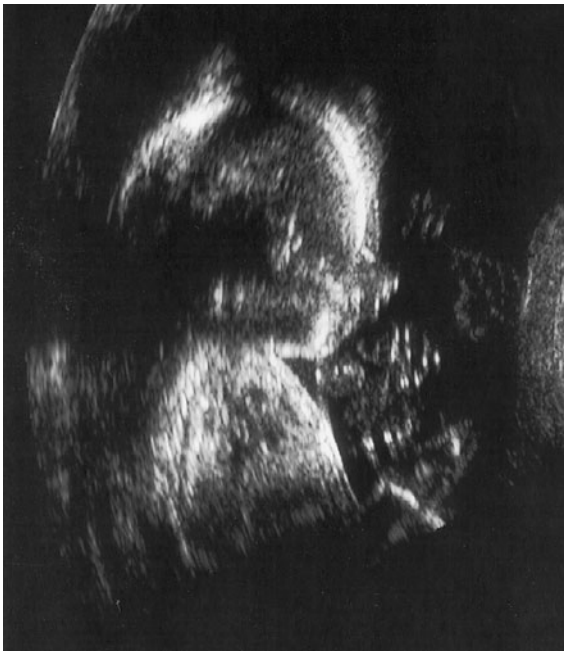

Figure 130-1 Prenatal sonographic profile of a fetus with trisomy 18. Note the micrognathia and the suggestion of a prominent occiput.

A single umbilical artery (see Chapter 109) is seen in 38% to 50% of fetuses with trisomy 18 (Baty et al., 1994a). Yeo et al. (2003) showed that a short ear length (<10% for gestational age) was present in 96% of fetuses with trisomy 18.

Several investigators have described findings that in combination tend to predict a high risk of trisomy 18. These include the combination of polyhydramnios, abnormal hand posturing, and other major structural abnormalities (Carlson et al., 1992), and abnormalities of the fetal face and extremities (Figures 130-1 and 130-2) (Benacerraf et al., 1986, 1988). Benacerraf and colleagues (1994) developed a scoring system to identify fetuses with trisomy 18 based on the presence of certain sonographic findings. Her group specifically looked for the presence of nuchal translucency, long-bone shortening, choroid plexus cysts, echogenic bowel, and other major anatomic defects. They prospectively evaluated 60 fetuses with various autosomal trisomies between 14 and 21 weeks of gestation and 106 normal fetuses at the same gestational age. A sonographic score of 2 or more enabled the prospective identification of trisomy 18 in 11 of 13 affected fetuses. DeVore (2000) identified six sonographic markers (choroid plexus cysts, central nervous system malformations, abnormal nuchal skin fold, ventricular septal defect, outflow tract abnormalities, and right to left chamber disproportion of the heart) that collectively identify 93% of fetuses with trisomy 18 at a false-positive rate of 8.9%. Snijders et al. (1994) calculated a risk of trisomy 18 relative to maternal age and the number of additional sonographic abnormalities present.

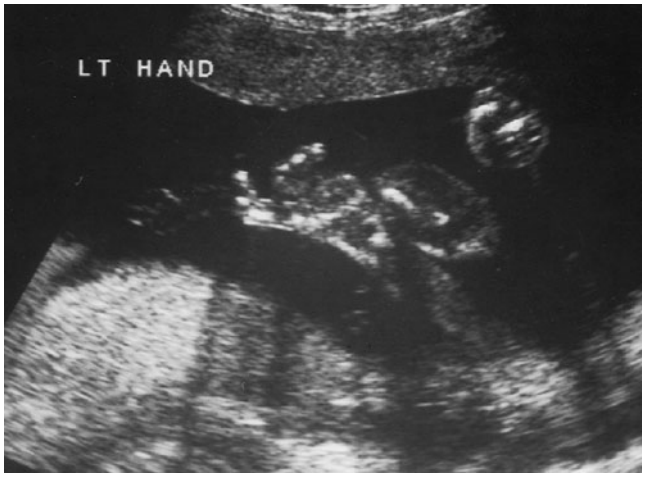

Figure 130-2 Prenatal sonographic image of same fetus shown in Figure 130-1. Note the flexed fingers, which were fixed in position, indicating the presence of camptodactyly.

First trimester sonographic findings observed in fetuses with trisomy 18 include increased nuchal translucency thickness and pulsatile blood flow in the umbilical vein (Sherod et al., 1997; Brown et al., 1999).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of trisomy 18 includes Pena–Shokeir I syndrome, pseudotrisomy 18, and arthrogryposis multiplex congenita (see Chapter 101).

Pena–Shokeir I syndrome is an autosomal recessive syndrome whose hallmark features include IUGR, low-set malformed ears, a depressed tip of the nose, small mouth, micrognathia, multiple flexion contractures, camptodactyly, rocker-bottom feet, pulmonary hypoplasia, and cryptorchidism (Muller and deJong, 1986). This condition is highly lethal—30% of affected fetuses are stillborn. The prenatal sonographic findings described for this condition include polyhydramnios, scalp edema, retrognathia, feeble limb movements, flattened nasal bridge, deformed ears, flexion deformities of the extremities, small thorax, and absent fetal respiratory movements. The distinguishing features between trisomy 18 and Pena–Shokeir I syndrome are scalp edema and lung hypoplasia. Prenatal sonographic diagnosis of Pena–Shokeir I syndrome is possible only in cases of a known family history for this condition.

Pseudotrisomy 18 is a diagnosis of exclusion after a karyotype has revealed normal chromosomes. This is an autosomal recessive lethal condition that presents with micrognathia, flexion contractures of the fingers, low-set malformed ears, and IUGR (Le Marec et al., 1981). To distinguish between pseudotrisomy 18 and trisomy 18, a normal karyotype is necessary. There are an equal number of affected females and males with pseudotrisomy 18. This differs from the excess of females seen with trisomy 18. Also, cardiac abnormalities are not characteristic of pseudotrisomy 18. Pseudotrisomy 18 is associated with consanguinity. A history of advanced maternal age is more typical for cases of trisomy 18.

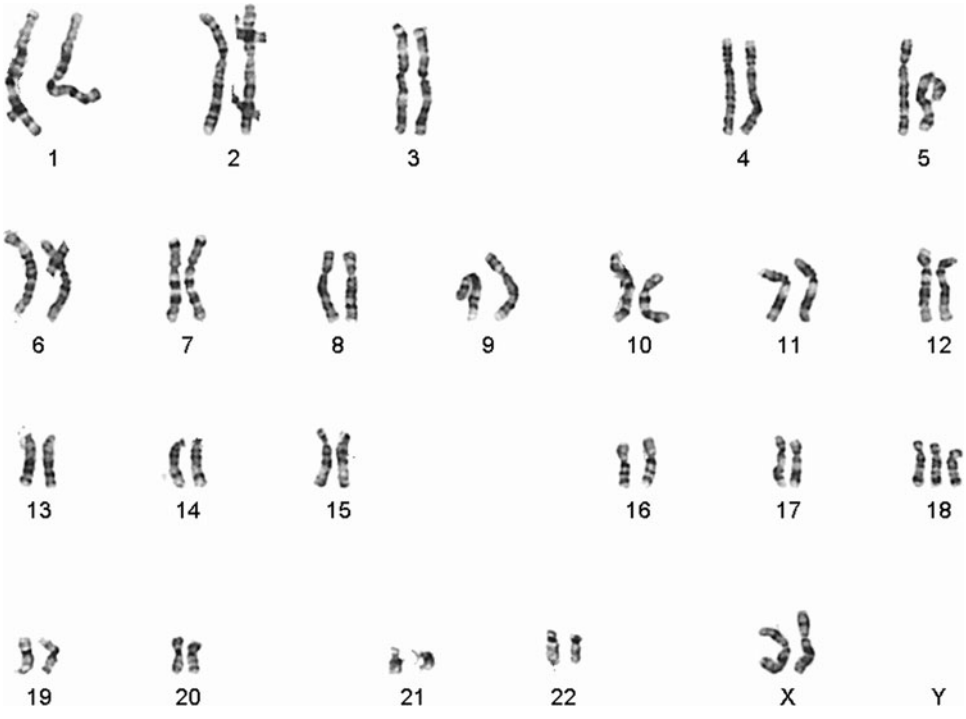

Figure 130-3 Karyotype demonstrating full trisomy 18 in a female. (*Courtesy of Dr. Janet Cowan.*)

The multiple flexion contractures seen in fetuses in which trisomy 18 is suspected may also be characteristic of arthrogryposis multiplex congenita (see Chapter 101). Fetuses affected with arthrogryposis may have camptodactyly, small thorax, and micrognathia.

ANTENATAL NATURAL HISTORY

Trisomy 18 is highly lethal in utero, although fetal demise does not occur at any specific gestation (Won et al., 2005; Yamanaka et al., 2006). In a survey of the rates of spontaneous death of fetuses with chromosomal abnormalities detected at second-trimester amniocentesis in which the mother did not elect to terminate the pregnancy, Hook et al. (1989) determined an excess risk of 63.8% (range, 49.3% to 79.8%) of in utero death of fetuses with trisomy 18. There is significant loss of male fetuses with trisomy 18 during the second half of pregnancy (Huether et al., 1996).

Hyett et al. (1995) studied the cardiac defects in fetuses with trisomy 18 that were identified by increased nuchal translucency measurement and were terminated between 11 and 14 weeks of gestation. There was an unusually high frequency of perimembranous ventricular septal defects and polyvalvular abnormalities, which were consistent with the developmental arrest of the cardiovascular system occurring between 6 and 8 weeks of gestation. These investigators studied 50 apparently normal fetuses and 19 fetuses with trisomy 18. All 19 had cardiac defects. A ventricular septal defect was demonstrated in 16 of 19 (84%) fetuses, and valvular abnormalities were also seen in 84% of fetuses. Fourteen of 16 fetuses with abnormalities had more than one valve affected. In addition, 10 of 18 fetuses studied had a hypoplastic aortic isthmus or pulmonary trunk and 6 of 18 fetuses had persistence of the left superior vena cava. It was hypothesized that hemodynamic changes due to valvular abnormalities and hypoplasia of the great vessels may be the mechanism for the increased nuchal translucency seen in trisomic fetuses (Hyett et al., 1995).

Although 80% to 85% of fetuses with trisomy 18 have a full trisomy when their amniocytes or lymphocytes are studied (Figure 130-3), when the placenta is studied it has been documented that 5% of the fetuses have a mosaic placenta with a normal diploid cell line. The use of cytogenetic analysis has demonstrated that this diploid cell line is confined to the cytotrophoblast in viable pregnancies with trisomy 18. This suggests that a normal diploid component of the trophoblast may facilitate the prolonged intrauterine survival in cases of trisomy 18 (Harrison et al., 1993). This postzygotic loss of the trisomic chromosome in a progenitor cell of a trophectoderm facilitates intrauterine survival of a trisomy 18 conceptus. It is placental function, therefore, that determines intrauterine survival (Kalousek et al., 1989).

MANAGEMENT OF PREGNANCY

Clinical suspicion of trisomy 18 can develop because of increased nuchal translucency measurement (Moyano et al., 2005), IUGR in the third trimester, or an abnormal

serum integrated screen. Multiple abnormalities of serum screening have been associated with trisomy 18, including low pregnancy-associated plasma protein A (PAPP-A) and α-fetoprotein (AFP) levels, low unconjugated estriol values, and a low β human chorionic gonadotropin (β-hCG) level. In one study, the maternal serum free β-hCG level was 0.37 multiples of the median (MoM) and the AFP level was 0.71 MoM in trisomy 18 (Spencer et al., 1993). These results were validated by Leporrier et al. (1996), who documented a low mean hCG and a mean unconjugated estriol 3 (UE3) of 0.4 MoM. With these abnormal values, the detection rate for trisomy 18 is 48% for a 0.8% false-positive rate and 79% for a 3% false-positive rate. Therefore, serum screening is more sensitive and specific for the detection of trisomy 18 than for trisomy 21. More recently, using integrated screening with the results of the first and second trimester markers, the combination of low PAPP-A, low AFP, low estriol, and low hCG detected 90% of trisomy 18 fetuses at a false-positive rate of 0.1% (Palomaki et al., 2003).

Fetuses in which trisomy 18 is suspected either on the basis of abnormal serum screen or by IUGR and evidence of fetal distress should be referred to a center capable of performing detailed anatomic scanning of the fetus. Furthermore, a karyotype should be performed, even when the abnormalities are detected during the third trimester. This is important, because it is well documented that fetuses with trisomy 18 have an excess of postterm deliveries and fetal distress prompting emergency cesarean section. In two separate studies performed in two different countries, the incidence of cesarean delivery for fetuses with trisomy 18 was on the order of 50% (David and Glew, 1980; Schneider et al., 1981). Therefore, a definitive diagnosis of a fetus with trisomy 18 may help the obstetrician and prospective parents to avoid unnecessary fetal monitoring and emergency cesarean delivery. Furthermore, antenatal knowledge that the infant has trisomy 18 will help to appropriately plan newborn resuscitation and further management.

FETAL INTERVENTION

There are no fetal interventions for trisomy 18.

TREATMENT OF THE NEWBORN

If the karyotype has not been performed antenatally, it should be performed at birth. A complete physical examination is indicated. Typically it will demonstrate the presence of intrauterine growth restriction, a prominent occiput, and a short sternum. No single physical finding is pathognomonic for trisomy 18. The major clinical features include hypertonia, anteroposterior elongation of the skull, partial syndactyly of the toes, hypoplastic toenails, narrow chest, micrognathia, short sternum, congenital heart disease, and renal anomalies (Taylor, 1968). The presence of low-arch dermal ridges, which can be seen only with a magnifying lens, is a helpful diagnostic finding, as it is generally seen in most of the fingers of affected patients with trisomy 18. Because of the delay in obtaining chromosome analysis, Marion et al. (1988) developed a bedside score for the clinical diagnosis of trisomy 18 during the immediate neonatal period. Points are given for features reported in a majority of infants with trisomy 18. The maximal attainable score is 160. In this report, in 11 patients with trisomy 18, the average score was 94.3 (range, 70 to 113). In 11 patients without trisomy 18, the average score was 41.4 (Marion et al., 1988).

Infants in whom trisomy 18 is suspected should undergo echocardiography because of the 90% incidence of congenital heart disease in affected patients. In one study of 15 autopsied cases of trisomy 18, all infants were shown to have congenital polyvalvular heart disease. Membranous VSDs were present in 87% of infants, patent ductus arteriosus (PDA) in 73%, and a high takeoff of the right coronary ostium in 80% (Matsouka et al., 1983). The most severe changes were present in the tricuspid and mitral valves with derangement of the spongiosa and fibrosa and defective elastic fibers. The heart valves are dysplastic in trisomy 18 and are noted to be thickened, gelatinous, and nodular. Other findings include long chordae tendineae and hypoplastic or absent papillary muscles (Van Praagh et al., 1989) (see Figure 130-3). Musewe et al. (1990) reviewed the role that cardiac anomalies play in the early death seen in cases of trisomy 18. They noted that most VSDs and PDAs were large and valvular dysplasia of one or more valves was seen in 68% of cases. However, the valvular dysplasia was not associated with evidence of significant regurgitation or stenosis on Doppler studies. Interestingly, several large-scale studies on long-term outcome in trisomy 18 have shown that the presence of a heart defect does not affect survival (Rasmussen et al., 2003; Niedrist et al., 2006).

There is a high incidence of 11 pairs of ribs in cases of trisomy 18 (Ho, 1989). Because of the severity of the clinical consequences of trisomy 18 and the poor prognosis, we recommend that chromosome analysis be performed as soon as possible after birth if it was not performed antenatally. If a surgical emergency is present, consideration should be given to performing fluorescence in situ hybridization (FISH) using chromosome 18–specific probes. This will provide rapid confirmation of the clinically suspected diagnosis, and in this setting, emergency surgery should be avoided if possible (Bos et al., 1992). Major surgery is likely to inflict suffering in an infant whose life expectancy is otherwise poor.

SURGICAL TREATMENT

As discussed above, surgical treatment to prolong life should be discussed with the family. In the relatively rare long-term survivors, surgical treatment may ultimately be indicated to improve their quality of life.

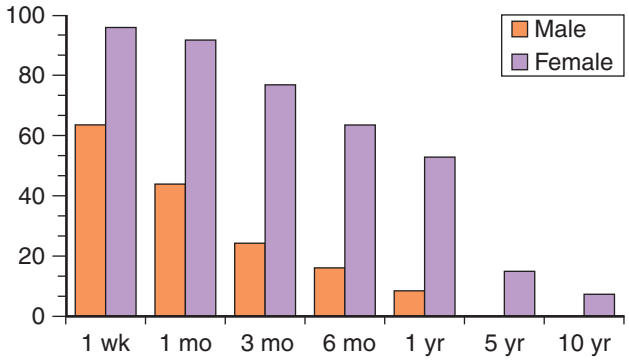

Figure 130-4 The longer-term survival of female versus male infants with trisomy 18 is clearly demonstrated in this graph. Data are based on 70 cases.

LONG-TERM OUTCOME

In an extensive survey of 98 families with an index case of trisomy 18, Baty et al., (1994a) documented an average length of survival of 1.4 months for males with trisomy 18 and 9.6 months for females with trisomy 18 (Figure 130-4). Many obstetricians and pediatricians mistakenly think that trisomy 18 is lethal during the newborn period. Although 55% to 65% of newborns with trisomy 18 die during the first week of life, 5% to 10% of infants are alive at 1 year of age (Root and Carey, 1994; Rasmussen et al., 2003).

In Baty et al.'s (1994a) study of the long-term medical outcome for infants with trisomy 18, the average neonatal hospital stay was 19.6 days, with an average number of 10.1 days on a ventilator. Eighty percent of their trisomy 18 cases went home from the hospital. Of these, 5% went home on oxygen, 12% went home on a cardiac monitor, and 44% were bottle- or breastfed. Nineteen percent of patients eventually required placement of a gastrostomy tube, but the average age of insertion of this tube was 8.4 months. Of long-term survivors, 17% had a known hearing loss, and of these patients, 41% eventually obtained a hearing aid. The major medical problems for long-term survivors with trisomy 18 include scoliosis, gastroesophageal reflux, hearing loss, and Wilms' tumor (Carey, 1992).

Baty et al. (1994a) generated growth curves for long-term survivors with trisomy 18. These demonstrate that the weight and height curves for patients with trisomy 18 are consistently below the normal curve, except for an overlap at birth (Figure 130-5). Long-term survivors were given immunizations in the first 6 months of life and there were no adverse complications directly attributable to the immunization.

In a related study, Baty et al. (1994b) collected developmental data on 50 individuals with trisomy 18. The developmental quotient (DQ), developmental age divided by the chronologic age, was on average 0.18. The developmental ages were studied in seven skill areas, and these differed significantly among the areas. Daily living skills and receptive language had the highest values, whereas motor and communication skill had the lowest values. During the first year of life, affected individuals with trisomy 18 achieved the following skills: following, cooing, rolling, social smile, reaching, and recognition of close adults. During the next 2 years, these individuals were able to sit unsupported, object permanence developed, and they were able to imitate actions and to recognize words. By the age of 4 to 6, affected individuals began to crawl and to follow simple commands, began helping with hygiene, and were capable of both independent playing and the use of signs. These investigators concluded that patients with trisomy 18 achieved some psychomotor maturation and continued to learn, although very slowly (Baty et al., 1994b).

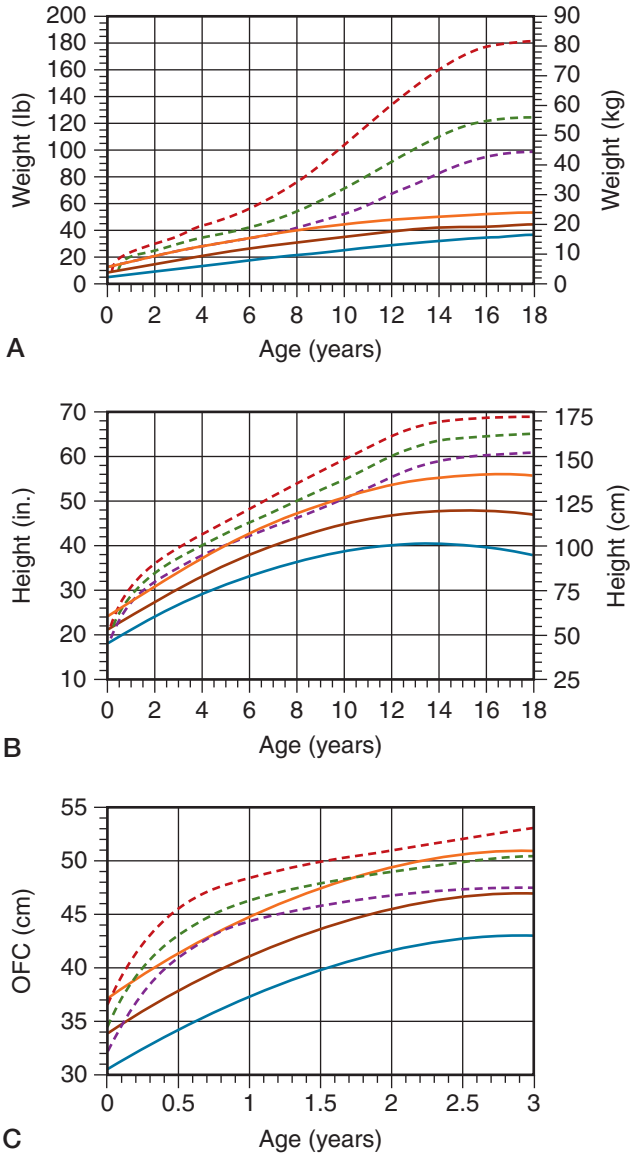

Figure 130-5 Growth curves for infants and children with trisomy 18.

Recently, studies have begun to appear in the literature that document a more aggressive approach to the treatment of infants and children with trisomy 18 (Goc et al., 2006; Kosho et al., 2006). These studies, originating in newborn intensive care units, document the use of mechanical ventilation,

cardiovascular drugs, parenteral nutrition, and surgical treatment of congenital anomalies. Graham et al. (2004) reported on cardiac surgical results in 24 infants with trisomy 18. The overwhelming majority of infants survived the surgery and were discharged alive. Although there may be slightly increased 1-year survival rates with aggressive treatment, it is important to realize that all long-term survivors with trisomy 18 are profoundly retarded.

The most common causes of death in individuals with trisomy 18 are apnea, cardiopulmonary arrest, congenital heart disease, and pneumonia (Baty et al., 1994a; Embleton et al., 1996). Many long-term survivors develop secondary protective lesions, such as pulmonary artery stenosis in the presence of a large VSD (Kelly et al., 2002).

GENETICS AND RECURRENCE RISK

Trisomy 18 is due to the presence of an extra chromosome 18, which is demonstrated on karyotyping. The recurrence risk for full trisomy 18 is commonly quoted as 1% or the age-related maternal risk, whichever is higher. The data from Baty et al. (1994a) on recurrence risk for trisomies 13 and 18 was 0.55%, based on one affected sibling from 181 subsequent pregnancies.

The origin of the extra chromosome in trisomy 18 is almost always maternal. Using molecular analysis and DNA polymorphisms, the origin of the extra chromosome was studied in 23 individuals with trisomy 18. Twenty of 23 were informative. In 19 of 20 the extra chromosome was maternal in origin (Kupke and Müller, 1989). Using DNA repeat sequences and a polymerase chain reaction-based assay, Nöthen et al. (1993) traced the parental origin in 30 cases of trisomy 18. The extra chromosome was maternal in 26 of 30 (86.7%) of cases and paternal in the remainder. When the nondisjunction resulting in trisomy 18 is due to a meiotic error, Eggermann et al. (1996) demonstrated that there was an increased number of meiosis II errors. This is somewhat different from trisomy 13 and 21, in which errors in the first meiotic division predominate.

To date, the specific region of chromosome 18 that is needed to produce the full phenotype of trisomy 18 has not been identified using molecular techniques (Boghosian-Sell et al., 1994). Duplication of part of the long arm of chromosome 18 may be associated with the mental retardation seen in trisomy 18.

There is an increasing appreciation of trisomy 18 mosaicism in women who have normal intelligence but a history of amenorrhea or miscarriages (Satge et al., 1996; Uehara et al., 1996). Kohn and Shohat (1987) described a 30-year-old woman with minor dysmorphic features and normal intelligence who had karyotyping because of a history of three miscarriages. Trisomy 18 was present in 18% of her lymphocytes and 2% of her skin fibroblasts. Several patients have been diagnosed because they gave birth to a child with trisomy 18 or have had infertility workups (Bettio et al., 2003).

Prenatal diagnosis in subsequent pregnancies is by karyotyping. Prospective parents can be offered chromosome analysis on chorionic villus cells or amniocytes, which will give a definitive diagnosis in a subsequent pregnancy.

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Trisomy 21 (Down Syndrome)

131 CHAPTER

Key Points

- Ninety percent of individuals with Down syndrome have three full copies of chromosome 21. Three to 4% have an unbalanced translocation, and 1% have mosaicism.
- Prevalence in the United States is 13.65 per 10,000 livebirths.
- Fetuses with Down syndrome are more likely to die in utero than normal fetuses.
- Karyotype analysis is diagnostic.
- Once trisomy 21 is diagnosed, prospective parents should be offered an echocardiogram and a detailed sonographic evaluation of fetal anatomy (if not performed previously). Fifty percent of fetuses have cardiac anomalies.
- If no structural heart disease or gastrointestinal obstruction is present, delivery can occur in the community. If structural anomalies in the heart or other organs are present, delivery should occur in a tertiary center.
- Newborns often have feeding difficulties due to hypotonia.
- There is an increased risk of hematologic disorders and hypothyroidism.
- Affected children have mild to moderate mental retardation (IQ 40–70).
- The precise number and function of genes of 21q is not fully known.
- Recurrence risk for full trisomy 21 is 1%, or the maternal age-associated risk (whichever is greater).

CONDITION

Trisomy 21 is an abnormality due to the presence of an extra copy of chromosome 21 (Figure 131-1). Individuals with the clinical characteristics of what we now know as Down syndrome were first described by Dr. John Langdon Down in 1866. Dr. Down was a physician at the Earlswood asylum in Surrey, England. His erroneous ideas about a racial cause for Down syndrome, along with a superficial similarity in facial appearance to persons of mongoloid origin, led to the term mongolism (Cooley and Graham, 1991). Interestingly, Dr. Down eventually had a grandson who was also named John Langdon Down, and he had Down syndrome (Patterson and Costa, 2005).

The association between the clinical entity Down syndrome and an extra copy of chromosome 21 was noted simultaneously in 1959 by Drs. Jerome Lejeune in France and Patricia Jacobs in Scotland. Ninety-five percent of individuals with Down syndrome have three copies of chromosome 21, which results from meiotic nondisjunction of the pair of number 21 chromosomes in the formation of an egg or sperm prior to fertilization (Sherman et al., 2005). Ninety-four percent of the time, the extra copy of the chromosome 21 is maternal in origin (Antonarakis, 1991). Approximately 3% to 4% of cases of Down syndrome are due to an unbalanced translocation involving chromosome 21. Fifty percent of the translocation cases occur spontaneously (de novo) and 50% are inherited from a parent with a balanced translocation. One percent of cases of Down syndrome are due to mosaicism, beginning as a trisomic conceptus with selective loss of one copy of chromosome 21 ("disomic rescue") or as mitotic nondisjunction occurring after fertilization in a specific cell line or lines.

A full extra copy of chromosome 21 is not needed to cause the symptoms of Down syndrome. The phenotype of Down syndrome is thought to be due to triplication of the genes expressed in a relatively small region of chromosome 21, band 21q22. However, recent gene expression studies using cell-free fetal RNA in amniotic fluid of second trimester affected fetuses suggests that the fetal phenotype is due to differential regulation of many genes that are not on chromosome 21 (Slonim et al., 2009). Furthermore, second trimester

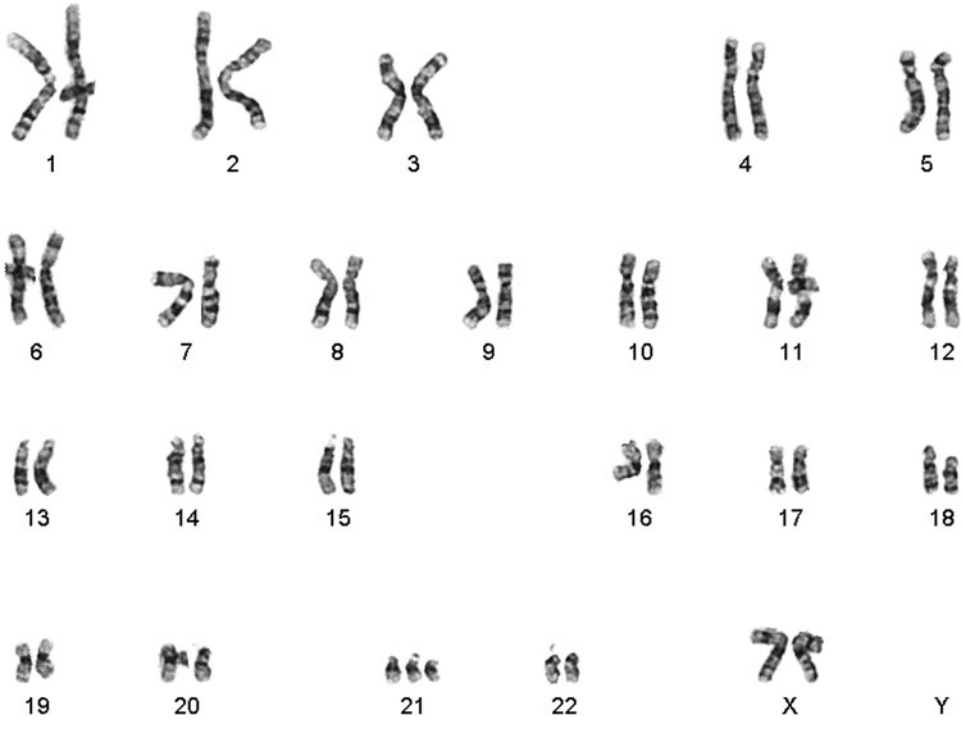

Figure 131-1 Karyotype from a female individual with Down syndrome, indicating the presence of three copies of chromosome 21. (*Courtesy of Dr. Janet Cowan.*)

fetuses with Down syndrome experience significant oxidative stress.

Currently, there is much interest in the noninvasive detection of Down syndrome, by first and second trimester serum screening and nuchal translucency measurement (Nicolaides et al., 1992a) (see Chapters 2 and 3). The analysis of cell-free fetal nucleic acids in maternal blood may eventually have a role in the noninvasive prenatal diagnosis of Down syndrome (Maron and Bianchi, 2007; Lo, 2009).

INCIDENCE

The incidence of trisomy 21 is 1 in 920 livebirths (Krivchenia et al., 1993). The frequency of Down syndrome increases with advanced maternal age. The incidence of Down syndrome is somewhat similar in all ethnic and racial groups, although population-based data from the United States National Birth Defects Prevention Network suggest that there is a higher incidence in Hispanics and a lower incidence in blacks compared to non-Hispanic white women (Canfield et al., 2006).

Cuckle et al. (1991) estimated the "natural birth prevalence" of Down syndrome, which they defined as the birth prevalence that would be expected in the absence of prenatal diagnosis or induced abortion. In their study, performed in England and Wales from 1974 to 1987, the natural birth prevalence of Down syndrome increased from 12.2 in 10,000 to 13.2 in 10,000—an average of 12.6 in 10,000 births. Fourteen percent of cases of Down syndrome were avoided by prenatal diagnosis and termination of affected pregnancies. The actual birth prevalence, which reflected the utilization of prenatal diagnosis, was 10.8 in 10,000 births in this population (Cuckle et al., 1991). In a more recent U.S. population-based study, the prevalence of Down syndrome was 13.65 per 10,000 livebirths (Canfield et al., 2006).

SONOGRAPHIC FINDINGS

The major sonographic findings seen in fetuses with trisomy 21 are listed in Table 131-1. Many of these findings are discussed in individual chapters and in Chapters 2 and 3. The frequency of major internal congenital malformations is less than with trisomies 13 or 18 (Hill, 1996). In general, in cases of trisomy 21, sonographic defects tend to be more subtle than in cases of Trisomies 13 or 18, such as flattening of the facial profile (Figure 131-2). These "soft" markers include nuchal edema, hydronephrosis, clinodactyly, sandal gap (wide space between first and second toes), macroglossia (Nicolaides et al., 1992b), as well as absent or shortened nasal bone (Sonek and Nicolaides, 2002) and increased frontomaxillary facial angle (Sonek et al., 2007).

DIFFERENTIAL DIAGNOSIS

Relatively long differential diagnoses exist for each individual sonographic finding that has been reported to be associated with Down syndrome. A karyotype that demonstrates the presence of an extra chromosome 21 is diagnostic and highly accurate. Once the chromosomes have been studied, there is no longer a need for a differential diagnosis. Postnatally,

Table 131-1

Sonographically Detectable Malformations Associated with Trisomy 21

Craniofacial
Absent or hypoplastic nasal bone
Increased frontomaxillary facial angle
Thickened nuchal fold
Increased nuchal translucency measurement
Cystic hygroma
Protuberant tongue
Central nervous system
Choroid plexus cysts
Mild ventriculomegaly
Cardiovascular system
Ventricular septal defect
Atrial septal defect
Endocardial cushion defect
Calcification of the chordae tendinae
Gastrointestinal system
Duodenal atresia
Echogenic bowel
Imperforate anus
Urogenital system
Pyelectasis
Skeletal system
Brachycephaly with flat occiput
Shortened long bones
Clinodactyly
Syndactyly
Short, thick fingers
Gap between 1st and 2nd toes
Elongated ischial bones
Nonimmune hydrops
Amniotic fluid volume
Polyhydramnios
Intrauterine growth restriction

however, findings such as muscular hypotonia in the newborn may suggest a diagnosis of congenital muscular dystrophy. Furthermore, abnormalities in the facial profile may suggest a diagnosis of Zellweger syndrome.

ANTENATAL NATURAL HISTORY

The incidence of Down syndrome in clinically recognized pregnancies is reported to be as high as 1 in 225 (Hecht and Hecht, 1987). The difference between the incidence of Down syndrome in conceptuses and livebirths indicates the strong selection pressure against this chromosomal abnormality.

Fetuses with Down syndrome have a higher rate of spontaneous abortion or stillbirth than normal fetuses (Figure 131-3). This has been studied extensively by Hook et al. (1989, 1995). This group reported the results of an ongoing survey of rates of spontaneous death of fetuses with trisomy 21 that were detected at second trimester amniocentesis in which the mother did not elect termination of pregnancy. The loss rates were ~50% for fetuses ascertained at 15 to 17 weeks, 43% at 18 weeks, 31% at 19 weeks, 25% at 20 weeks, and 21% to 25% at 21 to 28 weeks (Hook et al., 1995). This was adjusted for the likelihood that spontaneous fetal death would occur in a fetus with a normal karyotype in a population of women with advanced maternal age.

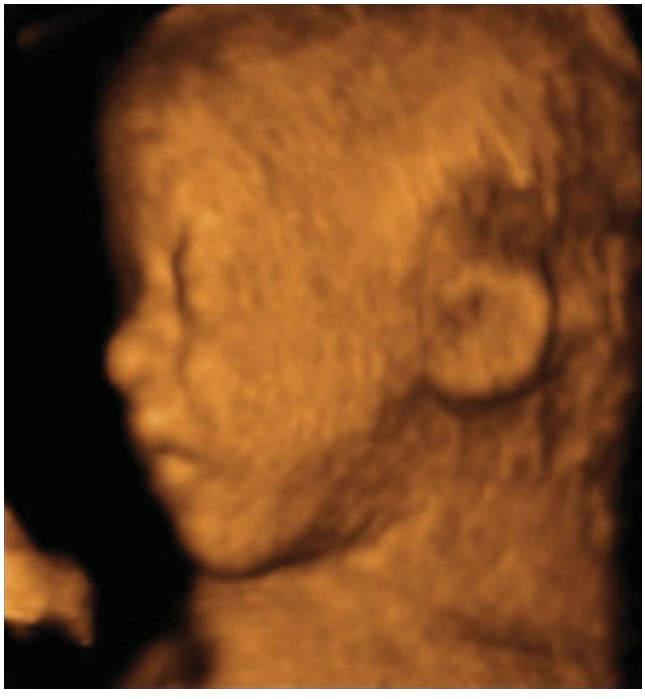

Figure 131-2 Three-dimensional sonographic image of a 20-week fetus with trisomy 21 showing the flattening of the face. The characteristic small ears and overfolded helices seen in Down syndrome are also especially well seen.

MANAGEMENT OF PREGNANCY

In our practice, we routinely offer a genetic amniocentesis or CVS to all pregnant women carrying a fetus with a major or multiple minor sonographic abnormalities that are associated with trisomy 21. If an isolated minor sonographic finding is present, the subsequent course of action is less clear (see Chapter 3).

Once the chromosomal analysis reveals trisomy 21, the prospective parents should be given the opportunity to meet with a medical geneticist to fully discuss the expected medical outcome for a child with Down syndrome prior to making

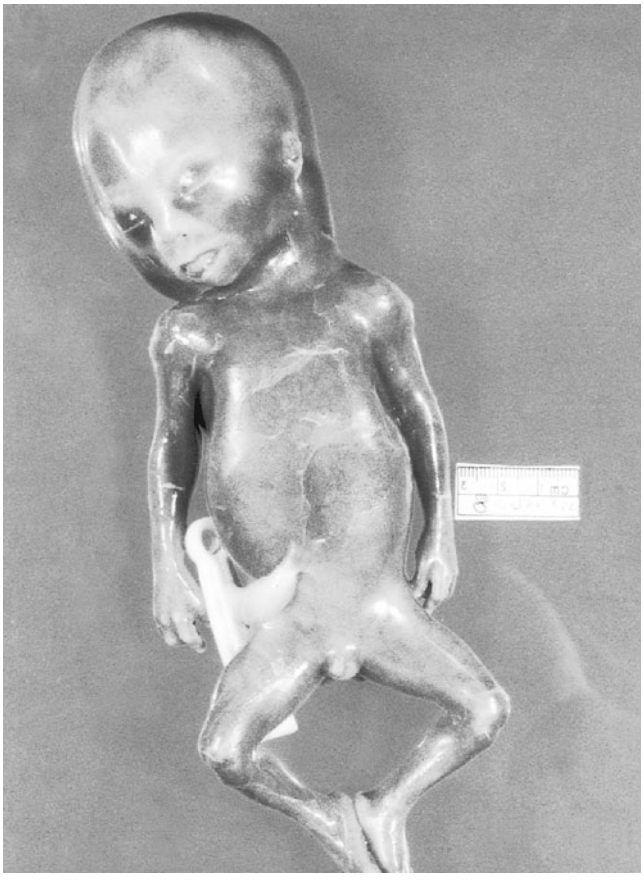

Figure 131-3 Nineteen-week-old fetus with trisomy 21. Note the relative nasal hypoplasia, small mouth, prominent tongue, and cystic hygroma. (*Courtesy of Dr. Joseph Semple.*)

a decision regarding continuation of pregnancy. Also, it is often helpful to have the prospective parents speak to parents who are raising a child with Down syndrome. Options for pregnancy termination should also be presented.

Once the fetus is diagnosed with trisomy 21, the pregnant patient should be referred to a center capable of diagnosing cardiac and other anatomic defects. Unless the fetus is known antenatally to have a severe congenital heart malformation or a malformation that will require immediate surgical repair, such as duodenal atresia, there is no reason to deliver the infant with trisomy 21 at a tertiary care center. We also recommend prenatal consultation with a pediatric cardiologist if a cardiac abnormality is present.

FETAL INTERVENTION

At present, there are no fetal interventions for trisomy 21.

TREATMENT OF THE NEWBORN

The newborn with Down syndrome should receive a complete physical examination (Figures 131-4 and 131-5). If a chromosome analysis has not been obtained prenatally, it should be obtained at birth. A chromosome analysis based on peripheral blood lymphocytes in the newborn should take a maximum of 48 hours. Fluorescence in situ hybridization (FISH) using chromosome-21-specific probes should enable a diagnosis to be made within a few hours. Prior to the availability of FISH, several diagnostic bedside tests based on the presence of certain physical examination findings were described

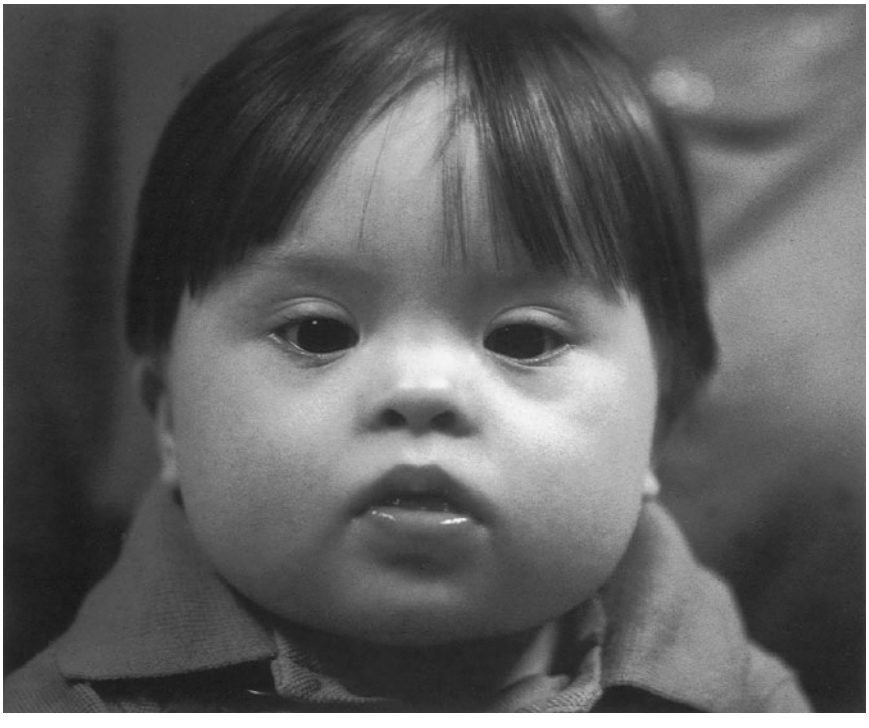

Figure 131-4 An infant with Down syndrome. Note the round face with midface hypoplasia and the epicanthal folds.

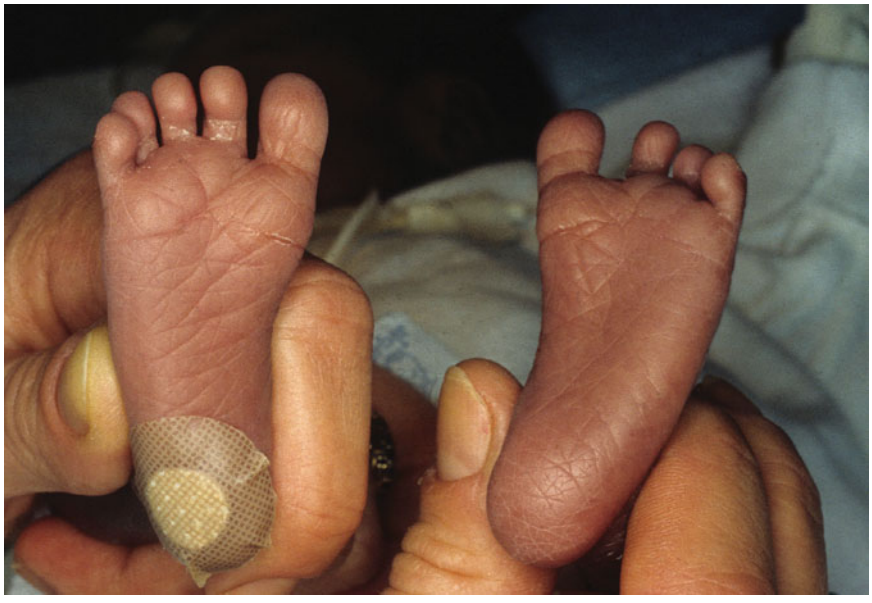

Figure 131-5 The "sandal gap" in a premature newborn with Down syndrome.

(Jackson et al., 1976; Preus, 1977; Rex and Preus, 1982). The newborn with Down syndrome is almost always hypotonic. Many of these infants have feeding difficulties, which result in their eventual transfer to a tertiary care center. Twelve percent of infants with Down syndrome have gastrointestinal abnormalities, including duodenal atresia, celiac disease, Hirschsprung disease, annular pancreas, and imperforate anus (Cooley and Graham, 1991).

An infant with Down syndrome may have breathing difficulties due to the presence of pulmonary hypoplasia. In one study, six of seven patients had hypoplastic lungs (Cooney and Thurlbeck, 1982). The presence of pulmonary hypoplasia is independent of the presence or absence of congenital heart disease. Structural abnormalities that have been described in cases of Down syndrome include a decreased number of alveoli in relation to pulmonary acini. There is a smaller alveolar surface area, which results in reduced capillary surface area. This can cause aggravation of pulmonary hypertension, which is a significant problem in children with Down syndrome.

The 50% incidence of congenital heart disease in cases of Down syndrome mandates that a chest X-ray examination, electrocardiography, and echocardiography be performed during the first month of life. Cardiac symptoms may be masked by the presence of physiologic pulmonary hypertension. In 40% to 60% of the cases of congenital heart disease, the underlying problem is an atrioventricular canal defect (see Chapter 45). The rest of the cardiac anomalies in Down syndrome are due to ventricular septal defect, tetralogy of Fallot, or atrial septal defect (Carey, 1992).

With regard to routine blood tests during the newborn period, a complete blood count should be performed to rule out hyperviscosity syndrome and a transient myeloproliferative disorder, which has a 10-fold to 30-fold greater incidence in individuals with Down syndrome, as compared with the general population. Other common hematologic abnormalities observed among neonates with Down syndrome include neurophilia, thrombocytopenia, and polycythemia (Henry et al., 2007). Transient megakaryoblastic leukemia is found in 10% of newborns with Down syndrome. In most cases the leukemic cells disappear spontaneously within a few months. However, in 20% of these individuals, irreversible acute megakaryoblastic leukemia develops within 4 years (Hitzler and Zipursky, 2005). The leukemic cells carry specific mutations of the hematopoietic transcription factor *GATA1*, which surprisingly maps to the X chromosome and not to 21. *GATA1* mutations have been detected in erythroblasts studied antenatally. Thus, the mutational event occurs in utero. The type of leukemia seen in Down syndrome shows increased sensitivity to chemotherapy (Hitzler and Zipursky, 2005).

There is an increased incidence of congenital hypothyroidism in Down syndrome infants. Therefore, a special effort must be made to check the results of the newborn screening for hypothyroidism. All infants with Down syndrome should be referred to early intervention services in the family's home community. The cardinal physical findings in the newborn with Down syndrome are listed in Table 131-2. Recommendations for the routine health care management of children with Down syndrome have been published (Committee on Genetics, 1994; American Academy of Pediatrics, 2001). Universal screening for celiac disease, starting at age 2 years, is recommended.

SURGICAL TREATMENT

Surgical treatment depends on the presence of structural abnormalities that are amenable to surgical repair, such as duodenal atresia or the presence of an atrioventricular cardiac defect. For specific treatment of each condition, please refer to the appropriate chapter (Chapters 72 and 45, respectively).

Table 131-2

Cardinal Physical Findings in the Newborn with Down Syndrome

Finding	Frequency (percent of cases)
Flat facial profile	90
Absent Moro reflex	85
Muscle hypotonia	80
Oblique palpebral fissures	80
Excess skin at back of neck	80
Joint hyperflexibility	80
Dysplastic pelvis on X-ray examination	70
Dysplastic ear	60
Dysplastic middle pharynx of 5th finger (on X-ray examination)	60
Simian crease	45

Source: Hall B. Mongolism in newborn infants: an examination of the criteria for recognition and some speculations on the pathogenic activity of the chromosomal abnormality. Clin Pediatr. *1966;5:4-12.*

Table 131-3

Life Expectancy for Individuals with Down Syndrome

Age	Chance of Survival with Congenital Heart Disease (%)	Chance of Survival Without Congenital Heart Disease (%)
1 year	76.3	90.7
5 years	61.8	87.2
10 years	57.1	84.9
20 years	53.1	81.9
30 years	49.9	79.2

Source: Baird PA, Sadovnick AD. Life expectancy in Down syndrome. J Pediatr *1987;110:849-854.*

LONG-TERM OUTCOME

Eighty percent of individuals with Down syndrome survive to age 30 or beyond (Cooley and Graham, 1991). The life expectancy for individuals with Down syndrome differs based on the presence or absence of congenital heart disease. This is summarized in Table 131-3. The median age at death has increased to 49 years of age (Yang et al., 2002). Although there is an increased risk of leukemia early in life, there is a lower risk of all other solid tumors, such as breast and colon.

All individuals with Down syndrome have delayed growth, and many have problems with obesity. They are generally followed as outpatients with specific growth charts designed for individuals with Down syndrome (Cronk et al., 1988). All individuals with Down syndrome have mental retardation. Their IQs are in the mild to moderate mentally retarded range (IQ = 40–70). Children with Down syndrome walk, talk, and toilet train, but all of these milestones occur later than average as compared with individuals who do not have Down syndrome. Individuals with Down syndrome are better at visual tasks as compared with tasks that require auditory processing. There is an increased incidence of behavioral and psychiatric problems such as attention deficit/hyperactivity disorder and depression (Roberts et al., 2007).

Individuals with Down syndrome are at risk for hearing loss. This is partly due to the development of serous otitis media, which causes a conductive hearing loss. This finding has a 50% to 70% prevalence in individuals with Down syndrome. Patients with Down syndrome should be referred for audiology and tympanometry before 8 months of age (Carey, 1992), as hearing problems affect language development (Roberts et al., 2007). There is also an increased risk of ocular abnormalities. Patients with Down syndrome are at risk for cataracts, strabismus, nystagmus, and myopia. An annual thyroid screen is also recommended, because of the increased prevalence of hypothyroidism that continues throughout life (Carey, 1992), although the recommendation has been challenged (Van Vliet, 2005).

A controversial area is the screening for atlanto-axial instability, which is caused by a ligamentous laxity in the C1-C2 area. The diagnosis is generally made radiographically if the atlanto-dens interval is 5 mm. The concern is that this instability will lead to dislocation and will develop into an upper spinal cord injury. Atlanto-axial instability reportedly affects 10% to 30% of patients with Down syndrome (Carey, 1992). The Special Olympics organization has made screening for atlanto-axial instability a requirement prior to participation in active sports. However, much controversy exists as to whether neck radiography is an effective screening tool for this abnormality. In most patients who have atlanto-axial instability, neurologic symptoms will develop well in advance of any problems that lead to dislocation.

Fertility is very rare for a male with Down syndrome (Pradhan et al., 2006). However, pregnancy is possible for a

female, for whom the recurrence risk is 50%. Contraceptive measures should be discussed for a sexually active adolescent female with Down syndrome.

With regard to neurologic abnormalities, 5% to 10% of patients with Down syndrome will develop myoclonic seizures. Ultimately, the brains of nearly all adults with Down syndrome who are older than 35 years of age will have senile plaques and neurofibrillary tangles consistent with Alzheimer disease (Antonarakis and Epstein, 2006). Down syndrome is unique in that it confers a 100% risk of developing early onset Alzheimer disease. The mean onset of dementia in patients with Down syndrome is 51.3 years (range, 46–57 years).

GENETICS AND RECURRENCE RISK

Despite the completion of the Human Genome Project, the precise genetic composition of the long arm of chromosome 21 (21q) is not fully known. The total number of protein-coding genes is estimated to be between 271 and 364 (Antonarakis and Epstein, 2006). Recent studies of the transcriptional activity of 21q suggest that there are nonprotein coding RNA molecules present.

The recurrence risk for Down syndrome depends on whether an extra whole chromosome 21 is present or whether a translocation is noted on the karyotype. For the more common situation of a full or "free" trisomy 21, the recurrence risk is 1% or the maternal age–associated risk, whichever is greater (Eunpu et al., 1986). In one study, the recurrence risk in second-degree relatives (uncles and aunts of individuals with trisomy 21) was not increased (Eunpu et al., 1986). Cytogenetic studies, using chromosome heteromorphisms, show that 70% to 80% of cases of trisomy 21 are maternal in origin (Juberg and Mowrey, 1983). However, molecular studies show that the incidence is 94% maternal in origin (Antonarakis, 1991).

If a translocation is documented in the fetal or infant karyotype, parental blood studies must be obtained. The risk of recurrence is 16% if the mother is a carrier of the translocation and 5% if the father is a carrier of the translocation (Cooley and Graham, 1991).

In a subsequent pregnancy, parents who have had either a stillbirth, a spontaneous abortion, or a pregnancy or liveborn infant affected with Down syndrome should be offered prenatal genetic diagnosis for a subsequent pregnancy.

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132 CHAPTER Triploidy

Key Points

- Occurs in 1% to 2% of clinically recognized conceptions but only 1/10,000 livebirths. Not associated with advanced maternal age.
- Most cases are 69, XXY (60%) or 69, XXX (37%); only 3% of cases are 69, XYY.
- In the type I phenotype the fetus is relatively well grown with a large cystic placenta.
- In the type II phenotype the fetus is markedly growth restricted with a disproportionately large head and a small, noncystic placenta.
- One third of cases survive beyond 15 weeks and are associated with abnormal maternal serum screen results.
- The longest postnatal survival for an affected infant was 10½ months.

CONDITION

Triploidy is defined as the presence of three complete sets of the normal haploid genome found in gametes. Triploidy occurs in one of three ways: (1) failure of division in meiosis I or II in the spermatocyte, resulting in an extra set of paternal chromosomes (diandry); (2) failure of division in meiosis I or II in the oocyte, resulting in an extra set of maternal chromosomes (digyny); or (3) double fertilization of a normal haploid ovum (dispermy). Using special chromosome-staining techniques, it has been shown that the extra set of chromosomes is paternal in origin in three quarters of cases (Jacobs et al., 1982). Most of the paternally derived cases are due to dispermy (Kajii and Niikawa, 1977). The distribution of karyotypes seen in triploid conceptuses is 69, XXY (60%), 69, XXX (37%), and 69, XYY (3%) (Jacobs et al., 1982). The infrequent occurrence of XYY suggests that either diandry must be uncommon or that XYY carries a disadvantage for survival.

Triploid fetuses can present with a broad spectrum of phenotypic features that can range from near normalcy to multisystem involvement. McFadden and Kalousek (1991) have described two distinct fetal and placental phenotypes that appear to correlate with the parent of origin in the extra set of chromosomes. In the type I phenotype, the fetus is relatively well grown and has a proportionate head size or microcephaly. The placenta is large, with cystic changes. At the microscopic level there is trophoblastic hyperplasia, scalloping of the villus surface, and focal hydropic change (Sergi et al., 2000). These cases are generally associated with diandry (Figure 132-1A). The type II phenotype predominates in the cases diagnosed after the first trimester; it consists of a markedly growth-restricted fetus

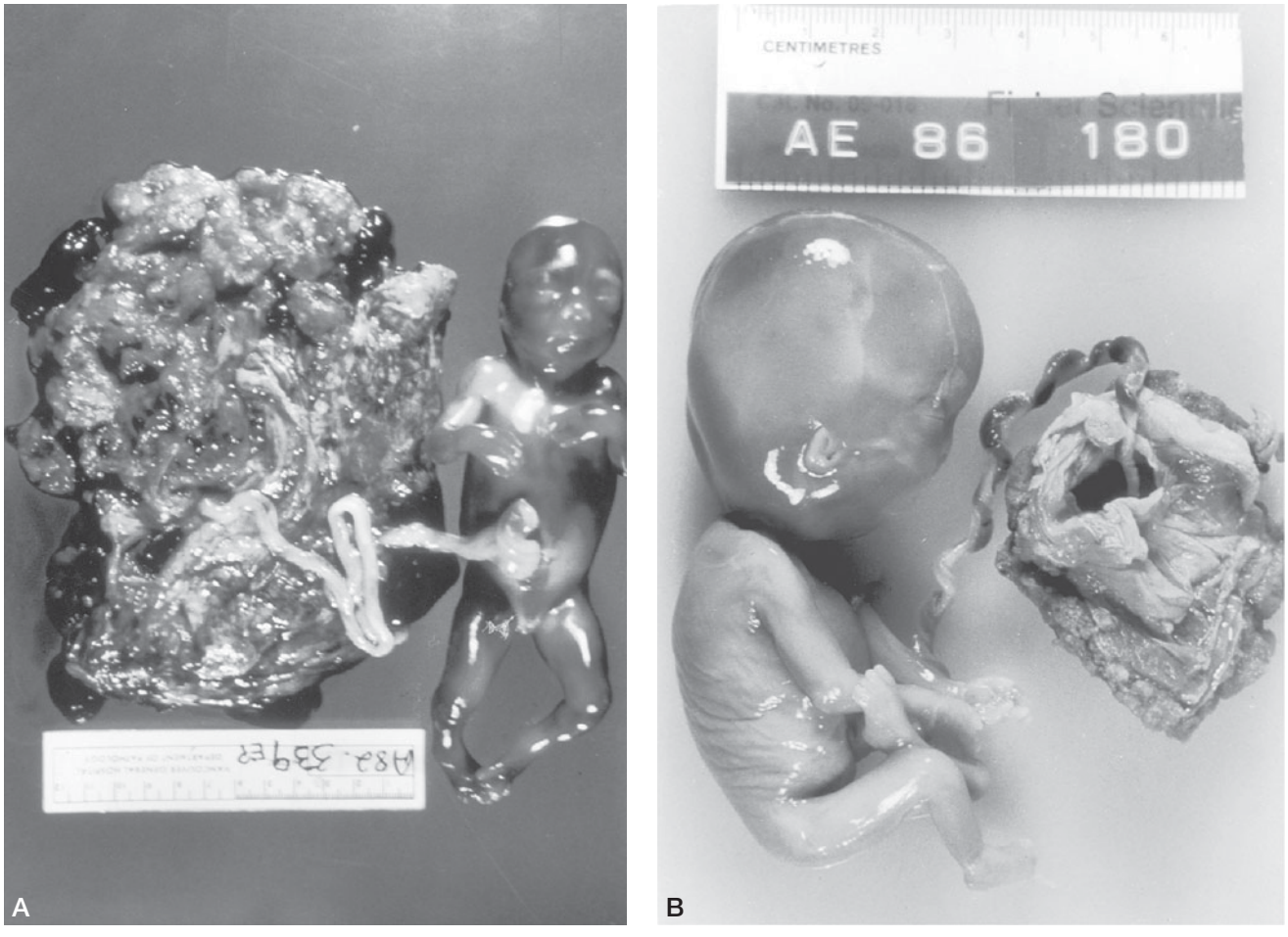

Figure 132-1 **A.** Relatively well-grown fetus with large cystic placenta seen in type I triploidy. **B.** Markedly growth-restricted fetus with a disproportionately large head and a small, noncystic placenta seen in type II triploidy. (*Reprinted from McFadden DE, Kalousek DK. Two different phenotypes of fetuses with chromosomal triploidy: correlation with parental origin of the extra haploid set.* Am J Med Genet. *1991;38:535-538. Copyright 1991 John Wiley & Sons. Reprinted, by permission, of John Wiley & Sons, Inc.*)

with a disproportionately large head and a small, noncystic placenta (Figure 132-1B). In their series, McFadden and Kalousek were able to demonstrate that one case of type II triploidy originated from an error in maternal gametogenesis.

INCIDENCE

Human triploidy is a relatively common condition, occurring in 1% to 2% of all clinically recognized conceptions (Jacobs et al., 1978). Triploidy accounts for approximately 20% of spontaneous abortions due to chromosomal abnormalities (Niebuhr, 1974; Wertelecki et al., 1976). After Turner syndrome (45, X), triploidy and trisomy 16 are the most common chromosomal abnormalities diagnosed in first trimester products of conception (Lindor et al., 1992). The early pregnancy wastage is high—for each triploid infant born alive, it is estimated that 1200 are miscarried (Doshi et al., 1983).

Although triploid conceptions are very common, the incidence is only 1 per 10,000 livebirths (Jacobs et al., 1982). There is no evidence for an increased risk due to advanced maternal age (Rochon and Vekemans, 1990). In experimental animals, triploidy has been induced by colchicine administration, hypoxia, and heat shock (Niebuhr, 1974). There is a questionable association between triploidy and delayed fertilization, due to prolonged menstrual cycles or discontinuation from oral contraceptives (Niebuhr, 1974). Uchida and Freeman (1985) have described an association between preconceptual diagnostic abdominal X-ray exposure and subsequent triploid conceptuses.

SONOGRAPHIC FINDINGS

No single anomaly on sonographic examination is pathognomonic of triploidy (Pircon et al., 1989a). The diagnosis of triploidy should be suspected in any pregnancy with cystic placental changes and fetal anomalies. Similarly, severe intrauterine growth restriction and a markedly increased head:body size ratio should elicit consideration of triploidy (Figure 132-2).

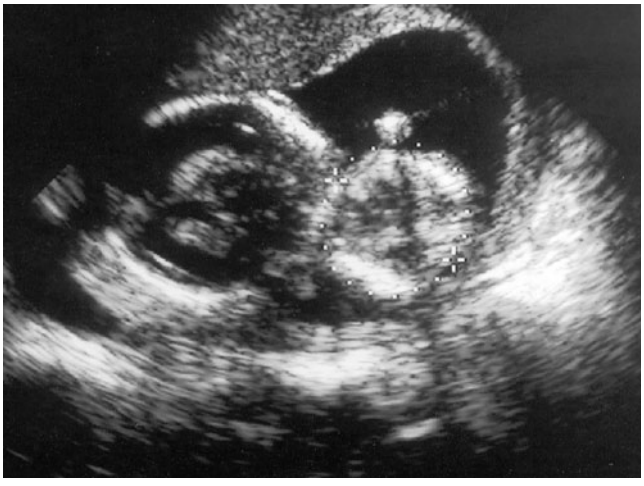

Figure 132-2 Prenatal sonographic image demonstrating increased head to body size ratio.

Intrauterine growth restriction in triploidy has been reported as early as the first trimester (Benacerraf, 1988), but the classic presentation is in the second trimester. Crane et al. (1985) have described growth curves for triploid fetuses studied on several occasions during gestation. The characteristic finding is an abnormally increased head:abdominal circumference ratio that gives the appearance of relative macrocephaly. Oligohydramnios has been reported in as many as 60% of cases (Mittal et al., 1998). Hydrocephalus is common and can be seen in the first trimester (Crane et al., 1985; Benacerraf, 1988). Facial anomalies include micrognathia, microphthalmia (Wertelecki et al., 1976), a bulbous nose, and a small mouth (Bendon et al., 1988). A relatively specific finding is syndactyly of the third and fourth digits (Figure 132-3) (Bendon et al., 1988). Approximately 25% of triploid fetuses have a neural tube defect (Gosden et al., 1976) and 10% to 18% have associated omphalocele or gastroschisis (Blackburn et al., 1982). Male triploid fetuses may have genital abnormalities. Ambiguous genitalia may also be due to the presence of a mosaic karyotype, with two cell lines that contain different sex chromosomes. Both polyhydramnios and oligohydramnios have been described. Other fetal findings that may be apparent sonographically include cardiac anomalies (ventricular septal defect and atrial septal defect), pulmonary hypoplasia, and renal cystic changes. It should also be noted that the absence of anomalies does not preclude a diagnosis of triploidy.

Figure 132-3 Syndactyly of the third and fourth digits seen in an infant with triploidy.

Placental abnormalities are typical of type I (diandric) triploidy (Mittal et al., 1998). Characteristic findings include placental enlargement, hydropic changes (Wertelecki et al., 1976), a generalized hyperechoic appearance, and the presence of multiple small or a single large cyst (see Figure 132-1) (Rubenstein et al., 1986). Abnormal placental Doppler studies are also common (Jauniaux, 1999).

In cases in which triploidy is suspected, sonographic examination of the maternal ovaries may reveal the presence of associated theca lutein cysts (Meizner et al., 1991).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes severe intrauterine growth restriction due to uteroplacental insufficiency, infection, or other genetic syndromes, or other aneuploidies such as trisomy 18. The possibility of a complete mole, with its risk for malignant change, must also be excluded.

ANTENATAL NATURAL HISTORY

The majority of triploid conceptions are lost during the first trimester, but one-third survive beyond 15 weeks of gestation (Warburton et al., 1994). Approximately 1 in 200 ongoing pregnancies at 15 weeks involve a triploid fetus, although some of these fetuses are already dead (Hassold et al., 1980; Jacobs et al., 1982). Between 16 and 19 weeks of gestation, triploidy is found in 8.1% of all spontaneous abortions. In one study, 43% of the chromosomally abnormal fetuses lost between 16 and 19 weeks were shown to be triploid (Warburton et al., 1994).

Development of hydatidiform changes in the placenta ("partial mole") is primarily associated with the presence of two paternal sets of chromosomes (diandry or dispermy). These moles rarely undergo malignant change, as opposed to diploid moles that are not associated with the formation of a fetus.

Abnormalities in maternal serum testing are present in triploid pregnancies that survive to the second trimester. Increased maternal serum α-fetoprotein (AFP) levels have been demonstrated in several reports (O'Brien et al., 1988; Freeman et al., 1989; Pircon et al., 1989b). In most cases, amniotic fluid AFP levels have been normal unless an associated neural tube defect is present (Freeman et al., 1989). It is important to consider triploidy in the differential diagnosis of elevated maternal serum AFP levels, as in several reported cases, the sonographic examination was within normal limits (Pircon

et al., 1989a). Low levels of human chorionic gonadotropin (hCG) and estriols are also associated with triploidy (Fejgin et al., 1992). It has been questioned whether this finding is due to an extra set of maternal chromosomes impairing placental function (Schmidt et al., 1994). As first trimester prenatal diagnosis has become more common it has also become appreciated that triploidy is associated with very low levels of pregnancy-associated plasma protein A (PAPP-A) (De Graaf et al., 1999; Campbell et al., 1999).

MANAGEMENT OF PREGNANCY

Prenatal diagnosis of triploidy is important, as this condition carries serious medical risks for the mother. These risks include vaginal bleeding and severe pre-eclampsia (Jauniaux, 1999). Prenatal recognition also prevents unnecessary cesarean delivery (Graham et al., 1989). The abnormally large cystic placenta can cause severe postpartum hemorrhage and may be retained after birth (Niebuhr, 1974).

We recommend that prenatal karyotyping be performed for the following clinical situations: (1) severe intrauterine growth restriction with or without fetal anomalies documented on second trimester sonographic examination; (2) hydatidiform placental changes noted on sonography; (3) abnormally increased maternal serum AFP levels (greater than 3.5 MoM); and (4) severe pre-eclampsia with fetal anomalies or hydatidiform placental changes. A full metaphase karyotype will make a definitive diagnosis and also rule out the presence of mosaicism. If a rapid diagnosis is necessary, fluorescence in situ hybridization (FISH) analysis using chromosome probes has been used on uncultured amniocytes to diagnose triploidy (Christensen et al., 1992; Gersen et al., 1995).

Once the diagnosis of triploidy has been made, the poor prognosis and maternal risks should be discussed with the parents, and termination of pregnancy should be offered if the gestational age is less than 24 weeks. Early induction of labor is recommended if the diagnosis is made after 24 weeks because of the maternal medical risks associated with continuing the pregnancy. Cesarean section is not indicated except to facilitate delivery for maternal health. Delivery in a tertiary care center is not necessary. The advantages of delivering in a tertiary care center are that: (1) if the infant survives postnatally, neonatal transfer will not occur; (2) when the infant dies, perinatal pathologists are available for autopsy; (3) many tertiary care centers offer coordinated services for bereavement and genetic counseling; and (4) appropriate subspecialty referral is available for the mother if she has medical complications.

FETAL INTERVENTION

There are no fetal interventions for triploidy.

TREATMENT OF THE NEWBORN

Given the relative infrequency of this condition in the liveborn population and the subtlety of the associated dysmorphic features, the diagnosis of triploidy in the newborn is sometimes unsuspected. The severe growth restriction usually prompts an investigation of the chromosomes, but results are usually not available for 3 to 7 days. The phenotypic features of infants presenting with complete triploidy are summarized in Table 132-1. The typical infant who survives postnatally has the "type II" phenotype of McFadden and Kalousek, with growth restriction, relative macrocephaly, dysplastic calvarium, ocular colobomas, cleft palate, micrognathia, hypotonicity, and genital abnormalities (if male) (Graham et al., 1989). Gosden et al. (1976) have also described an unusual appearance of the thighs due to muscular hyperplasia. They termed this physical finding "wine bottle thighs."

Hematologic abnormalities in triploid infants have also been reported. Typical findings include macrocytosis, anisocytosis, polychromasia, an increase in platelet size, and abnormalities of the granulocytes (Strobel and Brandt, 1985).

Doshi et al. (1983) have documented pathologic findings in 43 complete and 11 mosaic triploid fetuses or infants delivered after 22 weeks of gestation. In addition to the anomalies already mentioned, they reported ovarian, adrenal, and pulmonary hypoplasia as well as testicular Leydig cell hyperplasia. True hermaphroditism has also been reported (Petit et al., 1992).

Importantly, the diagnosis of complete triploidy is considered lethal. There have been no survivors beyond the age of 10.5 months (Sherard et al., 1986). Newborn resuscitation and mechanical ventilation are not indicated. Warmth, nutrition, and comfort measures are recommended. Faix et al. (1984) have eloquently described the ethical dilemmas in a case of triploidy in which the parents insisted on employment of the full range of life-support technology. Even with their aggressive support, the infant survived for only 4 months and had marked impairment of his growth and development.

SURGICAL TREATMENT

The lethal nature of complete triploidy precludes intervention in surgically correctable anomalies such as abdominal wall defects. A more aggressive approach to surgically correctable lesions may be considered in cases of diploid/triploid mosaicism.

LONG-TERM OUTCOME

The longest reported survival of an infant with triploidy is 10.5 months (Sherard et al., 1986). This male infant was small for gestational age, with a complete cleft lip and palate, digital abnormalities, and a large ventricular septal defect (Figure 132-4). His medical problems included congestive

Table 132-1

Phenotypic Features of Infants with Complete Triploidy

General
Intrauterine growth restriction
Head
Relative macrocephaly
Malformed, low-set ears
Microophthalmia
Ocular coloboma
Micrognathia
Chest
Pulmonary hypoplasia
Cardiac
Ventricular and atrial septal defects
Abdomen
Omphalocele
Renal anomalies
Adrenal hypoplasia
Ovarian hypoplasia
Genitalia
Normal in females
Anomalies in males include
Hypospadias
Micropenis
Cryptorchidism
Extremities
3rd and 4th digit syndactyly of the hands and/or feet
Simian crease
"Wine bottle" thighs
Neurologic
Hypotonicity
Myelomeningocoele
Hydrocephalus

Modified from Doshi N, Surti U, Szulman AE. Morphologic anomalies in triploid liveborn fetuses. Hum Pathol. *1983;14:716-723.*

heart failure (treated with digitalis and diuretics), seizures (treated with phenobarbital), and upper respiratory infections. He died from respiratory complications.

Genotyping studies demonstrated that the extra set of chromosomes was maternal in origin. In three of the longest-surviving infants with triploidy, the extra genome was also maternal (Fryns et al., 1977; Galan et al., 1991) although at least one other case was paternally derived (Niemann-Seyde et al., 1993). In the future, we may understand the importance

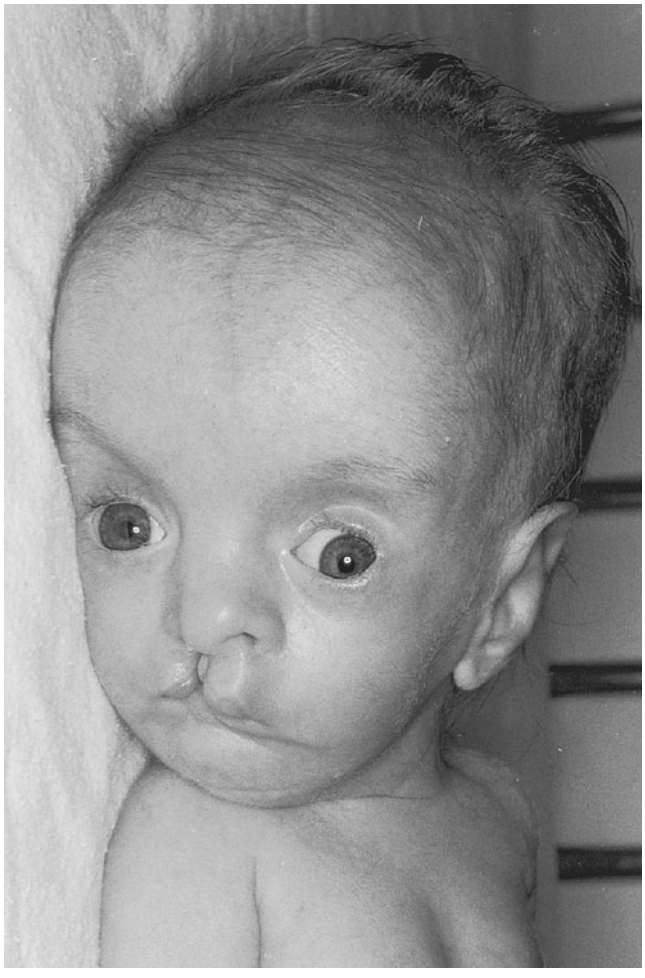

Figure 132-4 Facial appearance of a triploid male infant who survived for 10.5 months. (*Reprinted from Sherard J, Bean C, Bove B, et al. Long survival in a 69, XXY triploid male.* Am J Med Genet *1986;25:307-312. Copyright © 1986 John Wiley & Sons. Reprinted, by permission, of John Wiley & Sons, Inc.*)

of the parent of origin differences in the extra chromosome set. Imprinting of certain genes may play a role.

Infants who are shown to have diploid/triploid mosaicism on their karyotype will, in general, have a milder phenotype that may permit prolonged survival to adulthood (Tantravahi et al., 1986). The majority of the patients reported have had developmental delay. Other features described in these diploid/triploid individuals include hemihypertrophy, syndactyly, ambiguous genitalia, and mild craniofacial abnormalities (Dewald et al., 1975).

GENETICS AND RECURRENCE RISK

The issue of whether triploidy is a random event or whether it affects future reproductive performance is currently unresolved. Three studies have suggested a slightly increased risk for other chromosomal abnormalities in future pregnancies (Boué et al., 1973; Stene et al., 1984; Uchida and Freeman,

1985). We recommend prenatal cytogenetic diagnosis in subsequent pregnancies. Genetic counseling is indicated so that the family can understand the cause of the triploidy and the risk of recurrence.

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133 CHAPTER Other Autosomal Aneuploidies

Key Points

- Trisomies 8, 9, 14, 16, and 20, if present in mosaic form, are compatible with postnatal survival.
- Mosaic trisomies are generally associated with nondisjunction due to advanced maternal age.
- Trisomy 16 occurs in at least 1.5% of all clinically recognized pregnancies and 31% of all spontaneous losses due to chromosome abnormalities.
- Trisomy 20 accounts for 2% of trisomic miscarriages and is a common cause of true mosaicism in amniotic fluid cultures.
- For mosaic trisomies 8, 9, and 14, a detailed sonographic survey of fetal anatomy and consultation with a medical geneticist are indicated.
- Women carrying fetuses with mosaic trisomy 16 are at risk for developing pre-eclampsia.
- Phenotype does not correlate with percent of mosaic cells except for trisomy 20. The presence of more than 60% of cells with trisomy 20 is associated with a poor prognosis.
- All continuing pregnancies should have involvement of the medical genetics team.
- Survivors with trisomy 16 have excellent postnatal catch-up growth and the majority have a good developmental outcome. Mosaic trisomies 8, 9, and 14 have variable outcomes. Mosaic trisomy 20 has a normal outcome if there are less than 60% abnormal cells.

CONDITION

In this chapter, information will be discussed regarding trisomies 8, 9, 14, 16, and 20. These are the trisomies that, if present in a mosaic form, are compatible with fetal survival at least until the end of the first trimester. They present with sonographic abnormalities or abnormalities of maternal serum screening analytes. All of these conditions are detected by cytogenetic analysis. Mosaic trisomies account for around 5% of the trisomies detected in human spontaneous abortions. In general, they are associated with advanced maternal age (James and Jacobs, 1996). For most of the trisomies, the general mechanism is nondisjunction in maternal meiosis I. This is then followed by a second mitotic error in chromosome division. The second division corrects the trisomy, but about a third of the time results in leaving behind two maternal copies of the particular chromosome. This is known as uniparental disomy (UPD). UPD can then cause an abnormal phenotype through homozygosity for recessive genes or if there are areas of imprinted genes on that particular chromosome (Reish et al., 1998). In contrast, current evidence seems to indicate that trisomy 8 has a different underlying mechanism. It appears to be due to postzygotic nondisjunction with a gain of a chromosome in some tissues.

Trisomies 8, 9, 14, 16 and 20 are generally lethal when present as a full trisomy. In this chapter only the mosaic trisomies will be discussed, as those are what is encountered clinically. For most of the mosaic trisomies, there is no relationship between the percent mosaicism and the clinical outcome, with the exception of trisomy 20.

Interestingly, all of the mosaic trisomies may present with postnatal skin pigmentation defects, such as hypomelanosis of Ito. The precise connection between mosaicism and the skin pigmentation defects is unknown. Also, a number of the mosaic trisomies can demonstrate subtle body asymmetries.

INCIDENCE

It is difficult to get accurate livebirth incidences for the mosaic trisomies. Most of the data that have been reported are from the prenatal diagnosis or the pathology literature. For example, full trisomy 16 is the most common trisomy that is found in spontaneous abortions. Trisomy 16 occurs in at least 1.5% of all clinically recognized pregnancies (Wolstenholme, 1995). This condition comprises 31% of all autosomal trisomies in products of conception. Similarly, trisomy 20 is one of the most common forms of autosomal mosaicism diagnosed at amniocentesis (Hsu et al., 1987). Mosaic trisomy 20 accounts for 2% of all trisomic miscarriages (Hsu et al., 1987; Robinson et al., 2005). Mosaicism for trisomy 8 has been detected in approximately 1 in 3870 amniocenteses (van Haelst et al., 2001). Trisomies 9 and 14 account for 2.7% and 3.7%, respectively, of chromosomally abnormal miscarriages (Fujimoto, 1992; Chitayat et al., 1995).

SONOGRAPHIC FINDINGS

Trisomy 8

The sonographic findings for trisomy 8 include nuchal fold thickening, hemivertebrae, ventriculomegaly (Southgate et al., 1998), reversed end-diastolic ductus venosus blood flow (Campbell et al., 2001), pyelectasis, hydronephrosis, ureteral reflux, and cardiac abnormalities (Miller et al., 2001).

Trisomy 9

Stipoljev et al. (2003) reviewed the sonographic findings in 12 nonmosaic and 13 mosaic fetuses with trisomy 9. The sonographic abnormalities seen in full trisomy 9 included intrauterine growth restriction, microcephaly, increased nuchal translucency measurement, cystic hygroma, micrognathia, hydrops, decrease in the long bone measurements for age, congenital heart defects, skeletal abnormalities, and Dandy–Walker malformation. Dandy–Walker malformation (see Chapter 11) is seen in 12% to 15% of fetuses with trisomy 9. For the mosaic fetuses, the characteristic abnormalities are Dandy–Walker malformation, intrauterine growth restriction, micrognathia, and hydronephrosis. Other abnormalities associated with trisomy 9 include hepatic calcifications, diaphragmatic hernia, and male genital abnormalities.

Trisomy 14

There have been no comprehensive reports of prenatal sonographic findings in trisomy 14. However, from the postnatal literature, what might be expected would be intrauterine growth restriction, micrognathia, congenital heart disease (especially tetralogy of Fallot), polyhydramnios, and micropenis.

Trisomy 16

Characteristic pathologic findings associated with trisomy 16 include intrauterine growth restriction, congenital heart disease (atrial septal defect, ventricular septal defect, and tetralogy of Fallot), single umbilical artery, and renal anomalies. Astner et al. (1998) reported on sonographically associated anomalies associated with confined placental mosaicism for trisomy 16. They noted the presence of a thickened and enlarged cystic placenta. The cysts that were present in the second trimester but disappeared in the third trimester had an unusual appearance in that they were multiple and round without a hyper-reflective border. They speculated that this might be a sonographic marker for trisomy 16.

Trisomy 20

For the majority of cases of mosaic trisomy 20, the sonographic findings have been normal. James et al. (2002) reported on 14 cases of trisomy 20 mosaicism. Of these, three had an increased nuchal translucency measurement on a first trimester scan. The remaining 11 cases had a detailed second trimester anatomy scan that was normal. What might be expected from the postnatal literature would also be the possibility of a heart or renal malformation.

DIFFERENTIAL DIAGNOSIS

The diagnosis of each of these conditions is based on highly accurate cytogenetic analysis.

ANTENATAL NATURAL HISTORY

For all of these conditions, full trisomy is generally lethal in utero. Whether or not the fetus survives depends on a number of factors. These include whether or not the trisomy is confined to the placenta, whether or not there is a rescue disomy, and whether or not UPD of the remaining disomic chromosomes exists. Because trisomies 16 and 20 are more common than trisomies 8, 9, and 14, relatively more information is available.

Trisomy 16

In cases of mosaic trisomy 16, placental mosaicism is always present. In spontaneous abortions with trisomy 16, the extra copy of 16 is always maternal in origin (Hsu et al., 1998). The mosaic trisomy 16 cases that derive from full trisomy and undergo disomic rescue have approximately a 30% to 40% chance of maternal UPD for chromosome 16. If UPD for 16 is present, there is an increased incidence of both intrauterine growth restriction and congenital anomalies (Yong et al., 2002). Most cases of trisomy 16 spontaneously abort between 8 and 15 weeks of gestation (Wolstenholme, 1995;

Benn, 1998). Trisomy 16 detected at amniocentesis is more likely to be associated with anomalies as compared with trisomy 16 detected at CVS, which is more likely to be due to confined placental mosaicism. It has been shown by many investigators that adverse fetal outcomes are more common when the trisomy is detected in the amniotic fluid (Yong et al., 2003; Langlois et al., 2006; Neiswanger et al., 2006).

Trisomy 20

Trisomy 20 is more frequently detected in specific fetal tissues, such as kidney, rectum, and esophagus. Trisomy 20 cells have not been detected in fetal blood. Interestingly, there is a clear association between the percent trisomy and outcome in mosaic trisomy 20. Several investigators have shown that a percent mosaicism above 60% is associated with an abnormal outcome (Hsu et al., 1987; Robinson et al., 2005).

MANAGEMENT OF PREGNANCY

In general, the cytogenetic detection of a mosaic aneuploidy mandates that a detailed sonographic assessment of fetal anatomy should be performed in a tertiary center. As stated earlier, clinical phenotype does not correlate with the percentage of mosaicism for most autosomal trisomies; the only exception to this is trisomy 20. For the mosaic trisomies 8, 9, and 14, there are no specific recommendations, other than to perform a detailed sonographic assessment of fetal anatomy and to meet with a clinical geneticist for the prognosis for an infant with these conditions. For a woman carrying a fetus with mosaic trisomy 16, the pregnancy is at significant risk for developing pre-eclampsia (Yong et al., 2006). In one study, 25 cases of prenatally diagnosed mosaic trisomy 16 were reviewed and 6 of the pregnant women (24%) developed pre-eclampsia compared with 3 of 44 (7%) of controls. No clinical variables were predictive of which women carrying fetuses with mosaic trisomy 16 would develop pre-eclampsia. Therefore, the recommendation is that all women carrying fetuses with mosaic trisomy 16 who continue their pregnancies should be monitored for this complication. Percutaneous umbilical blood sampling (PUBS) is not recommended to determine the prognosis for trisomy 16, as it is not helpful. Also, it is not currently recommended to test fetal material for the presence of maternal UPD for chromosome 16 (Yong et al., 2002). Furthermore, it should be noted that pregnancies affected by mosaic trisomy 16 generally have extremely high hCG values with a median multiple of the median (MOM) of 8.62. These pregnancies also have high α-fetoprotein levels and low unconjugated estriol levels (Benn, 1998).

Similarly, there is insufficient evidence to warrant testing for UPD in mosaic trisomy 20 (Robinson et al., 2005). Because mosaic trisomy 20 has only rarely been shown to be present in fetal blood, PUBS is also not recommended for mosaic trisomy 20. For cases of mosaic trisomy 20, the results of the fetal anatomic survey will dictate further management. One study showed that if the fetal anatomy appears normal on prenatal ultrasound examination, the prospective parents should be counseled that the risk of a fetal abnormality is less than 10% (James et al., 2002). Several other studies have examined the correlation between the percent mosaicism in the amniocentesis and CVS sample and outcome. If the mosaicism is less than 40%, there is a 4% chance of an abnormal outcome (Robinson et al., 2005); however, even in cases with high levels of mosaicism in the amniotic fluid culture, half of the cases will have a normal outcome.

FETAL INTERVENTION

No fetal interventions are indicated for the mosaic aneuploidies.

TREATMENT OF THE NEWBORN

Newborns with the mosaic trisomies should be delivered in a tertiary center capable of pediatric subspecialty care or transferred to an institution with these services. A complete physical examination is indicated, as well as consultation with a medical geneticist. An echocardiogram and an abdominal sonogram should be considered to evaluate for the presence of cardiac and renal anomalies.

Trisomy 8

Newborns with trisomy 8 have several characteristic anomalies, including deep plantar and palmar creases, a prominent forehead, large dysplastic ears, agenesis of the corpus callosum, and skeletal abnormalities, including camptodactyly and clinodactyly.

Trisomy 9

Infants with trisomy 9 have intrauterine growth restriction, a dysmorphic face with retromicrognathia and small palpebral fissures, microcephaly, dislocated hips, knees and elbows, and abnormal genitalia (Chitayat et al., 1995). The typical trisomy 9 facial phenotype includes a bulbous nose, microophthalmia, and dislocated limbs (Arnold et al., 1995) (Figures 133-1 and 133-2).

Trisomy 14

The major clinical findings in trisomy 14 include a normal birth weight, but with postnatal failure to thrive, a dysmorphic face that consists of a broad nose, micrognathia, hypertelorism, small palpebral fissures, a prominent forehead, and a large mouth. Affected infants sometimes have a cleft or a high arched palate, congenital heart disease, micropenis, cryptorchidism, body asymmetry, and abnormal skin pigmentation (Fujimoto et al., 1992).

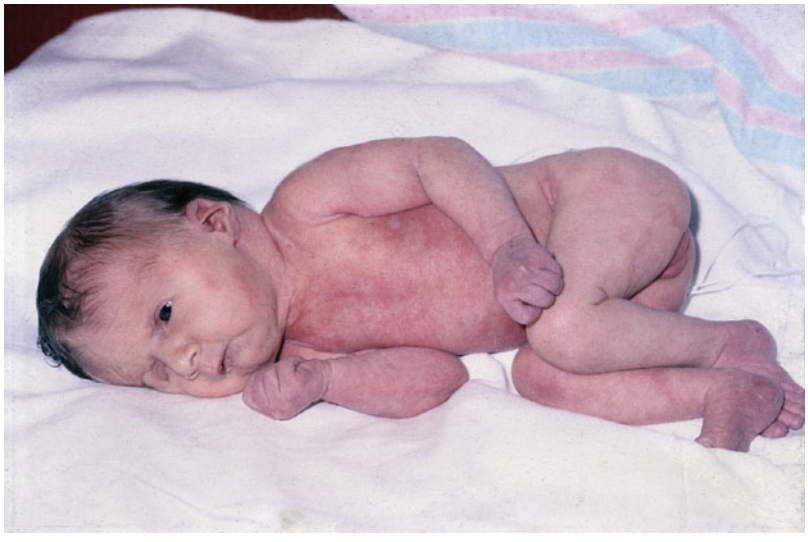

Figure 133-1 Term infant with mosaic trisomy 18 showing growth restriction, dislocated hips, and clenched hands. These infants are sometimes initially suspected of having trisomy 18.

Trisomy 16

Yong et al. (2003) reviewed 162 cases with a prenatal diagnosis of trisomy 16. Two-thirds of the cases resulted in a live-birth at an average gestational age of 35.7 weeks. Among the infants that were liveborn, 45% had at least one congenital anomaly. The most common malformations were ventricular septal defects, atrioseptal defects, and hypospadias. One of the biggest characteristics of mosaic trisomy 16 is severe intrauterine growth restriction. In this study, the average birth weight was approximately 2 standard deviations below the population mean. Other malformations that were present in eight or more of the cases in the study included two-vessel cord, clinodactyly, and pulmonary hypoplasia (Yong et al., 2003).

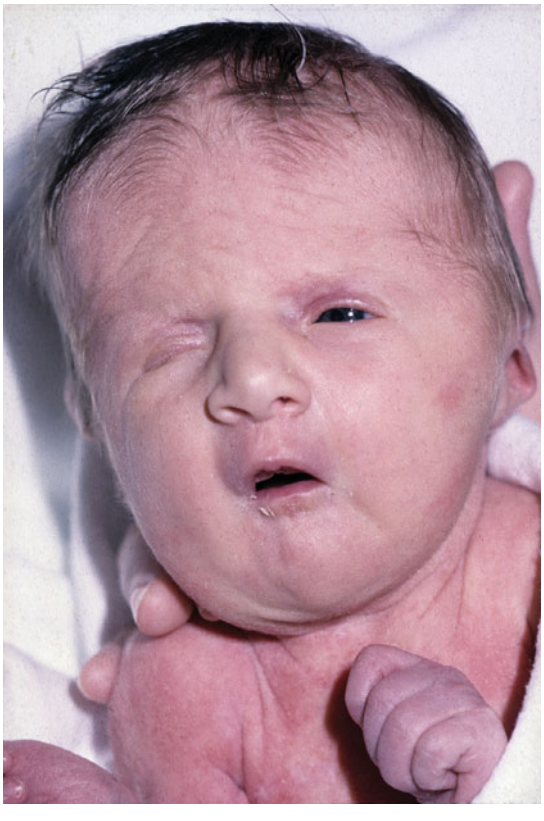

Figure 133-2 Same infant shown in Figure 133-1, showing dysmorphic face with microphthalmia, micrognathia, and low-set ears.

Trisomy 20

Most cases of trisomy 20 have been associated with a normal phenotype (Reish et al., 1998).

SURGICAL TREATMENT

There is no surgical treatment that is typical for the mosaic autosomal trisomies. Surgical treatment will depend on whether or not a congenital anomaly is present. The most likely organ systems to require surgical treatment are the cardiac and genitourinary systems.

LONG-TERM OUTCOME

Long-term survival is possible for each of the mosaic trisomies described in this chapter.

Trisomy 8

The long-term outcome for trisomy 8 is very variable. The outcome ranges from mental retardation and failure to thrive to normal development and function. Rauen et al. (2003) described a 23-year-old woman with mosaic trisomy 8 who had cleft palate, mixed bilateral hearing loss, short stature, developmental delay, and dysmorphic features. However, she became pregnant and had a relatively uncomplicated pregnancy. Her daughter had a normal karyotype.

Trisomy 9

In general, long-term survivors with mosaic trisomy 9 have mental impairment that can range from mild to severe. The oldest reported survivor with mosaic trisomy 9 is 9 years old (Saneto et al., 1998).

Trisomy 14

Individuals with trisomy 14 have postnatal failure to thrive and show growth restriction before the completion of their first year of life. For long-term survivors, congenital heart disease is the major issue (Fujimoto et al., 1992). The oldest known surviving woman with mosaic trisomy 14 is 29 years old and has an IQ of 60.

Trisomy 16

Langlois et al. (2006) performed a study of the long-term outcome for children with mosaic trisomy 16. They were able to ascertain 36 cases in which the child was older than 1 year of age. Of the 36, 19 were diagnosed by CVS and 17 cases were diagnosed by amniocentesis. Almost all affected infants were severely growth restricted at birth, but 80% to 90% of the children showed significant catch-up growth. Of the children in which mosaicism was diagnosed at CVS, none had global developmental delay and one had a delay in speech development. The prognosis was worse for those detected at amniocentesis in which 4 of 17 had global developmental delay. None of these children had maternal UPD for chromosome 16. These investigators concluded that the majority of infants and children with mosaic trisomy 16 have a good outcome. Mosaicism at amniocentesis is associated with a greater risk for developmental delay especially if accompanied by the presence of major congenital anomalies on a level II sonogram. Most infants with this condition are not dysmorphic (Figure 133-3).

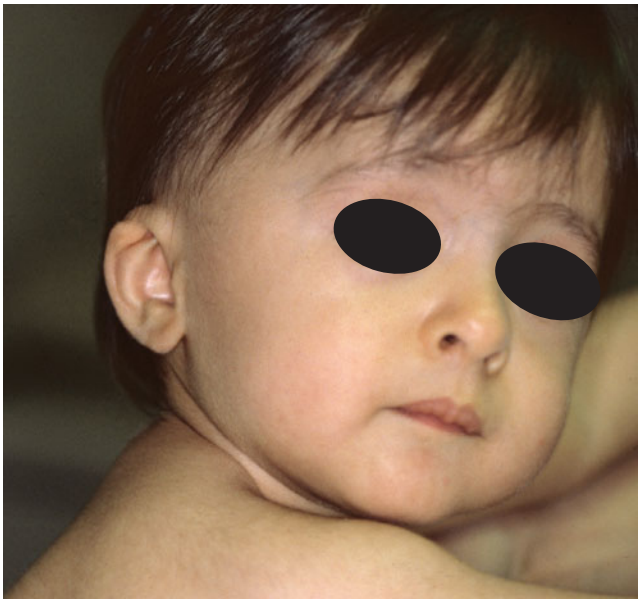

Figure 133-3 Infant with mosaic trisomy 16 demonstrating a normal facial appearance.

Trisomy 20

The long-term outcome for mosaic trisomy 20 is, in general, good. Robinson et al. (2005) described the outcome for 206 affected pregnancies that ended in a livebirth. Of the 206, only 9 had an abnormal outcome. These included three cases of multiple congenital anomalies, three cases of intrauterine growth restriction, one case of intrauterine growth restriction with hypotonia and micrognathia, one case of cleft lip, and one case of Williams syndrome (which was—in all likelihood—unrelated to the mosaic trisomy 20). Similarly, in a follow-up study performed in New Zealand, James et al. (2002) identified 14 children with mosaic trisomy 20. The longest follow-up period was 10 years. Twelve of the affected children were physically and developmentally normal and 2 cases had only minor abnormalities.

GENETICS AND RECURRENCE RISK

In general, the mosaic autosomal aneuploidies derive from maternal meiosis I errors as the result of advanced maternal age. The exception to this is trisomy 8, in which 50% of the cases are due to maternal meiosis I and 50% are due to a postzygotic mitotic gain of chromosome 8 (James and Jacobs, 1996). In general, the recurrence risk for these conditions is related to maternal age. The exception is when one of the parents has a balanced translocation that involves the affected chromosomes. Parents of fetuses with trisomy 9 have an increased incidence of structural variations in chromosome 9, such as a large heterochromatic region of the long arm of chromosome 9 and/or pericentric heterochromatic inversions of chromosome 9 (Arnold et al., 1995).

If the fetal karyotype shows the presence of a full free-standing extra chromosome, parental chromosome studies are not indicated. However, if the fetus shows the presence of a translocation, parental studies are then indicated.

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45, X (Turner Syndrome)

134 CHAPTER

Key Points

- Most common chromosomal abnormality that occurs in females. Only 1% of conceptuses with Turner syndrome survive to term.
- Incidence is 1 in 2500 female livebirths. No association with advanced maternal age.
- Approximately 50% of cases have full 45, X, 30% to 40% have mosaicism, and 10% to 20% have a structural abnormality of one X chromosome. Severity of clinical phenotype cannot be predicted from the karyotype.
- Characteristic sonographic abnormalities include very large cystic hygroma, hydrops fetalis, short femur, coarctation of the aorta, hypoplastic left heart, and renal anomalies.
- In the presence of lymphatic or cardiac malformations, delivery should occur at a tertiary center.
- Major considerations for long-term follow-up include: growth hormone treatment for short stature, estrogen treatment for feminization and bone health, monitoring for cardiovascular complications such as aortic dilatation and rupture, severe hypertension, and propensity toward autoimmune disease.
- Intelligence is normal, but there may be mild learning difficulties related to visual-spatial issues.
- Phenotype may differ depending upon whether the maternal or paternal X is retained. In ~75% of women the maternal X remains.

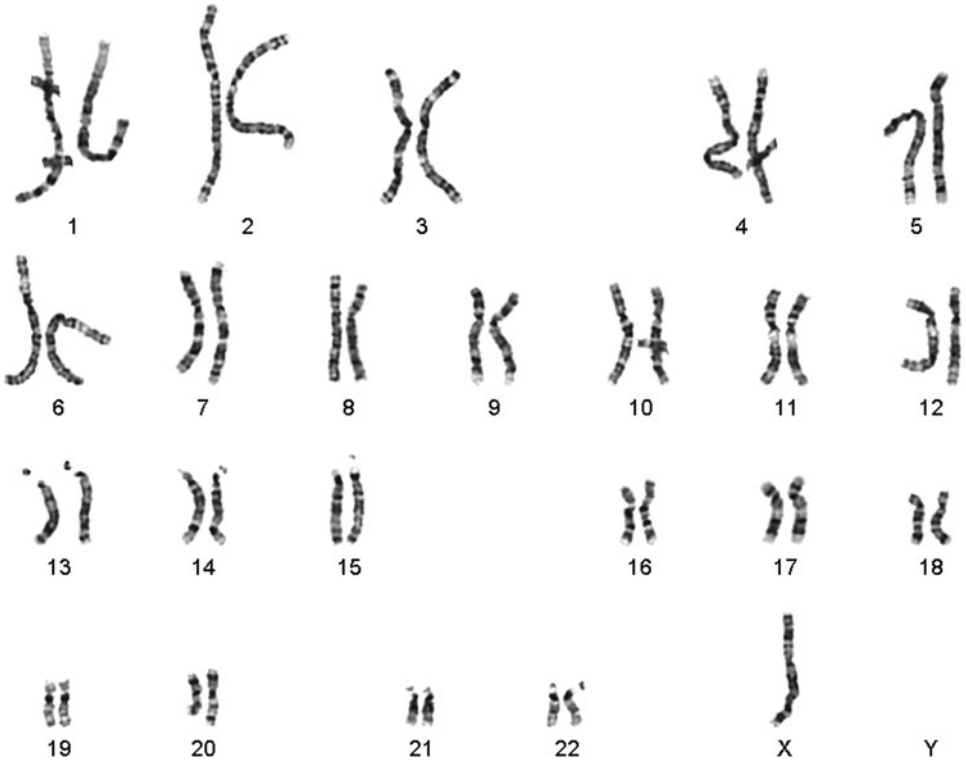

Figure 134-1 Chromosome analysis demonstrating 45, X, which is found in about 50% of cases of Turner syndrome. (*Courtesy of Dr. Janet Cowan.*)

CONDITION

Turner syndrome is named for Henry Turner, who in 1938 recognized the combination of sexual infantilism, webbed neck, and cubitus valgus to be a distinct entity. However, the underlying chromosomal abnormality in the condition was not recognized until 1959 (Ford et al., 1959). Turner syndrome exclusively affects females, and affected patients are generally missing all or part of the X chromosome in all or part of their cells. Postnatally, Turner syndrome is clinically suspected because of short stature, gonadal dysgenesis, or lymphedema. There are no pathognomonic clinical features (Hall and Gilchrist, 1990).

Turner syndrome is the most common chromosomal abnormality that occurs in females. It affects an estimated 3% of all females conceived, but only 1% of these survive to complete a full-term gestation. There are between 50,000 and 75,000 girls and women with Turner syndrome in the United States (Saenger, 1996).

INCIDENCE

The prevalence of Turner syndrome in Denmark is 392 in 100,000 cases ascertained at chorionic villus sampling (CVS), 176 in 100,000 amniocentesis cases, and 32 in 100,000 live female births (Højberg-Gravholt et al., 1996). The incidence of Turner syndrome of 1 in 2500 female livebirths is the most commonly quoted figure (Hall et al., 1982). Turner syndrome does not increase in incidence with advanced maternal age (Koeberl et al., 1995).

Turner syndrome is highly lethal in embryonic and fetal life. Although 1% to 2% of all conceptuses have 45, X, 98% to 99% of affected fetuses miscarry. When spontaneous abortuses are karyotyped, approximately 10% of them are shown to have Turner syndrome (Hall et al., 1982).

Of patients diagnosed with Turner syndrome, approximately 50% have 45, X (monosomy X) (Figure 134-1). An additional 30 to 40% of patients have mosaicism with a normal cell line. However, it is postulated that the incidence of mosaicism is in reality much higher, and that cases that survive to a full-term delivery have placental mosaicism. Of the remaining cases of Turner syndrome, 10% to 20% have a structural rearrangement of the X chromosome, most commonly, isochromosome X (duplication of one arm of the X chromosome with loss of the other arm). Any combination of physical features can be seen with any X chromosomal abnormality. The severity of the clinical phenotype cannot be predicted from the karyotype (Hall et al., 1982).

SONOGRAPHIC FINDINGS

Sonography is the most useful tool to detect cases at risk for Turner syndrome. The prenatal sonographic findings

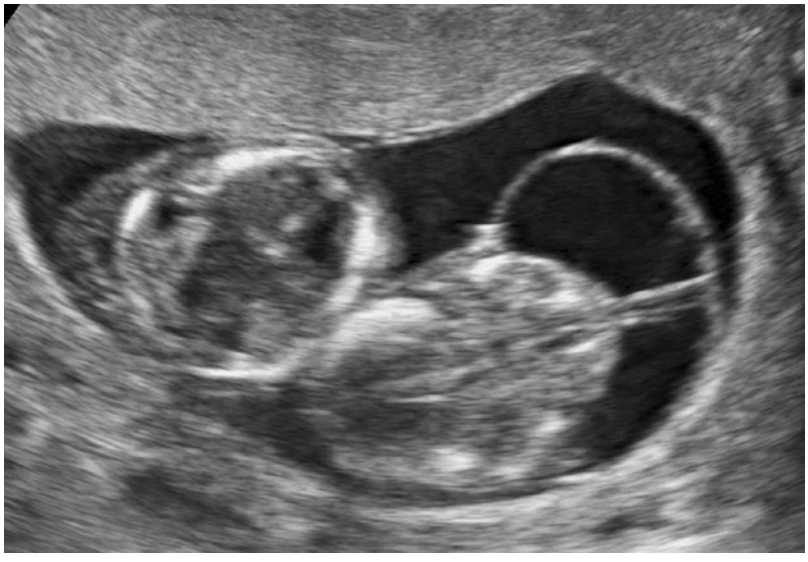

Figure 134-2 Septated cystic hygroma in the posterior nuchal region, as demonstrated by a fetal sonographic image. This fetus was shown to have 45, X.

that are characteristically found in Turner syndrome include increased nuchal translucency measurement (Kagan et al., 2006), cystic hygroma, renal malformations, and left-sided cardiac anomalies (Papp et al., 2006).

Bronshtein et al. (2003) described a "classic" cluster of abnormalities visualized by transvaginal sonography in 13 fetuses with Turner syndrome studied at 14 to 16 weeks. These included very large cystic hygroma, severe subcutaneous edema, hydrops fetalis, short femur, and narrow aortic arch. Cystic hygromas are the fetal expression of anomalous lymphatic development (see Chapter 31). The most common anatomic site for cystic hygromas is the nuchal region (Figure 134-2). Cystic hygroma is an ominous prenatal finding. In one study, 93% of continuing pregnancies with cystic hygroma resulted in fetal or neonatal death (Cohen et al., 1989). However, several cases have documented resolution of the cystic hygroma in Turner syndrome. For example, Brookhyser et al. (1993) described the spontaneous resolution of a nuchal cystic hygroma and pleural effusion during the third trimester in a fetus with Turner syndrome. There was a good outcome for this case. Similarly, Chodirker et al. (1988) also described resolution of a cystic hygroma, but demonstrated the postnatal appearance of a webbed neck (pterygium colli) and a rotated ear. Other manifestations of lymphatic malformations include transient bilateral pleural effusion, which has been demonstrated as early as the first trimester using transvaginal imaging (Shimizu et al., 1997).

The sonographic diagnosis of cystic hygroma is made by the demonstration of a thin-walled multiseptated asymmetrical fluid-filled mass attached to the lateral aspect of the fetal head or neck (see Figure 134-2). The mass is in a constant location with respect to the fetal occiput and is independent of fetal motion (Garden et al., 1986; Donnenfeld and Mennuti, 1988).

A somewhat rarer presentation of the fetal lymphatic malformations seen in Turner syndrome is isolated fetal ascites. Wax et al. (1992) presented a case of massive fetal ascites and polyhydramnios detected at 32 weeks of gestation resulting from congenital intestinal lymphangiectasia. The diagnosis was later shown to be Turner syndrome.

Other manifestations of Turner syndrome include cardiovascular anomalies. In 2003, Surerus et al. reported on 53 fetuses with 45, X; 47 of them were ascertained by the presence of an increased nuchal translucency measurement. Cardiac malformations were detected in 33/53 fetuses (62.2%). Nuchal translucency measurement was greater in the fetuses with congenital heart disease than in those without. Coarctation of the aorta was observed in 24/53 fetuses (45.3%). Hypoplastic left heart syndrome was the next most common finding (seen in 7/53, or 13.2% of cases). These authors concluded that structural heart disease is more common in prenatal than postnatal life, and that the type of lesions observed was different. For example, postnatally, bicuspid aortic valve is the most common abnormality in Turner syndrome (Gøtzsche et al., 1994).

Approximately 30% to 60% of patients with Turner syndrome have a structural or positional renal anomaly (Hall et al., 1982; Hall and Gilchrist, 1990). Horseshoe kidney is especially common, seen in 20% of patients with Turner syndrome. Other typical malformations include duplication of the collecting system (20% of cases) and malrotation (seen in 50% of kidneys). Renal anomalies seen in Turner syndrome rarely result in renal malfunction but may predispose to postnatal urinary tract infections.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis varies according to the age at presentation of symptoms. Prenatally, the lymphatic malformations predominate. The differential diagnosis for cystic hygroma includes cystic teratoma, meningocele, encephalocele, and neural tube defect (Bluth et al., 1984). Cystic hygroma

can be differentiated from neural tube defects by the demonstration of bilateral echo-free spaces divided by septae. In addition, with a cystic hygroma there is an intact cranial vault and an intact spinal canal. Ascites and an edematous placenta can be seen in association with cystic hygroma, but is generally not seen in association with neural tube defects or cystic teratoma.

At birth, peripheral lymphedema has the differential diagnosis of Milroy disease, and other single-gene disorders associated with lymphedema, such as lymphedema with recurrent cholestasis or lymphedema with intestinal lymphangiectasia.

Turner syndrome can be detected later in life because of short stature or amenorrhea. The differential diagnosis of short stature includes familial short stature, Noonan syndrome, dyschondrosteosis (Leri–Weill syndrome), growth hormone deficiency, and hypothyroidism (Hall et al., 1982).

Noonan syndrome can be distinguished from Turner syndrome on the basis of a normal chromosome analysis.

ANTENATAL NATURAL HISTORY

Turner syndrome results from haploinsufficiency for specific genes located on the X chromosome. It is highly lethal in utero (Committee on Genetics, American Academy of Pediatrics, 1995) (Figure 134-3). It is estimated that as many as 80% of liveborn infants with Turner syndrome have an additional normal cell line that permits postnatal survival (Amiel et al., 1996). In one study of four fetuses with Turner syndrome, three were phenotypically normal and one had malformations. All three that were phenotypically normal had the presence of an additional normal cell line. In the one fetus with malformations, no normal cell line could be demonstrated in any of the tissues examined (Amiel et al., 1996). In a study of 16 first trimester fetuses with a variety of chromosomal abnormalities, a monoclonal antibody was used to study the distribution syndrome of lymphatic vessels (von Kaisenberg et al., 1999). In the 3 fetuses with Turner syndrome, the vessels were hypoplastic in the upper dermis.

It is thought that the lymphatic malformations originate from hypoalbuminemia. In a study by Shepard and Fantel (1986), fetuses with Turner syndrome had lower albumin levels in their plasma as compared with control fetuses. These investigators postulated that early edema resulting from hypoalbuminemia may interfere with the normal development of the lymphatics. In fact, most of the congenital anomalies seen in Turner syndrome can be explained on the basis of lymphedema at critical points in development (Hall and Gilchrist, 1990). Some investigators hypothesize that the lymphedema is the result of failure to open embryonic lymph channels. Pterygium colli (webbed neck) results from an in utero persistence of embryonic lymph sacs.

A correlation between neck webbing and the presence of coarctation of the aorta has been noted by Clark (1984), who postulated that large lymph channels adjacent to the aortic outflow tract misdirect blood flow to the aorta, thus producing an abnormal blood flow through the ductus arteriosus. In a study of 12 fetuses terminated between 16 and 26 weeks of gestation because of a prenatal finding of cystic hygroma or hydrops, 8 demonstrated a consistent constellation of cardiac defects. These included a small ascending aorta, relatively large pulmonary arteries that were 1.5 to 3 times the size of the aorta, a large patent ductus arteriosus, and a juxtaductal coarctation of the aorta (Lacro et al., 1988). The high incidence of left-sided flow defects among the fetuses in this study supports the hypothesis that there is a pathogenetic relationship between lymphatic obstruction and the subsequent development of congenital heart disease. In this study, lymphatic distention was demonstrated on histologic sections obtained through the base of the heart and the pulmonary hila. These data support the concept that hydrostatic pressure occurring within the jugular lymphatic sac can also distend the cardiac lymphatics (Lacro et al., 1988).

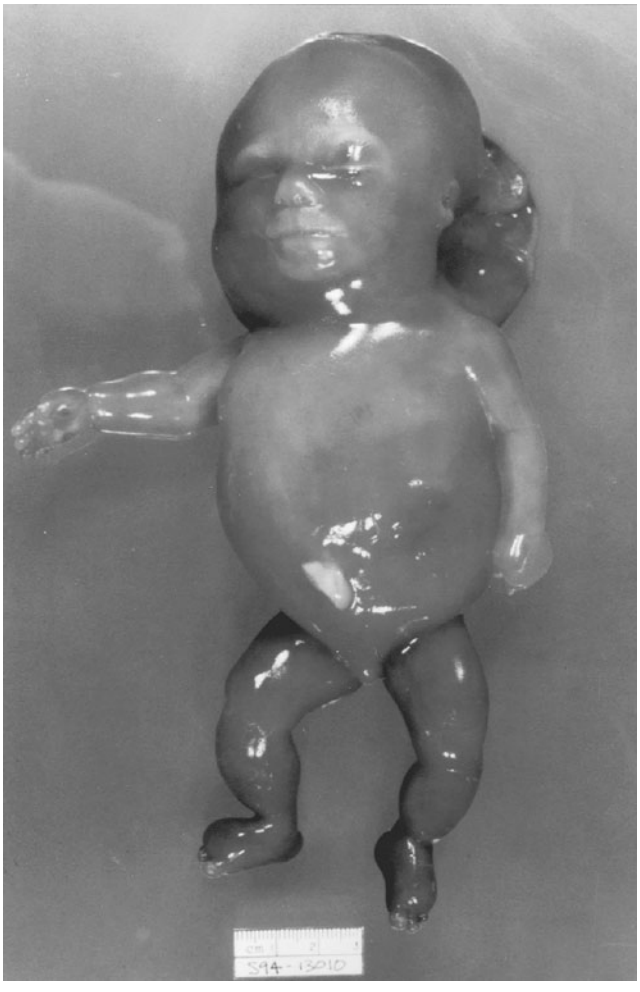

Figure 134-3 Postmortem photograph of a fetus with Turner syndrome. Note the large septated cystic hygroma, body wall edema, and presence of pedal edema. (*Courtesy of Dr. Joseph Semple.*)

MANAGEMENT OF PREGNANCY

In general, Turner syndrome is suspected because of the presence of an abnormal sonogram or an abnormal serum screening result. Some cases of Turner syndrome are also unexpectedly detected at amniocentesis for advanced maternal age. A unique pattern of serum screening markers is present in both hydropic and nonhydropic cases of Turner syndrome. Typically, there is a slightly reduced α-fetoprotein level, markedly reduced estriol, and increased human chorionic gonadotropin (hCG) levels in hydropic cases of Turner syndrome (Saller et al., 1992; Ruiz et al., 1999). Free β-hCG is thought to be the most effective serum marker for Turner syndrome (Laundon et al., 1996). In Laundon et al.'s study of 17 cases of Turner syndrome, the median level for the multiple of the median for free β-hCG was 4.04.

In the setting of either an abnormal sonogram or an abnormal serum screen, prospective parents should meet with a genetic counselor to discuss the indications for an invasive diagnostic procedure. Turner syndrome is definitively diagnosed by prenatal karyotype. Once the chromosome analysis confirms the finding of Turner syndrome, prospective parents should meet with a medical geneticist to discuss the long-term implications of the findings, which will differ according to the karyotype. In general, parents should know that a diagnosis of Turner syndrome implies short stature, some congenital anomalies, infertility without assisted reproductive technology, and some learning difficulties. However, girls with Turner syndrome have normal intelligence.

If mosaicism is present, the implications of the specific karyotype should be discussed. For example, Koeberl et al. (1995) described their experience with 12 patients diagnosed with amniocentesis for advanced maternal age or maternal serum screen and a documented fetal karyotype of 45, X/46, XX. They compared the long-term outcome for the prenatally diagnosed group with a group of 41 postnatally diagnosed girls with mosaic Turner syndrome. The patients that were diagnosed prenatally had less severe findings than the postnatal patients. These girls all had normal linear growth. Only 4 of the 12 had structural anomalies, which included atrial septal defect, ptosis, labial fusion, dysplastic kidneys, and hydrometrocolpos. None of the prenatally diagnosed group had physical findings that would have warranted karyotyping for a clinical suspicion of Turner syndrome at birth. This contrasted with the postnatally diagnosed group, who presented with a variety of congenital anomalies and short stature. These investigators suggested that most individuals with 45, X/46, XX would normally escape detection during the newborn period.

A study of 76 cases of 45, X/46, XY mosaicism was published by Chang et al. (1990). Of these patients, 95% had normal male genitalia. Four patients had significant genital anomalies, which included three cases of hypospadias and one female with clitoromegaly. The degree of amniotic fluid mosaicism did not predict the degree of genital or gonadal abnormality. It is commonly stated that patients with 45, X/46, XY are at risk for gonadoblastoma. In 11 patients who underwent gonadal biopsy, 3 had abnormal gonadal histology.

There is no indication for a cesarean section based on the diagnosis of Turner syndrome alone. The decision about whether to deliver in a tertiary care center is made on the basis of the significance of the lymphatic malformations and the presence of cardiac disease. If the fetus has hydrops fetalis, delivery should occur at a tertiary care center. Similarly, if there is concern that the cystic hygroma may interfere in any way with airway management in the newborn infant, delivery should occur at a tertiary care center. For a patient with a known fetal diagnosis of Turner syndrome, but no sonographic abnormalities, delivery can safely occur in a community medical center. However, plans should be made for postnatal consultation with a pediatric cardiologist and a medical geneticist.

FETAL INTERVENTION

There are no fetal interventions for Turner syndrome.

TREATMENT OF THE NEWBORN

The average birth weight of newborns with Turner syndrome is 2.8 kg (around 500 g below average) and the average length is 48 cm (2.8 cm below average) (Hall and Gilchrist, 1990). Untreated infants with Turner syndrome tend to remain small, generally at the 3rd to 10th percentile for age. At birth, a complete physical examination is indicated and congenital hip dysplasia should be ruled out. We recommend consultation with a pediatric cardiologist at birth and echocardiography to rule out left-sided cardiac defects. The published percentage of individuals with Turner syndrome who have cardiovascular malformations is between 17 and 47% (Gøtzsche et al., 1994). The specific abnormalities that are greatly increased in this population of patients include aortic coarctation and bicuspid aortic valve. In a large retrospective review, Sybert (1998) demonstrated that 136 of 244 patients with Turner syndrome (56%) had cardiovascular abnormalities. Of these, 71% were structural and 29% were functional. The functional abnormalities included hypertension, mitral valve prolapse, and conduction defects. Sybert confirmed that coarctation of the aorta and bicuspid aortic valve comprised greater than 50% of the structural abnormalities.

Eighty percent of babies with Turner syndrome are born with lymphedema. The pedal lymphedema is treated symptomatically. The cystic hygroma generally recedes, leaving folds of skin in the neck and a low hairline on the back of the neck. The protruberant ears with upturned lobules are a residual manifestation of the lymphatic abnormalities that were present in utero (Figure 134-4).

During the newborn period, an abdominal ultrasound examination is also indicated to look for the presence of

Figure 134-4 Photograph of a young girl with Turner syndrome, demonstrating the postnatal appearance of the neck webbing. (*Courtesy of Dr. Patricia Wheeler.*)

renal malformations. In a postnatal study of 141 patients with Turner syndrome, Lippe et al. (1988) demonstrated renal abnormalities in 47 (33%) of patients. Ten of these patients had a horseshoe kidney, 1 had a double collecting system, 4 had complete absence of one kidney, 3 had crossed ectopia, 3 had ureteropelvic obstruction, 2 had ureterovesical obstruction, and 1 had a pelvic kidney. The 7% incidence of horseshoe kidney in patients with Turner syndrome can be compared to a prevalence of 1 in 600 normal individuals (Lippe et al., 1988).

Additional problems that can exist during the newborn period for patients with Turner syndrome include feeding difficulties due to the presence of a high arched palate and inefficient sucking and swallowing. Also, patients with Turner syndrome are subject to recurrent otitis media due to anatomic alterations at the base of the skull that change the angle of the eustachian tube.

Routine pediatric management recommendations for females with Turner syndrome have been published (Committee on Genetics, American Academy of Pediatrics, 1995; Frias and Davenport, 2003; Bondy, 2007).

SURGICAL TREATMENT

Thomson et al. (1990) described the surgical treatment for the simple neck webbing found in Turner syndrome. In four cases, they excised the excess neck skin and closed the defect to flatten the web against the side of the neck. In patients with Turner syndrome, they found that a defined band of fibrous tissue ran from the acromion to the mastoid process and was present in all cases studied. The underlying muscle and superficial layer of deep cervical fascia were noted to be normal and separate from the web. The skin anterior to the web was normal but the skin posterior to the web was freely mobile. When they biopsied the fibrous bands, they were demonstrated to consist of fibrous tissue and no other abnormalities (Thomson et al., 1990). These investigators achieved excellent cosmetic results. They recommended the lateral approach to elevate the hairline.

LONG-TERM OUTCOME

The major considerations regarding long-term follow-up include treatment of short stature, cardiovascular abnormalities, including complications due to vascular malformations and hypertension, specific issues related to cognitive development, the propensity toward autoimmune disease, and issues surrounding fertility.

With regard to short stature, familial height plays a role in the ultimate height of patients affected with Turner syndrome (Hall et al., 1982). In other words, taller parents have taller daughters. For most patients with Turner syndrome, the bone age is within normal limits until ages 12 to 14 but without the influence of pubertal hormones there is no adolescent growth spurt. In a large survey taken in United States, untreated patients with Turner syndrome achieved an adult height of 143.0 cm (4 ft 8 in.). With growth hormone, patients achieved a mean height of 151.9 cm (4 ft 11.5 in.), a net gain of 8.1 cm (Saenger, 1993). Growth hormone treatment should be initiated when the child's height drops below the fifth percentile of the normal female growth curve. This generally occurs between ages 2 and 5 years (Saenger, 1996). Most endocrinologists recommend treatment with growth hormone until the bone age is greater than 15 years and the growth slows to less than 2 cm per year. In addition, estrogen therapy is recommended beginning at around age 14 to induce the secondary sexual characteristics and to promote bone health. Only natural estrogens are recommended for these patients, as synthetic estrogens are incompletely metabolized. Approximately 20% to 25% of patients with Turner syndrome have spontaneous pubertal development and 2% to 5% have spontaneous onset of menstrual periods (Saenger, 1996).

Patients with Turner syndrome are predisposed to vascular malformations, which include intestinal telengiectasias and hemangiomas, and they have an increased incidence of ulcerative colitis and Crohn disease. The incidence of

hypertension in adults with Turner syndrome is 30% (Hall et al., 1982). Individuals with Turner syndrome need to be monitored for hypertension on a lifelong basis (Sybert, 1998). Magnetic resonance angiography in addition to ultrasonography is currently recommended for periodic follow-up of the cardiovascular system (Bondy, 2007). The majority of patients with aortic dilation have associated risk factors, such as bicuspid aortic valve or coarctation or systemic hypertension (Lin et al., 1998).

With regard to specific learning difficulties in patients with Turner syndrome, Bender et al. (1984) studied an unselected group of 16 patients with Turner syndrome. They noted a slight delay in walking and average development of language skills, but a striking deficit in perceptual organization and fine motor skills. Patients with Turner syndrome have a type of space–form blindness. They have difficulties identifying position in space, mentally rotating geometric shapes, and orienting to left–right directions. This visual-spatial impairment may be due to bilateral small volumes of the hippocampus and caudate, lenticular, and thalamic nuclei as well as parieto-occipital brain matter, as measured by MRI (Murphy et al., 1993). Importantly, intelligence is normal in Turner syndrome, unless a specific X chromosome abnormality is present.

Other complications in patients with Turner syndrome include otitis media, progressive sensorineural hearing loss in more than 60% of patients (Morimoto et al., 2006), conductive middle ear disease (Sculerati et al., 1996), strabismus and other eye findings, such as ptosis, hypertelorism, and red–green color deficiency (Chrousos et al., 1984). Scoliosis is present in 10% of cases (Saenger, 1996) and specific dermatologic abnormalities such as pigmented nevi and increased keloid formation are also characteristic. In addition, there is an increased incidence of autoimmune thyroid disease (Gruñeiro de Papendieck et al., 1987). Adult women with Turner syndrome have a high incidence of undiagnosed lipid, thyroid, and bone mineral density abnormalities (Garden et al., 1996). Women with Turner syndrome have a high incidence of coronary artery disease (Aligeti and Horn, 2007).

Fertility issues are significant for adult patients with Turner syndrome (Sutton et al., 2005). Several studies have performed pelvic sonography in childhood (Massarano et al., 1989; Mazzanti et al., 1997). During childhood, the ovaries can be classified as streak or nonstreak. Nonstreak ovaries retain a range of function. Patients with mosaicism have the highest percentage of detectable ovaries, as compared with patients with full monosomy 45, X (Mazzanti et al., 1997). Patients with Turner syndrome are infertile due to the streak ovaries, which result in an inability to ovulate. With the addition of hormonal replacement during early adolescence, patients can achieve secondary sexual characteristics and establish menses. Spontaneous pregnancy is rare, but possible. Reported cases of spontaneous pregnancy in Turner syndrome patients are associated with an increased incidence of miscarriage, perinatal fetal death, and malformations (Tarani et al., 1998).

Over the past decade, fertility has become possible using assisted reproductive technology and oocyte donation. In one study of 29 patients with Turner syndrome, Khastgir et al. (1997) documented 28 clinical pregnancies, including two sets of triplets. These investigators achieved a pregnancy rate of 41.2% per treatment cycle and a 17.1% implantation rate per embryo transferred. The recipient's age, specific karyotype or uterine anomaly had no influence on the treatment outcome. However, as more women with Turner syndrome undergo pregnancy, previously unknown complications have emerged (Practice Committee of the American Society for Reproductive Medicine, 2006). These include aortic rupture and dissection, significant hypertension, and risk of death. Women with Turner syndrome who are interested in oocyte donation need careful cardiac evaluation prior to comtemplating pregnancy.

GENETICS AND RECURRENCE RISK

In general, Turner syndrome is considered to be a sporadic condition. It is not associated with advanced maternal age. Genes that are important in the phenotype of Turner syndrome include the short-stature-homeobox (*SHOX*) gene, which maps to Xp22.2, and *USP9X*, which maps to Xp11.4, and is a candidate for gonadal dysgenesis. *D1APH2*, located at Xq, is required for normal ovarian function (Baena et al., 2004).

In several studies, the role of genetic imprinting has been investigated. On average, about 75% of Turner syndrome patients retain their maternal X chromosome (Sagi et al., 2007; Jacobs et al., 1997). There is a highly significant correlation between the child's height and the maternal height percentile when the X chromosome is inherited from the mother but not from the father. Similarly, there is also a strong correlation between the presence of cardiovascular abnormalities, neck webbing, and renal malformations with retention of the maternal X chromosome. In addition, the retention of the paternal X chromosome results in better social adjustment and superior verbal and higher-order executive function skills (Skuse et al., 1997). These data indicate that there is a genetic locus for social cognition, which is imprinted, and not expressed from the maternally derived X chromosome.

Patients who have Turner syndrome and have mosaicism for a small portion of the Y chromosome face a risk of gonadoblastoma. Cytogenetic analysis can fail to detect rare cells bearing a normal or structurally abnormal Y chromosome. Binder et al. (1995) screened 53 individuals with Turner syndrome for the presence of the sex-determining region Y (*SRY*) sequence. Of the 53 individuals, none were positive for Y specific loci after the first round of polymerase chain reaction (PCR) but 2 were positive *SRY* after the second round of PCR. This indicates that the distal short arm of the Y chromosome is occasionally present. More recent studies of girls who

were 45, X by conventional karyotype showed that up to 35% had evidence of hidden Y chromosome mosaicism by PCR (Bianco et al., 2006). These data suggest that PCR should be considered in girls with Turner syndrome to determine who is at risk for gonadoblastoma.

Patients with Turner syndrome who conceive spontaneously have a 30% chance of having a fetus with chromosomal abnormalities or congenital anomalies (Saenger, 1996). Any woman with Turner syndrome who conceives spontaneously should be offered amniocentesis. Women who conceive using oocyte donation will only need amniocentesis if their donor is over age 35.

Patients who have had a previous fetus or infant with Turner syndrome may be offered chromosome analysis in a subsequent pregnancy for reassurance.

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47, XXY (Klinefelter Syndrome)

135 CHAPTER

Key Points

- Results from meiotic nondisjunction that occurs in the sperm (44% of cases) or egg (56% of cases).
- About 10% of all cases are diagnosed prenatally and 26% of cases are diagnosed postnatally. The majority of cases are never diagnosed, which suggests that symptoms are mild.
- Incidence of 47, XXY is 1 in 500 to 1 in 800 male births. Incidence of 48, XXXY is 1 in 20,000.
- No sonographic findings are characteristic. Nuchal translucency measurement may be increased.
- The most significant factors regarding the decision whether or not to terminate the affected pregnancy are the presence of sonographic abnormalities and the medical specialty of the person providing the genetic counseling.
- Affected males are tall, but phenotypically normal, with an increased risk for developmental delays in speech, neuromotor, and learning disabilites.
- Testosterone treatment is recommended, beginning at puberty.
- 50% to 80% of affected males develop gynecomastia, but it is usually mild.
- Fertility is now possible with assisted reproductive technology.
- Motor impairment and speech and language problems are more common if the extra X chromosome is paternally derived.

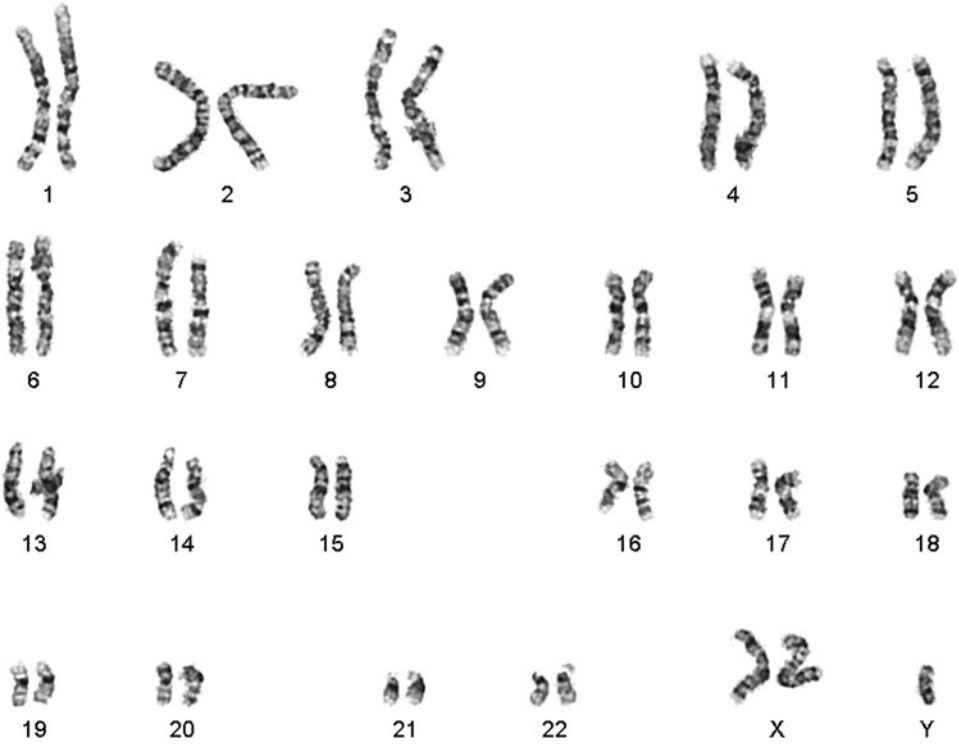

Figure 135-1 Karyotype obtained from a patient with Klinefelter syndrome, demonstrating presence of two X and one Y chromosomes. (*Courtesy of Dr. Janet Cowan.*)

CONDITION

Klinefelter syndrome (47, XXY karyotype) is the spectrum of phenotypic features resulting from a sex chromosome complement that includes two or more X chromosomes and one Y chromosome (Figure 135-1). It results from meiotic nondisjunction occurring during gametogenesis of the egg or sperm with subsequent fertilization of an XX ovum by a Y bearing sperm, or fertilization of an X ovum by a sperm bearing both the X and Y chromosomes (Mandoki et al., 1991). There are no known predisposing factors except advanced maternal age in some, but not all, cases. The condition was first described in nine men with gynecomastia, infertility with normal Leydig cells, a normal to low 17-ketosteroid level, and a high follicle stimulating hormone level in the urine (Klinefelter et al., 1942; Schwartz and Root, 1991). It was not until 1956 that the chromosomal basis of this abnormality was appreciated by noting the presence of the Barr body on buccal smears obtained from affected patients, which represented the inactive extra X chromosome (Arens et al., 1988). The specific chromosomal abnormality reponsible for the disorder was not known until 1959.

The phenotype in Klinefelter syndrome is extremely variable and may be subtle. Most cases are never diagnosed. In general, affected males are identified by age-related clinical concerns (Table 135-1). Infant patients are identified by either prenatal cytogenetic testing for advanced maternal age or by the presence of mild genital abnormalities (Schwartz

Table 135-1

Clinical Features of Klinefelter Syndrome Across the Lifespan

Age	Features
Fetus	Usually none
Infant	Usually none; occasionally, small penis; hypotonia
Toddler	Delay in expressive speech development
Child	Accelerated linear growth velocity (long legs); learning disabilities
Adolescent	Sparse facial, axillary, pubic hair Gynecomastia (50% to 80%) Small testicular volume (<5 mL) Long legs, narrow shoulders, wide hips
Adult	Infertility (azoospermia) Leg ulcers

and Root, 1991). During school-age years, affected patients may be identified by the occurrence of learning disabilities and behavioral problems, whereas in adolescence, the clinical diagnosis is usually suspected from gynecomastia, a taller than average stature, and a possible delay in pubertal development. However, a large number of patients with Klinefelter syndrome are identified as adults when they present during a workup for infertility (Schwartz and Root, 1991).

INCIDENCE

A study of 34,910 newborns performed over 13 years in Arhus, Denmark, put the incidence of Klinefelter syndrome at 1 in 576 newborn male infants (Nielsen and Wohlert, 1991). 47, XXY is generally described as occurring in 1 in 500 to 1 in 800 live male births (Mandoki et al., 1991). About 7% of cases are mosaic (46, XY/47, XXY) (Bojesen et al., 2003). Other variants of Klinefelter syndrome include the karyotypes 48, XXXY, which occurs in 1 in 20,000 live male births, and the karyotype 49, XXXY, which occurs in 1 in 85,000 live male births (Kleczkowska et al., 1988). For a review of the more severe clinical manifestations of 48, XXY, the reader is referred to a study by Linden et al. (1995). In the variant Klinefelter karyotypes, it has been shown that a single parent contributes all of the extra chromosomes present.

The incidence of 47, XXY is increased in twins. In one large study of fetal karyotypes obtained at amniocentesis performed primarily for advanced maternal age, 2 cases of 47, XXY were seen in 1821 singleton fetuses. Three cases of 47, XXY were seen in 21 pairs of twins, giving an incidence of 7.1% in the twin population (Flannery et al., 1984).

Two large, population based studies using national cytogenetic registries have shown that most boys and men with Klinefelter syndrome are not clinically recognized. In the United Kingdom, Abramsky and Chapple (1997) demonstrated that 10% of 47, XXY cases are diagnosed prenatally and 26% are diagnosed in adolescence or adulthood. In Denmark, where all karyotype results are recorded in a central registry, a marked discrepancy between the prevalence of prenatally ascertained cases (153/100,000 male fetuses) and postnatally ascertained cases (40/100,000 males) was shown (Bojesen et al., 2003). Thus, only about a fourth of cases are diagnosed postnatally, which suggests that symptoms are mild.

SONOGRAPHIC FINDINGS

No sonographic findings are characteristic for a fetus with Klinefelter syndrome. In a review of 35 cases of fetal omphalocele, one fetus had a 47, XXY karyotype, but this is probably unrelated (Gilbert and Nicolaides, 1987). Another study has suggested that the median nuchal translucency measurement is increased in cases of sex chromosome abnormalities (Spencer et al., 2000). In general, the fetal phenotype is extremely mild and difficult to distinguish from normal.

ANTENATAL NATURAL HISTORY

In cases of 47, XXY, the phenotype is not distinctly recognizable, even in fetuses studied at autopsy. In one fetus terminated at 20 weeks of gestation, the clinical features of Klinefelter syndrome noted in the fetus included an arm span less than its height, a minor ear abnormality, fifth-finger clinodactyly, and undescended testes (which is not unusual for a fetus at this point in gestation). Significantly, the testicular histology was normal (Flannery et al., 1984). Amniotic fluid testosterone levels do not differ between 46, XY and 47, XXY fetuses (Ratcliffe, 1999).

Using older data, there is a suggestion that there is a slightly increased risk of miscarriage in fetuses with Klinefelter syndrome (Simpson et al., 2003). The risk was derived by comparing the incidence of 47, XXY at amniocentesis and at birth in newborn studies. However, a more recent Danish dataset did not find any cases of spontaneous abortions or stillbirths among prenatally diagnosed cases that were not electively terminated (Bojesen et al., 2003).

MANAGEMENT OF PREGNANCY

Fetuses with Klinefelter syndrome are most commonly identified during amniocentesis performed for advanced maternal age, where it is the third most common chromosomal abnormality diagnosed, after trisomies 21 and 18 (Robinson et al., 1992; Linden and Bender, 2002). It is unlikely that an affected fetus will be identified on the basis of an abnormal sonographic finding. Occasionally, Klinefelter syndrome is associated with abnormalities in maternal serum screening. Reported maternal serum abnormalities include elevated levels of α-fetoprotein (Fejgin et al., 1990) and human chorionic gonadatropin (hCG) (Ben-Neriah et al., 1991; Barnes-Kedar et al., 1993).

The main concern regarding management of pregnancy is the parental decision whether to continue or terminate the pregnancy. One of the difficulties in this area has been the ascertainment bias that exists in the medical literature, overreporting of the more extreme phenotypic aspects of Klinefelter syndrome, and underreporting of patients who have few or no symptoms related to the condition. Ongoing studies regarding developmental outcome for children who have been prenatally diagnosed with 47, XXY suggests a milder phenotype and considerable variability in physical and psychologic development (Robinson et al., 1992; Linden and Bender, 2002). Approximately 30 to 55% of well-informed couples opt to continue their pregnancy after an antenatal diagnosis of 47, XXY (Holmes-Siedle et al., 1987; Lancet editorial, 1988; Robinson et al., 1992; Meschede et al., 1998; Marteau et al., 2002). The most significant factors that influence the decision to terminate the pregnancy include the presence of sonographic abnormalities (Christian et al., 2000; Hamamy and Dahoun, 2004) and the medical specialty of the person providing the genetic counseling following the

karyotype results. In general, the pregnancy is more likely to be continued if the counseling is provided by a geneticist instead of an obstetrician (Hall et al., 2001; Marteau et al., 2002). Robinson et al. (1992) suggest that the following information be given to prospective parents during prenatal counseling for a fetal diagnosis of 47, XXY:

1. Their son will likely be tall but phenotypically normal.
2. Puberty is usually entered normally, but testosterone supplementation therapy may be desirable after midadolescence.
3. Their son will be infertile without the use of assisted reproductive technology.
4. Their son will be at risk for gynecomastia, but this will most likely be mild.
5. Their son will belong to a group of children who are at risk for developmental problems and delays in speech, neuromotor, and learning abilities.
6. Due to some of the language issues, boys with 47, XXY may be shy and insecure.

However, these investigators write that a stable, nurturing, and stimulating environment will considerably enhance developmental outcome (Robinson et al., 1992).

In cases of 46, XY/47, XXY mosaicism, the prognosis is better than for the nonmosiac karyotype, with fewer developmental abnormalities and potential spontaneous fertility (Robinson et al., 1992).

If the decision is made to continue the pregnancy, there is no need for a particular route of delivery. Arrangements should be made to have the parents discuss the prenatal finding of 47, XXY with a medical geneticist.

FETAL INTERVENTION

There are no fetal interventions for 47, XXY.

TREATMENT OF THE NEWBORN

Most newborn male infants with 47, XXY not ascertained by prenatal chromosome analysis will be missed during the neonatal period. In general, findings are normal on physical examination, although the incidence of minor congenital abnormalities may be increased as compared with siblings (Mandoki et al., 1991). Newborns with Klinefelter syndrome may have minor abnormalities of the genitalia, including cryptorchidism and hypospadias (Kleczkowska et al., 1988). A minority of infants with 47, XXY has a small penis, but penile growth occurs with local systemic testosterone treatment (Ratcliffe, 1999). The mean birth weight and height for affected newborns falls well within the range of normal, although the head circumference may be and remain slightly on the small side (Ratcliffe, 1999). A complete physical examination is necessary to ascertain the presence of additional congenital anomalies, but otherwise there is no indication for specific treatment during the newborn period. Exogenous testosterone therapy should not begin until around 11 to 12 years of age (Winter, 1991).

SURGICAL TREATMENT

Gynecomastia may be treated surgically in adolescence or adulthood. The other symptoms of Klinefelter syndrome do not require surgical treatment.

LONG-TERM OUTCOME

There have been several recent, comprehensive review articles that summarize primary care issues for children and adults with Klinefelter syndrome (Visootsak et al., 2001; Simpson et al., 2003; Lanfranco et al., 2004). Adult individuals with 47, XXY have a moderate increase in stature due to excessive growth of the lower extremities, resulting in a height that is greater than or equal to the arm span (Schwartz and Root, 1991). The mean adult height for men with 47, XXY is at the 75th percentile (Lancet editorial, 1988).

Most males enter puberty normally. Basal serum gonadotropins and response to gonadotropin-releasing hormone are normal until 12 years of age, when they rapidly elevate to reach uniformly hypergonadotropic values by age 14 (Winter, 1991). With the onset of puberty, there is an initial increase in testicular volume, but during this time the seminiferous tubules undergo irregular progressive hyalinization and fibrosis, which restricts further growth beyond 2.5 cm (Rutgers, 1991; Schwartz and Root, 1991; Winter, 1991). Patients with nonmosaic Klinefelter syndrome are almost always infertile without the use of assisted reproductive technology. In a large review of 544 Belgian 47, XXY males diagnosed between 1966 and 1987, the majority (397) of affected patients were adults who were diagnosed only by an infertility workup performed for azoospermia (Kleczkowska et al., 1988). There is no increase in homosexual preference in males with 47, XXY (Ratcliffe, 1999). Successful pregnancies in the partners of affected men have been achieved by testicular fine needle aspiration, intracytoplasmic sperm injection, and preimplatation genetic diagnosis (Reubinoff et al., 1998) (see Genetics and Recurrence Risk, below).

Adult men with Klinefelter syndrome demonstrate persistently low circulating testosterone and dihydrotestosterone levels, together with normal or elevated estradiol levels (Hsueh et al., 1978; Winter, 1991). The increased ratio of estradiol to testosterone may play a role in the development of gynecomastia, a condition that affects 50% to 80% of XXY males (Winter, 1991). Gynecomastia most often regresses spontaneously, and cosmetic surgery is rarely needed (Lancet editorial, 1988).

Prospective parents facing a fetal diagnosis of 47, XXY are frequently most concerned regarding the implications for developmental outcome. Individuals with 47, XXY have, in general, average to above average intelligence. In one study, 18.7% of affected individuals had an IQ of less than 90, but the

scores were lowered by verbal deficits (Mandoki et al., 1991). It is now appreciated that 47, XXY males have difficulties with language production more than language comprehension (Graham et al., 1988). They may have delayed speech development, poor short-term auditory memory, and difficulties with reading and spelling (Graham et al., 1988; Lancet editorial, 1988; Ratcliffe, 1999). It is recommended that special attention be paid to language development in affected males and that early referral to a speech therapist be considered. The neurocognitive problems seen are not unique to 47, XXY individuals and management is the same as that for individuals with language problems and normal chromosomes. Less than 4% of 47, XXY males are considered mildly to moderately retarded (Kleczkowska et al., 1988). The overwhelming majority of the adult patients reported in the long-term Belgian study was employed and had a normal work life, and 43% were married (Kleczkowska et al., 1988). In a 20-year follow-up of 47, XXY males, considerable improvement in mental health, working capacity, social adjustment, and activity level was noted between the ages of 27 and 37 years (Nielsen and Pelsen, 1987).

Testosterone therapy is currently recommended, beginning in adolescence. It improves concentration, mood, social interaction, and libido, and prevents osteoporosis, autoimmune disease, and the development of gynecomastia and a eunuchoid body habitus (Winter, 1991; Lanfranco et al., 2004). It does not, however, affect fertility.

The incidence of breast cancer is increased in affected individuals (Evans and Crichlow, 1987; Rutgers, 1991; Bojesen et al., 2006). In one study of 93 males with breast cancer, 7 had 47, XXY, as ascertained by FISH analysis of surgically removed lymph nodes. This represents a 50-fold increased risk above the normal male population (Hultborn et al., 1997). 47, XXY males also have an increased risk for the development of extragonadal germ cell tumors, including mediastinal teratocarcinoma, choriocarcinoma, and cerebral germinoma (Arens et al., 1988; Rutgers, 1991; Hasle et al., 1992; Swerdlow et al., 2005). It is hypothesized that these midline tumors develop in 47, XXY males because of an alteration in testicular gonadal ridge differentiation, which subsequently leads to abnormal migration of primordial germ cells from the yolk sac. Instead of advancing toward the gonads, these germ cells migrate caudally along the midline, and may undergo malignant transformation when they settle in a nonphysiologic location (Arens et al., 1988; Rutgers, 1991).

GENETICS AND RECURRENCE RISK

Klinefelter syndrome is due to nondisjunction occurring during meiosis. Counseling about recurrence risk should incorporate consideration of maternal age, although 50% of cases are paternal in origin. Females known to be carriers of the fragile X mutation have an increased tendency toward nondisjunction of the affected X chromosome. The incidence of the simultaneous occurrence of XXY and fragile X is 1 in 153 males with the XXY karyotype (Kleczkowska et al., 1988).

The parental origin of the extra X chromosome was assessed using 26 DNA probes that detected X chromosome restriction-site polymorphisms in a total of 111 47, XXY individuals (Harvey et al., 1991). In 61 XXY males ascertained by large-scale newborn cytogenetic surveys, 27 (44%) were paternal and 34 (56%) were maternal in origin. In 41 XXY males who presented with clinical features of Klinefelter syndrome, 171 (41%) were maternal and 22 (54%) were paternal in origin. Of a group of 9 cases ascertained by amniocentesis for advanced maternal age, 4 (44%) were maternal, 4 (44%) were paternal, and 1 was unknown in origin (Harvey et al., 1991). Thirty-nine of the maternally derived cases were studied to determine the source of the nondisjunctional error. In 78% of cases it occurred during meiosis I and in 22% of cases it occurred during meiosis II. In another study, the origin of the X chromosome in 41 paternally derived cases of 47, XXY was studied using six different polymorphic genetic loci. Most cases of paternal origin were shown to result from meioses in which the X and Y chromosomes failed to recombine (Hassold and Sherman, 1993).

Until recently, it was thought that there was no phenotypic difference in cases in which the extra X chromosome was maternally versus paternally derived. In 2006, Stemkens et al. studied 54 men with Klinefelter syndrome, and showed that motor impairment and speech and language problems were significantly more common in the men with an extra paternal X chromosome. Similarly, a number of anthropometric parameters related to body size were larger in the paternal X group. This was not surprising, as animal data has shown that paternally expressed genes enhance growth. This study suggested that there is an imprinting effect of the X chromosome on educational performance and body size.

It is possible for men with Klinefelter syndrome to biologically father children using surgical sperm recovery, coordination with egg retrieval, and use of intracytoplasmic sperm injection (ICSI) (Lanfranco et al., 2004). The outcome data on liveborn infants conceived in this way indicates that the overwhelming majority is healthy and has a normal karyotype. The use of preimplantation genetic diagnosis on biopsied blastocysts should be considered, due to data suggeting that embryos derived from men with Klinefelter syndrome have an increased rate (9/23) of both sex chromosome and autosomal aneuploidy (Kahraman et al., 2003). For couples with a previously affected child but in which the father does not have Klinefelter syndrome, prenatal cytogenetic diagnosis by amniocentesis or CVS can be offered in subsequent pregnancies.

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47, XXX (Triple X Syndrome, Trisomy X)

136 CHAPTER

Key Points

- Incidence is 1 in 1000 females.
- Most cases are undiagnosed.
- Associated with advanced maternal age (70% are due to a meiosis I error).
- There are no characteristic fetal sonographic findings in this condition, except for occasional genitourinary anomalies.
- IQ of affected women is in the normal range, but 10 to 15 points lower than siblings.
- Mild learning disabilities are primarily verbal.
- Adult women with 47, XXX are tall and fertile.

CONDITION

The chromosome constitution 47, XXX was first described by Jacobs et al. (1959) in a woman of average intelligence with secondary amenorrhea. Since that time, several hundred cases have been reported in the medical literature. The phenotype of infants who are prenatally diagnosed with 47, XXX is significantly different from infants who are diagnosed by newborn screening or clinical symptomatology (Robinson et al., 1992; Linden and Bender, 2002). In general, the prenatally diagnosed infants have a more normal developmental profile. This may be due to factors unrelated to the chromosomes, such as socioeconomic status and level of parental education.

The sex chromosome aneuploidies are the most common group of abnormalities found in prenatal karyotypes, with an incidence of 1 in 250 amniocenteses (Robinson et al., 1992). Despite their frequency, sex chromosome aneuploidy is rarely discussed in preprocedural genetic counseling. Thus, the finding of a fetal sex chromosome abnormality is usually not expected by the pregnant patient (Krone et al., 1975). This diagnosis prompts anxiety and ambivalence because, although the karyotype is abnormal, the phenotype of the affected child can be quite variable. Trisomy X can be associated with a normal outcome. In fact, most cases of 47, XXX are undiagnosed (Ratcliffe, 1999).

INCIDENCE

The incidence of 47, XXX is approximately 1 in 1000 at midtrimester amniocentesis (Hook and Hamerton, 1977) and 0.7 in 1000 livebirths (Tennes et al., 1975). These differences reflect different study populations and are not thought to reflect an increased perinatal mortality for 47, XXX fetuses. Using X-linked restriction fragment length polymorphisms, May et al. (1990) determined the parental origin of the extra X chromosome in 28 individuals with 47, XXX. Maternal nondisjunction was demonstrated in 26 of 28 cases. Seventy percent of these cases were due to an error in meiosis I. Thus, the etiology of trisomy X more closely resembles the autosomal trisomies. In this regard, trisomy X differs from the other sex chromosome aneuploidies, in that there is a maternal age effect. Mitotic errors do not play a significant role in 47, XXX (May et al., 1990).

SONOGRAPHIC FINDINGS

In general, there is no characteristic phenotype associated with trisomy X. The overwhelming majority of fetuses with trisomy X will have normal results on sonographic examination. The diagnosis is typically made at amniocentesis for advanced maternal age. In one study, the fetal nuchal

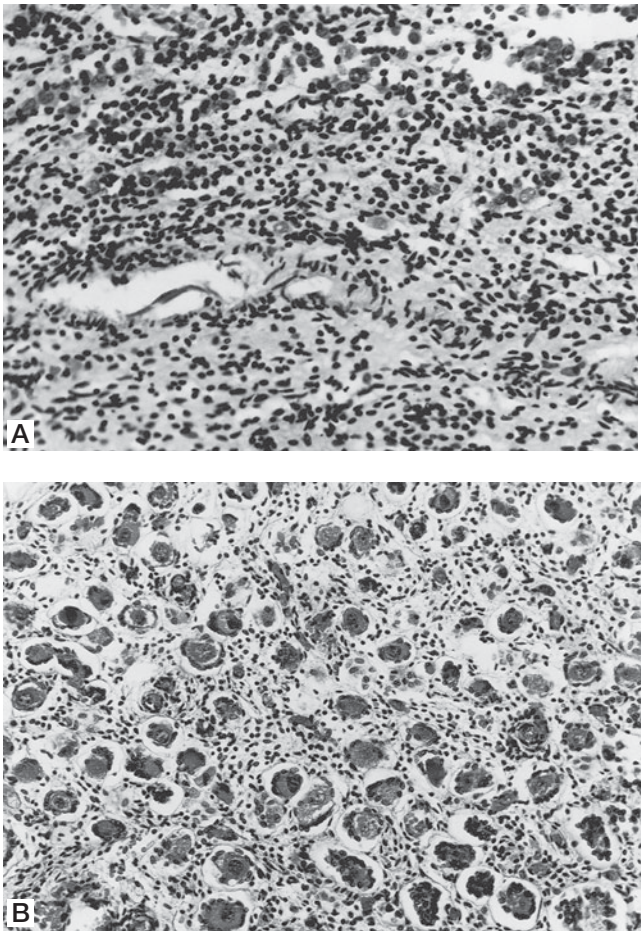

Figure 136-1 **A.** Postmortem photomicrograph of the cortex of the ovary from a fetus who spontaneously died in utero with 47, XXX. Note the relative absence of primordial follicles and germ cells. **B.** Comparison view of an ovary from a stillborn female fetus at 26 weeks of gestation, demonstrating numerous primordial follicles. (*Reprinted from Spear GS, Porto M. 47, XXX chromosome constitution, ovarian dysgenesis, and genitourinary malformation.* Am J Med Genet. *1988;29:511-515. Copyright 1988 by Wiley-Liss, Inc. Reprinted, by permission, of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.*)

translucency measurement was above the 95th percentile in 40% of the cases with 47, XXX, 47, XYY, or 48, XXXY (Sebire et al., 1998). In rare cases, structural abnormalities of the genitourinary tract have been described. These include bilateral renal agenesis and developmental arrest of the mesonephric and paramesonephric systems (Hogge et al., 1989); ovarian dysgenesis (Figure 136-1), urinary tract malformation, meconium peritonitis, and nonimmune fetal ascites (Spear and Porto, 1988); exstrophy of the cloaca with unilateral renal agenesis (Lin et al., 1993); and unilateral renal agenesis, hydrometrocolpos, ovarian dysgenesis, laryngeal atresia, pulmonary hypoplasia, and craniofacial anomalies (Hood et al., 1990). Because of the apparent clustering of cases with abnormalities in the genitourinary system, it has been suggested that the developing urogenital field may be affected by the presence of an extra X chromosome (Lin et al., 1993).

DIFFERENTIAL DIAGNOSIS

When the karyotype is 47, XXX, the main consideration in the differential diagnosis is whether the abnormality is present in all cells or in a fraction of the cells (mosaicism). A 46, XX/47, XXX mosaic karyotype will result in a significantly reduced likelihood of clinical symptoms (Salbenblatt et al., 1989; Robinson et al., 1992).

ANTENATAL NATURAL HISTORY

The antenatal natural history does not differ from fetuses with a normal karyotype. If a level II sonogram was not performed at the time of the original amniocentesis, it should be offered. The parents should be counseled regarding the expectation that the remainder of the pregnancy will not be different from pregnancy with a chromosomally normal fetus.

MANAGEMENT OF PREGNANCY

The main dilemma in management is the parental decision whether to continue the pregnancy (see "Long-Term Outcome"). Robinson et al. (1989, 1992) have reported their clinical experience with 530 phone consultations for a prenatal diagnosis of sex chromosome aneuploidy. In these series, 162 of the 530 consultations were reported for a diagnosis of trisomy X. Although their sample was admittedly biased, in that their patient population consisted of women who elected to undergo prenatal cytogenetic diagnosis, 85% of whom were college graduates and in an upper socioeconomic class, certain trends emerged. In general, the affected patients were developing in a manner that was comparable to their normal siblings. They also had better peer relations than the previously reported group of children with sex chromosome abnormalities (Robinson et al., 1979). In the prenatally diagnosed group of children with sex chromosome abnormalities, only 2 of 20 had intellectual quotients (IQ) as low as 90. The remainder of the children were in the normal range, greater than 110. Robinson et al. (1992) hypothesized that the improved developmental outcome was related to the supportive home environment provided by parents who knew the diagnosis and decided to continue the pregnancy. For the couples faced with a diagnosis of trisomy X in their fetus, 65% continued the pregnancy after phone consultation with Robinson's group.

Several recent studies have indicated an overall decreased trend in termination for fetal sex chromosome abnormalities. All three studies, performed in Canada, Switzerland, and Hungary, showed significantly lower rates of termination for 47, XXX compared to 45, X and 47, XXY fetuses (Christian et al., 2000; Hamamy and Dahoun, 2004; Mezei et al., 2004). In general, the decision to terminate in this condition was strongly influenced by the presence of a fetal anomaly on sonographic examination.

FETAL INTERVENTION

There are no fetal interventions for 47, XXX karyotype.

TREATMENT OF THE NEWBORN

In a study of 43 infants with trisomy X, the mean birth weight at term was 2.97 kg. There was no recognizable phenotype at birth. These infants were identified by prospective cytogenetic screening of all newborns in Denver. Their karyotype would not have been suspected from their physical examinations. Congenital heart disease was diagnosed in two infants and congenital hip dislocation in one. There was an increased frequency of epicanthal folds and clinodactyly (Robinson et al., 1979). The presence of minor anomalies such as these is possibly increased in 47, XXX females as compared with controls (Chudley et al., 1990).

SURGICAL TREATMENT

There are no surgical treatments indicated for XXX alone.

LONG-TERM OUTCOME

The most important statement regarding the long-term prognosis for a fetus with 47, XXX is that the phenotype is very variable (Tennes et al., 1975; Puck et al., 1983; Linden et al., 1988). The developmental outcome has ranged from mild mental retardation to college graduation (Linden et al., 1988). The general health of these children is excellent. Although their birth lengths are in the normal range, they become progressively taller as compared with their peers. The mean adult height of 47, XXX women is 167.9 + 7.7 cm, as compared with that in a white British control population—162.2 + 6 cm (Ogata and Matsuo, 1993). The mean head circumference remains at 10% for age (Ratcliffe, 1999). In infancy, a slight delay in neuromotor development has been noted. Salbenblatt et al. (1989) described a delay in the age of independent walking. In a prospective study of 11 girls identified at birth and followed over 22 years, Linden et al. (1988) noted that only two walked before the age of 12 months. About 50% of 47, XXX females have delays in speech and language that requires speech therapy during the preschool years (Ratcliffe, 1999). These delays are due to a specific deficit in auditory perception and in the ability to process linguistic information (Pennington et al., 1980; Bender et al., 1983, Bender et al., 1989).

The difficulties with verbal expression are described as the most severe of those described for the sex chromosome abnormalities (Linden et al., 1988). In a long-term follow-up study of 17 affected females (ages 7–18) 11 had school difficulties (Linden and Bender, 2002). Most of the 11 females received grades of Bs or Cs but none failed or repeated a grade. The mean IQ in this group was 103. Fifteen of 17 girls were involved in sports. None required psychological counseling services. In 47, XXX, sexual development is normal, with an average age of menarche of 12 years 8 months. In one fetus studied with 47, XXX, the ovary was histologically normal (Autio-Harmainen et al., 1980). Fertility and reproductive outcome is surprisingly good, with a low incidence of aneuploidy among offspring (Dewhurst, 1978). One case has been reported of an individual with trisomy X, premature ovarian failure, and the presence of antithyroid and antinuclear antibodies (Michalak et al., 1983). Females with trisomy X have thicker tooth enamel than females with disomy X. This indicates that the extra X chromosome escapes inactivation to promote amelogenesis (Alvesalo et al., 1987).

GENETICS AND RECURRENCE RISK

Since the majority of cases are due to a maternal meiosis I error, the risk of recurrence is most strongly related to maternal age. Amniocentesis or chorionic villus sampling should be offered in a subsequent pregnancy. Theoretically, half the offspring of an individual with 47, XXX should be normal and half 47, XXX or 47, XXY. This has not been shown empirically. Scattered case reports exist of 47, XXX mothers who have had children with sex chromosome and autosomal aneuploidies (Singer et al., 1972; Zizka et al., 1975), but most offspring are cytogenetically normal.

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137 CHAPTER 47, XYY

Key Points

- Incidence is 1 in 1000 males.
- Most cases are undiagnosed.
- Not associated with advanced parental age.
- There are no characteristic fetal sonographic findings.
- IQ of affected males is in the normal range, but 10-15 points lower than siblings.
- Mild learning disabilities involve verbal but not mathematical skills.
- Adult males are tall, thin, and fertile.
- Pregnant partners of adult males with 47, XYY should be offered testing for the fetal karyotype due to the increased incidence of sex chromosome abnormalities in sperm.

CONDITION

The cytogenetic finding 47, XYY refers to the presence of an extra Y chromosome in the fetal cells. The extra Y chromosome is always paternal in origin and results from nondisjunction in the second meiotic division (84% of cases) or a postfertilization mitotic error (16%) (Robinson and Jacobs, 1999). XYY is one of the diagnoses included in the group of

disorders known as sex chromosome abnormalities. Anomalies involving the sex chromosomes are the most common abnormal findings in prenatal cytogenetic diagnosis, accounting for 25% of abnormal amniocentesis results, yet their existence is rarely discussed in preprocedural genetic counseling. Thus, while prospective parents are reasonably prepared for a prenatal diagnosis of autosomal trisomy, the diagnosis of XYY usually comes as a surprise.

Much of the confusion regarding prognosis for males with XYY stems from studies performed in the 1960s that were highly biased by ascertainment of patients in maximum security hospitals or prisons (Price and Whatmore, 1967). Fortunately, prospective longitudinal studies of newborns identified at birth do not support an increased incidence of aggression or criminality (Ratcliffe et al., 1990). As with all of the sex chromosome abnormalities, the developmental phenotype is variable and subject to many other influences, such as parental IQ, socioeconomic status, and family stability.

INCIDENCE

The incidence of 47, XYY is 1.45 in 1000 livebirths (Autio-Harmainen et al., 1980) and 1 in 1000 amniocenteses for advanced maternal age (Robinson et al., 1992a). The incidence is not increased among offspring of parents with advanced age. As opposed to the other sex chromosome abnormalities, the XYY karyotype does not carry an increased chance of in utero mortality (Ferguson-Smith and Yates, 1984). As many as 85% of cases are believed to be undiagnosed (Ratcliffe, 1999).

SONOGRAPHIC FINDINGS

There are no characteristic sonographic findings because the fetal phenotype in this condition is generally normal (Autio-Harmainen et al., 1980). In one study, the fetal nuchal translucency measurement was above the 95th percentile in 40% of the fetuses with 47, XXX, 47, XYY, or 47, XXY (Sebire et al., 1998). More recently, Maymon et al. (2002) reported on two fetuses with 47, XYY that had brain anomalies detected on prenatal sonographic examination. One had complete agenesis of the corpus callosum and one had a Dandy–Walker malformation. Both were terminated, so long-term developmental outcome is unknown.

DIFFERENTIAL DIAGNOSIS

47, XYY is a definitive diagnosis obtained by prenatal karyotype (Figure 137-1). Occasionally, cases of 46, XY/47, XYY mosaicism are detected, resulting from mitotic nondisjunction after fertilization. These patients are expected to have milder manifestations of the developmental abnormalities seen in this condition.

ANTENATAL NATURAL HISTORY

The antenatal natural history for these fetuses does not differ from normal fetuses. A few patients with 47, XYY have been identified through abnormally increased maternal serum

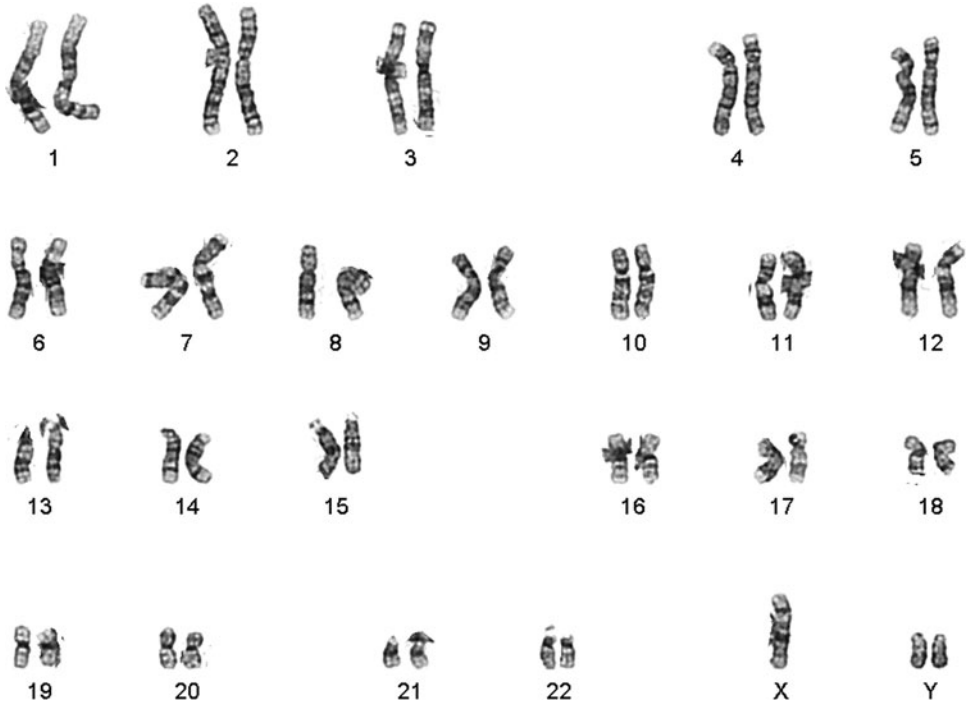

Figure 137-1 Karyotype obtained from a patient with 47, XYY demonstrating the presence of two identical Y chromosomes.

α-fetoprotein levels (Robinson et al., 1992a). It is unclear whether a true relationship exists between abnormalities in serum analytes and this particular chromosomal abnormality.

MANAGEMENT OF PREGNANCY

The subsequent management of the pregnancy should include subspecialty referral to a clinical geneticist for parental education and counseling. No additional maternal testing is necessary other than that indicated by standard obstetric practice. There is no need for delivery at a tertiary care center.

The major issue to be discussed with the expectant couple is whether or not to continue the pregnancy. Several recent studies have indicated an overall decreased trend over time in termination for fetal sex chromosome abnormalities. All three studies, performed in Canada, Switzerland, and Hungary, showed significantly lower rates of termination for 47, XYY compared to 45, X and 47, XXY fetuses (Christian et al., 2000; Hamamy and Dahoun, 2004; Mezei et al., 2004). In general, the presence of a fetal anomaly on sonographic examination correlated with a decision to terminate.

FETAL INTERVENTION

There are no fetal interventions indicated for a 47, XXY karyotype.

TREATMENT OF THE NEWBORN

The birth weights, head circumferences, and lengths of males with XYY are no different from control infants (Robinson et al., 1979; Ratcliffe et al., 1990). Although the phenotype is normal for this condition, an increased incidence of minor anomalies has been reported. In a study of 43 XYY infants identified by screening of all Denver newborns, one had congenital dislocation of the hip. Eight of the infants had one or more minor anomalies, including clinodactyly, inguinal hernia, abnormally formed ears, pectus carinatum, large or asymmetric head, strabismus, epicanthal folds, micrognathia, simian crease, and heart murmur (Robinson et al., 1979).

SURGICAL TREATMENT

There are no surgical treatments indicated solely for XYY.

LONG-TERM OUTCOME

XYY males tend to be tall and thin, with an average height of greater than the 75th percentile for age. This is due to an increased growth velocity from age 2 onwards as compared with normal individuals (Ratcliffe et al., 1992; Ratcliffe, 1999) and affects size rather than body proportions (Varrela and Alvesalo, 1985). XYY adult males achieve heights that are, on average, 13 cm taller than their fathers (Ratcliffe et al., 1990). The onset of puberty, defined as an increase in testicular volume to 4 ml or the appearance of pubic hair, occurs, on average, 6 months later than in controls (Ratcliffe et al., 1990; Robinson et al., 1992a; Ratcliffe, 1999). Testosterone production, pubertal development, and heterosexual interest have all been normal. The histology of the fetal testes in one case of 47, XYY was normal (Autio-Harmainen et al., 1980). The germ-cell depletion characteristic of other chromosome abnormality syndromes is apparently rarely affected by the presence of the extra Y chromosome (Coerdt et al., 1985). XYY males have normal spermatogenesis and have fathered normal infants. In one study, human sperm chromosomes were analyzed from a 47, XYY male and all of them contained only one sex chromosome. The frequencies of numerical, structural, and total abnormalities did not differ significantly from normal controls, suggesting that one Y chromosome is eliminated from the germ cells of males with XYY (Benet and Martin, 1988). Despite these encouraging findings, another study reported an increased incidence of miscarriage, stillbirth, perinatal death, and chromosomally abnormal offspring in pregnancies conceived with 47, XYY men (Grass et al., 1984). More recent analyses using 3-color probes and fluorescent in situ hybridization techniques suggest that there is an increased incidence of sperm carrying two sex chromosomes (Shi and Martin, 2000).

Interestingly, the presence of the extra Y chromosome affects dimensions of the palate and mandible. Palatal height and mandibular width are smaller in 47, XYY men as compared with their chromosomally normal first-degree male relatives (Laine and Alvesalo, 1993). In addition, there appears to be a regulatory influence of the Y chromosome on amelogenesis that results in thicker dental enamel and larger size in the permanent teeth of 47, XYY males (Alvesalo et al., 1985).

Early development in XYY infants is essentially within normal limits. Gross motor milestones are generally first noted to be slightly delayed, with an average age of walking at 14 to 16 months. Characteristic findings include hypotonia, motor planning dysfunction, primitive reflex retention, and difficulties with bilateral coordination and visual–perceptual–motor integration. This decreased muscle tone and joint proprioception diminishes joint stability, which particularly affects the shoulder and pelvic girdles and results in an awkward and inefficient gait (Salbenblatt et al., 1987). In addition, about 10% of affected individuals have an intention tremor (Ratcliffe, 1999).

In general, males with 47, XYY are not mentally retarded, but their IQs are 10 to 15 points lower than their chromosomally normal siblings (Robinson et al., 1992a). Intelligence level has a major effect on the development of psychosocial problems (Fryns, 1998). Specific risks exist for mild language impairment, affecting both receptive and

expressive function (Bender et al., 1983), and presenting initially as speech delay. In neurodevelopmental studies, Walzer et al. (1990) have shown that XYY males have difficulty understanding complex sentence structures, deficits in auditory memory, problems with word finding and narrative formulation, and persistent distractibility. Recommended educational intervention for 47, XYY males is no different than that for chromosomally normal children with reading and spelling difficulties.

In Ratcliffe's (1999) Scottish study of 19 affected males, followed from birth until early adulthood, 42% had speech delay and 54% had reading difficulties (compared to 18% of controls). However, a significant percentage of these young men went to college and had a wide range of employment. None had difficulty with mathematics.

With regard to concern over the association between aggressive behavior and XYY karyotype, prospective studies of thirty-nine 47, XYY probands have not revealed marked psychiatric disturbances. However, an increased frequency of distractibility, hyperactivity, and temper tantrums have been reported (Robinson et al., 1990; Ratcliffe, 1999). The importance of a supportive family environment has been noted by Robinson et al. (1992b), who have described significant developmental differences between 47, XYY males ascertained by prenatal diagnosis versus those discovered by newborn screening. All the children in this study who were diagnosed prenatally belonged to well educated and economically stable families. These children had fewer language deficits and learning problems, a mean IQ of 123 (range 109–147), and were getting As and Bs in school (Robinson et al., 1992b).

GENETICS AND RECURRENCE RISK

Although few data exist regarding the specific recurrence risk for XYY, the risk for nondisjunction involving any of the other chromosomes may be as high as 1%. Prenatal cytogenetic studies should be offered in subsequent pregnancies. Pregnant partners of 47, XYY men should also be offered prenatal karyotyping, due to the increased incidence of sex chromosome abnormalities seen in sperm studies (Shi and Martin, 2000).

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138 CHAPTER Tetrasomy 12p (Pallister–Killian Syndrome)

Key Points

- Characterized by tissue-specific presence of an abnormal extra chromosome, which consists of two copies of the short arm of chromosome 12.
- Abnormal (marker) chromosome is more likely to be found in amniocytes or fibroblasts than blood.
- Associated with advanced maternal age.
- Sonographic findings: polyhydramnios, diaphragmatic hernia, rhizomelic short limbs.
- Main consideration in differential diagnosis is Fryns syndrome.
- Very poor long-term prognosis. All survivors are mentally retarded.
- Sporadic inheritance.

CONDITION

Tetrasomy 12p is a multiple congenital anomaly syndrome characterized by the tissue-specific presence of a marker chromosome in fibroblasts, but not lymphocytes, of affected patients. The clinical symptoms associated with this condition were first recognized in 1977, when Pallister described two adults, aged 19 and 37, who had profound retardation, severe hypotonia, coarse facial features, and pigmentary abnormalities. Both of these patients had an extra chromosome that was identified as a probable isochromosome of the short arm of chromosome 12 (Pallister, 1977). Independently, Teschler-Nicola and Killian (1981) reported a 3-year-old with severe mental retardation, dysmorphic facies, and sparse, dystrophic hair. Buyse and Korf (1983) were the first to suggest that these two seemingly disparate clinical presentations actually represented different manifestations of the same syndrome. The discrepancy between the two was explained by the fact that the isochromosome 12p was demonstrable in fibroblasts but not lymphocytes from affected patients. The interesting and unique aspect of this syndrome is that mosaicism exists for the chromosomal abnormality, and diagnosis usually depends on performing a chromosome analysis on amniocytes or fibroblasts from a skin biopsy.

From the prenatal perspective, tetrasomy 12p is usually diagnosed in one of two ways: either it is a karyotype abnormality found at amniocentesis performed for advanced maternal age (32% of cases) or it is detected when karyotyping is performed because fetal anomalies have been detected on sonography (52% of cases) (Wilson et al., 1994; Doray et al., 2002). Advanced maternal age is known to be a risk factor for the development of the isochromosome 12p. In a review of 30 case reports of Pallister–Killian syndrome, Wenger et al. (1988) found that the average age of the mothers of affected patients was 30 years. It is currently thought that there is an initial nondisjunctional event that results in trisomy 12. This is then followed by a centromeric misdivision at meiosis I or II (Struthers et al., 1999). The abnormal extra isochromosome is progressively lost in vivo during embryogenesis and in vitro during tissue culture. This hypothesis has been proven in several cases using molecular markers (Cormier-Daire et al., 1998; de Ravel et al., 2004).

The diagnosis of tetrasomy 12p is made by karyotype (Figure 138-1). The extra chromosome in this syndrome was originally thought to be derived from the long arm of chromosome 21 based on similarities in the cytogenetic banding patterns between the short arm of chromosome 12 and the long arm of chromosome 21 (Zhang et al., 1989). Identification of the marker chromosome as 12p was initially based on the twice-normal expression of the lactate dehydrogenase-B (LDH-B) isoenzyme gene, which maps to chromosome 12. Normal levels of superoxide dismutase 1 (SOD-1), which maps to chromosome 21, ruled out an increased dosage effect from extra copies of chromosome 21 (Gilgenkrantz et al., 1985). Fluorescence in situ hybridization (FISH) studies using DNA markers specific to the short arm of chromosome 12

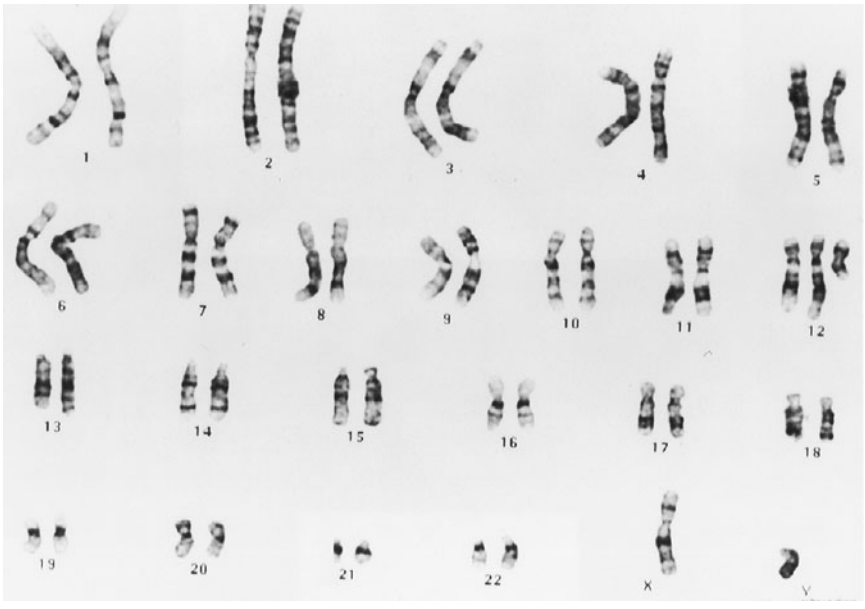

Figure 138-1 Karyotype obtained from amniocytes in an affected fetus with Pallister–Killian syndrome. Note the presence of an extra chromosome next to the normal chromosome 12 pair. (*Courtesy of Dr. Janet Cowan.*)

have now definitively identified the marker chromosome as the short arm of chromosome 12 (Tejuda et al., 1992; Larramendy et al., 1993; Ohashi et al., 1993; Butler and Dev, 1995). The ability to detect the isochromosome 12p is affected by the tissue type studied, the patient's age (fetal versus infant versus adult) and the in vitro age of the cells (Priest et al., 1992). Peripheral blood lymphocytes are continually dividing, and it has been hypothesized that they lose the extra chromosome with their frequent divisions. In contrast, fibroblasts obtained from a skin biopsy normally cycle less frequently. In addition, a time-dependent in vitro selection occurs against cells that contain the isochromosome. In one study, the percentage of cells containing the isochromosome went from 100% to 20% after only five passages in tissue culture (Speleman et al., 1991). Detection of the isochromosome 12p may be difficult in peripheral blood lymphocytes, although the marker has been seen in bone marrow aspirates obtained from newborns (Ward et al., 1988). Several authors have suggested the use of FISH analysis to detect the presence of the extra chromosome 12 short arm interphase nuclei as opposed to metaphase chromosomes (Reeser and Wenger, 1992; Larramendy et al., 1993).

INCIDENCE

The incidence of Pallister–Killian syndrome or tetrasomy 12p is unknown. Tetrasomy 12p is the most frequent autosomal tetrasomy in humans (Bresson et al., 1991). The disorder is being increasingly recognized in clinical medicine.

SONOGRAPHIC FINDINGS

The sonographic findings for fetuses with tetrasomy 12p are summarized in Table 138-1. The most consistent prenatal findings include polyhydramnios, short femurs, and diaphragmatic hernia (Figure 138-2) (Priest et al., 1992; Wilson et al., 1994). Wilson et al. reviewed 15 cases of tetrasomy 12p diagnosed prenatally. In six of the cases that were ascertained by amniocentesis performed for advanced maternal age, only one had fetal anomalies detected between 16 and 18 weeks of gestation. In the cases that were ascertained by the presence of fetal structural anomalies, the gestational

Table 138-1

Sonographic Findings Reported in Tetrasomy 12p

Dilated cisterna magna
Frontal bossing
Hypertelorism
Excess nuchal skin
Rhizomelic limb shortening
Postaxial polydactyly
Congenital heart disease
Diaphragmatic hernia
Cystic/dysplastic kidneys

Source: Wilson RD, Harrison K, Clarke LA, Yang SL. Tetrasomy 12p (Pallister–Killian syndrome): ultrasound indicators and confirmation by interphase FISH. Prenat Diagn. *1994;14:787-792.*

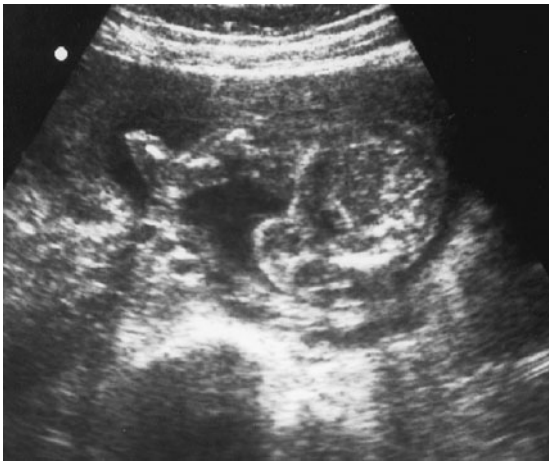

Figure 138-2 Prenatal sonographic image from a fetus with tetrasomy 12p demonstrating a shortened lower extremity.

age was more advanced, between 16 and 32 weeks (Wilson et al., 1994). The extensive range of sonographic findings described varies from normal to a large diaphragmatic hernia with shift of the heart to right side of the chest (see Chapter 37). Additional sonographic findings reported include congenital heart disease (Wilson et al., 1994) and increased cisterna magna, suggesting agenesis of the vermis or cerebellar hypoplasia (Gilgenkrantz et al., 1985; McLean et al., 1992). An additional clinical finding in fetuses with Pallister–Killian syndrome is hypertelorism. Many fetuses with tetrasomy 12p also have nuchal edema or other hydropic changes (Figure 138-3). In 2002, Doray et al. summarized the existing literature on 63 prenatally diagnosed cases of Pallister–Killian syndrome (Doray et al., 2002). Sonographic abnormalities were described in 31 cases. The three most commonly found abnormalities were: polyhydramnios (26/31, 84%), diaphragmatic hernia (5/31, 16%), and rhizomelic micromelia (3/31, 10%). Other anomalies detected at a frequency of less than 10% included: hydrops fetalis, cystic hygroma, increased nuchal translucency measurement (see Langford et al., 2000), fetal overgrowth, ventriculomegaly, dilated cavum pellucidum, absent stomach visualization, and presence of a sacral appendix. Importantly, intrauterine growth restriction has never been described in this syndrome.

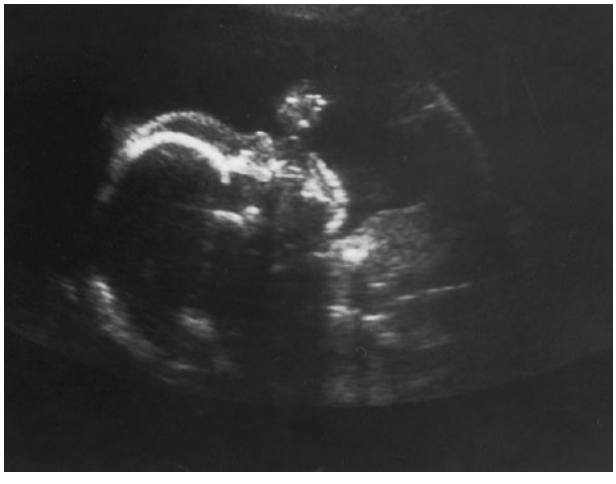

Figure 138-3 Prenatal sonographic image from the same fetus shown in Figure 138-2 demonstrating the fetal face in profile. Note the presence of frontal bossing and subcutaneous edema.

DIFFERENTIAL DIAGNOSIS

When isochromosome 12p is detected on an amniocentesis, it is diagnostic for Pallister–Killian syndrome. In the setting of an unknown marker chromosome with the presence of fetal anomalies, the possible diagnosis of tetrasomy 12p must be considered. It can be confirmed with the FISH technique using chromosome-specific probes for the short arm of chromosome 12 (Mowery-Rushton et al., 1997). In the setting of a fetus with sonographic anomalies suggestive of Pallister–Killian syndrome, the main consideration in the differential diagnosis is Fryns syndrome. However, Fryns syndrome is generally associated with growth restriction and Pallister–Killian syndrome is associated with normal, or even excessive growth for gestational age. Furthermore, Paladini et al. (2000) have described specific sonographic findings of the fetal face that aid in the diagnosis of Pallister–Killian syndrome. These include flat facial profile, small nose, and thin lips.

Fryns syndrome is a lethal condition inherited in an autosomal recessive pattern. Characteristic clinical findings during the newborn period include a coarse face, cleft palate, diaphragmatic hernia, distal digital hypoplasia, and neonatal death due to pulmonary hypoplasia. Chromosomes are normal in this syndrome. There is considerable clinical overlap between Fryns and Pallister–Killian syndromes. The diagnosis of Pallister–Killian syndrome is generally made in an older infant who has developmental delay and progressive coarsening of the facial features. Once the typical clinical findings of Pallister–Killian have been observed, karyotype studies generally include a skin biopsy for fibroblast culture. Babies who die during the neonatal period are more likely to have a diagnosis of Fryns syndrome, especially if a peripheral blood karyotype has been obtained and it is normal (Rodriguez et al., 1994). It has been suggested that newborn infants with clinical findings consistent with either Fryns or Pallister–Killian syndrome should have karyotypes performed on multiple tissue types to allow a correct diagnosis to be made (McPherson et al., 1993). This is important because Fryns and Pallister–Killian syndromes have different prognoses and different recurrence risks. Fryns syndrome is an autosomal recessive and Pallister–Killian syndrome (tetrasomy 12p) is considered to be a sporadic event.

ANTENATAL NATURAL HISTORY

In the review of Doray et al. (2002), 28/59 (47%) cases were terminated at an average age of 21 weeks. An additional 24

(41%) were liveborn, at an average gestational age of 30 weeks, but subsequently died. In three cases (5%) there was an intrauterine fetal death. Only four children survived past the neonatal period.

MANAGEMENT OF PREGNANCY

If polyhydramnios, short femur, and diaphragmatic hernia have been documented by prenatal sonographic examination, the diagnosis of Pallister–Killian syndrome should be considered. In this setting, an amniocentesis is more likely to be diagnostic of the chromosomal abnormality than cordocentesis, because the chromosomal abnormality is present in the majority of amniocytes but not in fetal lymphocytes (Donnenfeld et al., 1993; Wilson et al., 1994). However, at least one case has been detected at cordocentesis (Chiesa et al., 1998). If an unknown marker chromosome is detected on amniocentesis, consideration should be given to performing FISH studies using chromosome 12p-specific probes. This is best performed in a referral cytogenetics laboratory with experience in FISH analysis.

The abnormal marker chromosome can also be recognized in samples obtained by chorionic villus biopsy. The marker has been documented in 93% of cells derived from the direct preparation (Sharland et al., 1991) and 100% of cells derived from a cultured preparation (Bernert et al., 1992). In one case, however, karyotype results from chorionic villus sampling were normal, but the infant had clinical findings of Pallister–Killian syndrome. Fibroblast cultures obtained from a skin biopsy at 1 year of age demonstrated isochromosome 12p mosaicism (Horn et al., 1995).

Once a diagnosis of tetrasomy 12p has been made, the poor prognosis for a child with this condition should be discussed with the family. If the diagnosis is made at less than 24 weeks of gestation, termination of pregnancy can be offered. Cesarean section should not be performed for fetal distress. However, if the parents desire that everything be performed for the infant, delivery in a tertiary care hospital may be necessary because of the high frequency of associated pulmonary hypoplasia due to diaphragmatic hernia, which necessitates resuscitation by a neonatologist and treatment by a pediatric surgeon.

FETAL INTERVENTION

There are no fetal interventions for tetrasomy 12p.

TREATMENT OF THE NEWBORN

Because of the poor prognosis associated with this finding, resuscitation of the newborn infant with tetrasomy 12p should consist of basic supportive but not heroic measures. Recognition of the clinical features of Pallister–Killian syndrome during the newborn period is important because a normal peripheral blood karyotype does not exclude the diagnosis. To make the diagnosis in a newborn infant who did not have an amniocentesis performed prenatally, a fibroblast culture must be established from a skin biopsy (Bergoffen et al., 1993).

Newborns with tetrasomy 12p generally have a normal birth weight or they are large for gestational age. The average birth weight at term for affected infants is 3.6 kg (Reynolds et al., 1987). The typical physical findings in a newborn with Pallister–Killian syndrome include dysmorphic facies consisting of a high forehead with frontal bossing, sparse hair with bitemporal alopecia, hypertelorism, wide and flat nasal bridge, long philtrum, large mouth, short, webbed neck, supernumerary nipples, congenital heart disease, diaphragmatic hernia, proximal shortness of the upper and lower limbs, hypotonia, and imperforate anus (Reynolds et al., 1987; Schinzel, 1991). In time, skin pigmentary abnormalities (hypopigmentation and hyperpigmentation) may develop. These are best diagnosed by skin examination under a Woods lamp.

SURGICAL TREATMENT

Surgical treatment for infants with tetrasomy 12p is generally not indicated. Because of the overall poor prognosis, repair of a diaphragmatic hernia in a patient with known tetrasomy 12p is not advisable. Surgical treatment for these infants generally consists of supportive care, such as gastrostomy tube placement to permit feeding in cases in which survival beyond the immediate neonatal period is anticipated. A diverting colostomy in infants with imperforate anus may be necessary to permit normal bowel function.

LONG-TERM OUTCOME

The physical appearance of affected infants and children with tetrasomy 12p changes over time. The face becomes increasingly coarse and dysmorphic. Thick lips and a protruding tongue develop. The frontotemporal balding disappears, and hair growth becomes normal after a few years. Most affected children and adults have a generalized pigmentary dysplasia that may be evident only by Woods lamp examination. Some older patients with tetrasomy 12p are misdiagnosed as having hypomelanosis of Ito.

Most patients with tetrasomy 12p are profoundly retarded, and are completely bedridden, with flexion contractures. Almost all affected children and adults never speak or become continent and completely lack self-help skills (Schinzel, 1991). However, a few reports exist of affected individuals with a milder phenotype (Genevieve et al., 2003). The oldest reported patient is 45 years of age; thus, the chromosomal abnormality is in some cases compatible with prolonged survival.

GENETICS AND RECURRENCE RISK

Tetrasomy 12p is considered to be a sporadic condition with no increased risk of recurrence (Reynolds et al., 1987; Wenger et al., 1988; Bergoffen et al., 1993). There is also no history of recurrent miscarriage in affected families.

The isochromosome 12p is generally seen in 0% to 2% of lymphocytes in a peripheral blood karyotype but 50% to 100% of fibroblasts. Importantly, the proportion of tetrasomic cells present does not correlate with the severity of malformations, postnatal survival, or the extent of mental retardation.

For purposes of genetic counseling, the diagnosis of tetrasomy 12p can be made retrospectively on perinatal autopsy specimens in fetuses with hydrops, rhizomelic limb shortening, hypertelorism, diaphragmatic hernia, and congenital heart disease using FISH on fetal and placental tissues. This approach can be successful for diagnosis on formalin-fixed tissues (Wilson et al., 1994). Mothers who have given birth to an infant or fetus with tetrasomy 12p should be counseled that there is no increased recurrence risk. Amniocentesis is potentially indicated in a subsequent pregnancy, however, for reassurance.

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22q11.2 Deletion (DiGeorge Syndrome)

139 CHAPTER

Key Points

- Most common microdeletion syndrome reported in humans.
- 22q11.2 deletion is associated with DiGeorge syndrome, velocardiofacial syndrome (VCFS), Opitz G/BBB syndrome, and Cayler cardiofacial syndrome (also known as asymmetric crying facies syndrome).
- Incidence is 1 in 6000 livebirths.
- Deletion is associated with specific types of congenital heart disease, including tetralogy of Fallot, truncus arteriosus, absent pulmonary valve, and aortic arch abnormalities.
- Other associated sonographic findings include growth restriction, nuchal translucency, thymic hypoplasia, and renal anomalies. The presence of polyhydramnios is predictive of postnatal feeding difficulties.
- Once the deletion is found, both parents should also undergo cytogenetic analysis.
- Delivery should occur in a tertiary center.
- Affected neonates are at risk for seizure disorders due to hypocalcemia.
- Postnatal problems include speech defects due to palatal abnormalities, repeated infections due to immunodeficiency, developmental delay, feeding issues, and serious behavioral and psychiatric problems.
- 22q11.2 deletion is inherited as an autosomal dominant trait.
- The major causative gene is *TBX1*, a member of the T-box protein family of genes.

CONDITION

22q11.2 deletion is the most common microdeletion syndrome that has been reported in humans. It is also the most common syndrome associated with cleft palate and the most common syndrome associated with conotruncal anomalies (Shprintzen et al., 2005). Microdeletion syndromes are genetic disorders caused by the loss of a small chromosome segment contains multiple genes, but that is too small to be detected via the 400-band standard metaphase karyotype. 22q11.2 deletion is commonly thought of as being equivalent with DiGeorge syndrome.

DiGeorge syndrome was first described in 1965 by Dr. Angelo DiGeorge as a developmental field defect that affected structures derived from the 3rd and 4th pharyngeal arches. It is now known that 22q11.2 deletion is actually associated with a variety of different syndromes that appear to be phenotypic variants of the same disorder. 22q11.2 deletion encompasses DiGeorge syndrome, velocardiofacial syndrome (VCFS), conotruncal anomaly face syndrome, Opitz G/BBB syndrome, and Cayler cardiofacial syndrome, which is also known as asymmetric crying facies syndrome. Ninety percent of patients with DiGeorge syndrome who have an apparently normal karyotype actually have a microdeletion of chromosome 22q11.2 (Figure 139-1). This was not appreciated until the development of molecular cytogenetic techniques such as fluorescence in situ hybridization (FISH).

The clinical findings of 22q11.2 deletion are highly variable, both between families and within families (Yamagishi and Srivastava, 2003). Approximately 75% of patients with 22q11.2 deletion have congenital heart disease, most commonly abnormalities involving the outflow tracts and the aortic arch. Patients with this deletion have a characteristic facial appearance, immunodeficiency due to thymic hypoplasia, velopharyngeal dysfunction either with or without cleft palate, hypocalcemia due to hypoparathyroidism,

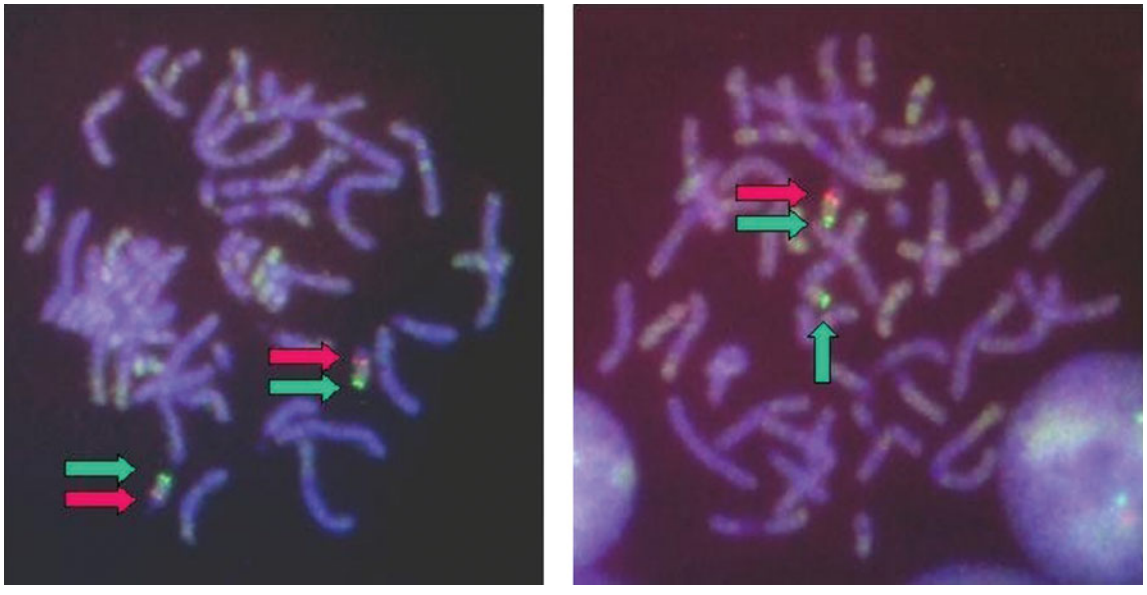

Figure 139-1 Chromosome analysis demonstrating the presence of the 22q11.2 deletion by FISH. On the left is a normal control. On the right is an affected individual. The green probes, as indicated by green arrows, map to the end of chromosome 22. The red probes, as indicated by the red arrows, map to the 22q11.2 region. The image on the right shows the presence of only one red probe, which indicates a deletion of this region on one copy of 22. This finding is diagnostic of DiGeorge syndrome. (*Photograph courtesy of Dr. Janet Cowan.*)

developmental and behavioral problems, and psychiatric disorders in adulthood (Yamagishi and Srivastava, 2003).

INCIDENCE

The minimum incidence of 22q11.2 deletion is 1 in 6395 livebirths, as described in the Flemish region of Belgium (DeVriendt et al., 1998a). In 2003, Botto et al. performed a population-based study, using matched records from the metropolitan Atlanta congenital defects program, the Sibley Heart Center, and the Division of Medical Genetics at Emory University School of Medicine. This group found 43 children with cytogenetic laboratory confirmed 22q11.2 deletion in a total population of 255,849 births. This gave an overall prevalence of 1 in 5950 births, with a slight racial difference observed. The prevalence was 1 in 6000 among white, black, and Asian individuals, and 1 in 3800 among Hispanics. The reason for the discrepancy was not known. The importance of the cytogenetic deletion was illustrated by the fact that 22q11.2 deletion was shown to contribute to 1 in 68 cases of congenital heart defects, 1 in 2 cases of interrupted aortic arch type B, 1 in 5 cases of truncus arteriosus, and 1 in 8 cases of tetralogy of Fallot.

SONOGRAPHIC FINDINGS

A deletion of 22q11.2 should be considered in fetuses with specific types of isolated congenital heart disease, such as tetralogy of Fallot, truncus arteriosus (Figure 139-2), aortic arch anomalies, absent pulmonary valve, or ventricular septal defect with pulmonary atresia or aortic arch anomalies (Goldmuntz, 2005). Deletion 22q11.2 should also be considered in any fetus with congenital heart disease and some other feature that has been described in fetuses with this condition, such as polyhydramnios (DeVriendt et al., 1998b), vertebral anomalies, holoprosencephaly, spina bifida, or renal anomalies (Stewart et al., 1999).

In one study, all fetuses with sonographically detected cardiac anomalies, an unremarkable family history and a normal metaphase karyotype were studied specifically for

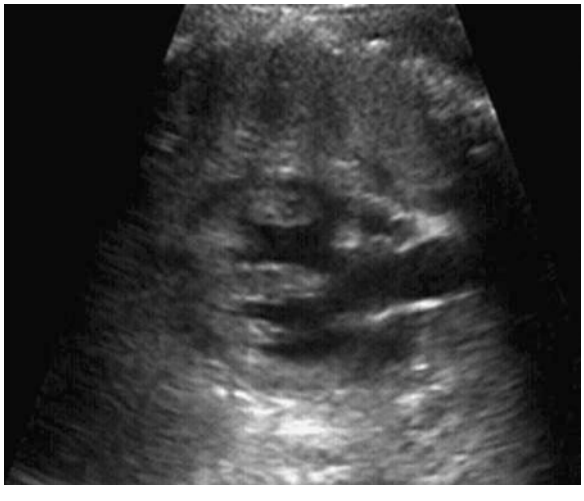

Figure 139-2 Sonogram demonstrating the presence of truncus arteriosus. A single cardiac outflow tract is seen straddling both ventricles. This finding prompted FISH testing for the 22q11.2 deletion, which was positive.

the incidence of the 22q11.2 deletion over a 3-year period (Manji et al., 2001). A total of 46 cases were studied by FISH. Five out of the 46 cases (10.8%) had the deletion. The fetal sonographic abnormalities found included tetralogy of Fallot, atrial ventricular canal defect, VSD with truncus arteriosus, and VSD and ASD. Parental chromosome studies showed that one case was maternally inherited, three represented de novo mutations, and in one case the parents declined cytogenetic testing. In another study, 261 consecutive fetuses with a conotruncal cardiac malformation and a normal karyotype were studied for the presence of the 22q11.2 microdeletion (Table 139-1) (Boudjemline et al., 2001). A microdeletion was found in 54 of 261 fetuses (20.7%). Recently, multiple studies have appeared that have taken specific fetal cardiac anomalies and analyzed the relative percentage of microdeletions present. For example, Galindo et al. (2006) studied 14 cases of the rare malformation of absent pulmonary valve; 3 of these had microdeletion 22q11.2. Similarly, in a study of 71 cases of antenatally presenting right aortic arch, 7 cases (10%) had the microdeletion (Berg et al., 2006). However, all of these seven cases had associated extracardiac anomalies. In a large study of 92 fetuses with tetralogy of Fallot that had cytogenetic studies performed, 15 had evidence of 22q11.2 microdeletion (16.3%) (Poon et al., 2007).

Table 139-1

Frequency of 22q11.2 Deletion in Congenital Heart Disease

Type of Heart Defect	Antenatal Data (%)*	Postnatal Data (%)†
Interrupted aortic arch	45	50
Truncus arteriosus	31	35
Tetralogy of Fallot	14	16
Absent pulmonary valve	38	
Isolated aortic arch anomaly		24
Ventricular septal defect (isolated)		10
With aortic arch anomaly		40
With pulmonary atresia	21.5	
Double outlet right ventricle		<5
Transposition of great arteries	4	<1

* *Data from Boudjemline Y, Fermont L, Le Bidois J, Lyonnet S, Sidi D, Bonnet D. Prevalence of 22q11 deletion in fetuses with conotruncal cardiac defects: a 6-year prospective study.* J Pediatr. *2001;138:520-524.*
† *Data from Goldmuntz E. DiGeorge syndrome: new insights.* Clin Perinatol. *2005;32:963-978.*

Other sonographic findings that are associated with the 22q11.2 microdeletion include increased nuchal translucency measurement (Lazanakis et al., 1998) and polyhydramnios (DeVriendt et al., 1998b). In the latter study, 52 fetuses that had cytogenetic analysis were retrospectively reviewed to determine whether polyhydramnios was present. This finding was seen in 8 of 52 (16%) fetuses. The severity and time of onset of the polyhydramnios was variable, but interestingly, it was predictive of postnatal feeding difficulties. Another sonographic finding associated with the microdeletion is an absent or hypoplastic thymus (Chaoui et al., 2002). The thymus can only be visualized after 15 or 16 weeks of gestation, so this is not an appropriate first trimester test. Chaoui et al. (2002) studied 149 fetuses with congenital heart disease. Of these, 76 had evidence of conotruncal abnormalities and 10 of the 76 (13.1%) had the 22q11.2 microdeletion. Thymic hypoplasia was suspected in 11 cases and of these 9 had the cytogenetic deletion. The absent or hypoplastic thymus provided an additional clinical finding to suggest the presence of a microdeletion. The thymic hypoplasia sign has a sensitivity of 90%, a specificity of 98.5%, a positive predictive value of 81.8%, and a negative predictive value of 99.2%. Only one fetus with the deletion had a normal thymus.

Sonographically detectable renal anomalies are also associated with the microdeletion. Two studies in postnatal patients suggested that renal abnormalities were part of this condition. In Europe, a large-scale study of 558 patients with 22q11.2 deletions had medical records reviewed to determine if renal imaging studies were performed. In 136, renal studies were performed and abnormalities were detected in 49 patients (36%) (Ryan et al., 1997). In a smaller study, 13 patients with a known cytogenetic deletion had renal sonography performed. Five of these 13 cases (a very similar 38.4%) had evidence of a renal anomaly. Specific anomalies seen in this population included bilateral duplex kidneys, unilateral renal agenesis, unilateral multicystic dysplastic kidneys, and bilateral extremely small kidneys (Stewart et al., 1999). Similarly, these findings have been observed in fetuses affected with the 22q11.2 deletion. Goodship et al. (1997) described three fetuses with renal anomalies as the main presenting symptom of the deletion. The findings in affected fetuses included absent kidneys, multicystic kidneys, obstructive abnormalities, and vesicoureteric reflux.

Another finding in affected fetuses is growth restriction. In an unbiased study of 27 consecutive growth-restricted fetuses with normal karyotypes, 3 of the 27 (11%) had the microdeletion (Chen et al., 2006).

DIFFERENTIAL DIAGNOSIS

In postnatal studies, it is of interest that the diagnosis of 22q11.2 deletion is made later in those individuals who do not have a heart defect. Overwhelmingly, the presence of the

heart defect triggers the diagnosis in a fetus or infant. Once speech begins, it is the presence of either nasal speech or the delay of speech development that usually prompts evaluation and testing. The diagnosis of 22q11.2 deletion is made by cytogenetic diagnosis (Figure 139-1). However, once this cytogenetic abnormality has been detected, it encompasses several different clinical conditions.

DiGeorge syndrome is characterized by a distinctive face, hypoplasia or aplasia of the thymus and parathyroid glands, and conotruncal cardiac defects. The essential triad consists of hypocalcemia, immunodeficiency, and congenital heart disease. VCFS is usually diagnosed in an older child with either cleft palate or velopharyngeal incompetence. Patients with VCFS also have a distinctive face that is long and narrow with a prominent nose, and long and tapering fingers. Conotruncal facial anomaly syndrome consists of a specific type of dysmorphism originally described in Japanese children in association with conotruncal cardiac anomalies. All three conditions are thought to be phenotypic variants of the same disorder. Cayler cardiofacial syndrome is characterized by an asymmetric appearance of the child while crying, along with the presence of cardiac anomalies. Lastly, Opitz G/BBB syndrome, the autosomal dominant form, has been shown to be associated with the 22q11.2 deletion. Affected patients manifest hypertelorism (see Chapter 25), laryngotracheal esophageal clefts, cleft palate, swallowing difficulties, genitourinary defects, and developmental delay.

ANTENATAL NATURAL HISTORY

The antenatal natural history of fetuses affected with a 22q11.2 deletion has not been studied prospectively nor systematically. Occasional case reports exist that document in utero demise secondary to the presence of complex congenital heart disease (Machlitt et al., 2002).

MANAGEMENT OF PREGNANCY

Current indications for prenatal testing for the 22q11.2 deletion include having had a previous child with the deletion or clinically diagnosed DiGeorge or VCFS, an affected parent with a 22q11.2 deletion, or the in utero detection of a conotruncal cardiac defect (Figure 139-2) (Driscoll, 2001). Approximately 6% to 10% of cases of the deletion are familial, and the deletion is transmitted as an autosomal dominant trait. Therefore, in pregnancies at risk for inheritance of the deletion, an amniocentesis or chorionic villus sampling should be performed. If the fetus is diagnosed as having the deletion, a fetal echocardiogram and consultation with a pediatric cardiologist should be offered (Goldmuntz, 2005). In addition, consultation with a medical geneticist is recommended. Furthermore, because of the high incidence of associated renal abnormalities, particular attention should be paid to the presence of renal malformations on a level II sonogram. As stated earlier, the presence of polyhydramnios is associated with postnatal feeding difficulties.

Fetuses diagnosed with the 22q11.2 deletion should be delivered in a tertiary center, because of the risk of developing hypocalcemic seizures as well as the availability of pediatric cardiology.

FETAL INTERVENTION

There has been no fetal invention reported for this condition.

TREATMENT OF THE NEWBORN

There are three major considerations for the treatment of a newborn with the 22q11.2 deletion. Cardiac disease, if present, must be treated. A neonatal cardiac consultation should be obtained to get better anatomic delineation of the cardiac anomalies present. Other major problems that occur in the newborn period include seizures due to hypocalcemia, and feeding difficulties due to the presence of either palatal abnormalities or dysmotility (Emanuel et al., 2001). Postnatal studies that should be performed include obtaining a renal sonogram, echocardiogram, electrocardiogram, ionized calcium level, and baseline immune profile. Consultations should be arranged with cardiology, ear nose and throat, audiology, and potentially immunology. In infants with repeated infectious illnesses secondary to immunodeficiency, a novel treatment is thymic transplant. This has been performed in at least one case of confirmed 22q11.2 deletion (Markert et al., 2004).

Patients with this deletion have a high percentage of palatal abnormalities, including submucosal cleft palate, isolated cleft palate, bifid uvula, cleft lip with cleft palate, and velopharyngeal incompetence. This latter finding is never diagnosed until speech develops.

SURGICAL TREATMENT

Surgical treatment is performed for the presence of specific cardiac abnormalities or palatal abnormalities.

LONG-TERM OUTCOME

22q11.2 deletion is a complex disorder that affects many organ systems. Affected individuals have a high incidence of associated congenital heart disease and may require medical treatment for congestive heart failure. Affected individuals have a variety of other problems associated with respiratory

abnormalities, such as stridor secondary to vascular ring. In addition, they have a variety of ear, nose, and throat abnormalities, including chronic otitis media, hearing loss, growth failure secondary to feeding problems, immunodeficiency, developmental delay, and later in life, serious behavioral and psychiatric problems. Early intervention is recommended. In 1 to 2% of individuals studied with schizophrenia, the 22q11.2 deletion is present (Shprintzen et al., 2005).

GENETICS AND RECURRENCE RISK

The 22q11.2 deletion is inherited as an autosomal dominant trait. Most of these cytogenetic deletions are de novo. It is now known that this particular part of the human genome is relatively unstable. 22q11.2 deletions and duplications arise simultaneously from proximal interchromosomal exchange during meiosis (Saitta et al., 2004). The 22q11.2 location is characterized by a large number of low copy repeat sequences. Unequal crossing over occurs between these low copy repeat sequences, and this results in a 3 Mb deletion in one 22 chromosome homolog and a reciprocal, similarly sized duplication in the other homolog. There are approximately 30 genes that have been mapped to the 3 Mb deletion of 22q11.2 (Yagi et al., 2003). In one study, 235 unrelated patients with rigorously clinically diagnosed 22q11.2 syndrome underwent cytogenetic analysis. Of these, 225 or the 235 (96%) had the characteristic deletion. This group then sequenced the gene *TBX1* in the 10 patients who had the clinical diagnosis but no evidence of the cytogenetic deletion. Three mutations in the *TBX1* gene were identified in two unrelated patients and three patients from one family. These mutations were three newly described point mutations. Yagi et al. (2003) therefore concluded that the *TBX1* mutation is a major determinant of clinical findings in nondeletion 22q11.2 syndrome. *TBX1* has been identified as the candidate gene responsible for the abnormal face, cardiac defects, thymic hypoplasia, velopharyngeal insufficiency, cleft palate, and hypocalcemia seen in this syndrome, but *TBX1* mutation alone is not associated with mental retardation. Therefore, the full DiGeorge syndrome phenotype results from a contiguous gene deletion, meaning that more that one gene is deleted and different genes are responsible for different components of the syndrome. *TBX1* is part of the T-box protein family of genes. The T-box proteins have a range of roles in early vertebrate development, including development of the heart and limbs. Mutations in *TBX3* are the underlying basis for ulnar mammary syndrome and mutations in *TBX5* are the cause of Holt–Oram syndrome.

Another interesting candidate gene, *COMT*, is also located within 22q11.2. *COMT* degrades synaptic dopamine in the brain. Two polymorphisms in the *COMT* gene have been described in patients with nondeletion "velocardialfacial" symptoms. The polymorphisms are *COMT* 158^{Met} and *COMT* 158^{Val}. The most severe form of mental illness in adults seems to be associated with *COMT* 158^{Met} (Shprintzen et al., 2005).

When a fetus is diagnosed with 22q11.2 deletion, parental cytogenetic testing should always be performed. As stated earlier, in 6% to 10% of cases one of the parents will be shown to be affected. However, even if both parents are negative by FISH studies, parents should be advised that germline mosaicism has been reported for this condition (Kasprzak et al., 1998; Sandrin-Garcia et al., 2002). Therefore, the recurrence risk is never zero after having had an affected fetus with this condition. This is why one of the indications for prenatal testing for 22q11.2 is having had a previously affected child.

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Index

Page numbers followed by italicized *f* and *t* refer to figures and tables.

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