Second Edition

# MULTIPLE *Pregnancy*

## Epidemiology, Gestation & Perinatal outcome

Edited by ISAAC BLICKSTEIN
and LOUIS G. KEITH
Associate Editor DONALD M. KEITH
Special photography by DAVID TEPLICA

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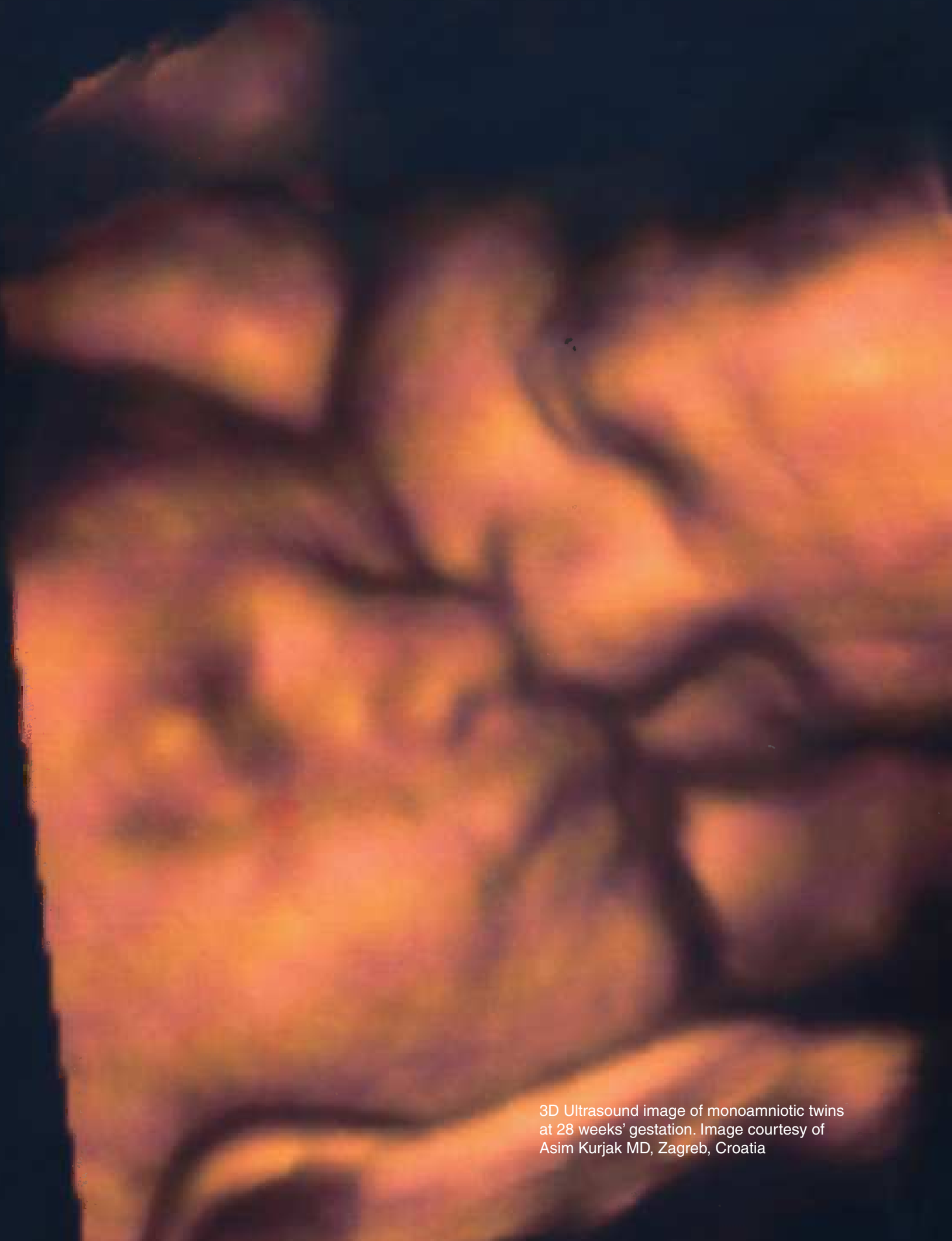

3D Ultrasound image of monoamniotic twins at 28 weeks' gestation. Image courtesy of Asim Kurjak MD, Zagreb, Croatia

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## Epidemiology, Gestation & Perinatal outcome


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# Dedications

This book is dedicated to the five individuals to whom I owe everything:

*To Noga, my first-born daughter, who turned into a charming young woman, and continues to bring light into my life;*

*To Ophir, my younger daughter, who turned into a lovely adolescent, and continues to color my life in gold;*

*To Dorit, who has ardently continued for more than 25 years to maintain our family cosmos, and to enable all these;*

*And to my parents, who have been there for me over 50 years.*

Isaac Blickstein MD

This book is respectfully dedicated to the individuals who made it all possible:

*John J. Sciarra, MD, PhD who, in his capacity as Professor and Chairman of the Department of Obstetrics and Gynecology of the Northwestern University Medical School, provided me and the Center for Study of Multiple Birth an unparalleled opportunity to study multiple gestation and to involve dozens of our students, residents and attending physicians in numerous scholarly efforts over a period of 28 years.*

*My brother, Donald: my thanks for being there along the way all these years. Our twinship is something that most other people do not have and fail to understand. Even so, it is the greatest thing in my life and I hope in yours too.*

*Catherine Brewer who, for more than 35 years, has represented far more than 'secretary' implies, in that she was there to listen, support, encourage, refine and implement my ideas and plans, not only for myself and my work at the University, but for the Center for Study of Multiple Birth.*

*My parents who, had they been here, would have been proud and delighted.*

Louis Keith MD PhD

# Special Thanks

I am extremely grateful to the Prentice Women's Hospital and Maternity Center of Northwestern Memorial Hospital in Chicago and its affiliate, the Kroch Twin Center, for their support and encouragement of my work on multiples.

L.G.K

# Preface

The first edition of this book was completed in 1992–93 and published in 1995. It attempted to provide a broad and inclusive perspective about the most common form of multiples, i.e. twins. At that time, no one, the editors included, could envision three dramatic events which changed the medical profession's opinions about multiples, a previously rare phenomenon. First was the emergence of the epidemic of multiple pregnancies observed worldwide, including high-order multiples. Second, and clearly a result of the first event, the relevant literature exploded, as shown in Figure 1. Finally, clinical management changed to embrace new technology, which was designed to care for these high-risk pregnancies and infants. Stated in other words, few areas in reproductive care encompassed modern technologies so intensively, so rapidly, and without geographic barriers.

The visionary foresight of David Bloomer, Managing Director of what was then the Parthenon Publishing Group, enabled the editors of this volume, working with others, to describe this epidemic in the monograph *Iatrogenic Multiple Pregnancy: Clinical Implications* (Figure 2a). Eventually, the co-editors, in association with Matria Healthcare, produced the first and only large-scale assessment of the most hazardous type of high-order multiples in the monograph *Triplet Pregnancies and Their Consequences* (Figure 2b).

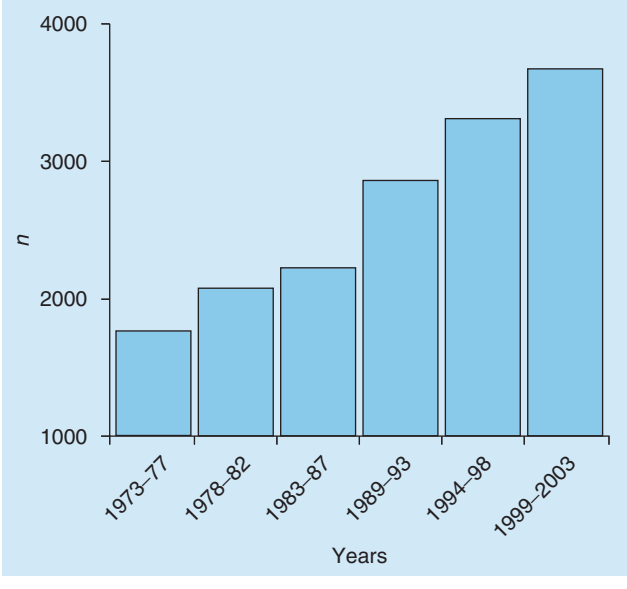


**Figure 1** Number of cited publications including the term 'multiple pregnancy'. Source: PubMed, National Library of Medicine

In November 2002 we decided that it was not only the right time but absolutely necessary to revise the original publication *Multiple Pregnancy: Epidemiology, Gestation and Perinatal Outcome*, which was almost 10 years old (Figure 2c). From the outset, it was clear that this should be a complete rewrite. Further, it became evident that the text should include as wide a knowledge base as possible, so that the new findings of the past decade could attain proper recognition. A comparison of the tables of contents of the respective first and second editions says it all.

Clearly, this type of effort could not be a two-man show, and the co-editors invited a galaxy of experts from around the world to share their experience. To avoid gaps, topics were assigned that occasionally overlapped. The editors, however, must acknowledge certain limitations of this plan. First and foremost is repetition, either in the introductions of specific chapters, or in their bodies. Readers must recognize, however, that in a multiauthor text, the removal of such material would have entailed significant rewriting of the book even before it was printed. We beg your indulgence.

Second, it is apparent that some chapters have a far greater clinical orientation than others. Nonetheless, as our intent was to produce a compendium of current knowledge and experience, we believe that the juxtaposition of these types of treatises is appropriate, as the readership of this volume will desire different types of information.

The co-editors, once again, wish to offer their sincere thanks, gratitude and appreciation to their good friend and colleague, David Teplica, MD, MFA for his gracious and continuous willingness to enhance the esthetic properties of our current and previous published productions. David's photographic work is in a class of its own, renowned throughout the world in the lay and medical press, in public art galleries and in private collections.

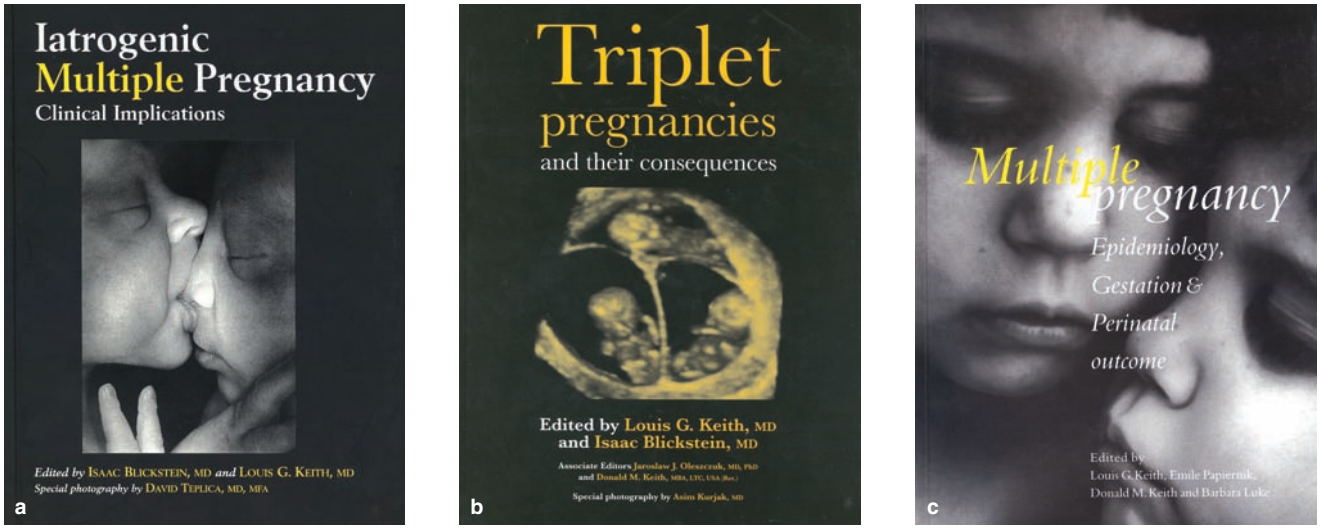


**Figure 2** (a) *Iatrogenic Multiple Pregnancy: Clinical Implications*. Parthenon Publishing Group, 2001; (b) *Triplet Pregnancies and Their Consequences*. Parthenon Publishing Group, 2002; (c) *Multiple Pregnancy: Epidemiology, Gestation & Perinatal Outcome*, 1st edn. Parthenon Publishing Group, 1995

Next, thanks go to Col. Donald Keith, the genetic copy of one of the co-editors (L.G.K.) and a dear friend of the other (I.B.), for his continuous support, constructive criticism, knowledgeable input and gallant camaraderie.

Last but not least, it is entirely appropriate to say thank you once again to the Parthenon team, starting with David Bloomer and Mrs Jean Wright, and currently transformed into Taylor and Francis with Mr Nick Dunton, Mrs Pamela Lancaster, and Mr Gerald Myers. Our numerous discussions have produced what we hope will be the 'definitive' text on multiples. The reader will especially appreciate the decision to include changes in textual format and style, and the addition of color images throughout.

Isaac Blickstein MD
Associate Professor
The Hadassah-Hebrew University
Jerusalem

and

Louis G. Keith MD PhD
Professor Emeritus at
Northwestern University, Chicago
Adjunct Professor, Mother and Child Health,
University of Alabama at Birmingham

**Figure 3** The Editors, Isaac Blickstein and Louis G. Keith

## Postscript

My career was advanced over the years by association with extremely talented co-workers, all of whom became my teachers. In the case of Isaac Blickstein, I have had the opportunity to be his teacher as well as his student. When we met, he was starting to develop his now enviable reputation for the subject of growth discordance in twins. As the years progressed, his talent and imagination led him in a variety of directions that amplified his early work. Reading Chapter 60 and its references brings me to realize the importance of his collected works over the years.

As an identical twin and co-Founder and President of the Center for Study of Multiple Births, it was always my ambition to promote scholarship in the subject of multiples with the goal of advancing knowledge. With the partnership of Isaac, my work has not only been easier, but has also brought me much closer to attaining my goal.

L. G. K.

Aristotle said, 'Wishing to be friends is quick work, but friendship is a slow-ripening fruit'. After many years of friendship and numerous collaborations, I find it still difficult to describe in a few sentences my friend and mentor – Louis Keith, MD, PhD. Perhaps the best way to appreciate the scholarship of Louis is to marvel at his decision to obtain a PhD on the verge of turning Professor Emeritus, after being a *full* professor for more than two decades, and after publishing *hundreds* of papers and editing *tens* of books. The only explanation for this formidable endeavor is Louis' insatiable quest for exploring every subject related to twinning. I was fortunate enough to be there for him in sheer admiration of his commitment to his scientific goals.

The unrivaled contribution of Louis to the research of multiple births is paralleled by his first-rate virtues as an editor. Over the years, I learnt from Louis, given in his own words, the well-known directions of Joseph Pulitzer: 'Put it before them briefly so they will read it, clearly so they will appreciate it, picturesquely so they will remember it and, above all, accurately so they will be guided by its light.' So I did.

I. B.

# Foreword

It is a pleasure once again to introduce this very important revised and updated text, *Multiple Pregnancy: Epidemiology, Gestation and Perinatal Outcome* edited by Professors Isaac Blickstein and Louis G. Keith.

Some years ago in the introduction to the first edition I wrote: 'This volume is a significant contribution to the study of twins and multiple pregnancies. It is the first major contribution on multiple pregnancy prepared after the widespread recognition that multiple births are presently more common then they have been, even in the recent past. It was also written after physicians and scientists realized that advances in neonatal care generally led to the survival of much smaller infants and the higher probability of these infants being handicapped. The authors and editors have provided a full discussion of these and other important problems.' Little did I realize at that time how accurate those words were. In the intervening years, the first edition of this text filled a scholarly void in the field of multiple pregnancy and unquestionably became the classic monograph on both twins and higher-order multiples for both clinicians and scientists.

The problems associated with multiple births are not limited to any single country. Indeed, multiple births are an issue worldwide and due primarily to the widespread introduction and enthusiastic public reception of assisted reproductive technologies for infertile couples. This volume, even more so than its predecessor, is truly international – with editors from Israel and the United States. Now more than ever it is vitally important that the international community of obstetricians and pediatricians clearly understand the issues relating to multiple pregnancy and their implications for health care. This volume addresses these issues in a comprehensive manner.

The editors deserve our compliments for assembling not only a truly scholarly volume but also a beautiful volume. This second edition has double the number of chapters that were published in the first edition and uses a two-color format and color illustrations throughout. It is thoroughly referenced so that the reader can easily find the background information on any of the many topics. The editors provide us with an in-depth discussion of difficult and important topics in the field of multiple pregnancy. Once again there are brilliant section dividers by Dr David Teplica, a friend and colleague of the editors.

In previewing this volume, I believe that it is most appropriate to say that the second edition of *Multiple Pregnancy: Epidemiology, Gestation and Perinatal Outcome*, is an encyclopedic reference. The section on epidemiology is international in scope and thorough in presentation with a comprehensive overview of multiple births resulting from assisted reproductive technologies in the United States in recent years. The section on biology expands greatly the information in the first edition with an excellent series of chapters on iatrogenic twinning, including a chapter on cloning by one of the editors. The section on perinatal diagnosis brings the reader fully up to date with ultrasound and genetic technology. Of particular importance, the sections on pregnancy management, delivery and postpartum concerns consist of an exceptional collection of chapters by recognized experts from many countries that will provide meaningful and practical guidance for clinicians dealing with twins and higher-order multiples. The concluding sections stressing childhood, familial and ethical concerns raise issues that deserve our attention. The editors, Professors Blickstein and Keith, draw on their own personal experience, both as clinicians and as members of numerous important national and international organizations dealing with multiples. As stated earlier, both editors should be congratulated on bringing together an array of world-class physicians and scientists. The editors' input and the intellectual contributions of the contributing specialists make this volume by far the most comprehensive and up to date resource on twins and multiple pregnancy.

In my Foreword to the first edition I indicated that it was my sincere hope that the first edition would serve as the basis for the continued discussion and study of the many complex medical and social issues surrounding the care of mothers with multiple pregnancy. The first edition was a fulfillment of that hope and I can only restate that hope for the present

expanded edition. The second edition of *Multiple Pregnancy: Epidemiology, Gestation and Perinatal Outcome* is easily destined to become a major reference for clinicians, scientists and other health-care professionals involved in the care of patients with multiple pregnancy. The editors have assembled an outstanding volume for both the present and the future.

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Past President of the International Federation
of Gynecology and Obstetrics (FIGO)
Editor, *International Journal of*
*Gynecology and Obstetrics*

# Foreword

Not only was I pleased to be asked to write this Foreword, but I was astonished to find 110 chapters and 11 sections in a book on multiple pregnancy that truly captures the entire world literature on multiple pregnancy in one volume. The editors are internationally well known for their expertise in this field and have assembled the chapters in a rational manner into different sections to give the reader an extensive discussion of the subject. The data in each chapter are new and based on recent evidence. Each chapter is written by an internationally renowned author or authors. The section on epidemiology is followed by biological considerations. From then onwards the journey of multiple pregnancy flows through prenatal diagnosis, pregnancy, labor, postdelivery and childhood issues including economic, legal and ethical issues.

The chapters are beautifully illustrated to give details, and the addition of numerous color photographs and figures makes it easy for one to read and understand the subject. Once you start reading, there is a tendency to continue reading till you finish that particular chapter or section. The arrangement of chapters is in such a way that one flows to the next with ease. Every chapter is well referenced.

This book makes an enormous contribution to our scientific knowledge on multiple pregnancy based on original research and collected data. As such, it should guide clinical practice and be of great value to people in different fields including investigational scientists, clinicians, sociologists, epidemiologists and health-care planners and providers.

I strongly believe that this book should be in every medical and hospital library and should also be widely available to the clinicians who look after multiple pregnancy. The editors should be commended for their enormous contribution to the literature on this subject.

Sabaratnam Arulkumaran PhD, FRCS, FRCOG, FACOG (Hon)
Professor and Head
Division of Obstetrics and Gynaecology
St. George's Hospital Medical School
University of London

and

Secretary General
International Federation of Gynecology
and Obstetrics (FIGO)

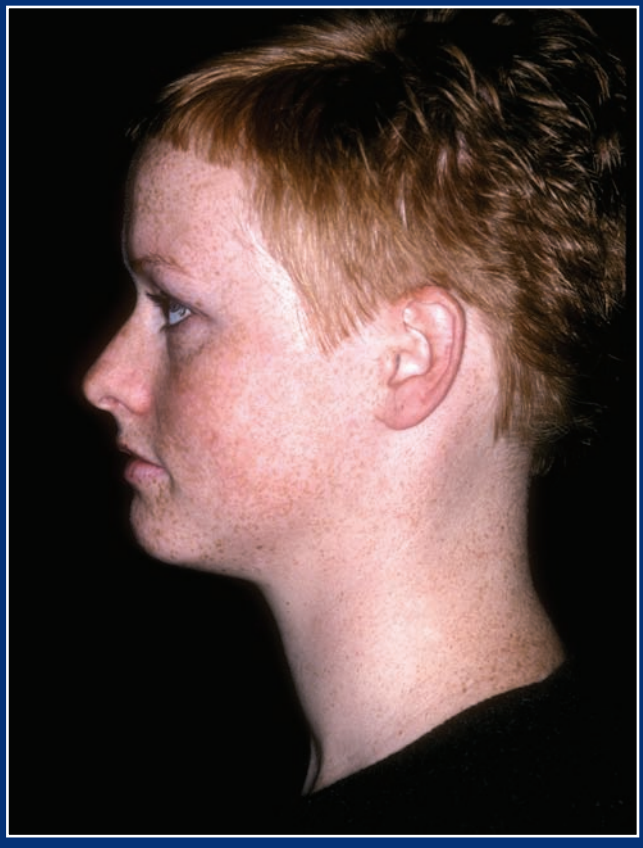
# Section dividers

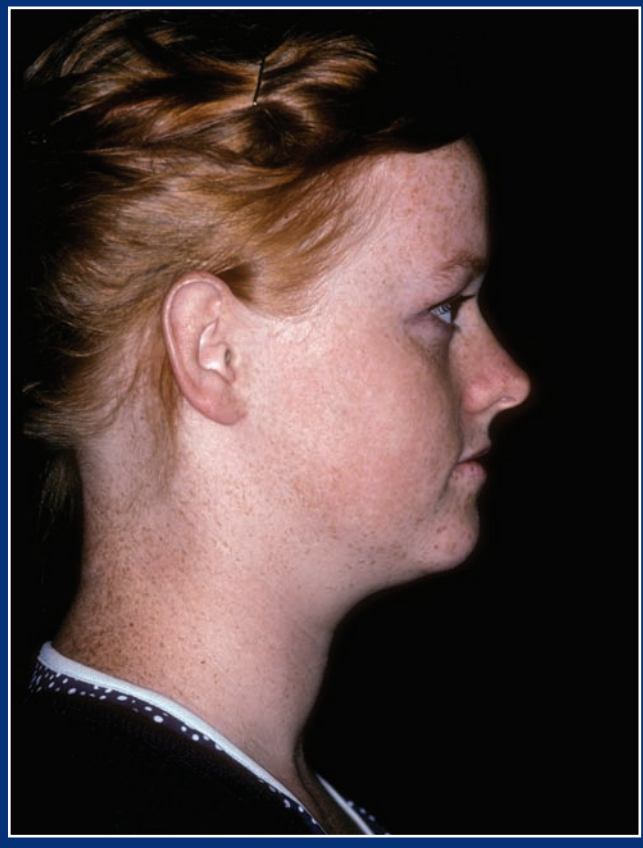
Recent advances in photographic standardization have opened new horizons for investigation of anatomic laterality and understanding of the mirror phenomenon in monozygotic twins (see Chapter 38). The paired photographic images of monozygotic twins selected for the section dividers are unique representations of this perplexing and fascinating phenomenon.

The images shown are from the 2004 Belgian Archive, a new extension of the Twinsburg Archive that was established in 1989 in collaboration with the Center for Study of Multiple Birth in Chicago. The co-Editors are grateful to David Teplica, MD, MFA for this unique contribution to the book.

I.B. and L.G.K.

# SECTION I
# EPIDEMIOLOGICAL AND DEMOGRAPHIC CONSIDERATIONS





**23-year-old female monozygotic, monochorionic, mirror twins, Belgium, 2004.**

Participants since birth in the East Flanders Prospective Twin Study. Twin A left, Twin B right.

An epidemic refers to the spread of a disease state, or anything resembling a disease, affecting many individuals in a community or population. Over time, increasing numbers of individuals are affected in a seemingly contagious nature. This definition, borrowed from the discipline of infectious diseases, seems quite suitable to describe recent changes in the incidence and distribution of multiple births:

- Multiple births resemble a disease state with increased likelihood of morbidity and mortality
- The incidence of multiple births has increased over time due to continuing exposure to a specific etiologic factor (in this case – all forms of assisted reproduction)
- The epidemic dimensions of multiple births are not entirely restricted to developed countries
- The propagation of the epidemic has had a 'contagious' nature, spreading from country to country where the etiologic factor is introduced

One of the major difficulties in comparative analysis of available data is the different registration of multiple births. In some countries, twins and triplets or more are registered separately, whereas in others, they are not registered at all. Because the likelihood is low that hospital-based data sets reflect the population at large, one should consider these sources of information with great caution.

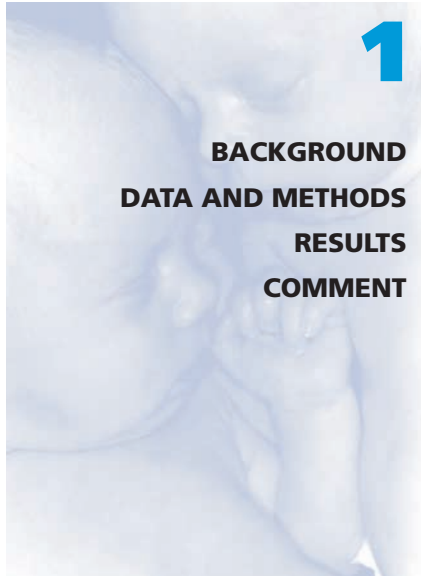
The present situation, however, is much better than that observed during the years preceding the first edition of this volume. This improvement is mainly due to the importance attributed in many countries to registering twins and high-order multiples as such. Based on this premise, the most suitable opening to this volume is an epidemiological account of multiple births. Obviously, a description of the epidemic in every country is impossible; however, a fair description from selected countries is presented, as well as that of major registries of assisted conceptions – the primary etiology of the epidemic.

*I.B. and L.G.K.*

# Contents of Section I

# Perinatal Outcomes of Singleton and Multiple Births in the United States, 1995–98

*G. R. Alexander and H. M. Salihu*




## BACKGROUND

The increases in both the rate and number of multiple births in the United States and elsewhere have been well documented in the literature and are described in detail in this book[1–7]. Several factors underlie the ascending incidence of multiple births in the USA, including the rapid growth in the use of assisted reproductive technologies (ART), the noticeable rise in the average age of women giving birth to their first child and the resultant and marked change in the distribution of the age of mothers at time of delivery[8–10]. Not only do older mothers have a greater likelihood of spontaneous multiple births, but also the necessity for employing ART increases as maternal age advances because of the accumulation of conditions that predispose to infertility[8–10].

Previous reports indicate that multiple births engender a greater risk of poor perinatal outcomes compared with singletons[11–16]. In addition to being associated with increased risks of maternal complications, including pre-eclampsia and toxemia, multiple births are associated with higher rates of preterm (< 37 weeks' gestation) delivery, low birth weight (< 2500 g) and fetal and infant death[1,11–15]. The distinct differences in the average length of gestation and mean birth weight of singletons, twins and triplets are documented, as are the marked variations in the fetal growth curves of multiple births[16].

This chapter addresses the perinatal outcomes of singleton and selected multiple births, specifically twins, triplets and quadruplets. Comparisons of maternal risk characteristics are provided for the mothers of the respective four infant groups under study, including both sociodemographic and behavioral risk indicators, measures of prenatal care utilization, previous pregnancy outcome and maternal complications. Infant mortality rates (deaths per 1000 live births) are contrasted for hebdomadal (within the first 7 days), neonatal (within the first 28 days) and infant (within the first year) periods of life. The chapter also examines common perinatal outcome measures, including mean birth weight and gestational age values, and percentages of low birth weight and very low birth weight (< 1500 g) and preterm and very preterm (< 33 weeks) birth. Furthermore, this report provides cause-specific infant mortality rates for infant deaths due to infections, congenital anomalies and perinatal conditions. Fetal growth curves for singletons and each multiple birth group are depicted, along with percentages of small-for-gestational-age birth, by using a US national fetal growth curve as an external reference for establishing the proportion of cases in each group that fall below the 10th centile of birth weight for gestational age. Finally, this chapter examines differences in gestational age-specific hebdomadal mortality rates among the study groups.

## DATA AND METHODS

Data on multiple births were obtained from the 1995–98 US Multiple Birth Data file, the latest multiple birth file available from the National Center for Health Statistics. Information on singleton births was selected from the 1995–98 US Birth Cohort Linked Birth/Infant Death files[11,12]. Live births to US resident mothers were selected for analysis.

Centiles of birth-weight distribution were calculated for each week of gestational age in order to estimate patterns of fetal growth. Centiles based on

**Table 1.1** Maternal characteristics by number at birth: 1995–98 US resident singleton, twin, triplet and quadruplet live births

| | *Singletons* | *Twins* | *Triplets* | *Quadruplets* |
|---|---|---|---|---|
| Non-Hispanic white mother (%) | 60.3 | 64.6 | 80.9 | 84.9 |
| Non-Hispanic black mother (%) | 15.0 | 16.9 | 7.5 | 3.6 |
| Hispanic mother (%) | 18.3 | 13.2 | 7.1 | 8.1 |
| Other race of mother (%) | 6.5 | 5.3 | 4.5 | 3.4 |
| Foreign-born mother (%) | 19.2 | 15.2 | 12.0 | 12.1 |
| Unmarried (%) | 32.6 | 27.9 | 8.9 | 3.8 |
| < 18 years of age (%) | 5.0 | 2.4 | 0.5 | 0.2 |
| ≥ 35 years of age (%) | 12.2 | 18.2 | 28.0 | 23.1 |
| High education for age* (%) | 44.3 | 52.5 | 73.5 | 71.4 |
| Low education for age† (%) | 20.0 | 15.4 | 4.8 | 3.0 |
| Primiparous (%) | 41.5 | 21.5 | 22.2 | 18.5 |
| High parity for age (%) | 2.9 | 6.0 | 3.9 | 5.1 |
| Previous pregnancy loss (%) | 2.7 | 3.7 | 4.9 | 5.2 |
| Smoked during pregnancy (%) | 13.5 | 11.8 | 3.7 | 1.7 |
| Cesarean delivery (%) | 19.7 | 53.6 | 89.4 | 91.1 |
| Hypertension (%) | 4.1 | 8.6 | 11.6 | 11.5 |
| Diabetes (%) | 2.6 | 3.3 | 5.8 | 7.1 |
| Incompetent cervix (%) | 0.2 | 0.8 | 4.0 | 7.1 |
| Male infant (%) | 51.2 | 50.2 | 50.0 | 50.6 |
| *Prenatal care utilization (R-GINDEX[18])* | | | | |
| Intensive (%) | 6.0 | 20.8 | 39.5 | 41.0 |
| Adequate (%) | 39.0 | 51.5 | 43.2 | 37.0 |
| Intermediate (%) | 39.5 | 16.1 | 5.2 | 5.9 |
| Inadequate (%) | 8.1 | 3.3 | 0.8 | 0.8 |
| No care (%) | 1.2 | 1.1 | 0.8 | 0.7 |
| Missing (%) | 6.3 | 7.2 | 10.6 | 14.7 |

*Less than 12 years of education (for adolescents, 2 or more years below expected grade level for age); †13 or more years of education (for adolescents, 2 or more years above expected grade level)

fewer than 50 cases and centiles for gestational ages less than 22 weeks and greater than 42 weeks are not given, owing to the potential for unstable or inaccurate fetal growth estimates because of insufficient numbers or gestational-age coding errors. Small for gestational age (SGA) was defined as the 10th centile of birth weight for gestational age, and percentage of SGA births was calculated using the 10th centile birth-weight values of the 1991 US birth weight for gestational age reference curve for singleton live births[17]. Cases with implausible or missing values for birth weight or gestational age, as well as cases with a birth-weight value inconsistent with gestational age, were deleted[17]. After these exclusions, 15 175 963 singleton births, 412 298 twins, 22 913 triplets and 2062 quadruplets were available for analysis.

Estimates of adequacy of prenatal care utilization were derived using the R-GINDEX, which incorporates data on the trimester in which prenatal care began and the number of prenatal care visits adjusted for gestational age[18]. Race and ethnicity were established using reported ethnicity and race of the mother. The $\chi^2$ test was used to establish whether there were significant differences in the proportion of maternal risk characteristics or adverse perinatal outcomes among the three multiple birth groups. Singleton births were excluded from significance testing, as the large number of births would typically result in significant findings.

## RESULTS

Table 1.1 details maternal characteristics according to singleton, twin, triplet and quadruplet live births. With one exception (gender of the newborn), significant ($p < 0.01$) differences were present in the proportions of these characteristics among the multiple birth groups. Whereas 60% of singletons were born to white mothers, this number increased to 85% of quadruplets. Compared with multiples, the mothers of singletons were more likely to be foreign-born, unmarried, less than 18 years of age and primiparous, have low education for age and use tobacco. The frequencies of these attributes tend to decrease

**Table 1.2** Gestational age, birth weight and infant mortality characteristics by number at birth: 1995–98 US resident singleton, twin, triplet and quadruplet live births

| | *Singletons* | *Twins* | *Triplets* | *Quadruplets* |
|---|---|---|---|---|
| Number of births | 15 175 963 | 412 298 | 22 913 | 2062 |
| Mean gestational age (weeks) | 39.0 | 35.6 | 32.2 | 30.4 |
| Median gestational age (weeks) | 39 | 36 | 33 | 31 |
| Very preterm (≤ 32 weeks) (%) | 1.81 | 14.7 | 45.1 | 73.6 |
| Preterm (< 37 weeks) (%) | 9.68 | 54.3 | 93.0 | 97.3 |
| Mean birth weight (g) | 3351 | 2367 | 1698 | 1339 |
| Median birth weight (g) | 3374 | 2460 | 1745 | 1332 |
| Very low birth weight (< 1500 g) (%) | 1.11 | 10.3 | 34.0 | 62.0 |
| Low birth weight (< 2500 g) (%) | 6.07 | 53.7 | 93.0 | 98.8 |
| Small for gestational age* (%) | 9.64 | 35.0 | 35.0 | 33.1 |
| Hebdomadal (day 7) mortality (per 1000 live births) | 3.2 | 21.8 | 50.6 | 57.2 |
| Neonatal mortality (per 1000 live births) | 4.0 | 25.6 | 59.2 | 75.2 |
| Infant mortality (per 1000 live births) | 6.4 | 31.1 | 66.4 | 82.4 |
| *Cause-specific infant mortality rates* | | | | |
| Infections (per 1000 live births) | 0.4 | 1.7 | 3.9 | 7.8 |
| Congenital anomalies (per 1000 live births) | 1.5 | 3.8 | 4.6 | 3.9 |
| Perinatal conditions (per 1000 live births) | 2.6 | 21.5 | 53.6 | 66.9 |

*10th centile of birth weight for gestational age, using a US singleton reference[17]

with increasing birth order. Mothers of triplets or quadruplets were more likely to be over 35 years of age, have high education for age, have incurred a previous pregnancy loss and report diabetes or an incompetent cervix. The proportion of mothers who reported hypertension was lowest among singletons.

Singletons had the lowest frequency of delivery by cesarean section (~20%). In contrast, over 50% of twins and approximately 90% of triplets and quadruplets were delivered by cesarean section. Intensive utilization of prenatal care increased with higher-order multiple births, as did the percentage of mothers with missing prenatal care utilization information (Table 1.1). Singletons were associated with the highest proportion of no and inadequate prenatal care use. The percentage of male births was not significantly different among the multiple birth groups.

Mean and median gestational age and birth weight decreased as multiple birth order increased (Table 1.2). On average, quadruplets were born approximately 2000 g lighter and 2 months earlier than singletons. The gestational age distribution of each study group highlights the distinct group differences in pregnancy duration (Figure 1.1). Correspondingly, percentages of preterm, very preterm, low birth weight and very low birth weight were the lowest for singletons and were significantly different and progressively higher among multiple birth orders. For quadruplets, nearly two-thirds were very low birth weight and three-quarters were very preterm (Table 1.2).

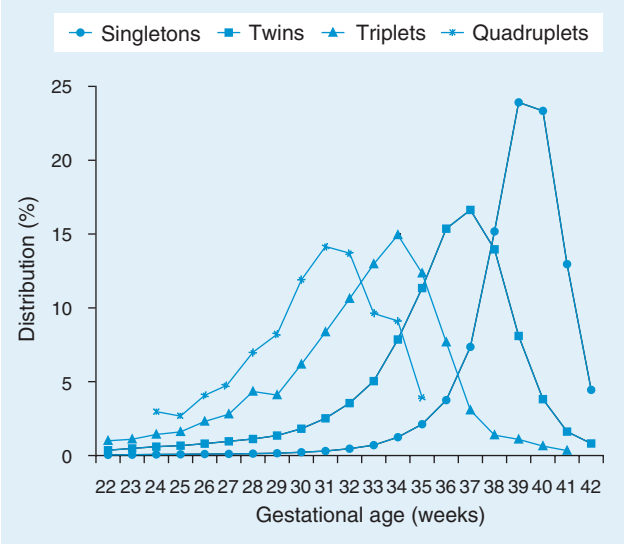



**Figure 1.1** Gestational age distribution for singletons, twins, triplets and quadruplets: 1995–98 US resident live births

Approximately one-third of multiple births fit the definition of small for gestational age (Table 1.2), using the 10th centile of birth weight for gestational age of US singletons[17]. The proportion of small for gestational age was not significantly different among the multiple birth groups. Notwithstanding, the percentages of small-for-gestational-age births according to gestational age, as defined by the 1991 US singleton births reference fetal growth curve,

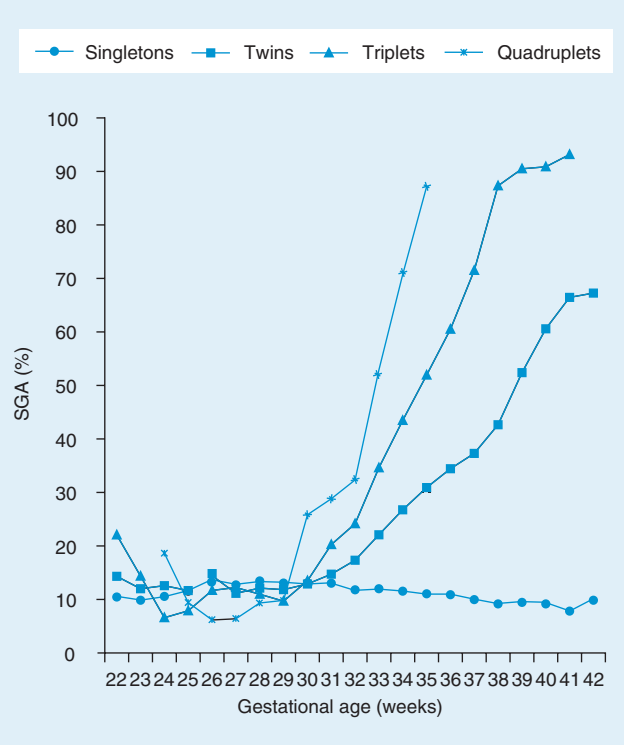



**Figure 1.2** Percentage of small for gestational age (SGA) according to gestational age: 1995–98 US resident singleton, twin, triplet and quadruplet live births

differed markedly among the four study groups (Figure 1.2). At 30 weeks, approximately 25% of quadruplets fit the definition of small for gestational age, with roughly corresponding proportions of small-for-gestational-age deliveries for triplets and twins observed at 32 and 34 weeks' gestation. Over 70% of quadruplets and triplets were delivered small-for-gestational-age by 34 and 37 weeks, respectively.

The risk of mortality in the first week, month and year of life increased notably as the number at birth increased (Table 1.2). The infant mortality rate of quadruplets was 82.4 infant deaths per 1000 live births, compared with 6.4 for singletons. Over 5% of triplets and quadruplets died in the first week of life. Infant death among higher-order multiples was predominantly attributed to perinatal conditions.

The 10th, 50th and 90th centiles of birth weight for gestational age for singletons, twins, triplets and quadruplets are provided in Table 1.3 and respective fetal growth curves in Figures 1.3–1.6. Among the four study groups, variation in median birth weight for gestational age was noted at quite early gestational ages. As shown in Figure 1.7, the 50th centiles of birth weight for gestational age for the multiple birth groups diverged markedly at around 32 weeks. By this time in the pregnancy, a

**Table 1.3** 10th, 50th and 90th Birth-weight centiles for gestational age, 1995–98 US resident singleton, twin, triplet and quadruplet live births

| | *Singletons* | | | *Twins* | | | *Triplets* | | | *Quadruplets* | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Week* | *10th* | *50th* | *90th* | *10th* | *50th* | *90th* | *10th* | *50th* | *90th* | *10th* | *50th* | *90th* |
| 22 | 370 | 510 | 765 | 352 | 482 | 653 | 330 | 454 | 595 | — | — | — |
| 23 | 440 | 588 | 851 | 425 | 567 | 737 | 415 | 539 | 652 | — | — | — |
| 24 | 484 | 660 | 907 | 482 | 650 | 870 | 510 | 629 | 834 | 473 | 607 | 851 |
| 25 | 539 | 765 | 1021 | 539 | 737 | 982 | 567 | 737 | 970 | 567 | 690 | 992 |
| 26 | 595 | 878 | 1247 | 583 | 851 | 1162 | 608 | 822 | 1050 | 652 | 794 | 992 |
| 27 | 652 | 992 | 1495 | 680 | 992 | 1361 | 652 | 964 | 1219 | 765 | 938 | 1134 |
| 28 | 737 | 1134 | 1814 | 765 | 1125 | 1588 | 794 | 1077 | 1385 | 816 | 1021 | 1295 |
| 29 | 865 | 1332 | 2268 | 880 | 1276 | 1777 | 936 | 1222 | 1559 | 935 | 1165 | 1440 |
| 30 | 1021 | 1559 | 2685 | 1021 | 1447 | 2040 | 1048 | 1385 | 1740 | 794 | 1276 | 1585 |
| 31 | 1200 | 1814 | 2977 | 1191 | 1637 | 2183 | 1134 | 1531 | 1905 | 1066 | 1420 | 1729 |
| 32 | 1446 | 2098 | 3175 | 1358 | 1800 | 2325 | 1276 | 1687 | 2080 | 1243 | 1616 | 1928 |
| 33 | 1670 | 2375 | 3345 | 1530 | 1985 | 2477 | 1417 | 1843 | 2255 | 1247 | 1701 | 2069 |
| 34 | 1899 | 2608 | 3487 | 1673 | 2155 | 2640 | 1559 | 1996 | 2410 | 1250 | 1745 | 2150 |
| 35 | 2126 | 2807 | 3600 | 1871 | 2353 | 2835 | 1673 | 2155 | 2595 | 1290 | 1759 | 2268 |
| 36 | 2340 | 2948 | 3657 | 2013 | 2515 | 3005 | 1729 | 2260 | 2750 | — | — | — |
| 37 | 2545 | 3119 | 3742 | 2155 | 2665 | 3165 | 1673 | 2268 | 2850 | — | — | — |
| 38 | 2722 | 3288 | 3884 | 2251 | 2778 | 3289 | 1503 | 2155 | 2791 | — | — | — |
| 39 | 2863 | 3402 | 3997 | 2240 | 2835 | 3374 | 1559 | 2145 | 2807 | — | — | — |
| 40 | 2948 | 3515 | 4110 | 2183 | 2807 | 3410 | 1640 | 2144 | 2863 | — | — | — |
| 41 | 3005 | 3572 | 4167 | 2126 | 2742 | 3345 | 1616 | 2211 | 2665 | — | — | — |
| 42 | 2947 | 3525 | 4167 | 2070 | 2721 | 3319 | — | — | — | — | — | — |

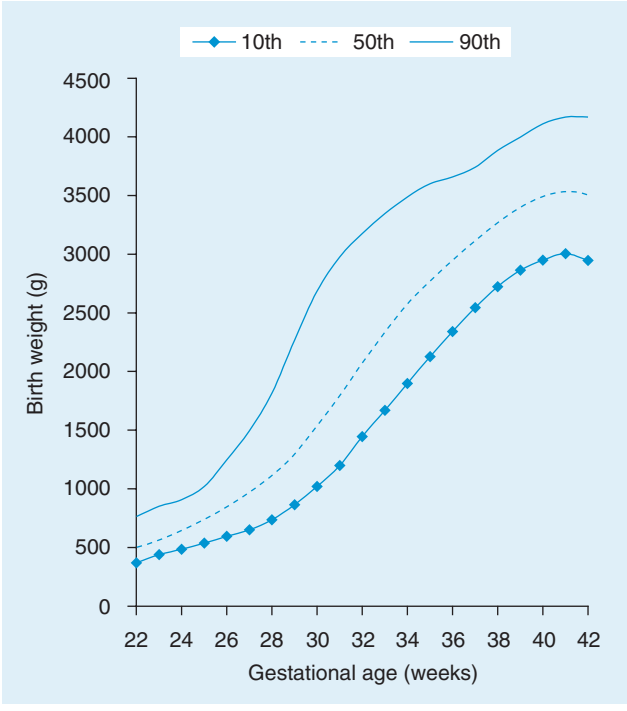



**Figure 1.3** 10th, 50th and 90th Birth-weight centiles for gestational age: 1995–98 US resident singleton live births

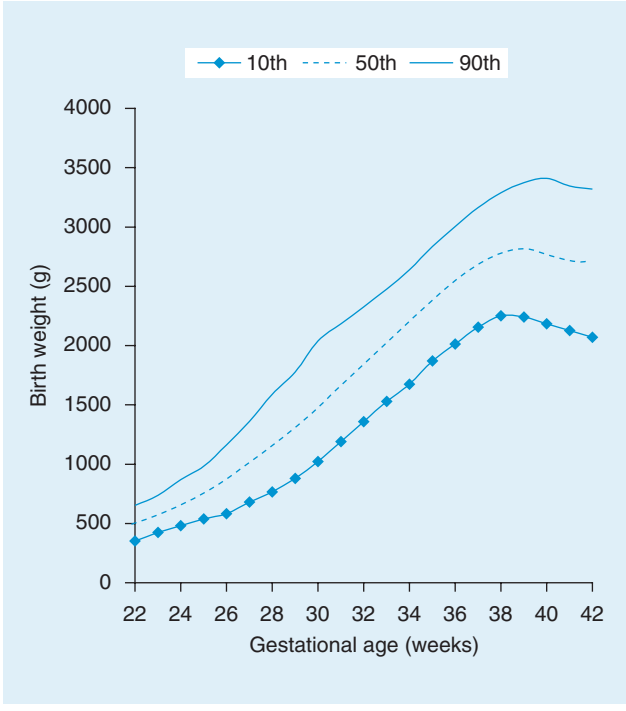



**Figure 1.4** 10th, 50th and 90th Birth-weight centiles for gestational age: 1995–98 US resident twin live births

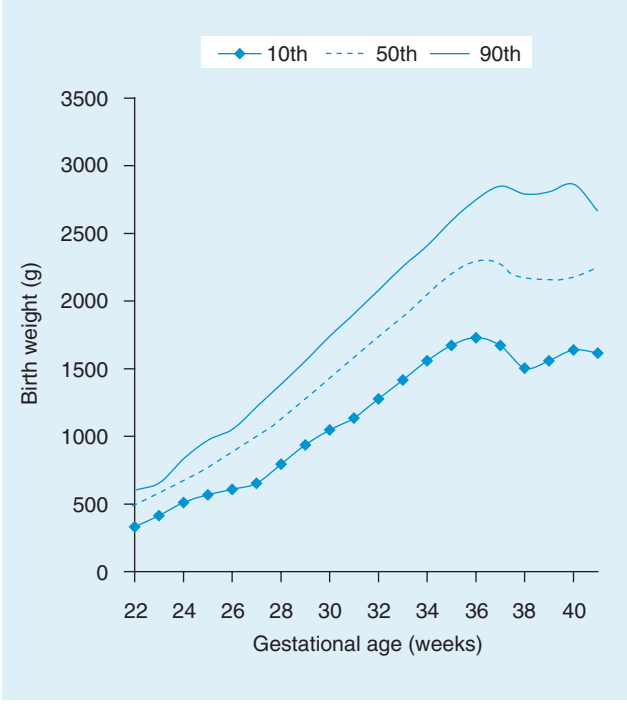



**Figure 1.5** 10th, 50th and 90th Birth-weight centiles for gestational age: 1995–98 US resident triplet live births

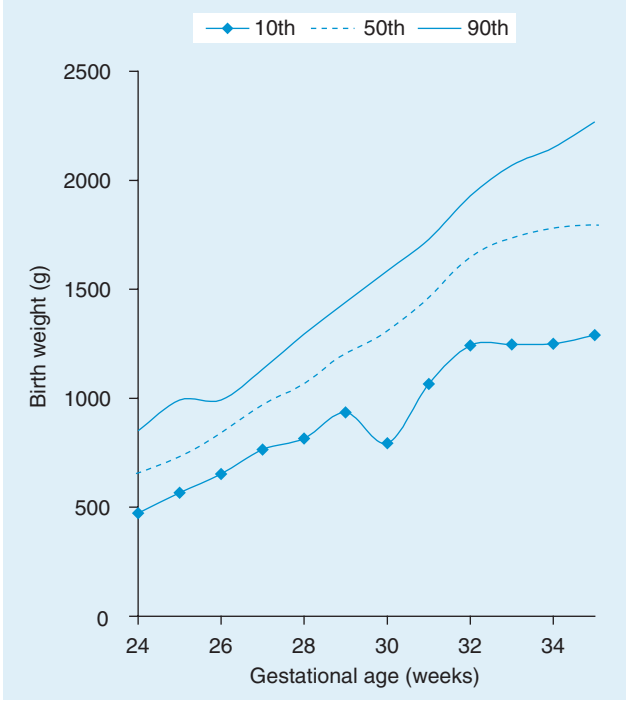



**Figure 1.6** 10th, 50th and 90th Birth-weight centiles for gestational age: 1995–98 US resident quadruplet live births

nearly 300-g difference was present in the median birth weight between singletons and twins and a 500-g difference was observed between singletons and quadruplets. Furthermore, the highest median birth weight value for triplets occurred at 37 weeks, compared with 39 weeks for twins and 41 weeks for

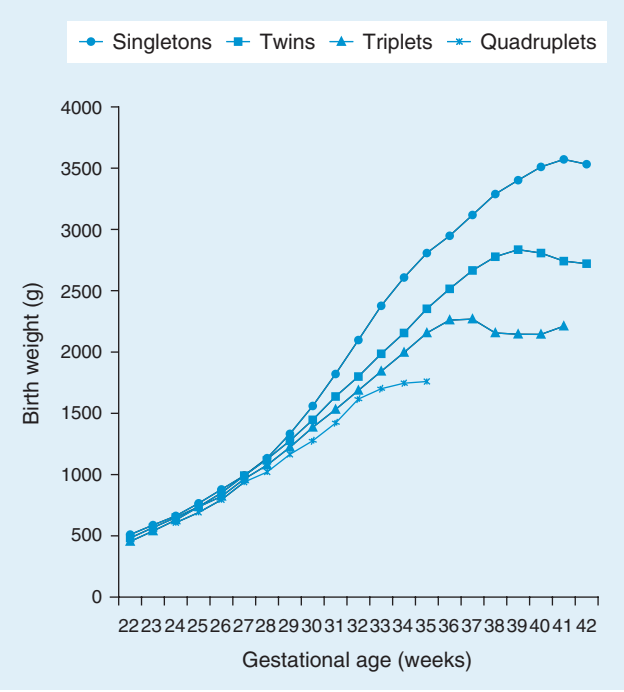



**Figure 1.7** 50th Birth-weight centile for gestational age: 1995–98 US resident singleton, twin, triplet and quadruplet live births

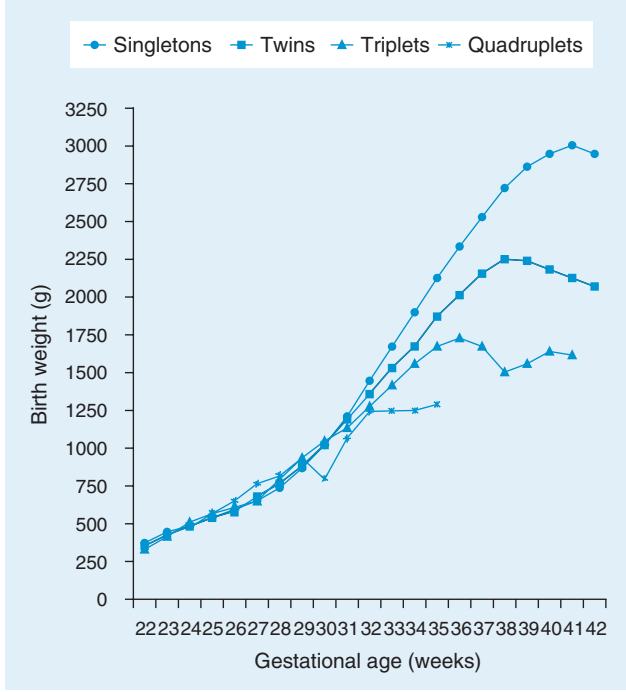



**Figure 1.8** 10th Birth-weight centile for gestational age: 1995–98 US resident singleton, twin, triplet and quadruplet live births

singletons. Similar patterns were apparent in the 10th centiles of birth weight for gestational age (Figure 1.8).

Figure 1.9 displays gestational age-specific hebdomadal mortality rates for each study group. Between 24 and 30 weeks' gestation, quadruplets had the lowest mortality rate, while singletons exhibited the highest risk of death. The risk of mortality reached its nadir at 30 weeks for quadruplets, 36 weeks for triplets, 38 weeks for twins and 40 weeks for singletons. Although demonstrating the highest mortality risk from 28 to 36 weeks, singletons had the lowest mortality risk after 38 weeks' gestation.

## COMMENT

Overall, the occurrence of several traditional maternal risk factors, e.g. race, marital status, low education and smoking, was lower among higher-order multiple births. Nevertheless, key risk factors are in evidence, including previous pregnancy loss, older age, diabetes, hypertension and incompetent cervix. As expected, higher-order multiple births were likely to experience more prenatal care visits than typically offered to low-risk pregnancies. Unexpectedly, however, they had more missing prenatal care utilization information, largely as a result of disproportionately higher amounts of missing data on the

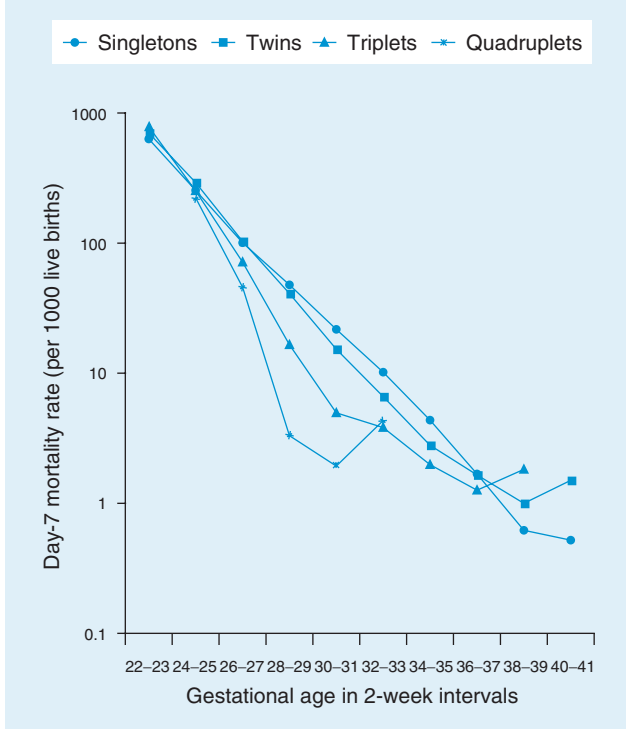



**Figure 1.9** Gestational age-specific day-7 mortality for singletons, twins, triplets and quadruplets: 1995–98 US resident live births

number of prenatal care visits. Such findings suggest progressively increasing difficulties in collecting

complete information on prenatal care visits with higher-order multiple births, possibly related to the more frequent number and types of visits associated with these high-risk pregnancies.

As observed in earlier reviews, pronounced differences were present among the study groups in terms of the frequency of low birth weight and preterm births[16]. Indeed, these outcomes were evident in over 97% of quadruplets. This study provides current fetal growth curves for twin and triplet births and the first fetal growth curve for quadruplet births based on national data. These centiles of birth weight for gestational age are derived from a large, national database including the most recent years available, and provide current, stable estimates of fetal growth for these groups. The intrauterine growth patterns of higher-order multiple births differ markedly from that of singletons, and divergence begins at about 28 weeks of gestation. By 38 weeks of gestation, the singleton 10th centile of birth weight is roughly equivalent to the twin 50th centile, and the singleton 50th centile is similar to the twin 90th centile. At 35 weeks, the singleton 10th centile of birth weight approaches the triplet 50th centile and the quadruplet 90th centile.

Marked disparities exist in the mortality risk between singletons and multiple births. Compared with singletons, the overall risk of infant death is approximately five-fold for twins, ten-fold for triplets and 12-fold for quadruplets. Notwithstanding, between 26 and 32 weeks, quadruplets have the best chances of early survival, followed in order by triplets, twins and then singletons. Such survival patterns suggest that the average optimal gestational age for delivery, in terms of early survival, is progressively earlier for multiple births as the birth number increases.

In light of the ongoing increase in the proportion of multiple births, clinicians are increasingly faced with the daunting question of what constitutes fetal growth impairment among higher-order multiples. This is particularly problematic, as fetal growth patterns for singletons and twins are substantially different from those of triplets and quadruplets. Applying singleton fetal growth standards not only may lead to the erroneous categorization of small for gestational age in higher-order multiples, but also calls into question the clinical validity of such a classification when based on a singleton fetal growth reference curve. Consequently, to determine whether a newborn of higher-order multiple gestation suffers from fetal growth restriction and to institute appropriate management options, the clinician requires population-based information on the normal growth trajectory for the given plurality class. Hence, the information contained in this study provides a heuristic tool for assessing, in the clinical setting, potential adverse fetal growth variation in multiple births.

## ACKNOWLEDGMENT

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# Demographic Trends in Western European Countries

*A. Macfarlane and B. Blondel*

2



## INTRODUCTION

In the countries of Western Europe, as in other developed countries, patterns of multiple pregnancy and births changed dramatically during the last quarter of the 20th century. This chapter outlines trends in twin, triplet and higher-order births, estimates zygosity in a range of countries, and then compares age-specific multiple birth rates in England and Wales and France before using data from France, England and Wales and Scotland to look at changes in the birth weight and gestational age distribution of multiple births and the impact of changes in multiple birth on trends in low birth weight and preterm birth. Before doing so, however, the chapter discusses differences between countries at the turn of the century. The sources of the data used are listed in the Appendix.

## VARIATIONS IN MULTIPLE BIRTH RATES IN WESTERN EUROPE

Multiple birth rates for a recent year in countries in the European Union were compiled for the PERISTAT Perinatal Indicator project. This project formed part of the European Union Health Monitoring Programme. It was set up to define and compile a range of indicators of the outcome of pregnancy in the 15 countries which were members of the European Union at the time it was under way[1–3]. Multiple birth rates were among the indicators specified in the project for comparisons between countries, and are shown in Table 2.1[3]. The data are expressed in terms of maternities, which are defined as pregnancies leading to one, two or more registrable births.

Table 2.1 shows wide variations in multiple birth rates from under 12 per 1000 in Portugal and Luxembourg to around 20 per 1000 in The Netherlands, Denmark and Greece. It also shows that the countries with the highest rates of triplet and higher-order births were not necessarily the same. The highest rate was observed in Spain, followed by Germany, the French-speaking community of Belgium, Ireland and Italy. This reflects the relatively small contribution made by triplet and higher-order births to the overall number of multiple births. In addition, rates for small countries, such as the Republic of Ireland, fluctuate considerably from year to year, as a result of the effect of random variation on the low numbers of triplet and higher-order maternities. Differences in the criteria for registering live and stillbirths and for inclusion of births in surveys also affect the differences observed between countries[1,2,4]. Although these factors should be taken into account in interpreting differences between countries, it is very likely that differences in practices for the medical management of subfertility and in the priority given to preventing triplet and higher-order pregnancies are a major influence.

As trends in multiple birth rates for Finland and the Scandinavian countries are the subject of a separate chapter, they are not considered here except to note that the rates for Finland and Sweden are lower than those for Denmark but all three are well above the European Union median. The high rates in Flanders are also discussed in detail in a separate chapter devoted to the birth register in East Flanders.

**Table 2.1** Multiple birth rates (per 1000 maternities) in the 15 member states of the European Union participating in the PERISTAT project[4]. For information on data sources see PERISTAT report[1–3]

| *EU Member State* | *Coverage, if not national* | *Year* | *Twin maternities* | *Triplet and higher-order maternities* | *All multiple maternities* |
|---|---|---|---|---|---|
| Austria | | 2001 | 14.95 | 0.42 | 15.37 |
| Belgium | Flanders | 2000 | 18.04 | 0.30 | 18.33 |
| Belgium | French community | 2000 | 13.31 | 0.55 | 13.86 |
| Denmark | | 2000 | 19.68 | 0.32 | 20.00 |
| Finland | | 2000 | 15.88 | 0.16 | 16.04 |
| France | | 2000 | 14.98 | 0.28 | 15.26 |
| Germany | nine Bundesländer | 2000 | 15.82 | 0.62 | 16.44 |
| Greece | perinatal survey | 1998 | 20.05 | 0.21 | 20.26 |
| Republic of Ireland | | 1999 | 13.00 | 0.52 | 13.52 |
| Italy | | 1998 | 11.73 | 0.52 | 12.25 |
| Luxembourg | | 2000 | 10.55 | 0.18 | 10.72 |
| The Netherlands | | 1999 | 18.98 | 0.38 | 19.37 |
| Portugal | | 1999 | 11.07 | 0.32 | 11.38 |
| Spain | | 1999 | 15.22 | 0.70 | 15.92 |
| Sweden | | 2000 | 15.99 | 0.20 | 16.19 |
| United Kingdom | | 2000 | 14.24 | 0.44 | 14.69 |

## TRENDS IN TWINNING RATES

Twinning rates for countries for which data were readily available are shown and compared in Figure 2.1. All depict a common pattern with a fall from the mid-1960s to the mid-1970s, followed by a continuing rise. The most striking feature is the rise in twinning rates for The Netherlands. These were among the highest in the 1950s and 1960s. From the mid-1970s onwards, they were increasingly higher than those for the other countries shown. In contrast, Italy, where twinning rates were also relatively high in the 1950s and 1960s, had relatively low rates in the 1980s and 1990s. France, which had experienced relatively low rates in the 1950s and 1960s, had one of the highest rates in the 1990s.

Twinning and other multiple birth rates for Scotland, the six counties of Northern Ireland which are included in the United Kingdom and for the Republic of Ireland are based on small numbers of births each year, and rates therefore fluctuate considerably from year to year. They are therefore shown as 5-year averages in Table 2.2, where they are compared with rates for England and Wales. In the 1970s, twinning rates for the Republic of Ireland, and to a lesser extent those for Northern Ireland, were higher than those for Scotland and England and Wales, but these rates converged by the late 1990s. It is notable that Ireland had the highest fertility rates in Western Europe, but these had fallen considerably by the late 1990s.

## TRENDS IN TRIPLET AND HIGHER-ORDER BIRTHS

Rates of triplet and higher-order births show a different pattern from twinning rates and also vary more between countries. They are therefore shown separately in Figure 2.2. In most countries, rates fluctuated around a relatively constant level up to the mid-1970s. This was followed by a steep rise, followed by a decline. The timing of the rise and decline varied between countries. The peak occurred earlier in The Netherlands and France than in Germany and England and Wales. Data for Italy are not available for years after 1998, and Figure 2.2 and Table 2.1 show that rates increased up to that year. Rates for Switzerland also show wide fluctuations about a rising trend, so it is difficult to see whether the lower rates in 2001 and 2002 are part of a sustained fall. Table 2.2 indicates evidence of a fall after 2000 in rates for Scotland and the Republic of Ireland, but not for Northern Ireland.

## ESTIMATED ZYGOSITY

Weinberg's method was used to estimate numbers of monozygotic and dizygotic sets of twins[5]. This assumes that the numbers of like-sexed dizygotic twins are equal in number to the numbers of sets of unlike-sexed dizygotic twins. The total numbers of dizygotic twins were estimated using this assumption. The estimated numbers of sets of monozygotic twins

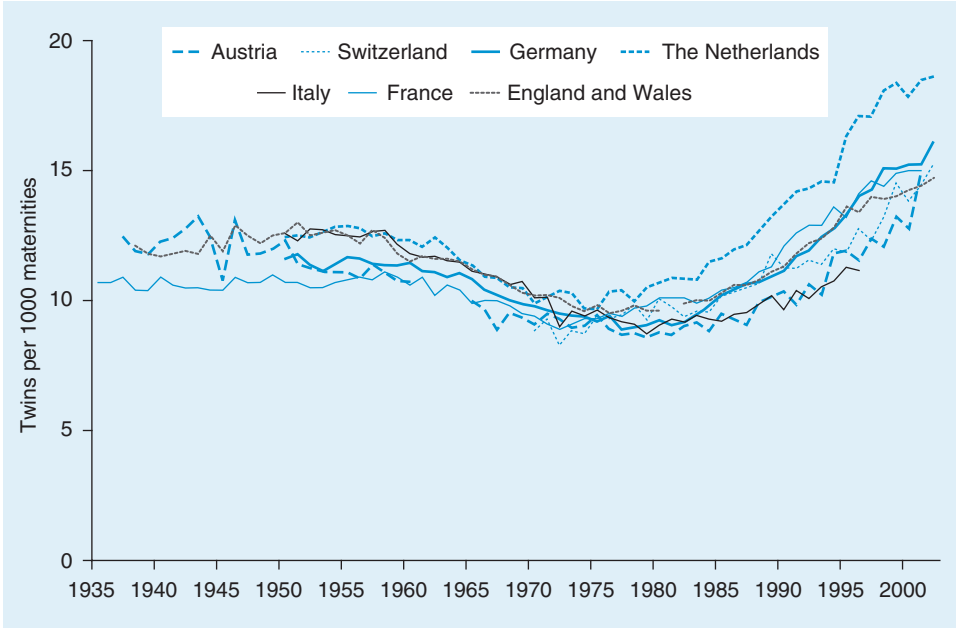


**Figure 2.1** Twinning rates in selected European countries

**Table 2.2** Multiple birth rates, England and Wales, Scotland and Ireland, 1971–75 to 2001–02. Source: Office for National Statistics, General Register Offices for Scotland and Northern Ireland, Central Statistics Office, Republic of Ireland

| | *England and Wales* | *Scotland* | *Northern Ireland* | *Republic of Ireland* |
|---|---|---|---|---|
| *Twins per 1000 maternities* | | | | |
| 1971–75 | 9.9 | 10.0 | 10.7 | 12.3 |
| 1976–80 | 9.6 | 9.4 | 10.1 | 11.2 |
| 1981–85 | 10.1* | 9.9 | 10.6 | 10.7 |
| 1986–90 | 10.9 | 11.0 | 10.7 | 11.5† |
| 1991–95 | 12.6 | 12.3 | 12.2 | 12.4† |
| 1996–2000 | 13.9 | 13.8 | 13.8 | 13.7† |
| 2001–02 | 14.6 | 14.8 | 15.0 | 15.6‡ |
| *Triplet and higher-order births per 1000 maternities* | | | | |
| 1971–75 | 0.11 | 0.08 | 0.08 | 0.12 |
| 1976–80 | 0.13 | 0.09 | 0.14 | 0.13 |
| 1981–85 | 0.14* | 0.10 | 0.12 | 0.11 |
| 1986–90 | 0.25 | 0.19 | 0.14 | 0.15† |
| 1991–95 | 0.37 | 0.31 | 0.31 | 0.25† |
| 1996–2000 | 0.45 | 0.36 | 0.33 | 0.44† |
| 2001–02 | 0.33 | 0.25 | 0.54 | 0.34‡ |

*Excluding 1981; †based on a revised methodology to take better account of multiple births including stillbirths; ‡2001 only

were estimated by subtracting these from the total. Estimated rates of monozygotic and dizygotic twins in England and Wales, Germany, The Netherlands and Scotland are shown in Figure 2.3. In each of these countries, there was a very marked rise in dizygotic twinning rates from the 1980s onwards and a small but consistent rise in monozygotic twinning.

The estimated percentages of sets of twins which were dizygotic in these countries plus Italy and Switzerland are shown in Figure 2.4. These all show marked rises from the early 1980s onwards, with fluctuations about an upward trend. The rise in Italy appears to be less than that for the other countries shown[6].

## AGE-SPECIFIC MULTIPLE BIRTH RATES

Twinning rates in France from 1902 onwards are plotted by age of mother in Figure 2.5, while overall age-specific multiple birth rates for England and

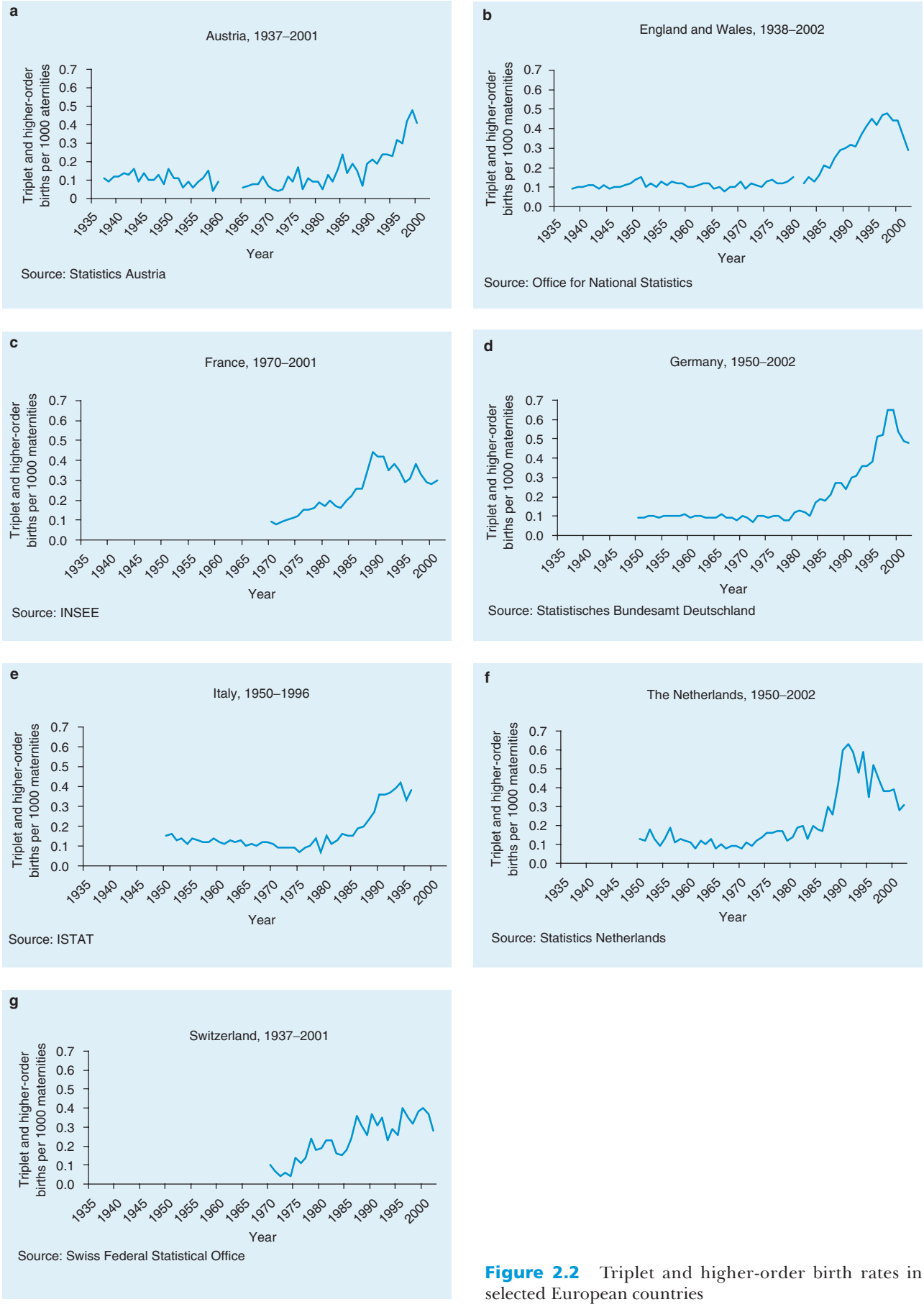


**Figure 2.2** Triplet and higher-order birth rates in selected European countries

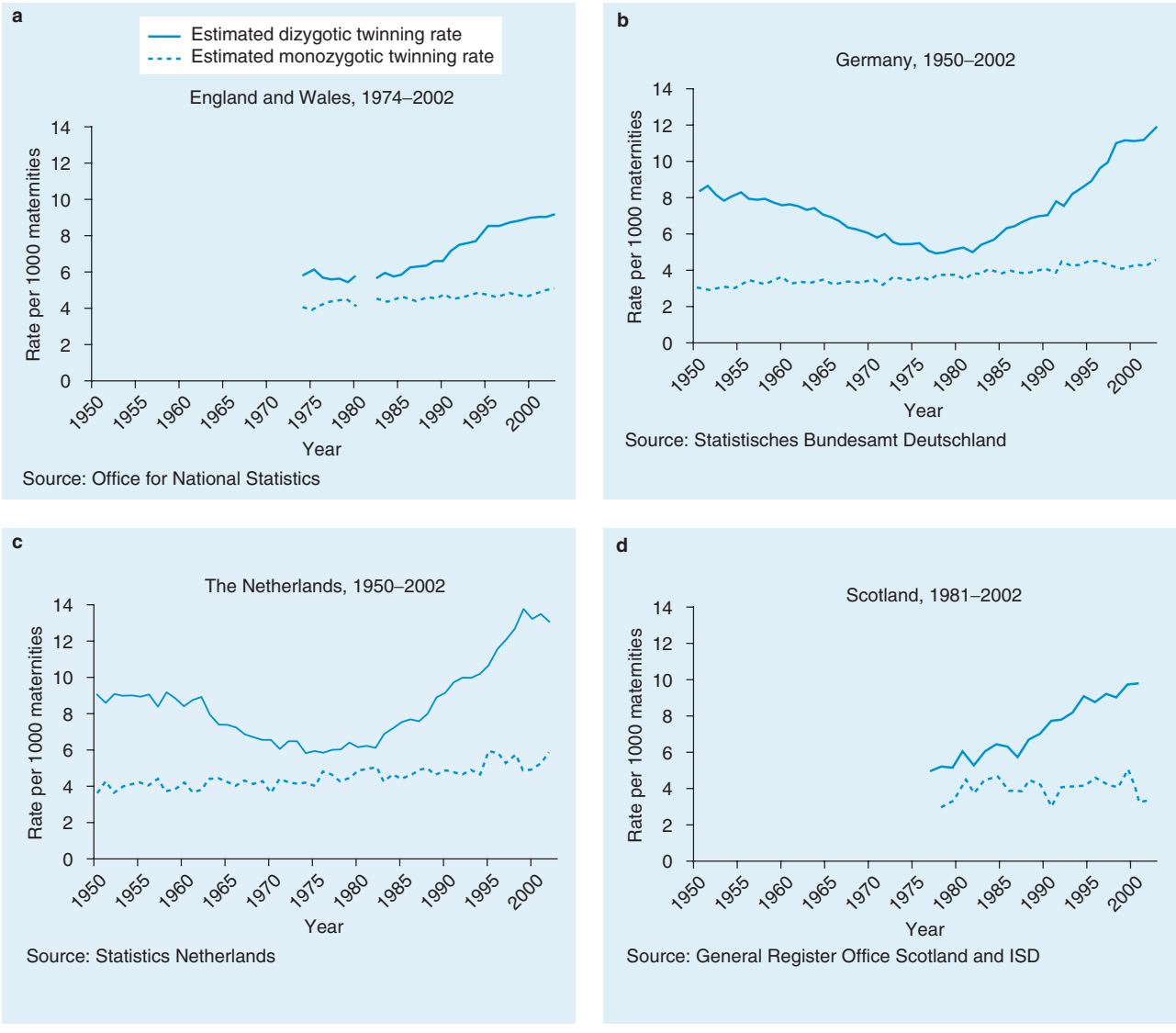


**Figure 2.3** Twinning rates by estimated zygosity

Wales from 1938 onwards are shown in Figure 2.6. As in many other analyses from the mid-19th century[7] onwards, rates were lowest for mothers aged under 20 and highest for those aged 35–39. Similar patterns were seen in an aggregated analysis of data for Scotland over the years 1981–2000[8]. This also analyzed multiple birth rates by parity, and found that, as in earlier analyses, multiple birth rates were lowest among women with no previous live and stillbirths and increased with parity.

In England and Wales and in France, rates for women in their 30s and 40s declined up to the late 1970s, and rates for women aged 25–29 decreased during the 1960s and 1970s. Then there were marked increases in rates from the early 1980s onwards in rates for women in the 25–29 and older age groups. There was also a smaller increase in the 1990s among women aged 20–24 in France.

Rates for women aged 45 and over were omitted from Figures 2.5 and 2.6. The relatively small numbers mean that year to year fluctuations in rates would obscure the trends in all other age groups. Rates for both countries for women aged 45 and over are compared in Figure 2.7, which shows marked differences. Whereas in France twinning rates among this group of older women fluctuated about a common level, multiple birth rates showed a dramatic rise from the early 1990s onwards in England and Wales.

## PRETERM BIRTH AND LOW BIRTH WEIGHT

An international study of preterm birth in France, the United States and Canada showed that the increase in multiple births in the 1980s and 1990s and the increase in preterm birth rates among multiple births made a major contribution to the rising rates

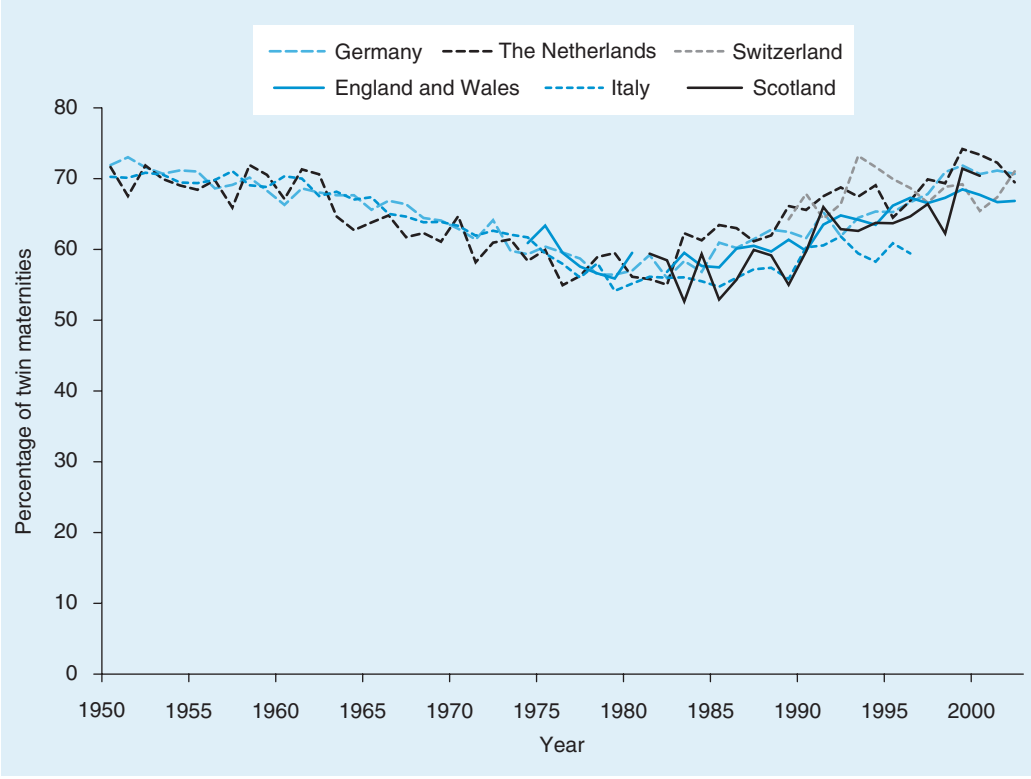


**Figure 2.4** Estimated percentage of twins which were dizygotic, selected European countries

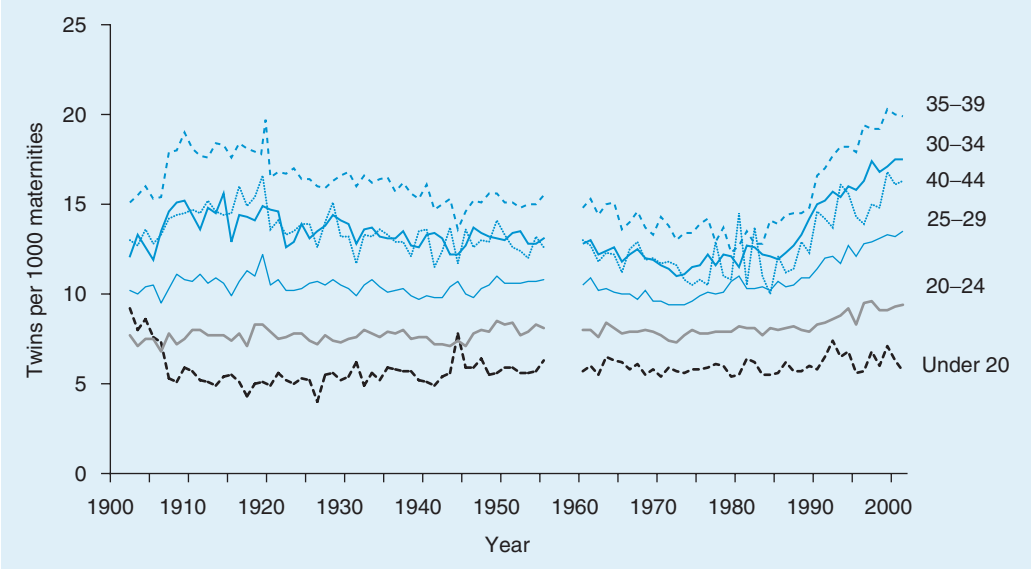


**Figure 2.5** Twinning rates by age of mother, France, 1902–2001. Source: INSEE

of preterm birth in these countries[9]. Rates of low birth weight in these countries and in England and Wales were also analyzed, and, here again, the increase in multiple births contributed significantly to the overall increase (Figure 2.8). Although rates of triplet birth increased markedly, their small numbers meant that their contribution to the overall increase in preterm birth and low-birth-weight rates was

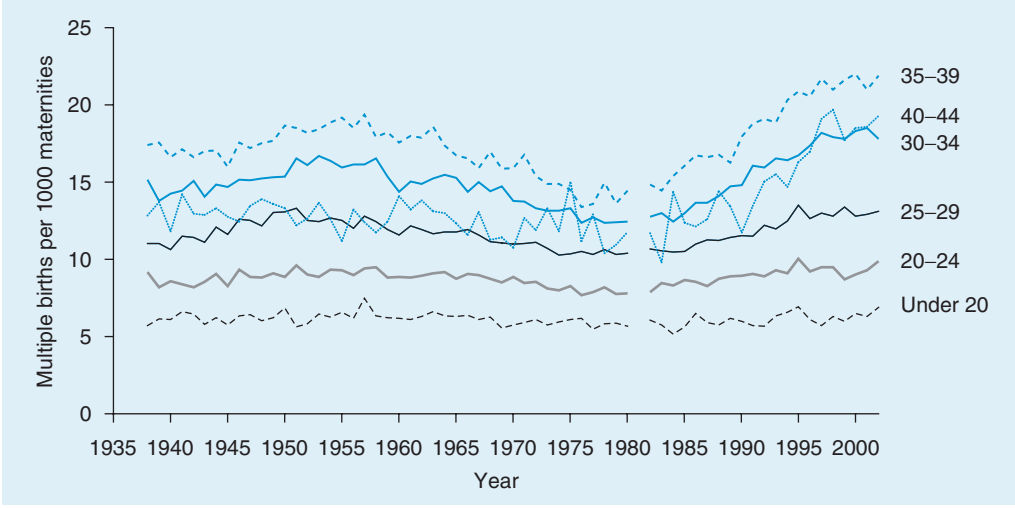


**Figure 2.6** Multiple birth rates by age of mother, England and Wales, 1938–2002. Source: Office for National Statistics

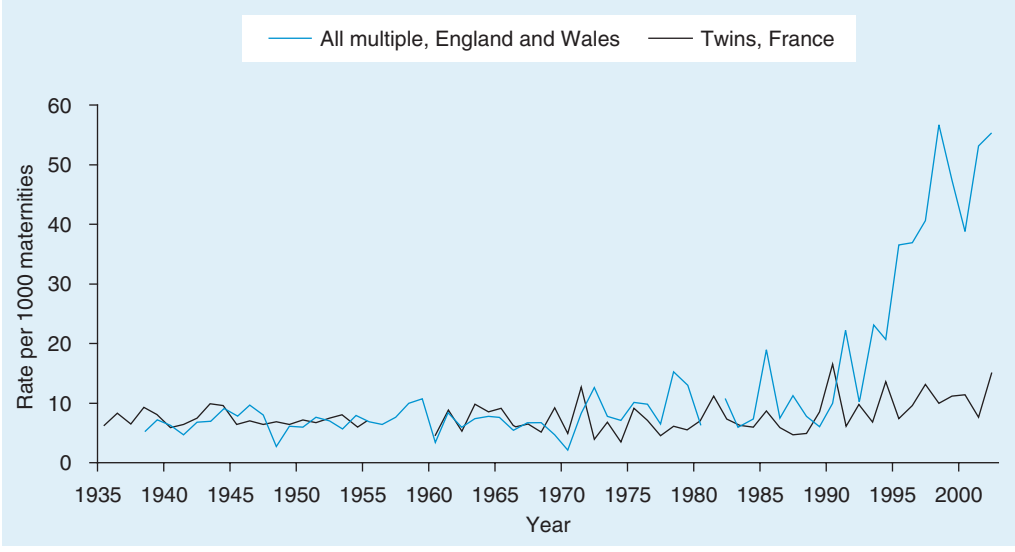


**Figure 2.7** Multiple birth rates among mothers aged 45 and over, England and Wales, 1935–2002 and France, 1938–2001. Source: Office for National Statistics and INSEE

relatively small. It was the rise in twinning which made a substantial population-based impact.

Trends in preterm birth in Scotland are shown in Table 2.3. They cover a short time period and are based on relatively small numbers of births, but they show an increase in all preterm births and in the proportions of both singleton and multiple preterm births. Figure 2.9 shows the substantial contribution of multiple births to the overall rise in preterm birth rates in Scotland.

These trends towards increasing proportions of preterm births have an impact on trends in low birth weight. Data on trends in preterm birth are not available for England and Wales, but data on birth weight are based on much larger numbers.Trends in low birth weight in singleton and multiple births from 1983 to 2001 in England and Wales are shown in Table 2.4. They show that among both singleton and multiple births, the increase was almost exclusively in the percentage of babies with birth weights under 1500 g. Although the percentage of missing birth weights rose to about 4% between 1989 and 1994, as a result of short-term changes in methods of data collection coupled with resource

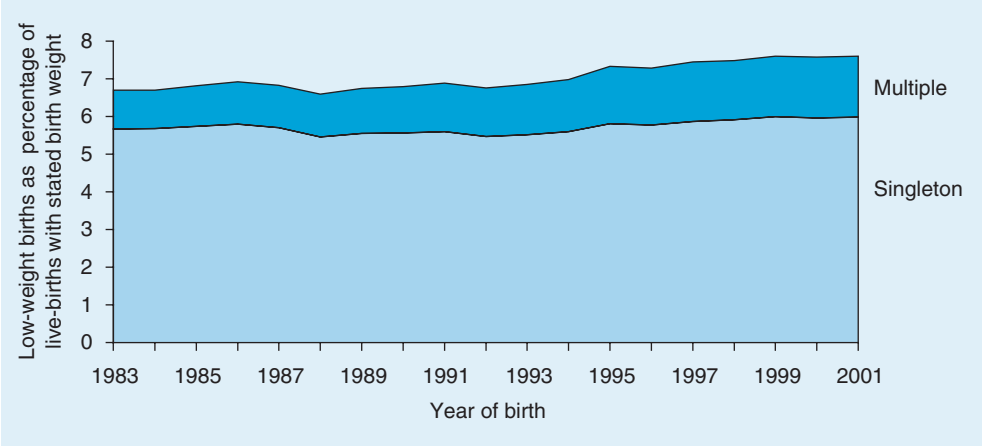


**Figure 2.8** Percentage of live births weighing under 2500 g by multiplicity, England and Wales, 1983–2001. Source: Office for National Statistics data reproduced from *Birth Counts*

**Table 2.3** Gestational age of live births in Scotland, 1990, 1995, 2002, 2003. Source: Information and Statistics Division, Scotland

| | | *Percentage of live births* | | | | | | |
|---|---|---|---|---|---|---|---|---|
| *Year* | *Total (n)* | *Less than 24 weeks* | *24–27 weeks* | *28–31 weeks* | *32–36 weeks* | *37–41 weeks* | *42+ weeks* | *Not known* |
| *All* | | | | | | | | |
| 1990 | 63 351 | 0.0 | 0.3 | 0.7 | 5.3 | 87.5 | 5.5 | 0.6 |
| 1995 | 60 261 | 0.0 | 0.3 | 0.8 | 5.7 | 88.2 | 4.7 | 0.2 |
| 2002 | 50 592 | 0.0 | 0.3 | 0.8 | 6.2 | 89.2 | 3.4 | 0.0 |
| 2003 (p) | 50 157 | 0.1 | 0.3 | 0.9 | 6.2 | 89.5 | 2.9 | 0.0 |
| *Singleton* | | | | | | | | |
| 1990 | 61 937 | 0.0 | 0.2 | 0.5 | 4.6 | 88.3 | 5.6 | 0.7 |
| 1995 | 58 712 | 0.0 | 0.2 | 0.7 | 4.8 | 89.2 | 4.9 | 0.2 |
| 2002 | 49 060 | 0.0 | 0.3 | 0.6 | 5.0 | 90.5 | 3.5 | 0.0 |
| 2003 (p) | 48 650 | 0.0 | 0.3 | 0.7 | 5.1 | 90.8 | 3.0 | 0.0 |
| *Multiple* | | | | | | | | |
| 1990 | 1 414 | 0.4 | 3.6 | 7.8 | 35.7 | 52.3 | 0.1 | 0.1 |
| 1995 | 1 549 | 0.6 | 4.1 | 5.4 | 39.3 | 50.6 | — | — |
| 2002 | 1 532 | 0.3 | 2.0 | 7.9 | 43.7 | 46.1 | — | — |
| 2003 (p) | 1 507 | 0.9 | 2.4 | 6.3 | 42.7 | 47.5 | 0.1 | — |

p, provisional

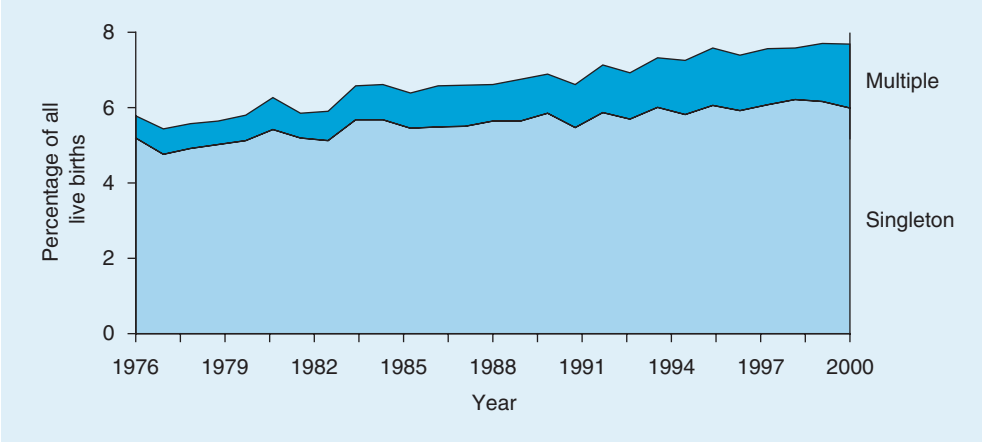


**Figure 2.9** Percentage of live births born before 37 weeks of gestation, by multiplicity, Scotland, 1976–2002. Source: Information and Statistics Division, SMR2

**Table 2.4** Singleton and multiple live births by birth weight, England and Wales, 1983–2001. Source: Office for National Statistics, Mortality Statistics, Series DH3 and *Birth Counts*

| | *Percentage of live births* | | | | | |
|---|---|---|---|---|---|---|
| *Year* | *Under 1500 g* | *1500–1999 g* | *2000–2499 g* | *Under 2500 g* | *All birthweights* (g) | *Percentage not stated* |
| *Singleton* | | | | | | |
| 1983 | 0.7 | 1.0 | 4.1 | 5.8 | 616 520 | 0.1 |
| 1984 | 0.7 | 1.0 | 4.0 | 5.8 | 624 148 | 0.1 |
| 1985 | 0.7 | 1.0 | 4.1 | 5.9 | 642 934 | 0.1 |
| 1986 | 0.7 | 1.1 | 4.1 | 5.9 | 646 924 | 0.1 |
| 1987 | 0.8 | 1.1 | 4.0 | 5.8 | 666 977 | 0.1 |
| 1988 | 0.8 | 1.0 | 3.8 | 5.6 | 678 386 | 0.1 |
| 1989 | 0.8 | 1.0 | 3.9 | 5.7 | 672 202 | 3.2 |
| 1990 | 0.8 | 1.0 | 3.9 | 5.7 | 689 866 | 4.1 |
| 1991 | 0.8 | 1.0 | 3.9 | 5.7 | 682 467 | 3.8 |
| 1992 | 0.8 | 1.0 | 3.8 | 5.6 | 672 598 | 3.9 |
| 1993 | 0.8 | 1.0 | 3.8 | 5.7 | 654 224 | 3.3 |
| 1994 | 0.9 | 1.1 | 3.8 | 5.8 | 646 888 | 2.6 |
| 1995 | 0.9 | 1.1 | 3.9 | 6.0 | 629 948 | 0.3 |
| 1996 | 0.9 | 1.1 | 3.9 | 5.9 | 631 760 | 0.2 |
| 1997 | 1.0 | 1.1 | 3.9 | 6.0 | 624 654 | 0.2 |
| 1998 | 1.0 | 1.1 | 4.0 | 6.1 | 617 754 | 0.1 |
| 1999 | 1.0 | 1.2 | 4.0 | 6.2 | 604 088 | 0.3 |
| 2000 | 1.0 | 1.1 | 4.0 | 6.1 | 586 868 | 0.2 |
| 2001 | 1.0 | 1.1 | 4.1 | 6.2 | 577 281 | 0.1 |
| *Multiple* | | | | | | |
| 1983 | 8.1 | 13.2 | 30.1 | 51.4 | 12 614 | 0.4 |
| 1984 | 8.0 | 13.6 | 29.7 | 51.3 | 12 670 | 0.3 |
| 1985 | 8.1 | 14.1 | 30.1 | 52.3 | 13 483 | 0.2 |
| 1986 | 8.9 | 14.2 | 29.9 | 53.0 | 14 094 | 0.2 |
| 1987 | 9.0 | 14.0 | 30.2 | 53.1 | 14 534 | 0.2 |
| 1988 | 9.0 | 13.9 | 29.1 | 52.0 | 15 191 | 0.3 |
| 1989 | 8.7 | 14.0 | 30.1 | 52.9 | 15 523 | 3.3 |
| 1990 | 8.9 | 14.3 | 29.7 | 52.8 | 16 274 | 3.7 |
| 1991 | 8.8 | 14.5 | 30.4 | 53.8 | 16 750 | 4.1 |
| 1992 | 8.4 | 13.2 | 30.7 | 52.3 | 17 058 | 4.3 |
| 1993 | 9.4 | 14.8 | 28.6 | 52.9 | 17 000 | 4.4 |
| 1994 | 9.7 | 14.2 | 29.2 | 53.1 | 17 368 | 3.3 |
| 1995 | 10.3 | 14.8 | 29.3 | 54.3 | 18 053 | 0.3 |
| 1996 | 11.0 | 14.5 | 29.6 | 55.1 | 17 729 | 0.3 |
| 1997 | 9.9 | 15.4 | 30.0 | 55.3 | 18 441 | 0.3 |
| 1998 | 10.3 | 14.9 | 29.9 | 55.0 | 18 147 | 0.1 |
| 1999 | 11.4 | 15.4 | 29.4 | 56.1 | 17 784 | 0.3 |
| 2000 | 10.5 | 14.9 | 30.2 | 55.7 | 17 573 | 0.1 |
| 2001 | 10.4 | 15.0 | 29.9 | 55.3 | 17 353 | 0.2 |

constraints[10], longer-term trends are based on years when few birth weights were missing. This means that the analysis of missing birth weights in the years 1993–95[11] may not be generalizable more widely. The contribution of multiple births to overall trends in low birth weight in England and Wales is illustrated in Figure 2.8, in which the overall rate of low birth weight is subdivided into singleton and multiple births. It confirms that the rise in multiple births has made an important contribution to the overall rise.

## COMMENT

Apart from Switzerland, where the multiple birth rates shown were based on live births only, other

rates were based on maternities with live and stillbirths. There were some changes in registration procedures over time. In Germany, for example, the criterion for registering a stillbirth was a birth weight of at least 1000 g from July 1 1979 to March 3 1994 and a minimum of 500 g from April 1 1994 onwards. In the countries of the United Kingdom, fetal deaths at 28 or more weeks of gestation were registrable as stillbirths before October 1 1992, when the limit was changed to 24 weeks. For those countries where registration of stillbirths is based on a gestational age criterion, the inclusion of macerated stillbirths and the difficulty in assessing their gender can affect estimations of zygosity[12].

The impact of these changes is likely to be small compared with those arising from the increasing age at childbirth and the use of ovarian stimulation from the late 1970s onwards and of assisted conception from the mid-1980s onwards. Although data are collected about assisted conception in most countries and are contributed to reports published by the European Society of Human Reproduction and Embryology[13], not all are collected on a national basis. In addition, the vast majority are unlinked to systems used to collect data about all births, and the data are not collected on a comparable basis[14]. Data about ovarian stimulation alone are particularly in short supply, as are data about selective termination and its possible contribution to the fall in rates of triplet and higher-order birth. This makes it difficult to monitor the impact of guidelines and codes of practice issued by professional and regulatory bodies. As a result, although it is possible to see that ovarian stimulation and assisted conception have undoubtedly made a major contribution to the rise in twinning rates as well as the increase and decrease in triplet and higher-order births, better data are needed to make it possible to quantify their impact[14].

Given the major impact of medical management of subfertility, it is all too easy to forget that other factors may also play a role. For example, it is possible that the increasing use of folates may have made a minor contribution to the rise[15]. It also has been suggested that the use of oral contraceptives may have contributed to the rise in monozygotic twinning[16]. In addition, an analysis of data for Italy found a rise in multiple births among younger women and suggested that there may have been a rise in natural fertility among younger women in Italy[17], although similar rises were not seen in France or England and Wales.

The continuing rise in multiple birth rates in Western European countries has been described as an epidemic. The rise in twinning has led to a major increase in the percentage of preterm birth and very-low-birth-weight babies, and the problems for mothers and babies associated with these[18,19].

## ACKNOWLEDGMENTS

The authors would like to thank Reinhold Zahn, Marcel Heiniger, Pat Casey and Laura Zonti for providing data from Germany, Switzerland, the Republic of Ireland and Italy, respectively.

## APPENDIX

### Data sources

| | |
|---|---|
| *Austria* | Statistics Austria |
| *France* | Institut National de la Statistique et des Etudes Economiques (INSEE) |
| *Germany* | Statistisches Bundesamt Deutschland |
| *Italy* | Istituto Nazionale di Statistica (ISTAT) data used in published analyses[17] |
| *The Netherlands* | Statistics Netherland, *Statistical Yearbook of The Netherlands 2004* |
| *Republic of Ireland* | Central Statistics Office |
| *Switzerland* | Swiss Federal Statistical Office, Statistik de Natürlichen Bevolkenungsbewegung (BEVNAT) |
| *United Kingdom* | |
| *England and Wales* | Office for National Statistics, *Birth Statistics*, Series FM1 and *Mortality Statistics*, childhood, infant and perinatal, Series DH3 |
| *Scotland* | General Register Office Scotland and Information and Statistics Division, Scotland |
| *Northern Ireland* | Northern Ireland Statistics and Research Agency |

Some data for the United Kingdom are based on tables published in *Birth counts: statistics of pregnancy and childbirth*[10,19].

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# Demographic Trends in Nordic Countries


*J. Kaprio and R. Marttila*

The demographics of multiple births are well studied in the Nordic countries. Indeed, marriages, births, deaths and migrations out of and into local parishes have been recorded for centuries, in Finland for example since 1686, but wider coverage exists since 1730–40. Further information on historical as well as current record-keeping is available at www.genealogia.fi, also in English. Eriksson and collaborators extensively documented multiple birth rates from historical times up to the 1990s for Finland and Sweden[1–5]. Twinning rates in Finland were quite high until the late 1950s, and corresponded to general European levels in the 1960s and 1970s. In Sweden, the twinning rate declined quite dramatically from the 1920s onwards from about 12/1000 maternities to around 8/1000 maternities in the 1960s. This decline occurred even after taking into account changes in maternal age distribution. Corresponding data on Denmark and Norway have also been published. A falling trend in the twinning rate was reversed in Denmark around 1970 and, from 1970 to 1984, an increasing trend was observed[6].

This chapter describes recent trends in twinning rates in Denmark, Finland, Norway and Sweden, with more detailed information from Sweden and Finland, based on official statistics and medical birth registry information. Table 3.1 describes the basic characteristics of these four neighboring countries in Northern Europe.

Twinning rates increased steeply in all Nordic countries (Figure 3.1). Rates averaged 10/1000 in 1980, increasing slightly during the next decade to be clearly above 10/1000 by 1990, after which the increase was uniformly steeper until 1998. Since that the time trends in each country have diverged. As data are available until only 2000 in Norway and 2001 in Sweden and Denmark, strong conclusions about the most recent developments cannot be made. Nonetheless, the increase in twinning rates appears to have continued most in Denmark, with some evidence for a levelling off in Sweden in the past 4 years. In contrast, a clear decline was observed after 1998 in Finland.

In 1999, based on early trends in the 1990s, it was predicted that, to the year 2015, 'twinning rates

**Table 3.1** Basic characteristics of multiple births in Denmark, Finland, Norway and Sweden according to the latest published data

| | *Denmark* | *Finland* | *Norway* | *Sweden* |
|---|---|---|---|---|
| Year | 2001 | 2002 | 2000 | 2001 |
| Maternities (*n*) | 64 283 | 54 698 | 58 756 | 89 128 |
| Twin births (*n*) | 1421 | 826 | 1036 | 1420 |
| Higher-order births (*n*) | 22 | 11 | 17 | 22 |
| Crude twinning rate/1000 | 22.1 | 15.1 | 17.6 | 15.9 |

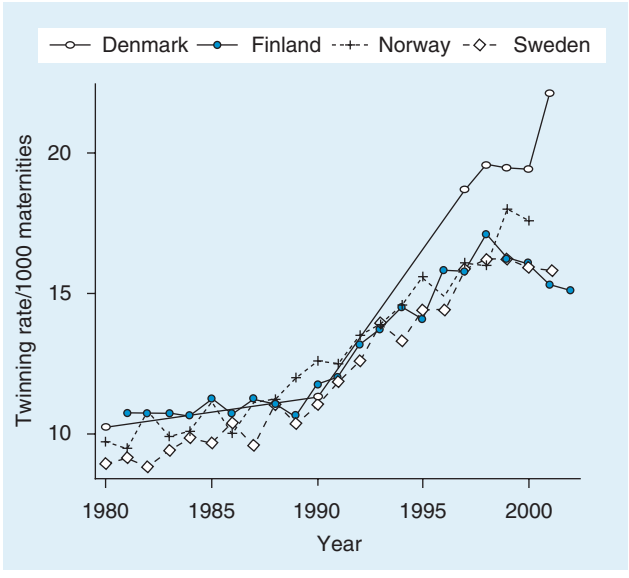



**Figure 3.1** Crude twinning rates (twin maternities/1000 maternities) in Denmark, Finland, Norway and Sweden during the past 2–3 decades

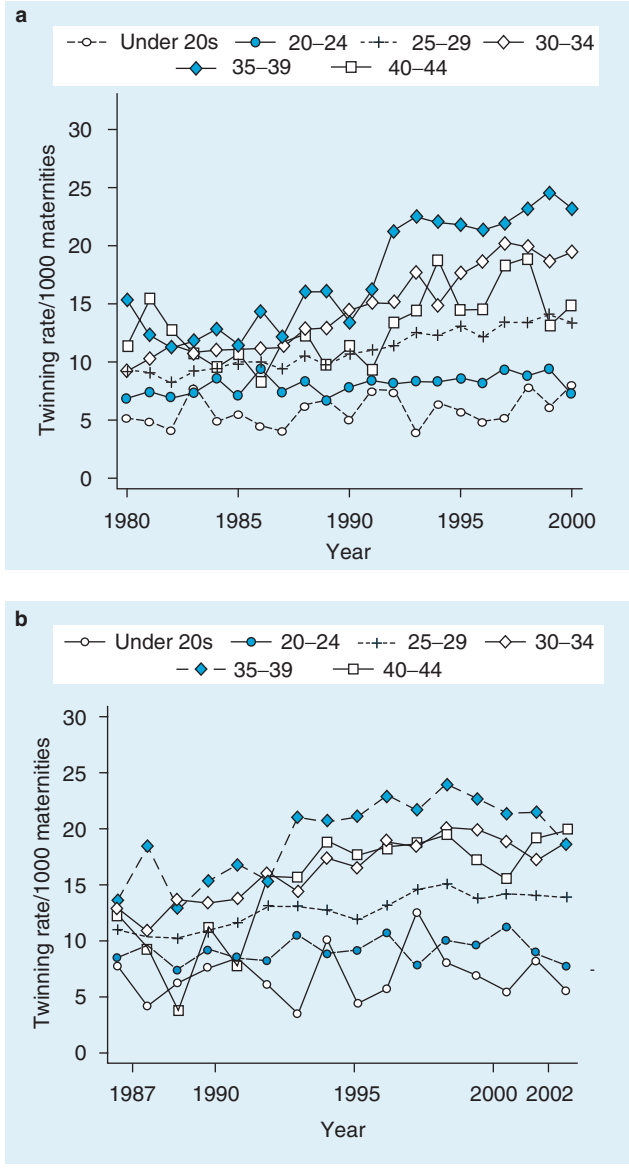



**Figure 3.2** Twinning rates by maternal age in (a) Sweden and (b) Finland

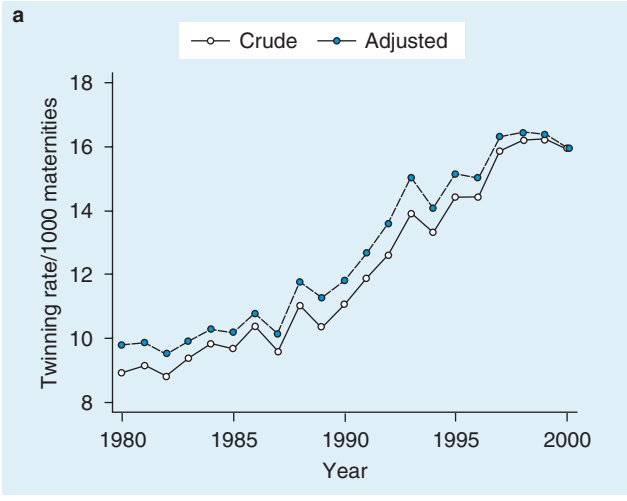
[would] reach figures that could best be described as derived from a Jules Verne novel: in this model Sweden would have four times more twin than singleton births'[7]. It is highly unlikely that such remarkable projections will become a reality.

Figure 3.2 shows that, in Finland and Sweden, maternal age-specific twinning rates appear to have increased along with the overall increase in twinning rate, but perhaps least so in the youngest age groups. In contrast, the highest rates are among 35–39-year-olds, followed by the 30–34- and 40–44-year-olds. Twins born to mothers aged 45 years and over are not shown in the figures because of small numbers and large variability in yearly rates.

The overall patterns of an increase and then levelling off in Sweden, and decline in Finland, are independent of maternal age distribution (Figure 3.3). Adjusted twinning rates were computed in order to summarize the twinning rate trends irrespective of changes in maternal age distribution. In both Finland and Sweden, adjusted rates are based on maternal age distribution in Sweden in 2000 and computed by direct standardization. This adjustment affects the twinning rate very little, albeit perhaps slightly more in Sweden than in Finland.

Because the variability in twinning rates is commonly ascribed to be due to the variability in dizygotic (DZ) twinning rates (see Chapter 24), the proportions of monozygotic (MZ) and DZ pairs were also computed during this time period. In Sweden, the proportion of pairs estimated to be MZ, based on the sex-ratios of twin births, has changed in the past 20 years. In 1980, 46.2% of twin pairs were estimated to be MZ, and 45.2% in 1985, but this number declined to 36.2% in 1990, and 36.3% in 1995, and reached 28.3% in 2000. A corresponding change was observed from 1987 to 2002 in Finland (Figure 3.4), with the proportion declining from over 40% to under 30%, with some variation from year to year. The changes in zygosity distribution are consistent with the changes in twinning rates, being primarily due to changes in DZ twinning.

We examined rates of triplet births, to find out possible reasons for the decline in twinning in Finland (Figure 3.5). Although based on relatively small numbers annually (10–20 triplet maternities),



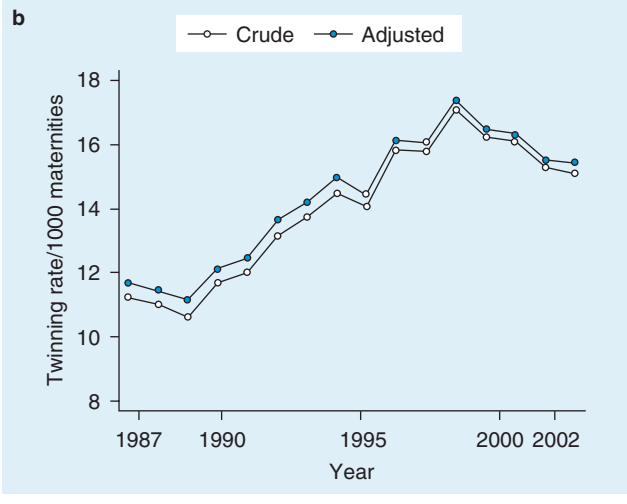




**Figure 3.3** Twinning rates in (a) Sweden and (b) Finland adjusted for maternal age. Direct age-standardization using the distribution of maternal age in Sweden in 2000

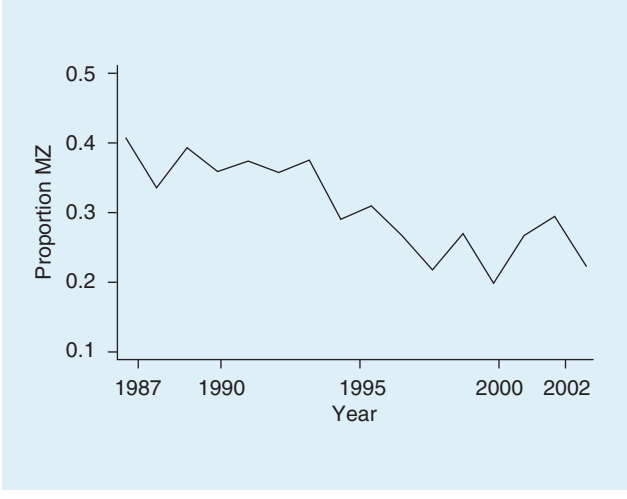



**Figure 3.4** Proportion of monozygotic (MZ) pairs estimated from sex-ratios of twin births in Finland in 1987–2002

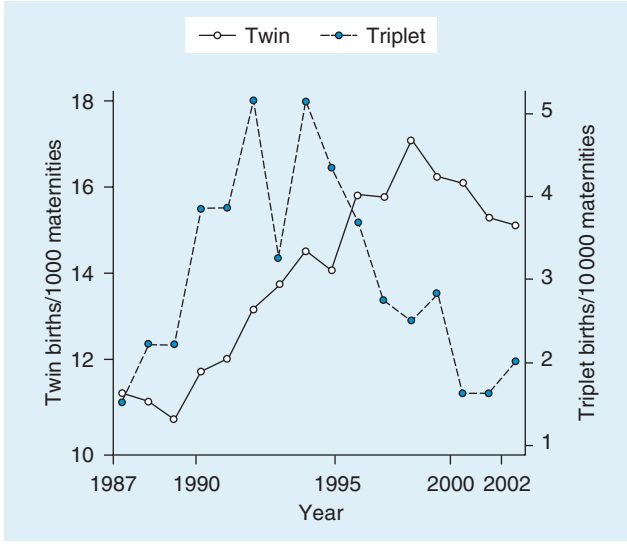



**Figure 3.5** Twin and triplet rates in Finland/1000 maternities and /10 000 maternities, respectively, from 1987 to 2002

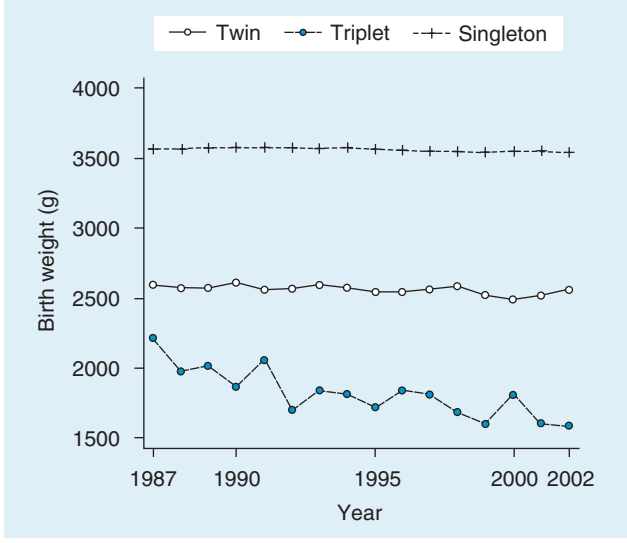



**Figure 3.6** Trends in birth weights among singletons, twins and triplets in Finland from 1987 to 2002

the decline in triplet rates began earlier than the decline of twinning in Finland. A peak in rates of triplets, 5/10 000 maternities, was reached in the early 1990s in Finland, but thereafter declined to under 2/10 000 maternities, a rate also present in the early 1980s. In Sweden, the triplet rate likewise peaked in 1992–93 (at 5/10 000), declining since then to slightly over 2/10 000 at the end of the decade. Even this is about double the rate that was present in Sweden between 1973 and 1985. Interestingly, mean triplet birth weights decreased,

compared with virtually no change in singleton and twin mean birth weights over the same time period (1987–2002). The number of *in vitro* fertilization treatments in Finland increased from 2331 to 7213 from 1992 to 1999[8], with most treatments for women aged 30–39 years. The number of transferred embryos decreased in these years, but two-embryo transfer was most frequent[8]. A Finnish randomized trial on the outcome of single- versus two-embryo transfer demonstrated that dizygotic twinning could be avoided, but treatment outcome was otherwise comparable[9]. Thus, a policy of elective single-embryo transfer has come into use[10] gradually since 1997, and Finnish consensus policy from 2000 onwards is that two-embryo transfer should be used for specific reasons only. These policy and treatment changes probably account for most of the decline in the twinning rate observed in Finland since the late 1990s.

## ACKNOWLEDGMENTS

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# Multiple Births in Australia

*M. P. Umstad and P. A. L. Lancaster*

4



## INTRODUCTION

Australia is a multicultural nation of 20 million people. Information about births and perinatal deaths is derived from registrations of births and perinatal deaths in the six states and two territories and from state and territory perinatal data collections. National data on birth registrations are compiled by the Australian Bureau of Statistics and, since 1991, on perinatal data by the Australian Institute of Health and Welfare, National Perinatal Statistics Unit (NPSU)[1–4]. Data on pregnancies after assisted conception are derived from the NPSU's national register for Australia and New Zealand[5].

## DEFINITIONS

In Australia, a stillbirth is classified as a fetal death prior to the complete expulsion or extraction from its mother of a product of conception of ≥ 20 weeks' gestation or ≥ 400 g birth weight; the death is indicated by the fact that after such separation the fetus does not breathe or show any other evidence of life, such as beating of the heart, pulsation of the umbilical cord or definite movement of voluntary muscles. A neonatal death is the death of a live-born infant within 28 days of birth. A perinatal death is a stillbirth or neonatal death.

## TRENDS IN MULTIPLE PREGNANCIES

In recent decades, the total number of confinements in Australia has remained constant at about 250 000 per year. The rate of twin pregnancies rose from 10.1 per 1000 confinements in 1983 to 15.7 per 1000 in 2000 (Figure 4.1)[1,2]. The higher rates of multiple births in 1991 and subsequent years are partly due to inclusion in the perinatal data collection of multiple pregnancies resulting in one or more fetal deaths. These are not recorded in the live-birth registrations.

The increase in triplet pregnancies during this period was substantially greater than that for twins (Figure 4.2)[1,2]. The number of quadruplet pregnancies was highest in the late 1980s then fell during the early 1990s as infertility specialists became more judicious in the application of assisted reproductive technologies (Figure 4.3)[5]. The complete data set for all multiple births in Australia from 1983 to 2000 is listed in Table 4.1.

## FACTORS INFLUENCING MULTIPLE PREGNANCY RATES

Australian data show the same influence of traditional factors on multiple pregnancy rates as in other countries. These include maternal age, parity, maternal country of birth, family history and the use of assisted reproductive technologies.

### Maternal age

The peak incidence of twins usually occurs for mothers in the 35–39-year age group (Figure 4.4). The 30–34-year and the age 40+ groups have the next highest rates, with lower rates in each successive younger age group for mothers in their 20s and teenage years. The complete data set for all twins by maternal age from 1971 to 2000 is given in Table 4.2[1,2].

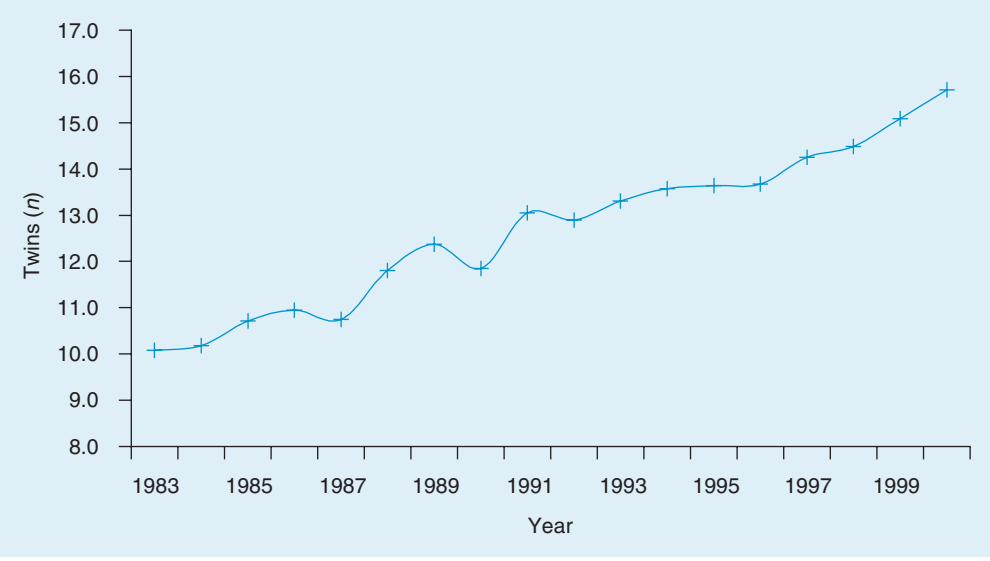


**Figure 4.1** Twins per 1000 confinements, Australia, 1983–2000

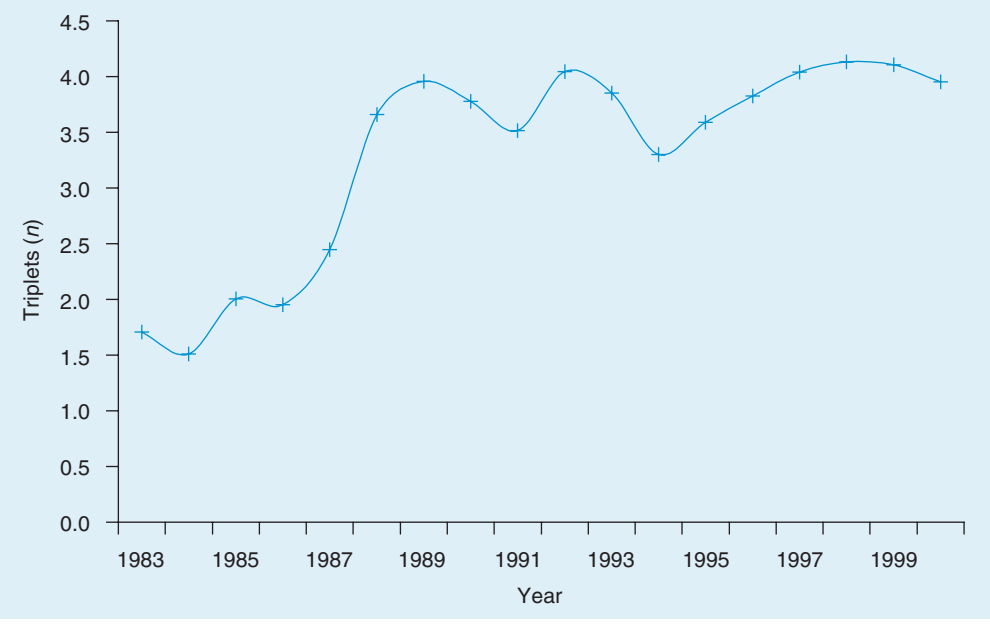


**Figure 4.2** Triplets per 10 000 confinements, Australia, 1983–2000

## Maternal country of birth

Australia is a multicultural society with almost one-quarter of mothers born overseas[2]. Data are collected for maternal country of birth and show that the highest rate of twin confinements is seen among women born in Europe. Based on aggregated data for 1991–96, mothers born in Italy had a twin confinement rate of 16.3 per 1000 confinements, mothers from the United Kingdom and Ireland 15.4 per 1000 and from Greece 13.7 per 1000. Lebanese women had a rate of 13.1 per 1000. The twinning rate was lowest for Asian women. Mothers born in China had 7.7 twins per 1000 confinements and women of Vietnamese origin the lowest at 7.4 twins per 1000 confinements. The twinning rate for women born in Australia was 13.4 per 1000 confinements. These variations by maternal country of birth are influenced

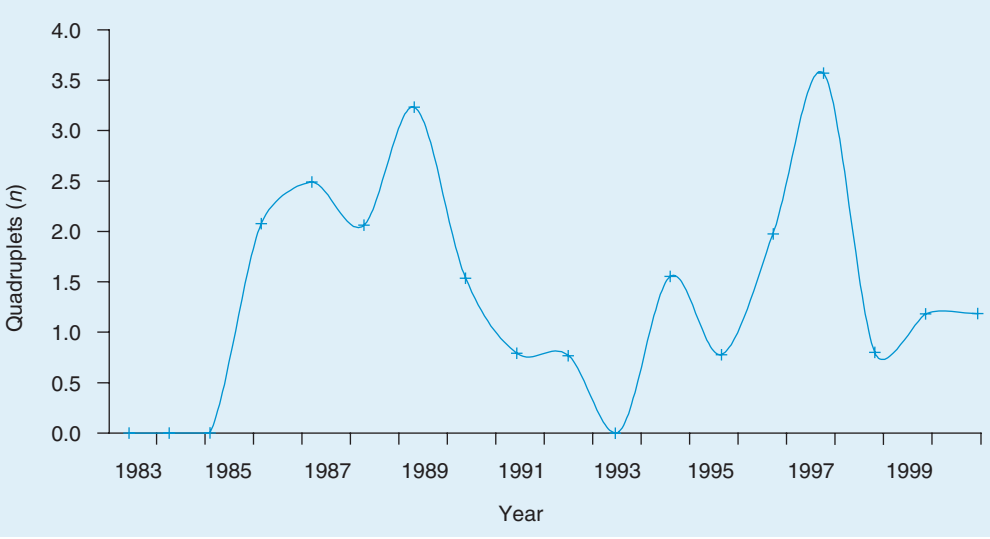


**Figure 4.3** Quadruplets per 100 000 confinements, Australia, 1983–2000

**Table 4.1** Multiple pregnancies in Australia: 1983–2000

| Year | Twin (n) | Twins per 1000 confinements (n) | Triplet (n) | Triplets per 10 000 confinements (n) | Quadruplet (n) | Quadruplets per 100 000 confinements (n) | All confinements (n) |
|---|---|---|---|---|---|---|---|
| 1983 | 2420 | 10.1 | 41 | 1.7 | 0 | 0.0 | 240 114 |
| 1984 | 2359 | 10.2 | 35 | 1.5 | 0 | 0.0 | 231 643 |
| 1985 | 2622 | 10.7 | 49 | 2.0 | 0 | 0.0 | 244 672 |
| 1986 | 2636 | 11.0 | 47 | 2.0 | 5 | 2.1 | 240 699 |
| 1987 | 2594 | 10.8 | 59 | 2.4 | 6 | 2.5 | 241 271 |
| 1988 | 2871 | 11.8 | 89 | 3.7 | 5 | 2.1 | 243 193 |
| 1989 | 3064 | 12.4 | 98 | 4.0 | 8 | 3.2 | 247 623 |
| 1990 | 3074 | 11.8 | 98 | 3.8 | 4 | 1.5 | 259 435 |
| 1991 | 3305 | 13.1 | 89 | 3.5 | 2 | 0.8 | 253 141 |
| 1992 | 3346 | 12.9 | 105 | 4.0 | 2 | 0.8 | 259 456 |
| 1993 | 3420 | 13.3 | 99 | 3.9 | 0 | 0.0 | 256 956 |
| 1994 | 3496 | 13.6 | 85 | 3.3 | 4 | 1.6 | 257 657 |
| 1995 | 3497 | 13.6 | 92 | 3.6 | 2 | 0.8 | 256 378 |
| 1996 | 3466 | 13.7 | 97 | 3.8 | 5 | 2.0 | 253 413 |
| 1997 | 3598 | 14.3 | 102 | 4.0 | 9 | 3.6 | 252 370 |
| 1998 | 3645 | 14.5 | 104 | 4.1 | 2 | 0.8 | 251 650 |
| 1999 | 3821 | 15.1 | 104 | 4.1 | 3 | 1.2 | 253 352 |
| 2000 | 3974 | 15.7 | 100 | 4.0 | 3 | 1.2 | 253 053 |

by differences in maternal age distribution, by the well-known geographical variations in twinning and possibly by differences in the use of assisted conception and other clinical infertility services.

### Indigenous mothers

The number of indigenous women giving birth each year in Australia has increased to more than 8600 in 2000[2]. Among almost 23 000 indigenous mothers in 1994–96, the twinning rate was 9.5 per 1000 confinements. While the usual trend of increasing twin confinements was apparent with advancing maternal age, more than 80% of all confinements in indigenous women occurred in those aged less than 30 years[6]. It also is likely that relatively fewer indigenous women are treated by assisted conception.

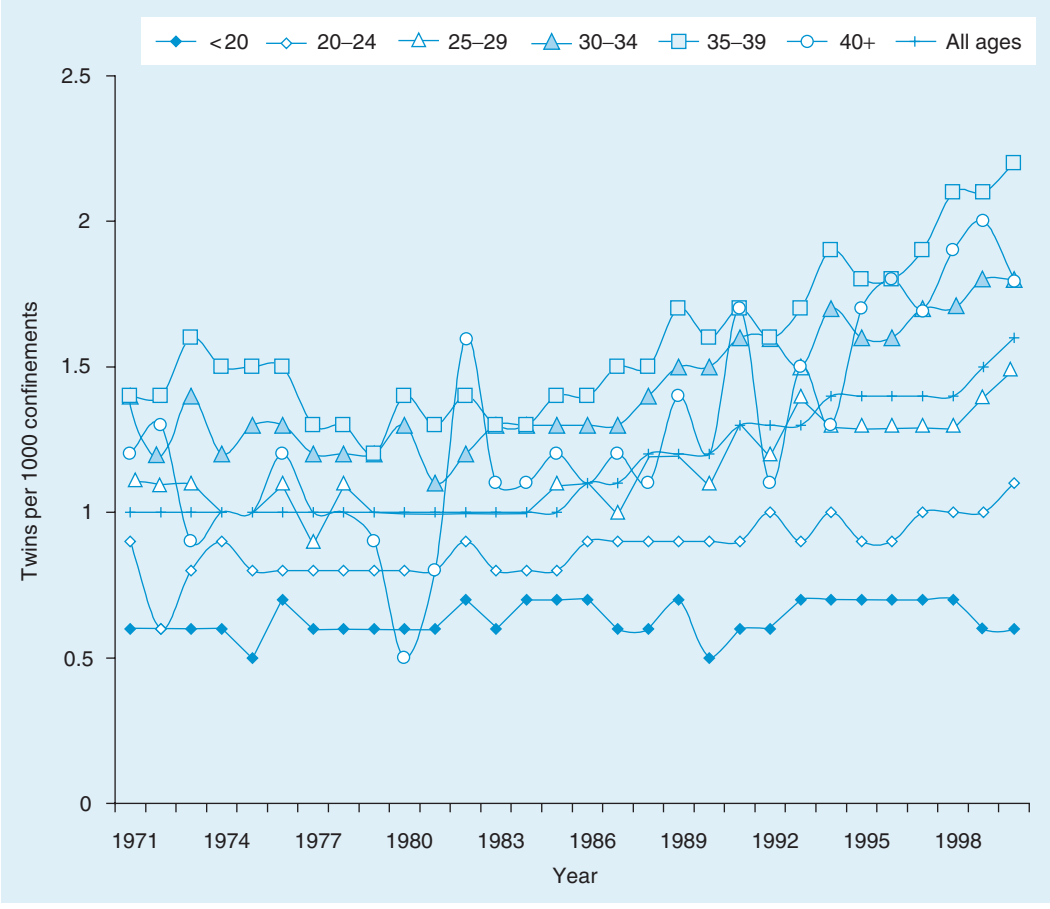


**Figure 4.4** Twins by maternal age, Australia, 1971–2000

### Sex ratio

The sex ratio of singleton and multiple births in Australia for the period 1991–98 shows a lower proportion of males with increasing plurality. For singletons, the male : female sex ratio was 106.1 : 100 with the proportion of males being 51.5%; for twins, the sex ratio was 102.6 : 100 (50.6% males); and for triplets, 97.7 : 100 (49.4% males)[2].

### Assisted conception

Australia has been at the forefront of assisted reproductive technologies for several decades. Of the 250 000 births in Australia annually, about 2% are a consequence of assisted reproduction. Between 1979 and 1999, the total number of assisted-conception pregnancies proceeding beyond 20 weeks was 30 684. Of these, 24 194 (78.8%) were singletons, 5797 (18.9%) were twins, 655 (2.1%) were triplets, 35 (0.1%) were quadruplets and there were three sets of quintuplets[5].

The perinatal mortality rate for singleton pregnancies following assisted reproduction is higher than for spontaneous conceptions (17.3 vs. 7.7 per 1000 confinements). The increase is primarily related to higher rates of preterm delivery in singleton pregnancies following assisted reproduction. No significant differences in perinatal mortality rates between spontaneous and assisted reproduction are seen for twins (34.1 per 1000 spontaneous vs. 32.3 per 1000 assisted-conception births) or triplets (72.7 per 1000 spontaneous vs. 95.2 per 1000 assisted-conception births)[5].

## DURATION OF PREGNANCY

Multiple pregnancies result in significantly higher rates of preterm births. Table 4.3 indicates that the rate of delivery prior to 28 weeks' gestation increases more than six-fold for twins (from 0.7 to 4.4%), 20-fold for triplets (from 0.7 to 14.1%) and almost 50-fold for quadruplets (from 0.7 to 33.3%). For pregnancies of at least 20 weeks' gestation in Australia in 2000, the mean gestational age at delivery was 39.0 weeks for singletons, 35.3 weeks for twins, 31.9 weeks for triplets and 27.0 weeks for quadruplets[2].

**Table 4.2** Twins by maternal age in Australia: 1971–2000 (per 1000 confinements)

| *Year* | *< 20* | *20–24* | *25–29* | *30–34* | *35–39* | *40+* | *All ages* |
|---|---|---|---|---|---|---|---|
| 1971 | 0.6 | 0.9 | 1.1 | 1.4 | 1.4 | 1.2 | 1.0 |
| 1972 | 0.6 | 0.6 | 1.1 | 1.2 | 1.4 | 1.3 | 1.0 |
| 1973 | 0.6 | 0.8 | 1.1 | 1.4 | 1.6 | 0.9 | 1.0 |
| 1974 | 0.6 | 0.9 | 1.0 | 1.2 | 1.5 | 1.0 | 1.0 |
| 1975 | 0.5 | 0.8 | 1.0 | 1.3 | 1.5 | 1.0 | 1.0 |
| 1976 | 0.7 | 0.8 | 1.1 | 1.3 | 1.5 | 1.2 | 1.0 |
| 1977 | 0.6 | 0.8 | 0.9 | 1.2 | 1.3 | 1.0 | 1.0 |
| 1978 | 0.6 | 0.8 | 1.1 | 1.2 | 1.3 | 1.0 | 1.0 |
| 1979 | 0.6 | 0.8 | 1.0 | 1.2 | 1.2 | 0.9 | 1.0 |
| 1980 | 0.6 | 0.8 | 1.0 | 1.3 | 1.4 | 0.5 | 1.0 |
| 1981 | 0.6 | 0.8 | 1.0 | 1.1 | 1.3 | 0.8 | 1.0 |
| 1982 | 0.7 | 0.9 | 1.0 | 1.2 | 1.4 | 1.6 | 1.0 |
| 1983 | 0.6 | 0.8 | 1.0 | 1.3 | 1.3 | 1.1 | 1.0 |
| 1984 | 0.7 | 0.8 | 1.0 | 1.3 | 1.3 | 1.1 | 1.0 |
| 1985 | 0.7 | 0.8 | 1.1 | 1.3 | 1.4 | 1.2 | 1.0 |
| 1986 | 0.7 | 0.9 | 1.1 | 1.3 | 1.4 | 1.1 | 1.1 |
| 1987 | 0.6 | 0.9 | 1.0 | 1.3 | 1.5 | 1.2 | 1.1 |
| 1988 | 0.6 | 0.9 | 1.2 | 1.4 | 1.5 | 1.1 | 1.2 |
| 1989 | 0.7 | 0.9 | 1.2 | 1.5 | 1.7 | 1.4 | 1.2 |
| 1990 | 0.5 | 0.9 | 1.1 | 1.5 | 1.6 | 1.2 | 1.2 |
| 1991 | 0.6 | 0.9 | 1.3 | 1.6 | 1.7 | 1.7 | 1.3 |
| 1992 | 0.6 | 1.0 | 1.2 | 1.6 | 1.6 | 1.1 | 1.3 |
| 1993 | 0.7 | 0.9 | 1.4 | 1.5 | 1.7 | 1.5 | 1.3 |
| 1994 | 0.7 | 1.0 | 1.3 | 1.7 | 1.9 | 1.3 | 1.4 |
| 1995 | 0.7 | 0.9 | 1.3 | 1.6 | 1.8 | 1.7 | 1.4 |
| 1996 | 0.7 | 0.9 | 1.3 | 1.6 | 1.8 | 1.8 | 1.4 |
| 1997 | 0.7 | 1.0 | 1.3 | 1.7 | 1.9 | 1.7 | 1.4 |
| 1998 | 0.7 | 1.0 | 1.3 | 1.7 | 2.1 | 1.9 | 1.4 |
| 1999 | 0.6 | 1.0 | 1.4 | 1.8 | 2.1 | 2.0 | 1.5 |
| 2000 | 0.6 | 1.1 | 1.5 | 1.8 | 2.2 | 1.8 | 1.6 |

**Table 4.3** Gestational age by plurality: all births, Australia, 2000. Data from reference 2

| *Gestational age* (weeks) | *Singletons* | | *Twins* | | *Triplets* | | *Quadruplets* | | *All births* | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *n* | *%* | *n* | *%* | *n* | *%* | *n* | *%* | *n* | *%* |
| 20–27* | 1 677 | 0.7 | 350 | 4.4 | 42 | 14.1 | 4 | 33.3 | 2 073 | 0.8 |
| 28–31 | 1 558 | 0.6 | 546 | 6.9 | 75 | 25.2 | 8 | 66.7 | 2 187 | 0.9 |
| 32–36 | 12 498 | 5.0 | 3331 | 42.0 | 172 | 57.7 | — | — | 16 001 | 6.2 |
| 37–41 | 228 561 | 91.8 | 3708 | 46.7 | 9 | 3.0 | — | — | 232 278 | 90.3 |
| 42 and over | 4 642 | 1.9 | — | — | — | — | — | — | 4 642 | 1.8 |
| Not stated | 54 | — | 3 | — | — | — | — | — | 57 | — |
| **All births** | **248 990** | **100.0** | **7938** | **100.0** | **298** | **100.0** | **12** | **100.0** | **257 238** | **100.0** |
| 20–36 weeks | 15 733 | 6.3 | 4227 | 53.3 | 289 | 97.0 | 12 | 100.0 | 20 261 | 7.9 |
| *Mean gestational age* (weeks) | | | | | | | | | | |
| 20+ weeks | 39.0 | | 35.3 | | 31.9 | | 27.0 | | 38.9 | |

*Includes seven babies of less than 20 weeks' gestation

**Table 4.4** Birth weight by plurality: all births, Australia, 2000. Data from reference 2

| | *Singletons* | | *Twins* | | *Triplets* | | *Other multiple births* | |
|---|---|---|---|---|---|---|---|---|
| *Birth weight* (g) | *n* | % | *n* | % | *n* | % | *n* | % |
| Less than 500 | 683 | 0.3 | 125 | 1.6 | 19 | 6.4 | 4 | 33.3 |
| 500–999 | 1 028 | 0.4 | 270 | 3.4 | 28 | 9.5 | 4 | 33.3 |
| 1000–1499 | 1 237 | 0.5 | 430 | 5.4 | 59 | 20.0 | 1 | 8.3 |
| 1500–1999 | 2 261 | 0.9 | 1075 | 13.6 | 90 | 30.5 | 3 | 25.0 |
| 2000–2499 | 7 865 | 3.2 | 2218 | 28.0 | 78 | 26.4 | — | — |
| 2500–2999 | 35 534 | 14.3 | 2671 | 33.7 | 18 | 6.1 | — | — |
| 3000–3499 | 89 372 | 35.9 | 995 | 12.6 | 3 | 1.0 | — | — |
| 3500–3999 | 79 072 | 31.8 | 140 | 1.8 | — | — | — | — |
| 4000–4499 | 26 891 | 10.8 | 3 | 0.0 | — | — | — | — |
| 4500 and over | 4 934 | 2.0 | — | — | — | — | — | — |
| Not stated | 113 | — | 11 | — | 3 | — | — | — |
| **All births** | **248 990** | **100.0** | **7938** | **100.0** | **298** | **100.0** | **12** | **100.0** |
| Less than 1000 | 1 711 | 0.7 | 395 | 5.0 | 47 | 15.9 | 8 | 66.7 |
| Less than 1500* | 2 948 | 1.2 | 825 | 10.4 | 106 | 35.9 | 9 | 75.0 |
| Less than 2500* | 13 074 | 5.3 | 4118 | 51.9 | 274 | 92.9 | 12 | 100.0 |
| *Mean birth weight* (g) | | | | | | | | |
| All birth weights | 3398 | | 2365 | | 1668 | | 930 | |

*Birth weights less than 1500 g and less than 2500 g are cumulative

**Table 4.5** Fetal, neonatal and perinatal deaths: singleton and multiple births, Australia, 1998–2000. Data from reference 2

| | *Singletons* | | *Twins* | | *Other multiple births* | | *All babies* | |
|---|---|---|---|---|---|---|---|---|
| *Year* | *n* | *Rate per 1000 births* | *n* | *Rate per 1000 births* | *n* | *Rate per 1000 births* | *n* | *Rate per 1000 births* |
| *Fetal deaths** | | | | | | | | |
| 1998–2000 | 3590 | 4.9 | 313 | 14.1 | 20 | 22.6 | 3923 | 5.2 |
| *Neonatal deaths** | | | | | | | | |
| 1998–2000 | 2006 | 2.8 | 343 | 15.7 | 27 | 31.6 | 2376 | 3.2 |
| *Perinatal deaths** | | | | | | | | |
| 1998–2000 | 5596 | 7.7 | 656 | 29.8 | 47 | 53.2 | 6299 | 8.4 |

*Fetal, neonatal and perinatal deaths from Australian Bureau of Statistics based on year of registration with 400 g/20 weeks' gestation definition

## BIRTH WEIGHT

As plurality increases, birth weight is reduced (Table 4.4). A twin pregnancy gives more than a seven-fold increase in the chance of a birth weight below 1000 g (from 0.7 to 5.0%), a triplet pregnancy a 23-fold risk (from 0.7 to 15.9%) and a quadruplet pregnancy almost a 100-fold increased risk (from 0.7 to 66.7%)[2].

The mean birth weight of singletons born in Australia in 2000 was 3398 g, of twins 2365 g, of triplets 1668 g and of quadruplets 930 g[2].

## PERINATAL MORTALITY

The perinatal mortality rate in Australia for 1998–2000 was 7.7 per 1000 singleton births. The rate was almost four times higher for twins (29.5 per 1000 births) and almost seven times higher (53.0 per 1000 births) for triplets and other multiple births (Table 4.5). In comparing these data with those for other countries, it must be remembered that Australia uses lower limits of ≥ 20 weeks' gestation or ≥ 400 g for its definition of perinatal mortality[2].

## SUMMARY

Multiple pregnancy usually has a satisfactory outcome. However, the consequences for some parents and children are devastating, and the costs to the community can be extreme. Multiple pregnancies reached epidemic levels in Australia in the late 1990s as a consequence of assisted reproductive technologies. The rate is now falling, and this trend must continue as practitioners respond with careful monitoring of ovulation induction and with reduced numbers of embryos transferred after *in vitro* fertilization[7].

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# Demographic Trends in Japan and Asia

*Y. Imaizumi*

5



## INTRODUCTION

The monozygotic (MZ) twinning rate is about 3.5–4 per 1000 births throughout the world, whereas variations exist in the dizygotic (DZ) twinning rate among races[1]. In one early survey, the DZ twinning rate in western Nigeria was very high with 40 per 1000 births, whereas the corresponding rates were 11 for Afro-American, 6–10 for Caucasian and 2.2–2.3 for Oriental people[1].

Ovulation-inducing hormones[2] and *in vitro* fertilization (IVF)[3] bring about a high rate of multiple births. In recent studies[4,5], twinning rates increased significantly after periconceptional multivitamin supplementation.

Imaizumi[6] examined the trend of twinning and triplet rates in 17 countries during the period from 1972 to 1996 using the vital statistics. Twinning and triplet rates increased in developed countries such as the four Scandinavian nations, Austria, Germany, The Netherlands, Switzerland, the UK, Canada, Australia, Israel, Japan, Singapore and Hong Kong after the 1970s[6], whereas the twinning and triplet rates were lower in Japan, Singapore and Hong Kong than corresponding values for Europe, Canada and Australia[6].

The present chapter focuses attention on recent trends in the overall twinning, triplet and quadruplet rates in Asian populations during the period 1972–2001. It also deals with trends in twinning and triplet rates according to zygosity in Japan, and the effects of maternal age on twinning rates in Asian populations.

## MATERIALS AND METHODS

For this analysis, staff of the statistics sections in three countries kindly supplied data on multiple births: the Health and Welfare Statistics and Information Department in Japan, Demographic Statistics Section in Hong Kong and National Registration Department in Singapore. Data on twinning[7–9] and triplet[9–11] rates according to zygosity in Japan were obtained from published papers[7–11].

## RESULTS

### Yearly changes in twinning and triplet rates

Table 5.1 lists yearly changes in the twinning and triplet rates in the three cited countries during the period from 1972 to 2001.

#### *Japan*

Twinning rates increased by 70% from 5.8 per 1000 births in 1974 to 9.9 in 2001. Triplet rates increased gradually from 58 per million births in 1974 to 109 in 1988, then increased rapidly to 280 in 1999 and decreased thereafter. The triplet rate increased 4.2-fold between 1974 and 2001.

#### *Hong Kong*

Twinning rates increased from 5.5 per 1000 births in 1972 to 8.7 in 1995 and remained nearly constant thereafter. The twinning rate increased by 62% during that period. Triplet rates remained constant between 1972 and 1980 (range 17–86 per million births), increased rapidly to 286 in 1997 and decreased thereafter. During the entire period the triplet rate increased by three-fold.

#### *Singapore*

With one exception, the twinning rate remained nearly constant between 1972 and 1990 (5.8–7.3

**Table 5.1** Twinning and triplet rates in Japan, Hong Kong and Singapore, and quadruplet rate in Japan, 1972–2001

| | *Twinning rate/1000 births* | | | *Triplet rate/million births* | | | *Quadruplet rate/million births: Japan* |
|---|---|---|---|---|---|---|---|
| *Year* | *Japan* | *Hong Kong* | *Singapore* | *Japan* | *Hong Kong* | *Singapore* | |
| 1972 | — | 5.54 | 6.54 | — | 86.33 | 86.53 | — |
| 1973 | — | 6.13 | 7.94 | — | 24.12 | 82.21 | — |
| 1974 | 5.79 | 6.48 | 6.97 | 57.95 | 47.50 | 53.48 | 3.27 |
| 1975 | 5.89 | 6.20 | 6.21 | 65.89 | 16.59 | 74.53 | 6.49 |
| 1976 | 5.82 | 6.69 | 5.94 | 66.85 | 63.27 | 115.97 | 2.97 |
| 1977 | 6.20 | 6.06 | 6.49 | 70.62 | 37.24 | 43.10 | 0.68 |
| 1978 | 6.18 | 6.38 | 6.43 | 71.64 | 24.57 | 75.53 | 4.18 |
| 1979 | 6.38 | 6.08 | 6.35 | 74.59 | 48.56 | 48.72 | 4.64 |
| 1980 | 6.40 | 7.07 | 5.82 | 76.16 | 81.61 | 40.18 | 2.42 |
| 1981 | 6.48 | 7.07 | 6.05 | 95.94 | 126.11 | 62.70 | 3.11 |
| 1982 | 6.53 | 7.45 | 6.34 | 103.75 | 92.42 | 69.88 | 4.86 |
| 1983 | 6.52 | 6.60 | 6.35 | 90.68 | 59.75 | 81.68 | 2.53 |
| 1984 | 6.54 | 7.25 | 6.36 | 87.06 | 128.82 | 0.00 | 2.56 |
| 1985 | 6.53 | 7.65 | 7.09 | 87.52 | 65.43 | 101.46 | 8.00 |
| 1986 | 6.49 | 7.26 | 6.38 | 90.43 | 55.62 | 103.68 | 8.28 |
| 1987 | 6.61 | 8.23 | 5.92 | 109.18 | 142.35 | 91.28 | 10.63 |
| 1988 | 6.72 | 7.14 | 6.60 | 109.44 | 158.47 | 106.60 | 8.74 |
| 1989 | 6.97 | 7.23 | 7.29 | 121.35 | 214.48 | 139.25 | 11.52 |
| 1990 | 7.00 | 7.94 | 6.85 | 168.04 | 176.44 | 188.26 | 13.33 |
| 1991 | 7.18 | 7.94 | 7.36 | 176.38 | 102.17 | 155.47 | 15.70 |
| 1992 | 7.50 | 7.67 | 7.48 | 228.69 | 154.30 | 221.89 | 19.68 |
| 1993 | 7.82 | 7.91 | 7.63 | 231.88 | 225.96 | 165.37 | 17.23 |
| 1994 | 8.32 | 7.45 | 7.57 | 274.98 | 222.26 | 201.12 | 26.73 |
| 1995 | 8.58 | 8.66 | 8.32 | 274.77 | 232.21 | 410.05 | 24.46 |
| 1996 | 8.90 | 8.13 | 8.42 | 257.61 | 267.69 | 424.13 | 6.42 |
| 1997 | 9.00 | 8.51 | 7.48 | 258.28 | 285.75 | 443.61 | 12.18 |
| 1998 | 9.09 | 8.46 | 8.72 | 274.53 | 187.96 | 297.70 | 8.05 |
| 1999 | 9.54 | 8.70 | 8.58 | 280.40 | 252.38 | 461.45 | 11.51 |
| 2000 | 9.85 | 9.09 | 9.74 | 266.90 | 240.1 | 531.84 | 6.51 |
| 2001 | 9.87 | 8.97 | 9.46 | 242.52 | 269.60 | 337.70 | 4.97 |

per 1000 births) and increased to 9.7 in 2000. The exception was 7.9 in 1973. The twinning rate increased by 33–67% during that period. With one exception, the triplet rate remained nearly constant between 1972 and 1988 (40–116 per million births) and increased to 532 in 2000. The exception was 0 in 1984. The triplet rate increased 6.1-fold from 1972 to 2000.

From Table 5.1, yearly changes in overall twinning and triplet rates indicate similar values comparing Japan, Hong Kong and Singapore in each year.

### Yearly changes in quadruplet rates

Table 5.1 also gives yearly changes in the quadruplet rate in Japan during the period from 1974 to 2001. The rate was 3.3 per million births in 1974, increased to 26.7 in 1994 and decreased thereafter. The quadruplet rate increased by eight-fold from 1974 to 1994.

Table 5.2 indicates the quadruplet rate in the three countries during the period from 1972–78 to 1993–2001. The quadruplet rate in Japan was about 4 per million births in 1979–85 and increased markedly to 12.4 in 1986–92, and 13.3 in 1993–2001. The rate increased 3.3-fold during that period. The quadruplet rate in Hong Kong was 3.1 per million live births in 1972–78 and gradually increased to 9.2 in 1993–2001. The rate increased three-fold during that period. The quadruplet rate in Singapore was 0 in 1972–78 and 3.4 per million births in 1979–85, and increased rapidly to 15.0 in 1986–92 and 19.0 in 1993–2001. The rate increased 5.6-fold from 1979–85 to 1993–2001 in Singapore.

### Yearly changes in twin and triplet rates according to zygosity in Japan

Figure 5.1 shows yearly changes in the twinning rate according to zygosity during the period from 1974 to 1998. The MZ twinning rate remained nearly constant (3.7–4.4 per 1000 births) during that

**Table 5.2** Quadruplet rate per million births in Asian populations, 1972–2001

| | Number of quadruplets | | | Quadruplet rate/million births | | |
|---|---|---|---|---|---|---|
| Year | Japan* | Hong Kong† | Singapore* | Japan | Hong Kong | Singapore |
| 1972–78 | 36‡ | 7 | 0 | 3.70 | 3.07 | 0.00 |
| 1979–85 | 45 | 9 | 1 | 4.01 | 3.88 | 3.41 |
| 1986–92 | 116 | 10 | 5 | 12.42 | 5.04 | 14.98 |
| 1993–2001 | 148 | 20 | 8 | 13.32 | 9.23 | 19.03 |

*Number of quadruplet sets; †number of live quadruplets; ‡1974–78

period, whereas the DZ twinning rate remained nearly constant from 1974 (1.86) to 1987 (2.29), and increased gradually to 1998 (4.64).

Figure 5.2 shows yearly changes in the rate of triplets according to zygosity during the period from 1974 to 1998. The MZ triplet rate remained nearly constant (18–42 per million births) during that period, whereas the trizygotic (TZ) triplet rate increased gradually from 12 per million births in 1974 to 52 in 1988 and then increased rapidly to 202 in 1998. As for DZ triplets, the rate remained constant (14–20) from 1974 to 1987 and increased to 39 in 1998, reflecting the corresponding increase in the DZ twinning rate during that period.

### Effect of maternal age on twinning rates according to zygosity in Japan

Figure 5.3 shows zygotic twinning rates according to maternal age in 1974 and 1998. DZ rates in 1998 increased rapidly with maternal age up to the age group 35–39 years, and decreased thereafter. On the other hand, DZ rates in 1974 increased slowly with maternal age up to the age group 35–39 years, and decreased thereafter. During that period of 24 years, the DZ rate increased three-fold for ages 35–39 years and 2.7-fold for ages 30–34 years. MZ twinning rates for both 1974 and 1998 were nearly the same for all maternal age groups. The higher DZ twinning rate was attributed to the higher proportion of mothers treated with ovulation-inducing hormones and IVF in Japan.

### Effect of maternal age on twinning and triplet rates in Asia

Figure 5.4 shows twinning and triplet rates according to maternal age in Hong Kong during the period 1976–2001, and Figure 5.5 shows these rates according to maternal age in Singapore during the period 1997–2001.

#### *Hong Kong*

Twinning rates increased significantly with maternal age in each period. The twinning rate for the group aged 35–39 years was 1.35 times higher in the period 1996–2001 than in the period 1976–80. As for triplets, the rate was significantly higher in the period 1996–2001 than in the period 1976–80 in each maternal age group except 25–29 years. The rate was nine times higher in the latter than in the former period in the group aged 35 years or more.

#### *Singapore*

Twinning rates increased rapidly with maternal age up to the age group 35–39 years, and decreased thereafter. As for triplets, the rate increased from the age group 20–24 years to that over 40 years of age.

## DISCUSSION

Table 5.1 shows that yearly changes in overall twinning and triplet rates were similar among the three Asian populations. According to Chen and colleagues[12], twinning rates in Taiwan remained nearly constant between 1972 and 1980 (3.6–5.6 per 1000 births) and increased from 1981 (6.4) to 1990 (11.5). Similarly, the triplet rate in Taiwan increased from 1975 (47 per million births) to 1990 (453 per million births)[12]. According to Ho and associates[13], 12% of 34 triplet pregnancies were the result of natural conception and 88% of ovulation induction (including IVF) during the period 1983–95 in Taiwan. According to a Japanese Perinatal Committee's Report[14], 18% of 280 triplet and higher-order multiple pregnancies resulted from natural conception, 47% ovulation induction and 35% IVF during the period 1990–92. Furthermore, a nationwide survey of infertility treatment in Japan was conducted between January and February 2000 by means of a questionnaire[15]. The total number of facilities providing infertility treatment was 494, and questionnaires were distributed

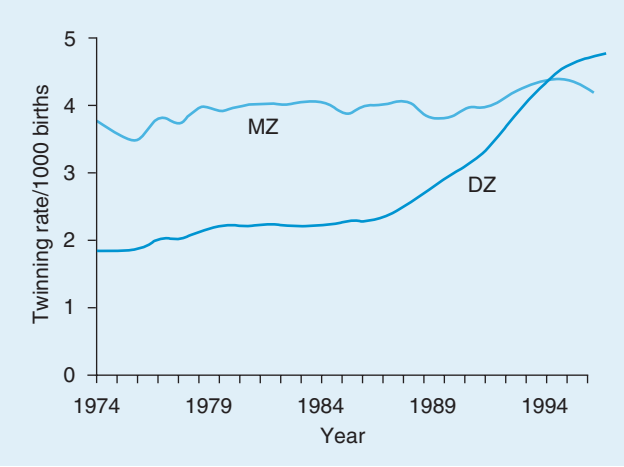



**Figure 5.1** Yearly changes in monozygotic (MZ) and dizygotic (DZ) twinning rates in Japan, 1974–98

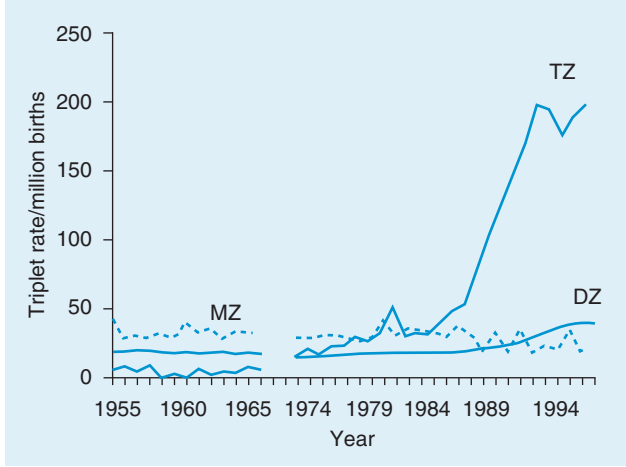



**Figure 5.2** Yearly changes in rate of triplets according to zygosity in Japan, 1974–98. MZ, monozygotic; DZ, dizygotic; TZ, trizygotic

to all of them. Of the 494, 297 (60.1%) were returned. Causes of 682 triplet and higher-order multiple pregnancies were IVF (73.2%), ovulation-inducing hormones (22.1%) and natural pregnancy (4.3%) during the period from 1997 to 1999. As for quadruplets and higher-order multiple pregnancies, 54.3% were the result of IVF and 44.4% of ovulation-inducing hormones.

Annual changes in twinning and triplet rates according to zygosity were investigated in Japan and seven European countries during the period 1972–99 using vital statistics[9]. With the exception of the Slovak Republic, the DZ twinning rate increased significantly year by year in each country. It was 2.9 times higher in Denmark and 1.5 times higher in Germany in 1999 than in 1972, and within this range in the other countries. With two exceptions, the MZ triplet rates remained more or less constant in each country. On the other hand, the DZ and TZ triplet rates increased significantly year by year in each country. The TZ rate increased 30-fold in Germany, 16.6-fold in Japan, 11.7-fold in Switzerland, 9.7-fold in the Czech Republic, 8.7-fold in The Netherlands, 6.4-fold in Denmark, 5.6-fold in England and Wales and 3.5-fold in the Slovak Republic. The higher DZ twinning rate and higher DZ and TZ triplet rates since 1983 were attributed to the higher proportion of mothers being treated with ovulation-inducing hormones and IVF in these six countries.

In February 1996, the Japan Society of Obstetrics and Gynecology recommended that only three and never more than four oocytes or embryos should be transferred per treatment cycle. On the other hand, the rate of selective reduction for triplet and

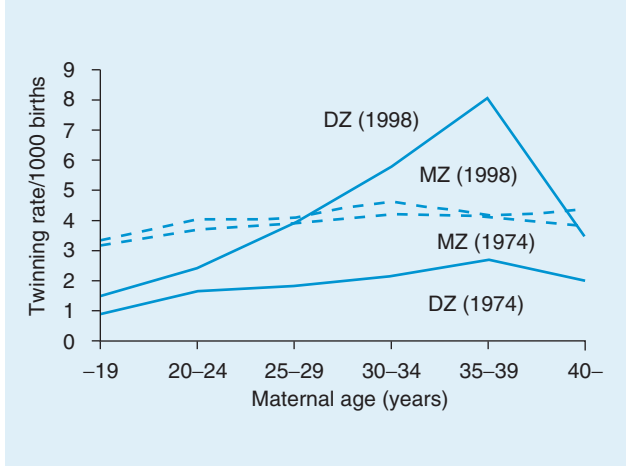
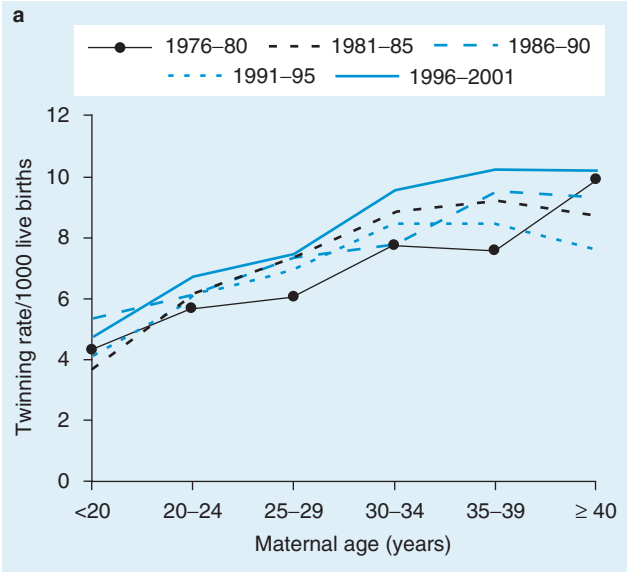



**Figure 5.3** Twinning rates by zygosity according to maternal age in 1974 and 1998 in Japan. MZ, monozygotic; DZ, dizygotic

higher-order multiple pregnancies ('supertwins') in Japan was 28.6% in 1997, 35.3% in 1998 and 36.2% in 1999[15]. The overall rate was 29.6% for triplets and 64.2% for quadruplets and more. These reductions were mainly to twins (80%, 188/235)[15]. From Table 5.1, it can be seen that the quadruplet rate increased rapidly up to 1994 and decreased thereafter. The declining tendency of the rate reflects the above selective reduction of 'supertwins' mainly to twins, and the recommendation of the Japan Society of Obstetrics and Gynecology in 1996.

Before the introduction of fertility drugs and IVF, the DZ twinning rate was higher than the MZ



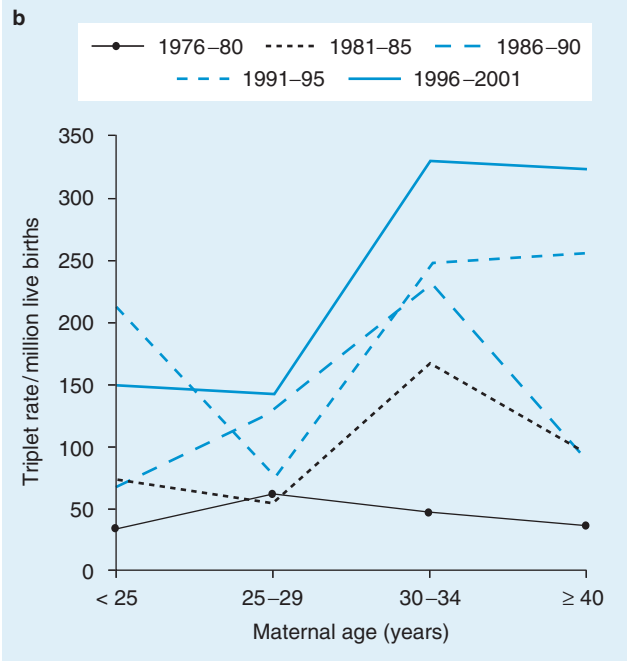




**Figure 5.4** Twinning (a) and triplet (b) rates according to maternal age in Hong Kong, 1976–2001

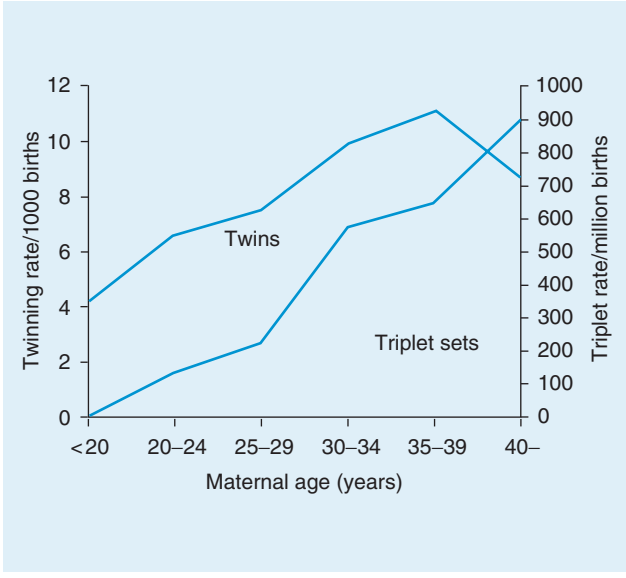



**Figure 5.5** Twinning and triplet rates according maternal age in Singapore, 1997–2001

twinning rate for Caucasian and African populations[1], whereas the opposite tendency was seen in Oriental populations. In Japan, the DZ twinning rate was 2.2 per 1000 births in 1980 and 4.6 in 1998, increasing 2.1-fold during that period. Also in Japan, the twinning rate was slightly higher for DZ twins than for MZ twins (4.3) in 1998. After the introduction of assisted reproductive techniques such as fertility drugs and IVF, the twinning and triplet rates have changed depending on how popular these techniques are in each country[6]. In other words, variations of these rates in each country are not only due to biological factors, but also depend on the popularity of the use of assisted reproductive techniques.

## SUMMARY

Yearly changes in twinning and triplet rates have been analyzed using vital statistics from Hong Kong, Japan and Singapore during the period from 1972 to 2001. In these three countries, the twinning and triplet rates increased significantly year by year during the period examined. The quadruplet rate in Japan increased by eight-fold from 1974 to 1994. In Hong Kong, the quadruplet rate increased three-fold from 1972–78 to 1993–2001, and the corresponding increase was 5.6-fold in Singapore from 1979–85 to 1993–2001. The rising twinning, triplet and quadruplet rates have been attributed to the higher proportion of mothers treated with ovulation-inducing hormones and IVF.

## ACKNOWLEDGMENTS

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# The East Flanders Prospective Twin Survey

*C. Derom and R. Derom*


## INTRODUCTION

### Geographic characteristics

The East Flanders Prospective Twin Survey (EFPTS) was established on July 15, 1964, in the Province of East Flanders in Belgium. The province covers 10% of Belgian territory, and is inhabited by approximately 13% (1 336 000 inhabitants) of the Belgian population; the great majority are Caucasian and tend to remain in the same residence for years, if not decades. As such, they are easily traceable, even after 40 years.

### Data collection

In Belgium, over 99%[1] of mothers deliver in a maternity ward. In the case of multiple births this percentage is even higher. In East Flanders, 19 maternity units deliver 14 000 births/year on average in the province. All obstetricians working in these units agreed to participate in the survey from its inception in 1964. Every multiple birth was reported to the EFPTS within 24 h and within 24 h after notification of such a delivery, a trained midwife visited the hospital and registered data in a standardized manner. All twin pairs in which at least one of the children, live- or stillborn, weighed 500 g or more, or, when birth weights were unknown, gestation was at least 22 weeks, were entered into the register. Birth date and time, birth weight, parental ages and parity were obtained from the obstetric records. Identification data of the parents were registered in a manner to conform to the law for the protection of privacy.

Structured questionnaires (answered by the obstetrician and pediatrician) were used to obtain information on the mode of conception, fetal presentation, mode of delivery, birth order, possible pathologies, ABO and rhesus (Rh) blood groups, health status of the mother before, during and after the delivery, and health and survival status of the children for the period they stayed in the maternity unit. Gestational age, calculated as the number of completed weeks, was obtained from the obstetrician's record. Placentas were collected and examined in the laboratory within 48 h after delivery. A full description of the examination of the placentas is given elsewhere (see Chapters 24 and 25).

### Placentation

Four groups of twins can be distinguished according to the zygosity and the number and structure of the placental membranes:

(1) Dizygotic (DZ);

(2) Monozygotic–dichorionic (MZ–DC);

(3) Monochorionic–diamniotic (MC–DA);

(4) Monochorionic–monoamniotic (MC–MA).

In DZ twins, who develop from the fertilization of two ova, each embryo develops within its own membranes: all DZ pairs are therefore DC. In contrast, all MZ twins arise from a single fertilized ovum. (Editor's note: For a revisionist point of view, see Chapter 36.) At some stage between fertilization and formation of the embryonic disk, the formative material divides into two parts, each giving rise to a complete embryo. It is commonly believed that, if the division occurs at an early stage (before the 4th day after conception), each embryo of the resulting

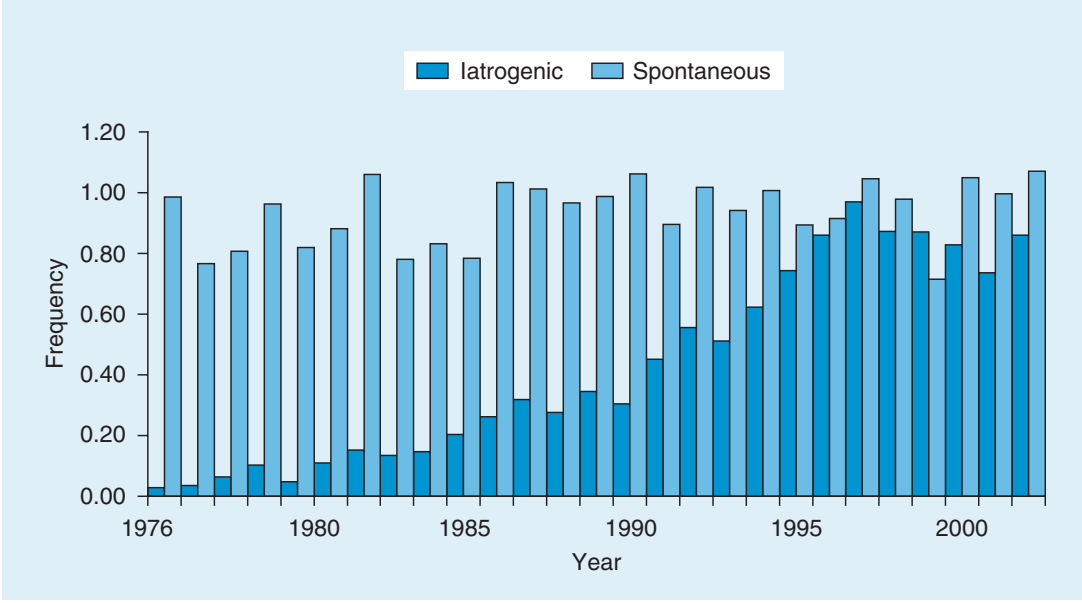


**Figure 6.1** Yearly frequencies of spontaneous and iatrogenic twin maternities (East Flanders Prospective Twin Survey)

MZ pair will have a separate set of membranes[2]. The two embryos are DC and, in this respect, resemble DZ twins. If, however, division of the ovum is delayed until the blastocyst has formed (between day 4 and day 8 after conception), the two embryos will share a single chorionic membrane but develop within two separate amniotic sacs. Such pairs are MC, albeit DA. Exceptionally, division of the formative material may be delayed until the embryonic disk separates from the cavities that will subsequently form the amniotic and chorionic sacs (after implantation into the endometrium)[2]. When this happens, the embryos will share a single chorionic and amniotic sac. They are MC–MA.

### Zygosity diagnosis

Until 1985, zygosity was determined through sequential analysis in live- and stillbirths based on sex, fetal membranes, umbilical cord blood groups (ABO, Rh CcDEe, MNSs, Duffy, Kell) and placental alkaline phosphatase. After that time, blood groups Kell and Duffy, and placental alkaline phosphatase were replaced by DNA fingerprints[3,4]. Unlike-sex twins and same-sex twins with at least one different blood group or, if blood groups were the same, at least two different DNA markers were classified as DZ; MC twins were classified as MZ. For all same-sex DC twins with the same genetic markers, a probability of monozygosity was calculated using a lod-score method[5]. After DNA fingerprinting, a probability of monozygosity of 0.999 can be reached. Owing to financial stringency, however, DNA fingerprints could not be determined systematically in all twin pairs. Therefore, in this study, only same-sex DC twins with the same markers, reaching a probability of 0.95 or more, were considered MZ. The remaining same-sex DC twins were classified as 'unknown'.

### Statistical analysis

The contingency $\chi^2$ test was used for comparisons of categorical data. When $\chi^2$ values appeared to be significant, odds ratios (ORs) and their two-sided 95% confidence intervals (95% CIs) were calculated to determine the strength of the association. For sex proportions in DZ twins, the proportion of male infants was considered, whereas in MZ twins, the proportion of male pairs was considered. Analyses were conducted using the Statistical Analysis System (SAS) 6.12 computer package. All reported $p$ values are two-sided, and were considered statistically significant when $p \leq 0.05$.

## FINDINGS

### Prevalences according to origin of pregnancy

In the EFPTS, the origin (spontaneous or induced) of the pregnancy has been recorded since 1976. Figure 6.1 shows the frequencies of spontaneous and iatrogenically induced twin maternities collected by the EFPTS since that time. The total numbers of twin and singleton deliveries for the province of East

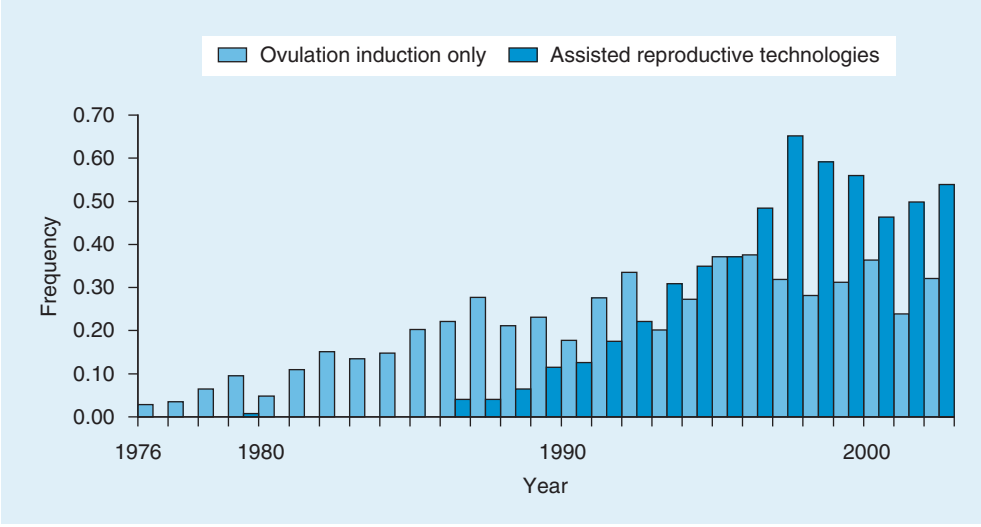


**Figure 6.2** Yearly frequencies of iatrogenic twin maternities according to ovulation induction and assisted reproductive technologies

**Table 6.1** Spontaneous and iatrogenic triplet maternities: East Flanders Prospective Twin Survey (1976–2002)

| | *Triplets* | | | |
|---|---|---|---|---|
| *Year* | *Spontaneous* | *AIO only* | *ART* | *Unknown* |
| 1976–84 | 10 (36%) | 18 (64%) | — | — |
| 1985–89 | 6 (18%) | 19 (58%) | 8 (24%) | — |
| 1990–94 | 5 (11%) | 25 (57%) | 14 (32%) | — |
| 1995–99 | 5 (12%) | 15 (35%) | 22 (51%) | 1 (2%) |
| 2000–02 | 2 (22%) | 5 (56%) | 2 (22%) | — |
| Total | 28 (18%) | 82 (51%) | 46 (30%) | 1 (1%) |

AIO, artificial induction of ovulation; ART, assisted reproductive technologies

Flanders were obtained from the National Institute of Statistics, Belgium, for the period between 1976 and 1987[5] and from the Flemish Center for Study of Perinatal Epidemiology (Flanders) for the period from 1989 to 2002. Before that period, very few iatrogenic twin maternities were recorded. The rate of spontaneous twin maternities has remained fairly constant during the past 25 years, i.e. between 0.8 and 1%. In contrast, the frequency of iatrogenically induced twinning has increased exponentially from 1976, to reach a maximum of nearly 1% of all maternities in 1997.

The frequency of iatrogenically induced twins resulting from the two principal types of infertility treatments shows differences over time (Figure 6.2). Twin births occurring after the use of ovulatory drugs without other interventions increased progressively from 1978 to reach a more or less stable maximum in the 1990s. In contrast, twins related to advanced assisted reproductive technologies (ART) appeared much later (1986), and rapidly became more numerous than those in the former group. Given these circumstances, the total number of twin births has almost doubled in recent years. The recent trend in stabilization of twinning frequencies after ART is most probably attributed to efforts aimed at better monitoring and management of follicular maturation, and to voluntary reduction of the number of embryos replaced in ART trials.

What is true for twin maternities is even more true for triplet maternities (Table 6.1). Before the use of fertility-enhancing agents, the EFPTS recorded one triplet delivery a year. In contrast, by 1992, 15 triplet maternities, of which only one was spontaneous, were registered. This means that more than 90% of triplet maternities result from artificial reproduction, and

**Table 6.2** Zygosity of spontaneous and iatrogenic twin and triplet maternities (1964–2000)

| | *Twins* | | | *Triplets* | | |
|---|---|---|---|---|---|---|
| *Zygosity* | *Spontaneous* | *AIO only* | *ART* | *Spontaneous* | *AIO only* | *ART* |
| Trizygotic | — | — | — | 9 (24%) | 71 (87%) | 38 (84%) |
| Dizygotic | 2360 (54%) | 637 (92%) | 602 (96%) | 22 (60%) | 11 (13%) | 3 (7%) |
| Monozygotic | 1924 (44%) | 49 (7%) | 14 (2%) | 6 (16%) | 0 (0%) | 1 (2%) |
| Unknown | 106 (2%) | 3 (1%) | 8 (1%) | 0 (0%) | 0 (0%) | 3 (7%) |
| Total | 4390 (100%) | 689 (100%) | 624 (100%) | 37 (100%) | 82 (100%) | 45 (100%) |

Difference between spontaneous and iatrogenic: $p < 0.001$ for twins and triplets; difference between artificial induction of ovulation (AIO) only and assisted reproductive technologies (ART): $p < 0.001$ for twins, not significant for triplets

it shows the contribution of ART therapies to the present epidemic. In the past few years the number of triplet maternities has decreased, due partly to selective embryo reduction and partly to limiting the number of embryos transplanted in IVF.

The increase in the rate of multiple pregnancies represents an important public-health problem not only in Belgium, but in other parts of the world as well. One of the major changes resulting from this increase is that the rates of very preterm births and very-low-birth-weight infants are rising, because the skew of multiple pregnancies with infants whose birth weight is less than 1500 g is dramatic, compared with singletons (see Chapters 1 and 90). Because very-low-birth-weight infants have high perinatal mortality and morbidity rates (see Chapter 90), they represent a high cost to the community in terms of increased patient load to the neonatal intensive-care units (see Chapter 90) and increased number of lifelong physical and mental handicaps[6,7].

## Zygosity and chorionicity distributions

Table 6.2 illustrates the distribution of zygosity types among spontaneous and induced twin and triplet maternities registered by the EFPTS between 1964 and 2000. By the end of 2000, the register had enrolled 5810 twin pairs and 165 sets of triplets. Twin pairs that resulted from selective embryo reduction ($n = 39$) and, since 1985, twin ($n = 68$) and triplet maternities ($n = 1$) of unknown origin, were excluded leaving 5703 twin pairs and 164 triplet sets for analysis. Of these, 1313 twin and 127 triplet maternities resulted from ovulation induction and/or ART. All DC–MZ twins and trichorionic DZ triplets had a probability of monozygosity and dizygosity, respectively, of at least 0.95.

The relative proportions of di- and trizygotic cases were significantly higher among induced twin and triplet maternities, respectively ($p < 0.001$). The use of ovulatory drugs alone induced a relative proportion of MZ twins which was significantly higher than that observed after ART (7% vs. 2%) ($p < 0.001$). Although showing the same trend, the difference in this regard between DZ triplets was not significant (13% vs. 7%).

**Table 6.3** Distribution of chorionicity in monozygotic (MZ) twins (1964–2000)

| | *MZ twins* | |
|---|---|---|
| *Zygosity* | *Spontaneous* | *Iatrogenic* |
| Monochorionic (MC) | 1280 (66%) | 49 (78%) |
| Dichorionic (DC) | 644 (34%) | 14 (22%) |
| Total | 1924 (100%) | 63 (100%) |

Ratio of MC/DC in iatrogenic cases compared with spontaneous cases, $p = 0.06$

The fact that a number of MZ twins were born after ART and that the frequency of zygotic division after ART was higher than after naturally occurring ovulation is of fundamental biological importance. To date, no conditions are known that could influence the MZ twinning rate. These findings are in agreement with those in at least one other population-based study[8].

Table 6.3 shows that, among MZ twins, the ratio of MC/DC placentas in induced cases was higher than in spontaneous cases. Although not statistically significant ($p = 0.06$), this difference needs further investigation. The increased risk of embryonic splitting associated with infertility treatment is not merely of academic interest, since the outcomes of twin maternities are markedly affected by zygosity and, more specifically, chorionicity[9]. Several disease processes are found in MC twins that do not occur in DC twins, and MC twins are notoriously prone to suffer from a number of special complications such

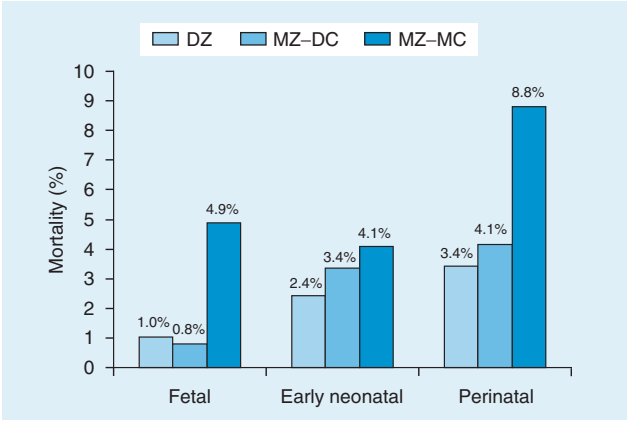


**Figure 6.3** Fetal, early neonatal and perinatal mortality of dizygotic (DZ), dichorionic–monozygotic (DC–MZ) and monochorionic (MC) infants. Data from reference 9

as, for instance, malformations and feto-fetal transfusion syndrome[9,10] (see Chapters 43 and 65).

## Perinatal mortality

In Figure 6.3, fetal, early neonatal and perinatal mortality are shown by type of twins: DZ, MZ–DC and MZ–MC. Fetal mortality is expressed as the proportion of all children in the survey that were stillborn; early neonatal mortality is the proportion of all live-born children who died within 7 days after delivery; and perinatal mortality is the proportion of all children who were stillborn or died within 7 days. Confirming a preliminary report[11], MZ–MC infants were at a significantly higher risk of dying perinatally than DZ infants ($p < 0.001$) (OR = 2.7), especially before birth (OR = 5.1), whereas MZ–DC infants had the same risk as DZ infants. This observation suggests that perinatal mortality is much more a matter of chorionicity than zygosity, which is in agreement with the findings of other investigators[9,12,13].

## The inheritance of spontaneous DZ twinning

DZ twinning is a highly heritable trait[2,14] (see also Chapter 36). The inheritance of spontaneous DZ twinning has been studied in collaboration with the Netherlands Twin Register by segregation analysis of 1422 three-generation pedigrees[15], ascertained through mothers of spontaneous DZ twins coming from East Flanders and The Netherlands. The observed frequencies of maternal and paternal grandmothers having DZ twins differed significantly from the expectations under an X-linked mode of inheritance. The segregation analysis showed that the parity-independent model was consistent with an autosomal monogenic dominant phenomenon, with a gene frequency of 0.035 and a female-specific penetrance of 0.10. Recessive, polygenic and sporadic models were rejected. This model was very robust against changes in population prevalence and loss of information due to the presence of same-sex twin pairs with unknown zygosity. When DZ twinning was modeled as a parity-dependent trait, the data were compatible with an autosomal dominant model with a gene frequency of 0.036 and a penetrance of 0.03 per birth for female carriers. Lewis and co-workers[14] published a review of the 'Genetic contribution to DZ twinning', and calculated risk ratios for relatives of DZ twins concluding that the genetic influence on DZ twinning is clearly discernible, even without accounting for maternal age and parity, and that the penetrance is compatible with the 10% penetrance for a dominant model described by our segregation analysis.

## Gender mix and length of gestation

Totally unexpected and contrary to the current vogue of intrauterine male dominance, we observed that the female fetus influences the birth weight of her male co-twin. It is well known that in singleton pregnancies the gestation length is slightly longer when the fetus is female[16]. The hypothesis of our study was that the same phenomenon would be present in like-sex twin pregnancies, female longer than male, but what happens to the unlike-sex cases? Birth weight and gestation length of same-sex and unlike-sex DZ twin pairs from the EFPTS were compared, to examine which sex of the unlike-sex twin pairs determined the length of gestation, and consequently the birth weight of the co-twin. We excluded pairs in whom one or both children were stillborn or had a major congenital malformation, when birth was by cesarean section (frequently on an elective basis near term) and whenever values were missing for gestation or birth weight of one child. The infants form four groups: same-sex males, same-sex females, boys of unlike-sex pairs and girls from unlike-sex pairs.

The mean gestation of unlike-sex pairs (36.8 weeks) was similar to that of girl same-sex pairs (36.9 weeks), but both unlike-sex and girl same-sex pairs had a significantly longer gestation ($p = 0.02$) than boy same-sex pairs (36.4 weeks). Boys from unlike-sex pairs weighed 78 g more than boys from same-sex pairs, whereas there was no difference in similar groups of girls. Most interesting are the unlike-sex pairs, showing that it is the girl who governs the length of gestation. She somewhat prolongs gestation,

to the benefit of her brother[17]. A series of studies have addressed this question, but the results are not in agreement[18–21]. Part of the discrepancy between studies may be explained by the selection of the cases. Only twins born vaginally have been considered in our study. Nowadays some 50% or even more twins are born by elective cesarean section, a procedure that can shorten gestation somewhat. A meta-analysis with the available data is then inappropriate, although such an analysis could be done if all the studies provided data on children not born by cesarean section.

**Table 6.4** Sex proportion of spontaneous twins in East Flanders Prospective Twin Survey (1970–2000) according to zygosity and placentation

| *Zygosity and chorionicity* | *Sex proportion* |
|---|---|
| Dizygotic | 0.514 |
| Monozygotic–dichorionic | 0.501 |
| Monochorionic–diamniotic | 0.499 |
| Monochorionic–monoamniotic | 0.212 |
| All monozygotic | 0.494 |
| All ($n$ = 3765 pairs) | 0.506 |

## Timing of splitting

MZ twinning events appear to occur very soon after fertilization, spanning a time-frame of as much as a week or more after conception[2]. Estimates for the timing of splitting of the embryo are based on examination of the placental anatomy of MZ twins at birth. To gain an insight into the timing of twinning, we have examined a closely related event, X chromosome-inactivation. Because of X-inactivation, tissues of females are normally a mosaic of two cell populations, each expressing gene alleles from either their paternal or their maternal X chromosome. This process of X-inactivation has been estimated to take place within the time-frame at which MZ is thought to occur[22].

X chromosome-inactivation patterns were investigated in the blood and buccal mucosa from 33 MZ and five DZ female twin pairs. While X-inactivation patterns in peripheral blood, which is mesodermal in origin, may differ among the members of a MZ twin pair, we reported that this phenomenon is restricted to those twins with a DC anatomy. Monochorionics do not differ substantially in their patterns of X-inactivation. The generally accepted explanation for this finding is that MC twins share their placental blood supply during intrauterine life, whereas DC–MZ twins do not, and therefore similar X-inactivation patterns in this shared hemopoietic cell population would be expected in MC twin pairs[13]. We therefore investigated X-inactivation patterns in the buccal mucosa of MZ twin girls, a tissue of ectodermal origin which is presumably not exchanged during intrauterine development. The intraclass correlation of X-inactivation patterns between members of MZ twin pairs for buccal mucosa is 0.4 ($p$ value 0.064) for DC–MZ and 0.92 ($p$ value 0.0001) for MC–MZ[23].

These data demonstrate that MC–MZ twins have strikingly correlated X-inactivation patterns in both ectodermal and mesodermal tissues, whereas DC–MZ twins do not. MC–MZ twins are thought to result from a later twinning event than DC–MZ twins[13]. Therefore, it is proposed that the timing of commitment to X-inactivation occurs between the time of DC– and MC–MZ twinning, possibly around 4 days after conception[22]. If this hypothesis is correct, the similarity in X-inactivation of MC–MZ pairs would be explained by the fact that splitting occurred after commitment to X-inactivation, with both embryos deriving from a cell population in which X-inactivation patterns were already established.

These conclusions were further confirmed by studying X-inactivation patterns in buccal mucosa of MA twin girls. MA–MZ twinning is a relatively rare event, and is thought to be the result of very late splitting of the human embryo (after day 7–8 post-fertilization). As hypothesized, the MA–MZ twins exhibit identical X-inactivation patterns (see also in Chapter 24)[24].

## Sex proportion

The proportion of males in multiple births has been, and still is, a matter of lively debate[25–28]. Clearly, there are differences between singleton and multiple births. The proportion of males in the human species decreases with each increase in the number of fetuses per pregnancy[29].

According to our data from East Flanders (Table 6.4) and data from the literature[25,26,30], it may be concluded that the sex proportion in MZ twins is lowered, albeit to a smaller extent in the DC and MC–DA and a much greater extent in the –MA variety. One can only speculate about the reasons for this remarkable biological phenomenon. Various hypotheses have been put forward. Guerrero[28] and James[27] independently suggest that the sex of a human zygote is influenced by the time of its formation within the menstrual cycle, with more male zygotes being formed, on average, both early and very late in the cycle, whereas more female zygotes are formed during the middle of the cycle. Experiments in lower vertebrates including fish, amphibians and chickens[27] led to MZ twinning

by retarding the development of the fertilized ova, depriving them of oxygen or maintaining them at a lower temperature (see Chapter 15). Delayed ovulation seems to induce MZ twinning in rabbits[31]. As suggested by James, it seems possible that the delay hypothesized as being associated with the formation of female zygotes runs parallel with the delay associated with the splitting of the ovum[27]. If this is the case, then MZ twins could be composed of a higher proportion of females.

One or two per cent of MZ pairs of twins share the chorion and the amnion at birth. They represent twinning that occurred after differentiation of the amnion (about day 7). Incomplete splitting of the embryo is generally considered as giving rise to conjoined twins, and could then occur even later, after the second week of development. However, we favor the more probable partial-fusion hypothesis[32], according to which no difference in time of splitting has necessarily to be considered. Because of the rarity of conjoined twins, it is as yet unknown whether further subdivision of the MA twins in unjoined and conjoined pairs will clarify the enigma of their very low sex proportion. As only three conjoined pairs (all of them female) emerged in our relatively large series, only a registry of almost continental scale could provide the amount of data needed to answer this question. It is well documented that conjoined twins include a high proportion of girls[25].

It is useful to inquire whether female embryos are more likely to undergo delayed splitting than male embryos, or whether embryonal or fetal mortality in the late-splitting group predominantly affects the male embryos. In their series of spontaneously aborted twins, Uchida and colleagues[33] found two male conjoined pairs with normal chromosomes, representing two consecutive abortions in the same mother. Because both conjoined twins and male MA twins are rare, this single finding could suggest a predominantly male early fetal mortality in MA twins. With regard to the first question, Burn and coworkers[34] hypothesized that unequal Lyonization may represent a cause of late twinning unique to female embryos. If this is true, analysis of the DNA methylation patterns of the X chromosome in MA twins should throw more light on the question. However, this hypothesis has recently been demonstrated to be non-probable by studying X-inactivation in MZ female pairs whereby X-inactivation is totally symmetric in MC–MA pairs, almost symmetric in MC–DA pairs and asymmetric in DC–MZ pairs[22–24].

Another more plausible explanation for the very low sex proportion in the MA twin group is the relative delay in early development of female embryos[17,35]. As a result, female embryos could be somewhat less mature at the time of formation of the amnion, and splitting of female embryos may be more compatible with survival at this stage. The delay in early female development has been ascribed to the absence of the Y chromosome[35]. However, the process of X-inactivation, since it may occur when there are fewer than 10 cells in the embryo[22], might itself contribute to a slight delay in early female development.

The proportion of same-sex and opposite-sex pairs found in DZ twins is in accordance with the Weinberg[30] rule as reported earlier by our group[36]. However, our data do not rule out subtle secular changes in that proportion as suggested by James[37] and Orlebeke and colleagues[38]. This discussion is not purely academic, because the Weinberg rule is the major tool available for the study of trends in MZ and DZ twinning rates when zygosity is not known although it has been criticized frequently, and with good cause (see Chapter 36).

The sex proportion discussed so far deals with spontaneous twinning, rather than iatrogenic twins. A series of studies have addressed this question, but the results are not in agreement. No large-scale population-based enquiries have been performed. Hence, one can question whether the samples are representative. In the EFPTS, the sex proportions of the iatrogenic and the spontaneous DZ twins do not differ significantly: 0.513 (95% CI 0.533–0.493) for iatrogenic DZ and 0.494 (95% CI 0.633–0.347) for iatrogenic MZ twins. This does not support James' hypothesis[26,30] that hormonal induction of ovulation increases the mother's gonadotropin levels at the time of conception, and that this in turn increases the probability of male offspring.

## FUTURE RESEARCH

Criticism has been addressed to the classic twin studies with regard to the circumstances of MZ twin gestation. In an often quoted paper, Price[39] reviewed the antenatal and natal difference-producing factors in MZ pairs. The most important of these is undoubtedly chorionicity. Other factors, however, must also be considered: gestational age, birth sequence, birth weight and, in those twins born vaginally, the presentation of both twins (cephalic, breech, transverse). Price concludes: 'It would seem to follow that part of the time and effort which will doubtless be expended on research with twins in the next decade or two could well be spent on identifying twin pregnancies 2 months or more before term, and obtaining much more complete information than we now possess as to the effects of prenatal and natal factors in the two types of MZ pairs. The results of such a study might show that the twin method, as ordinarily applied, is too crude for

purposes of modern nature–nurture studies. At the same time, pairs of MC type might prove to be of more interest and value for theoretical problems of developmental genetics than is commonly supposed.' Regrettably, despite Benirschke's[40] plea and our own which followed on more than one occasion[10,41], Price's expectation did not follow through. We hope that more twin registries will apply the messages of these two pioneers of fundamental twin research.

## ACKNOWLEDGMENTS

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# Multiple Births in Israel

*I. Blickstein and L. Baor*

7



*… and God said unto them, Be fruitful, and multiply, and replenish the earth, and subdue it.*

*Genesis 1:28*

*And when Rachel saw that she bare Jacob no children, Rachel envied her sister; and said unto Jacob, Give me children, or else I die.*

*Genesis 30:1*

These two Biblical passages epitomize the special connotation of fertility in Israel, and reflect the importance of reproduction in Judaism and Jewish culture[1]. Cultural as well as religious needs are satisfied by a politicosocial policy that promotes reproductive health. Within this construct, fertility treatments are fully subsidized by Israeli national health insurance and are available to all Israeli citizens, regardless of religion or marital status. As a result, more fertility centers per capita exist in Israel than in any other country in the world. Moreover, Israel has the world's highest per capita rate of *in vitro* fertilization (IVF) procedures[2]. Indeed, a survey of 48 countries found an average of 289 assisted reproductive technologies (ART) cycles per million of population per annum, whereas the figure for Israel was 1657 ART cycles per million of population per annum[3]. It has been estimated that in 1998 there were about 3500 ART cycles per million of population, representing at least a 5–12-fold higher rate than that observed elsewhere (V. Insler, MD, unpublished observation, cited with permission).

These extraordinary numbers do not represent evidence that Israeli women are plagued with infertility, but reflect the fact that the cultural milieu, as well as political issues and climate of statehood, took advantage of the availability of ART[1]. One might also say that the practice of ART took advantage of the centrality of thought regarding reproduction in Israel. A closer look at the maternal age distribution in Israel suggests that women undergoing IVF are significantly younger than their counterparts in the United States and Europe[4]. This fact may suggest that because ART is so widely available, Israeli women gain access to treatments earlier and perhaps more easily than elsewhere. At present, many Israeli women do not consider IVF treatment an unusual or exceptional means to achieve their reproductive expectations, and, interestingly, women from ultra-orthodox infertile married women to secular unmarried women share this view[1]. Based on these circumstances, it is no wonder that multiple pregnancy in Israel has reached an extraordinary rate[5].

## SOURCE OF DATA

Every birth in Israel is registered, and because the vast majority of births take place in hospitals, registry information is virtually complete. The data from the entire country are processed by the Israeli Central Chamber of Statistics and published in annual reports. Data related to multiple births were not recorded regularly between 1965 and 1985, but were recorded annually thereafter. Differentiation between twins and triplets or more began in 1994. Moreover, more recent information permits differentiation between the Jewish and Arab populations, between maternal age groups and between low-birth-weight categories (< 2500, < 1500 and < 1000 g).

## MULTIPLE BIRTH RATE, 1965–2001

Figure 7.1 shows the multiple birth rates in Israel during the years 1965–2001. The data indicate two periods. In the first, 1965–84, pregnancies were spontaneous, and the frequency of multiple births was about 1%. In the second, a steady increase, in almost a perfect linear trend, depicts an average annual increase of about 6.5%.

## JEWISH VERSUS NON-JEWISH POPULATIONS

Ethnic differences often accompany variable attitudes towards infertility. Figure 7.2 shows a comparison of multiple births during the years 1994–2001 between the Jewish vs. non-Jewish (mainly Arab) populations. These data indicate that twins and triplets are more prevalent among the Jewish population, probably because of more ART conceptions among Jewish women. However, because these data focus on the past decade, an interesting trend emerges whereby the rate of triplets among Jewish women declines, not only because of more judicious use of ART, but more importantly because of the widespread use of multifetal pregnancy reduction from triplets to twins. At the same time, however, the slightly increasing rate for the Arab population represents an increasing access of infertile Arab women to ART[6].

The differences in multiple birth rates attributed to ethnicity can also be translated to differing attitudes towards perinatal care[7,8]. In Israel, free access to antenatal care, facilities for delivery and neonatal care is available for the entire population. This potential effect on outcomes was studied in randomly selected, matched-controlled Israeli Jewish and Muslim mothers of twins. The data indicated no significant differences, suggesting that outcomes, in terms of birth-weight characteristics, do not depend on ethnic differences[8].

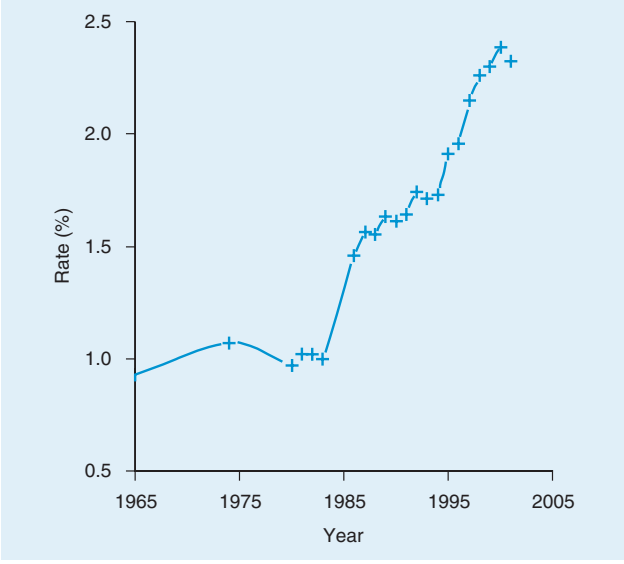


**Figure 7.1** Multiple birth rates in Israel (1965–2001)

## MATERNAL AGE

Figure 7.3 shows the distribution of ages in mothers of multiples during the years 1994–2001. There is a clear shift to the right for Jewish mothers, suggesting that Jewish mothers of multiples were older than Arab mothers. Of importance are the two extremes: there were almost eight times more Arab mothers in the group of less than 20 years (4.6 vs. 0.6%), and

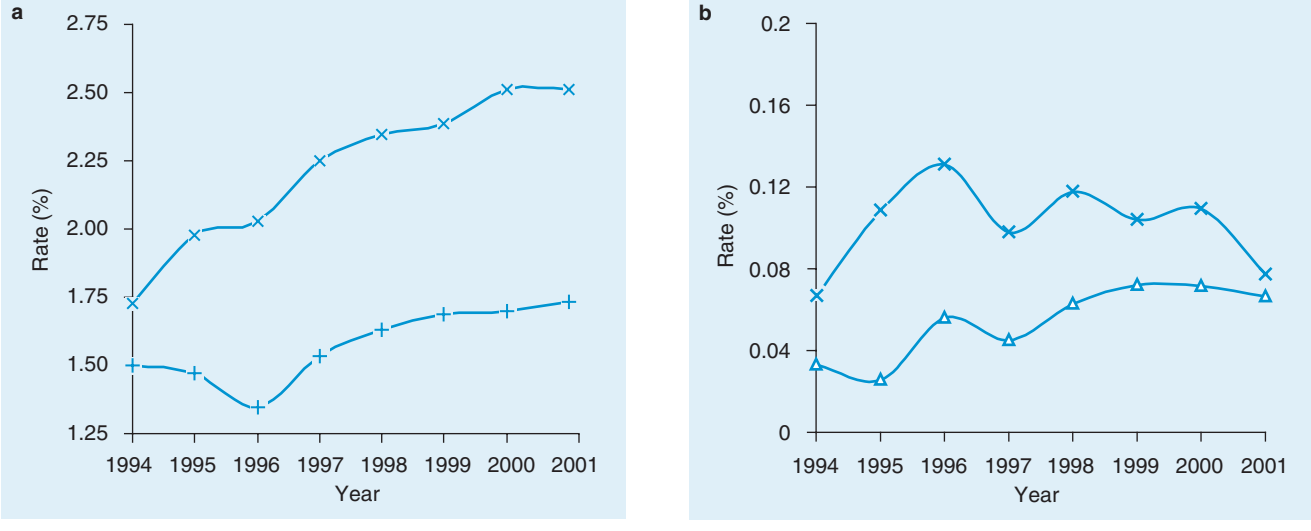


**Figure 7.2** Twin (a) and triplet (b) birth rates in the Jewish (upper curve) and Arab (lower curve) populations (1994–2001)

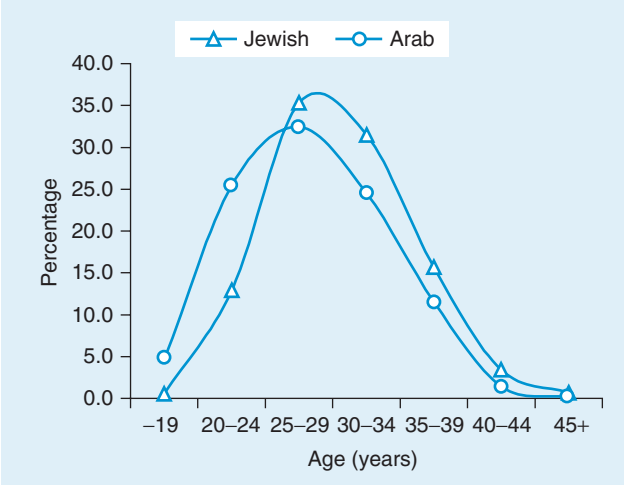


**Figure 7.3** Age distribution of mothers of multiples. Arab mothers were clearly younger compared with Jewish mothers

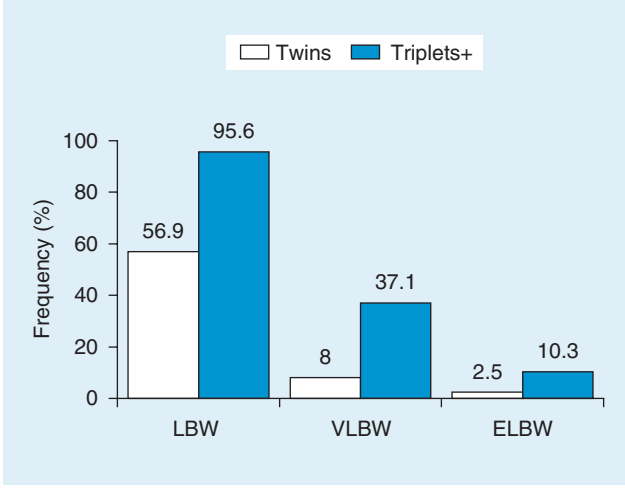


**Figure 7.4** Frequencies of twins and triplets or more weighing < 2500 g (low birth weight, LBW), < 1500 g (very low birth weight, VLBW) and < 1000 g (extremely low birth weight, ELBW)

twice in the age group 20–24 (25.5 vs. 12.9%). On the other hand, there were 2.5 times more Jewish mothers among the 40–44-year group (3.4 vs. 1.4%), and six times more at ages ≥ 45 years (0.6 vs. 0.1%).

## LOW BIRTH WEIGHTS

Data on low birth weights are available for the years 1993–2000, and are shown in Figure 7.4. As expected, the contributions of high-order multiples to the lower-birth-weight categories are significantly higher than those of twins. These figures can best be appreciated with regard to additional data from the Israeli Neonatal Network, which show that 34% of all admissions (of infants weighing < 1500 g) to the neonatal intensive-care units were multiples[9].

## COMMENTS

The data from Israel are a good example of how ART influences the multiple pregnancy rate, and how it may implicate overall outcomes in terms of low-birth-weight infants. It follows that Israel ranks first among the Western world countries in reported frequencies of multiple births. As was also found in recent US data, an onset of decline in the frequency of multiple births is seen (Figure 7.1). Although it is too early to establish if this change will remain undisturbed, it is not difficult to surmise that it might be due to more sensible use of ART and from implementing guidelines published by the Israel Society of Obstetrics and Gynecology, aimed to reduce the number of transferred embryos in IVF cycles.

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# Multiple Births in the Philippines

*C. Yabes-Almirante and B. B. Bautista-Zamora*


In the Philippines, of the 1 704 966 recorded deliveries in the year 2000, 40.7% were attended by midwives, 26.8% by doctors and 26.6% by trained traditional birth attendants. The remainder were attended by nurses and untrained traditional birth attendants (Table 8.1)[1]. These circumstances contribute heavily to the inability of government offices to develop population-based natality figures which include an accurate assessment of the number of multiple births. Years back, even more births were attended by traditional birth attendants rather than by trained health-care providers. Slowly, in the past decade, however, the role of these traditional birth attendants has been marginalized. This reduction, mainly in the rural areas, may be partially attributed to a more aggressive health-education campaign with better training of health attendants, midwives and doctors, especially at the primary health-care levels.

Despite this, national data on deliveries as well as maternal and neonatal outcomes remain poorly documented and under-reported, especially in the rural areas. Furthermore, many reports are incomplete and inaccurate, so much so that interpretation is difficult. Despite laws requiring compulsory reporting of births in the Philippines, it is possible that birth registration at the Department of Health could be 30% deficient[2].

In spite of inefficient collection and technical processing numerous and persistent efforts to use available data for administrative and research purposes have taken place. However, to date, not much attention has focused on multiple pregnancies. Collecting data on multiple pregnancies from local network hospitals is particularly difficult, as baseline recording is incomplete and pertinent data are often overlooked. Moreover, record keeping and documentation is lax and haphazardly completed, as there is no uniform or

**Table 8.1** Deliveries by attendance in the Philippines, 2000. Data are shown for the highest and the lowest attendance of doctors at birth (National Capital Region, NCR vs. Autonomous Region for Muslim Mindanao, ARMM). Data from reference 1

| Area | Total deliveries | Doctors | | Nurses | | Midwives | | Trained traditional birth attendant | | Untrained traditional birth attendant | | Others | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % |
| Total | 1 704 966 | 456 178 | 26.8 | 24 851 | 1.5 | 694 340 | 40.7 | 453 891 | 26.6 | 66 143 | 3.9 | 8530 | 0.5 |
| NCR | 234 804 | 120 625 | 51.4 | 5 450 | 2.3 | 80 107 | 34.1 | 22 860 | 9.7 | 5 555 | 2.4 | 207 | 0.1 |
| ARMM | 52 600 | 1 513 | 2.9 | 681 | 1.3 | 25 784 | 49.0 | 18 752 | 35.7 | 5 472 | 10.4 | 398 | 0.8 |

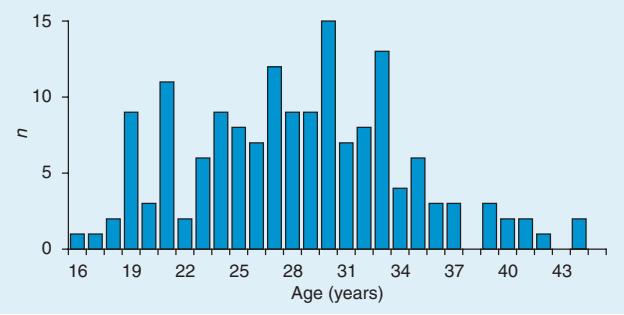


**Figure 8.1** Age distribution of mothers of multiple pregnancies admitted to the Perinatal Center, Philippine Children's Medical Center (1989–2003)

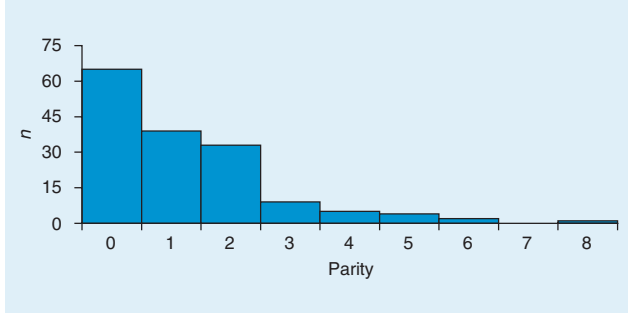


**Figure 8.2** Parity of mothers of multiple pregnancies admitted to the Perinatal Center, Philippine Children's Medical Center (1989–2003)

**Table 8.2** Medical and obstetric complications of multiple pregnancies admitted to the Perinatal Center, Philippine Children's Medical Center (1989–2003)

| *Complications* | *Number of cases* | *Percentage of multiple pregnancies* |
|---|---|---|
| Preterm delivery | 99 | 62.7 |
| Preterm premature rupture of the membranes | 21 | 13.3 |
| Twin-to-twin transfusion syndrome | 10 | 6.3 |
| Single intrauterine fetal demise | 10 | 6.3 |
| Pre-eclampsia mild | 8 | 5.1 |
| Pre-eclampsia severe | 8 | 5.1 |
| Anemia | 6 | 3.8 |
| Placenta previa | 4 | 2.5 |
| Premature rupture of the membranes | 4 | 2.5 |
| Cephalopelvic disproportion | 3 | 1.9 |
| Polyhydramnios | 3 | 1.9 |
| Oligohydramnios | 2 | 1.3 |
| Fetal distress | 2 | 1.3 |
| Diabetes mellitus | 2 | 1.3 |
| Chronic hypertension | 2 | 1.3 |
| Diffuse non-toxic goiter | 1 | 0.6 |
| Fetal hydrocephalus | 1 | 0.6 |
| Other congenital anomalies | 1 | 0.6 |
| Twin intrauterine fetal demise | 1 | 0.6 |
| Spontaneous abortion | 1 | 0.6 |

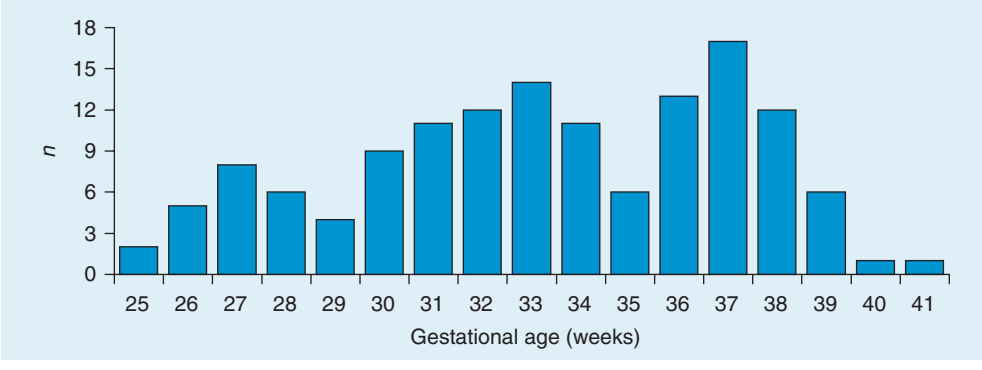


**Figure 8.3** Distribution by gestational age at delivery of multiple pregnancies admitted to the Perinatal Center, Philippine Children's Medical Center (1989–2003)

**Table 8.3** Outcomes of multiple pregnancies admitted to the Perinatal Center, Philippine Children's Medical Center (1989–2003): average birth weight (multiple pregnancies) by gestational age compared with standard Filipino birth weight[3] (singletons*) by gestational age

| *Age of gestation* (weeks) | *Lowest* (g) | *Highest* (g) | *Average* (g) | *10%** | *50%** | *90%** |
|---|---|---|---|---|---|---|
| 25 | 329 | 549 | 451 | — | — | — |
| 26 | 500 | 1620 | 909 | 666 | 906 | 1356 |
| 27 | 410 | 1340 | 887 | 727 | 1021 | 1641 |
| 28 | 420 | 1470 | 900 | 804 | 1147 | 1917 |
| 29 | 760 | 1900 | 1310 | 895 | 1286 | 2173 |
| 30 | 650 | 1980 | 1281 | 1001 | 1436 | 2402 |
| 31 | 940 | 1870 | 1504 | 1123 | 1596 | 2601 |
| 32 | 800 | 2000 | 1514 | 1259 | 1766 | 2771 |
| 33 | 820 | 2610 | 1690 | 1408 | 1942 | 2914 |
| 34 | 856 | 2340 | 1691 | 1569 | 2122 | 3033 |
| 35 | 998 | 2630 | 2085 | 1778 | 2303 | 3133 |
| 36 | 869 | 3080 | 2058 | 1912 | 2483 | 3220 |
| 37 | 920 | 3300 | 2148 | 2086 | 2656 | 3301 |
| 38 | 2040 | 2860 | 2425 | 2255 | 2819 | 3379 |
| 39 | 1600 | 2780 | 2387 | 2412 | 2969 | 3462 |
| 40 | 3350 | 3380 | 3365 | 2551 | 3100 | 3555 |
| 41 | 2009 | 2130 | 2069 | 2664 | 3209 | 3663 |

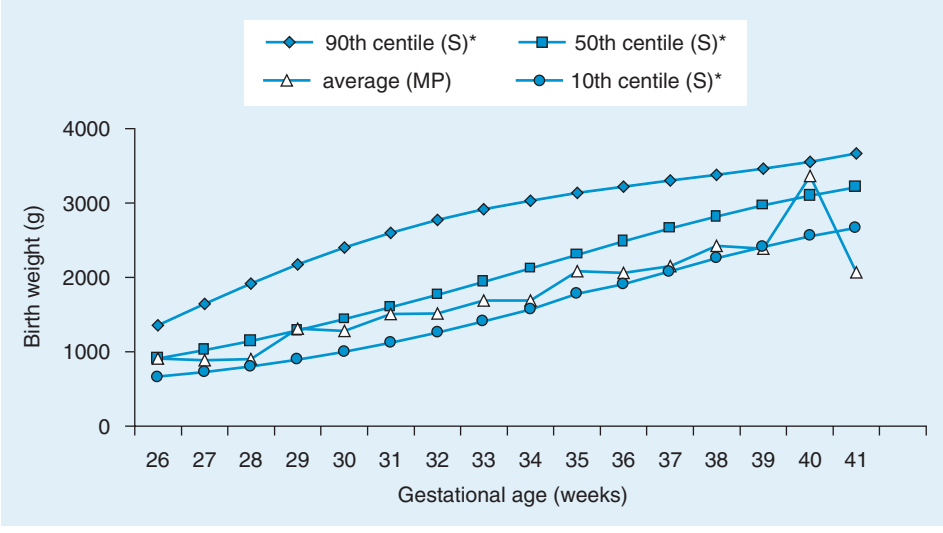


**Figure 8.4** Outcomes of multiple pregnancies admitted to the Perinatal Center, Philippine Children's Medical Center (1989–2003): average birth weight (multiple pregnancies, MP) by gestational age compared with standard Filipino birth weight[3] (singletons, S) by gestational age. *Reference 3

standard national form of data collection. In contrast, data available from our Perinatal Center have been more complete and adequately filed. Whereas these data may not be representative of the national picture, they do provide an interesting observation point of specialty practice in the Pacific Rim.

The Perinatal Center of the Philippine Children's Medical Center is one of the very few, if not the first, perinatal centers in a children's hospital in the world. It is located in the heart of one of the most populated cities of the National Capital Region. It is a medical facility that provides all aspects of perinatal

care, including services for high-risk pregnant patients, complicated deliveries and intensive care for infants with perinatal problems. The facility also provides educational programs and a broad range of continuously available subspecialty consultation services, as well as serving as a referral center for primary- and secondary-care units.

In the past 15 years, among the 6995 high-risk admissions, 158 or 2.26% were cases of multiple pregnancy. Ninety-one per cent of these were twin gestations and the remainder (9%) were triplets. Almost all were spontaneous pregnancies. Eighty-seven per cent were delivered, and 13% were managed medically and discharged for continued prenatal care. Among the twin gestations delivering at our institution, 56% had a cesarean section (9% as repeat cesarean section for a previous scar and the rest due to obstetric indications). Among the triplets, 79% were delivered abdominally.

The age range of these mothers was from 16 to 44 years. Most were between 24 and 33 years (Figure 8.1), primigravidas (41%) or secundigravidas (25%) (Figure 8.2).

As the Perinatal Center is a high-risk referral center, pregnancy admissions often had other medical and obstetric complications, the most frequent being preterm premature rupture of the membranes and preterm delivery, twin-to-twin transfusion syndrome and single intrauterine fetal demise. Among the medical complications, pre-eclampsia was the most common (Table 8.2).

Figure 8.3 shows the distribution of gestational age at delivery. Comparing the average birth weight by gestational age of multiple pregnancies with the standard birth weight among Filipino singletons, multiple pregnancies were almost always less than the 50th centile but more than the 10th centile of the standard for singletons (Table 8.3, Figure 8.4)[3].

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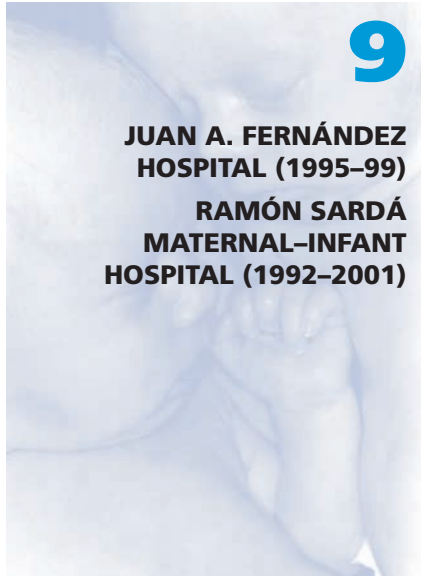
# Multiple Gestations: an Argentinian Point of View

*L. S. Voto, J. Ortí and M. Uranga-Imaz*




This chapter reviews the care of multiple pregnancies at two city hospitals in Buenos Aires, namely Juan A. Fernández Hospital, a referral center admitting high-risk obstetric patients, and Ramón Sardá Hospital, which admits low-risk patients. Although not population-based, the data describe the overall outcome of multiples in urban Argentina and thus reflect circumstances in other urban areas of South America.

## JUAN A. FERNÁNDEZ HOSPITAL (1995–99)

This report describes 231 sets of multiples (1.7%) and 13 270 singletons delivered during this period. The mean maternal age in both groups was similar, although slightly higher in the multiples. Mothers of multiples were of higher parity compared with mothers of singletons (81.7% of multiples were found in gravidas 1 and 2 and 7.3% in women with four or more previous gestations). The incidence of pregnancies without prenatal care was almost the same in both groups.

A comparison of complications affecting multiple and singleton pregnancies is given in Table 9.1. Only 24% of the multiple pregnancies had no perinatal morbidity. The relative risk of at least one hospital admission during pregnancy was twice higher than that for singletons (95% confidence interval (CI) 1.7–2.3), and the relative risk of preterm delivery was four times higher in multiple than in singleton pregnancies (95% CI 3.6–4.2). Twins and singletons had similar Apgar scores. The cesarean section rate was almost three times higher among multiple pregnancies (64.1 vs. 21.9%). The incidence of small-for-gestational-age babies was four times higher in multiples compared with singletons (21 vs. 5.4%). Because lower birth weights were observed in multiples more often (Table 9.2), pathologies related to preterm delivery were over-represented (Table 9.3). As a result, the relative risk of admission to the neonatal intensive-care unit was over five times higher in multiple than in singleton gestations. Fetal as well as neonatal mortality rates were increased in multiple (4.3 and 5.7%, respectively) compared with singleton pregnancies (1.9 and 1.4%, respectively). The risk of neonatal mortality was almost three times higher in multiple than in singleton pregnancies.

**Table 9.1** Maternal complications and gestational age at birth (%), Juan A. Fernández Hospital (1995–99)

| *Pathology* | *Multiple* | *Singleton* |
|---|---|---|
| None | 24.2 | 48.9 |
| Need for hospitalization | 54.6 | 25.8 |
| Hypertension | 14.4 | 7.1 |
| Diabetes | 1.1 | 0.4 |
| Anemia | 5.2 | 0.9 |
| Urinary infection | 11.8 | 6.9 |
| PROM | 12.8 | 6.9 |
| Preterm labor | 26.9 | 1.8 |
| Gestational age | | |
| ≥ 37 weeks | 29.6 | 84.8 |
| 33–36 weeks | 42.8 | 8.4 |
| 29–32 weeks | 18.4 | 2.4 |
| < 29 weeks | 9.2 | 1.7 |

PROM, premature rupture of the membranes

**Table 9.2** Birth-weight distribution (%), Juan A. Fernández Hospital (1995–99)

| *Weight* (g) | *Multiple* | *Singleton* |
|---|---|---|
| ≤ 1000 | 6.6 | 1.5 |
| 1001–1500 | 13.3 | 1.3 |
| 1501–2000 | 18 | 2.1 |
| 2001–2500 | 29.4 | 5.4 |
| ≥ 2500 | 32.7 | 88.7 |

**Table 9.3** Neonatal morbidity in twins, Juan A. Fernández Hospital (1995–99)

| *Pathology* | *Morbidity* (%) |
|---|---|
| None | 4.3 |
| Prematurity | 88.2 |
| Asphyxia | 6.0 |
| Respiratory distress syndrome | 10.6 |
| Jaundice | 25.6 |
| Congenital anomalies | 2.3 |
| Intrauterine infection | 4.6 |
| Hospital infection | 3.5 |

## RAMÓN SARDÁ MATERNAL–INFANT HOSPITAL (1992–2001)

A different population – women with low-risk pregnancy – is cared for at Ramón Sardá Maternal–Infant Hospital. This analysis is based on twin births between 1992 and 2001. Because infertility treatment is mainly practiced in private clinics, the incidence of triplets and higher-order births in public hospitals is very small, and therefore excluded from the analysis. During this period, a total of 66 882 deliveries were recorded, with an annual twin birth rate ranging from 0.94 to 1.29%. The average maternal age was 27.5 years (standard deviation, SD 6.1), with a median of 27 years, ranging from 14 to 43 years.

The mean birth weight was 2234 g (SD 620), with 11.9% weighing < 1500 g, 51.9% weighing 1500–2499 g and 36.2% weighing > 2500 g. The main difference between the two hospitals was in the very-low-birth-weight group (< 1500 g), reflecting the population at risk at the Juan A. Fernández Hospital. The incidence of low-birth-weight twins was high but similar in both hospitals. The mean gestational age was 35.3 ± 3.2 weeks and the primary cesarean section rate was 38.4%.

At birth, 97% of the infants had a 5-min Apgar score ≥ 7. The stillbirth rate was 2.7% and the early fetal mortality (occurring within 7 days) was 3%. The birth-weight-corrected prenatal mortality (for fetuses and neonates weighing 1000 g or more) during the period under study did not show significant differences over time, albeit a downward trend can be recognized (Figure 9.1). The average annual perinatal death rate was 4.9%. The data in Table 9.4 suggest that the main causes of neonatal death, as is the case in other published reports, are prematurity and its major complications including respiratory distress syndrome and hyaline membrane disease.

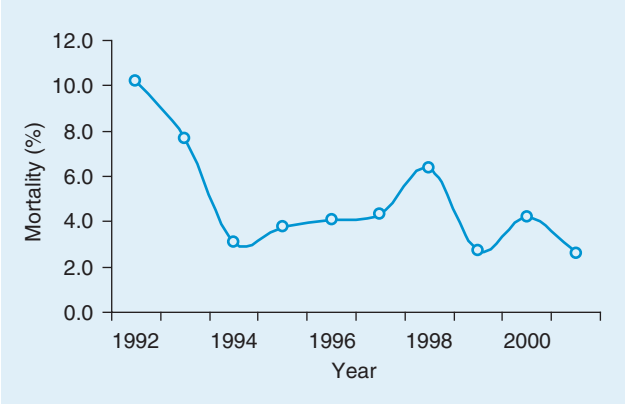



**Figure 9.1** Perinatal mortality of twins over the period 1992–2001, Ramón Sardá Maternal–Infant Hospital, Buenos Aires, Argentina

**Table 9.4** Causes of early and late neonatal death, Ramón Sardá Maternal–Infant Hospital (1992–2001)

| *Cause of death* | *Mortality* (%) |
|---|---|
| Immaturity | 23 |
| Respiratory distress syndrome (RDS) | 18 |
| Hyaline membrane disease (HMD) | 16.5 |
| Malformations | 14 |
| Sepsis | 7 |
| Cardiogenic shock | 7 |
| Intraventricular hemorrhage (IVH) | 3.5 |
| Other | 11 |
| Total | 100 |

The infant mortality rate for multiple gestations at Ramón Sardá Hospital was markedly higher than in the general population, and although unchanged over the 10-year study period, a steady decline has been observed[1]. Increased survival rates may be attributed to improvements in high-risk obstetric and neonatal care. However, current practice in Argentina, as well as in the rest of Latin America, still lags well behind that in developed countries[2,3].

## COMMENTS

The Department of Maternal–Fetal Medicine at Juan A. Fernández Hospital is a typical Argentinian

high-risk center, and provides medical care to numerous referral pregnant patients. Our data correspond to those of other nations and, once again, show that multiple gestations are high-risk.

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## COMMENT

The population of Latin America is one of extreme socioeconomic differences. At one end of the scale are the more affluent groups who have access to infertility treatment; at the other end of the scale, the resource-poor population often are unable to obtain basic perinatal care. A good example of the situation comes from the study of Colletto and colleagues[1], who compared the rates of multiple births in four Brazilian hospitals of different socioeconomic levels. Not surprisingly, the multiple pregnancy rates in the hospital caring for more affluent couples were much higher compared with the 'natural' rate observed among the poor population. In a similar, but totally unsurprising fashion, fetal death rate decreased as socioeconomic level increased. Another study, conducted at what the authors described as a 'first-class tertiary private hospital' in São Paulo, Brazil, found that the rate of twins was 21.6/1000 births and that for triplets was 2.1/1000 births. Of great importance was the very high rate (45.0/1000) of twins born to primigravid patients over 30 years of age, a strong indicator for the influence of assisted reproductive techniques[2].

The prenatal characteristics provided by Voto and colleagues in this chapter are quite similar to those reported by Campana and Roubicek[3] from another hospital in Buenos Aires, Argentina. The rate of twins, however, was higher than that reported in native Brazilians, where the mean annual incidence for the period 1984–93 was $8.8 \pm 0.9/1000$[4].

In a study conducted by the Latin American Center for Perinatology and Human Development, Conde-Agudelo and associates[5] examined the association between multiple gestation and frequency of adverse maternal outcomes in nearly one million pregnancies recorded in the Perinatal Information System database (Montevideo, Uruguay). Compared with singleton pregnancies, women with multiple gestations had an increased risk for hypertensive disorders, postpartum hemorrhage, preterm labor, anemia, urinary tract infection, puerperal endometritis and cesarean delivery[5]. These results correspond to the data presented by Voto and colleagues in this chapter.

It goes without saying that multiple gestations increase the risk of significant maternal morbidity in developing countries, as is the case in developed countries.

*Isaac Blickstein*

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# Multiple Births Resulting from Assisted Reproductive Technologies in the United States, 1997–2001

*J. Markovitz and A. Hershlag*

10



## BACKGROUND

A single, live birth is the ultimate goal of *in vitro* fertilization (IVF). However, the low probability of such an outcome in the early days of IVF became the root of multi-embryo transfers in order to increase the odds for a viable singleton. The rapid progression of physicians and embryologists along parallel learning curves resulted in IVF implantation rates that by now surpass natural implantation. This circumstance, in turn, led to increasingly higher rates of singleton deliveries, concomitant with an untoward increase in multiple pregnancies, a phenomenon, coupled with the exponential utilization of IVF, which became the basis of an epidemic-proportion increase in higher-order multiple pregnancies and overpopulation of high-risk clinics, antepartum units and above all neonatal intensive-care units across the USA.

Historically, IVF was utilized as a 'final common pathway'. Typically, patients had to fail a series of medical treatments and/or surgeries in order to become eligible for IVF. More recently, however, IVF has established itself as a reliable treatment with consistent and predictable pregnancy rates. For example, in older patients and those diagnosed with male factor infertility, the concept of 'IVF first' has become a clinical axiom. Impressively, in young patients with severe male factor infertility, per-cycle viable pregnancy rates have soared to above 50%.

In the United States, fertility clinics are pressured to demonstrate high per-cycle success rates. These demands are driven by the availability of clinic-specific outcomes to the general public. In addition, the higher cost of IVF in the USA compared with Europe or the UK, where much of the care is paid for by the state, also increased pressure to accelerate the pregnancy rate per cycle. This reality often contributes to the overzealous transfer of multiple embryos in the UK.

## THE SART–CDC REGISTRY

The United States Congress passed the Fertility Clinic Success Rate and Certification Act in 1992. This law mandates that all clinics performing assisted reproductive technologies (ART) in the United States must report their success rate annually to the Centers for Disease Control (CDC). This has been accomplished by the recruitment of a professional society, the Society for Assisted Reproductive Technology (SART), to assist in the collection and dissemination of this information. SART maintains a registry including all US clinics and individual practitioners who regularly perform ART. Each clinic enters its annual statistics into a standardized computer program, the Clinical Outcome Reporting System (CORS), first developed in 1995 and further refined in 1996. The information recorded consists of patient profiles including diagnosis and age, in addition to clinical pregnancy and live birth rates. Currently, the clinic-specific reporting system is about 2 years behind. One reason is that all live births have to be accounted for before data are submitted. A second reason is the rather elaborate process of data collection and verification, which currently involves both the CDC and SART. SART compiles the data and submits them to the CDC for analysis. In case of inconsistencies, SART proceeds

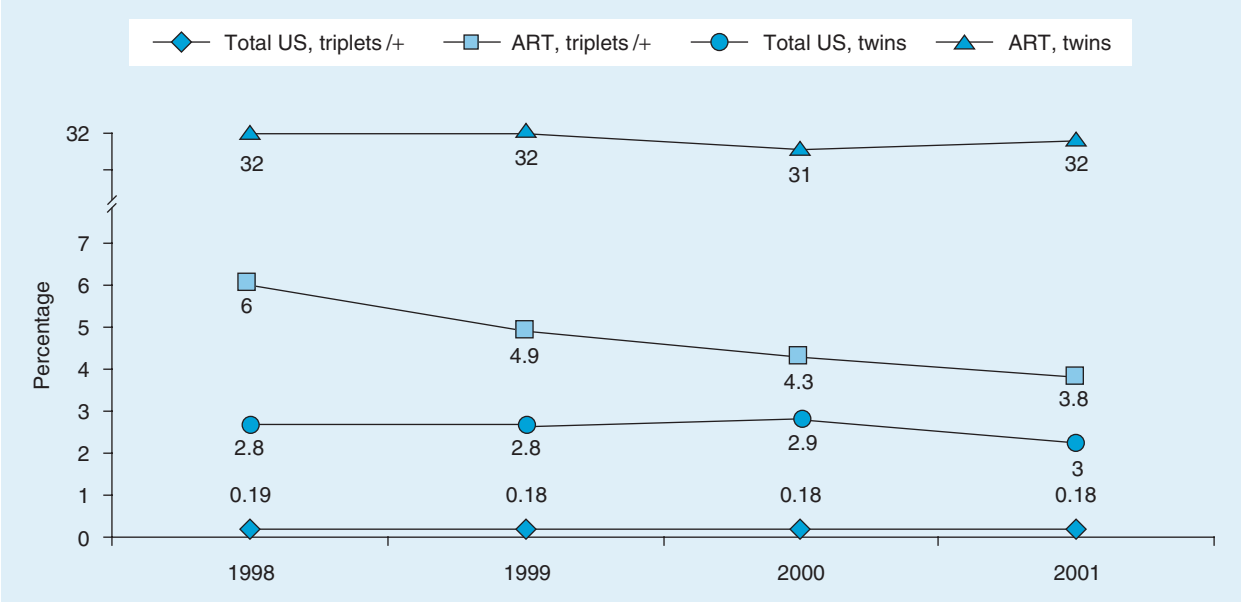


**Figure 10.1** Rate of twin births and triplet/+ births for the US and assisted reproductive technologies (ART) patients, 1998–2001

to review the office records of specific centers with the goal of subsequent correction of the data. Additionally, SART conducts audits of randomly selected clinics whose medical records are checked against reported data. Both the CDC and SART review all information a second time to ensure validity. Only then are the results compiled into tables and charts with accompanying explanatory texts. Eventually, the report is submitted to the Government Printing Office for publication and distribution.

A total of 384 fertility clinics were included in the most recently published SART report for the year 2001. Data from a small number of clinics nationwide were disqualified for failing to report data as required, but were ultimately included at the end of the report as 'non-reporters'. Several clinics that only functioned for a portion of the year were excluded from the report.

SART data report outcomes of individual ART treatment cycles. These cycles are defined by the onset of ovarian monitoring and/or the initiation of fertility medications with the intent of embryo transfer. To this end, all cycles are included, even those terminated before embryo transfer. If a woman were to have undergone several cycles throughout the year, each cycle is considered independently by SART.

SART considers two outcome measures: pregnancy and birth. Pregnancy is defined as the diagnosis through ultrasound of a viable fetus or multiple viable fetuses. Birth is defined as the reporting of a live infant by the patient or her obstetrician.

## DATA

### The impact of ART on multiple gestation rate

The rates of multiple births in ART compared with total rates of multiple births in the USA between the years 1998 and 2001 are charted in Figure 10.1. The overwhelming majority of multifetal births in the United States are twins[1]. Remarkably, the twin birth rate was increased 11-fold by ART in 1998 with a rise from 2.8 to 32%. In 2001, this rate of increase repeated itself with a rise from 3.0 to 32%. An even more dramatic impact of ART is evident in the case of triplets and higher-order multiples (triplets/+). For example in 1998, ART led to a triplets/+ increase of 32-fold (0.19% vs. 6%). Thus, what was a rather rare reproductive phenomenon among spontaneous pregnancies has become a rather common occurrence in ART. The triplet/+ rate has started to drop gradually, with 2001 seeing a rate of 3.8%, which is only a 21-fold increase compared with the overall US rate of 0.18%.

The data presented in Figure 10.1 represent actual *live birth* rates rather than the number of *heartbeats* observed through ultrasound, because national vital statistics, stored in the United States natality files, are reported as live births. In actuality, the numbers used for calculation of the rates of multiples do not include all cases diagnosed initially by ultrasound. Some multifetal pregnancies reduce spontaneously, while others are reduced iatrogenically. This circumstance results in a lower number of triplets/+ as well

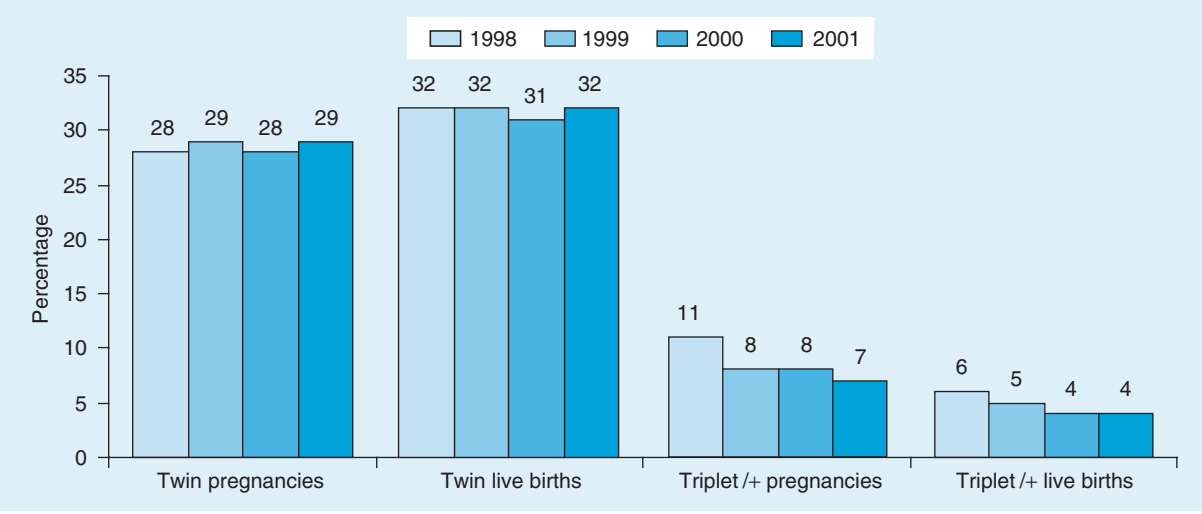


**Figure 10.2** Multiple fetal pregnancy and multiple-infant live birth rates from assisted reproductive technologies (ART), 1998–2001

as a potentially higher number of twins resulting from triplets/+ reduction.

### Delivery data versus ultrasound-detected heartbeats

Initial pregnancy rates prior to fetal reduction, either spontaneous or surgical, provide a much more accurate way of assessing the true extent of the problem. For this reason, all data presented from here on pertain to clinical pregnancies and the number of heartbeats counted during an ultrasound examination. Figure 10.2 represents the differences between pregnancy and live birth rates for ART patients. There is an obvious discrepancy in the reported incidence of both twin and triplet/+ pregnancies when compared with resultant births. For example, in the most recent SART report for the year 2001, the twin delivery rate was 32%, a figure which is 3% higher than the ultrasound-diagnosed twinning rate. The triplet/+ delivery rate during the same year decreased by exactly 3%. These findings confirm our suspicions that the rather common utilization of multifetal pregnancy reduction, as well as the occasional occurrence of spontaneous reduction, is responsible for discrepancies between the rates of viable multiples and multiples at the time of delivery.

### The effect of maternal age on the rate of multifetal pregnancies

Multiple pregnancies resulting from ART vary according to patients' age. Younger patients are more likely to deliver multiples than are older patients. The statistics presented below are based on data reported for fresh ART cycles using only non-donor eggs, which represent the overwhelming majority of the total number of ART cycles.

As shown in Figure 10.3, a slow yet consistent decrease in the multiple live birth rates was seen in younger patients. Over the years reported, in patients younger than 35, the 43% incidence in 1997 decreased to 39.7% in the year 2001. For patients between the ages of 35 and 37 years, the incidence of multiple births dropped from 36.8 to 34.7% for the corresponding years.

The rate of live-born multiples for the patient population over 38 years was lower than for younger patients, with some fluctuations between the years but no discernible trend so far: for patients 38–40 years old, 27.2–28.4%, and for 41–42 years old, 14.4–19%.

### The rate of twin deliveries

In reporting its pregnancy data, SART divides multiple gestations into two distinct categories, the first being the percentage of pregnancies resulting in twins and the second being the percentage of pregnancies resulting in triplets or more. During the 5 years of reporting (Figure 10.4), the twin pregnancy rates for the first two age categories, below 35 and 35–37, increased from 30.7 to 33.1% and from 26.4 to 28.6%, respectively. For patients aged 38–40 and 41–42, the rate of twins experienced slight fluctuations but ended approximately the same as at the beginning of the time period. This suggests that for most patients treated with ART up to 2001, the twin pregnancy rate had not declined but in fact had gone up.

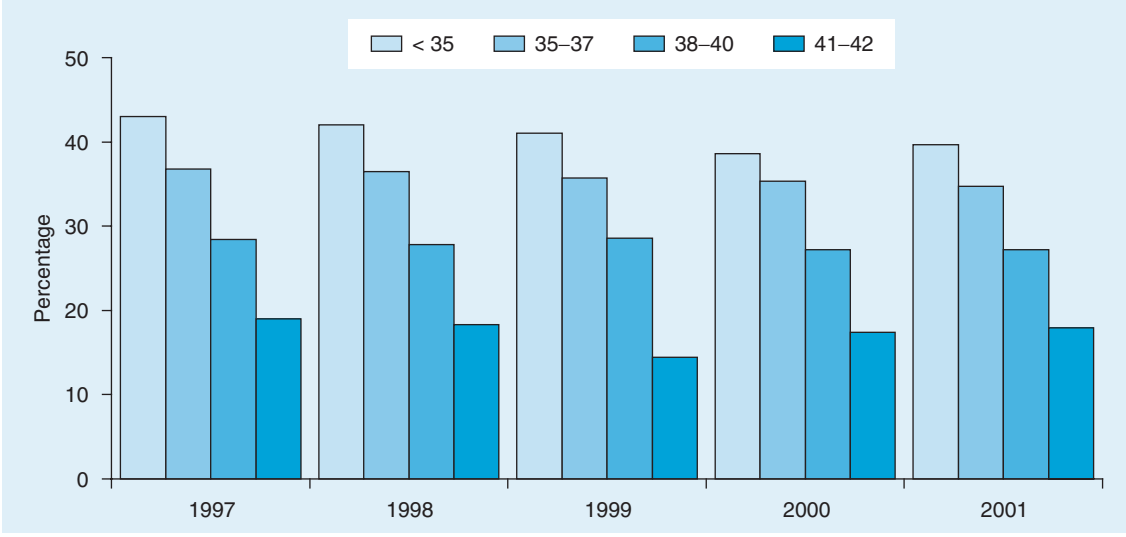


**Figure 10.3** Percentage of live births by maternal age (years) having multiple infants, 1997–2001

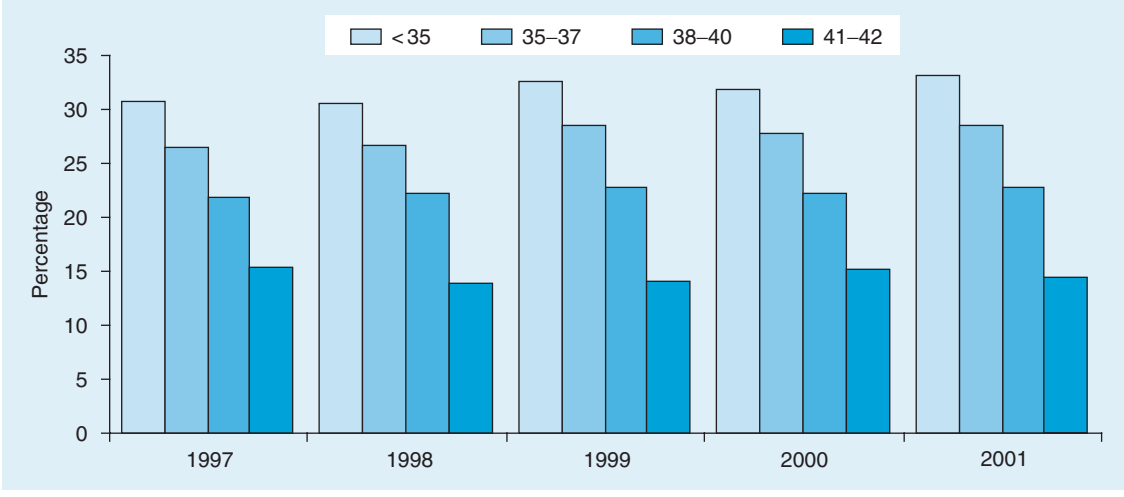


**Figure 10.4** Percentage of pregnancies with twins by maternal age (years), 1997–2001

### The rate of triplets and higher-order multiples

The rate of triplets or higher-order multiple deliveries declined between 1997 and 2001 for patients under 40 (Figure 10.5). An over 5% decline was evident in patients younger than 35, while for patients 35–37 years old, the rate of high-order multiples decreased by 3.5%. Patients between 38 and 40 reflected only a small drop of 0.6%. The rate of triplets and higher-order multiples in patients older than 40 ranged between 2 and 4% and thus shows no trend over the years.

### The effect of the number of embryos transferred on the delivery rate of multiples

Over a 5-year period, a lower rate of triplets and above is observed in the younger age group, concomitant with an increase in the pregnancy rate of twins during the same time period. This trend continues, to a lesser degree, in the intermediate-age group, and is absent in older patients. Thus, it is reasonable to ask whether the changes observed are the result of changes in embryo transfer practices across the United States?

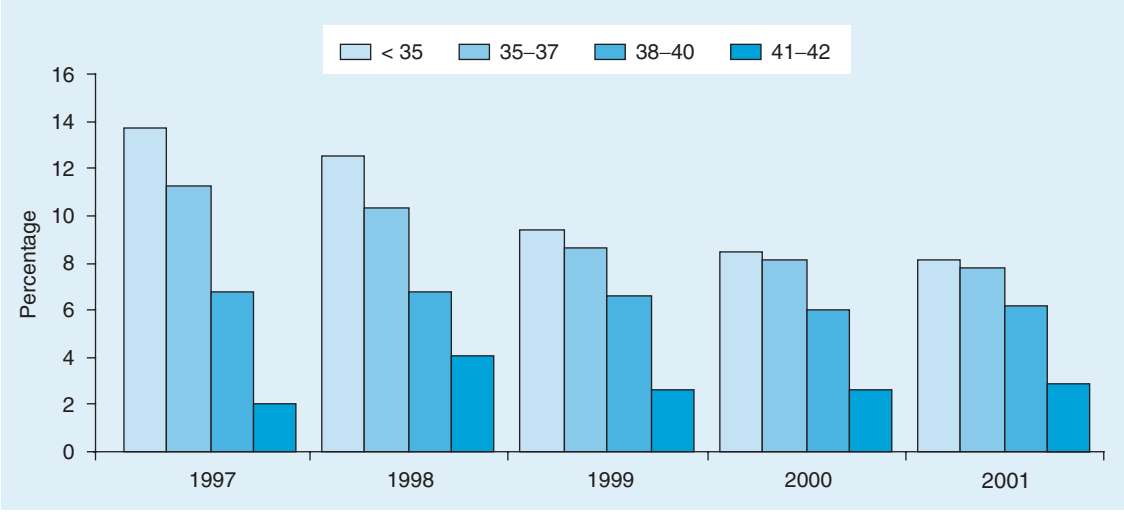


**Figure 10.5** Percentage of pregnancies with triplets or more by maternal age (years), 1997–2001

Figure 10.6 reflects an important change in transfer strategy in women younger than 35, whereby a steady drop in the number of embryos transferred is observed. The average number of embryos transferred dropped from 3.7 in 1997 to 2.8 in 2001. We suggest that in a direct cause-and-effect relationship, the pregnancy rate of triplets and higher-order multiples plummeted by 41%, whereas the twinning rate increased by 8%.

The number of embryos transferred declined across the board for all age groups. Figure 10.7 shows that for patients between the ages of 35 and 37, the number of embryos transferred decreased by 18%, the triplet and higher-order multiple pregnancy rate decreased 31% and the twin rate remained virtually the same. Between the ages of 38 and 40, a 13% reduction in the number of embryos transferred was associated with a 9% decrease in higher-order multiples and no change in the twin pregnancy rate was noted (Figure 10.8). Finally, for patients older than 40, no definitive trend was observed, despite a 7% decrease in the number of embryos transferred (Figure 10.9).

### The impact of embryo cryopreservation

Data for the year 2001 suggest that the transfer of fresh embryos was more likely to result in multifetal pregnancies than the transfer of frozen–thawed embryos. When utilizing patients' fresh embryos, 29.3% of all pregnancies were twins and 7.4% were triplets or higher-order multiples for women of all ages combined. In contrast, when frozen–thawed embryos were utilized, twin and triplet/+ pregnancy rates were lower at 22.2% and 4.4%, respectively. Delivery rates for fresh cycles were 32% for twins and 3.8% for triplets or higher orders. In frozen–thawed cycles, these numbers were 24.2% and 2.6%, respectively. The incidence of multiple-birth deliveries declined with the patients' age in both fresh and frozen cycles.

### The impact of donor eggs

Donor egg cycles result in high pregnancy rates along with high rates of multifetal pregnancies. In the published data for the year 2001, procedures utilizing donor eggs resulted in a 35.5% twin pregnancy rate and an 8.1% triplet/+ rate. Moreover, the percentage of infants born in twin deliveries reached 38.4%. This number, combined with the 3.3% of infants born as triplets/+, demonstrates a total multiple-infant live birth rate of 41.7% with donor eggs. These observations are best explained by the age of donors. The great majority of donors are less than 35 years old. Interestingly, fresh cycles in patients younger than 35 years for the year 2001 resulted in similar twin and triplet/+ pregnancy rates of 33.1% and 8.1%, respectively.

## DISCUSSION

### Trends

The utilization of ART in the United States has risen dramatically since 1981. This exponential increase in the number of cycles, coupled with much improved success rates, has resulted in a spectacular rise in the number of infants born through these procedures annually[2]. Since ART multiple birth rates continue to soar at above 40%, it is clear that ART has managed to bring the multiple pregnancy epidemic to a crisis proportion.

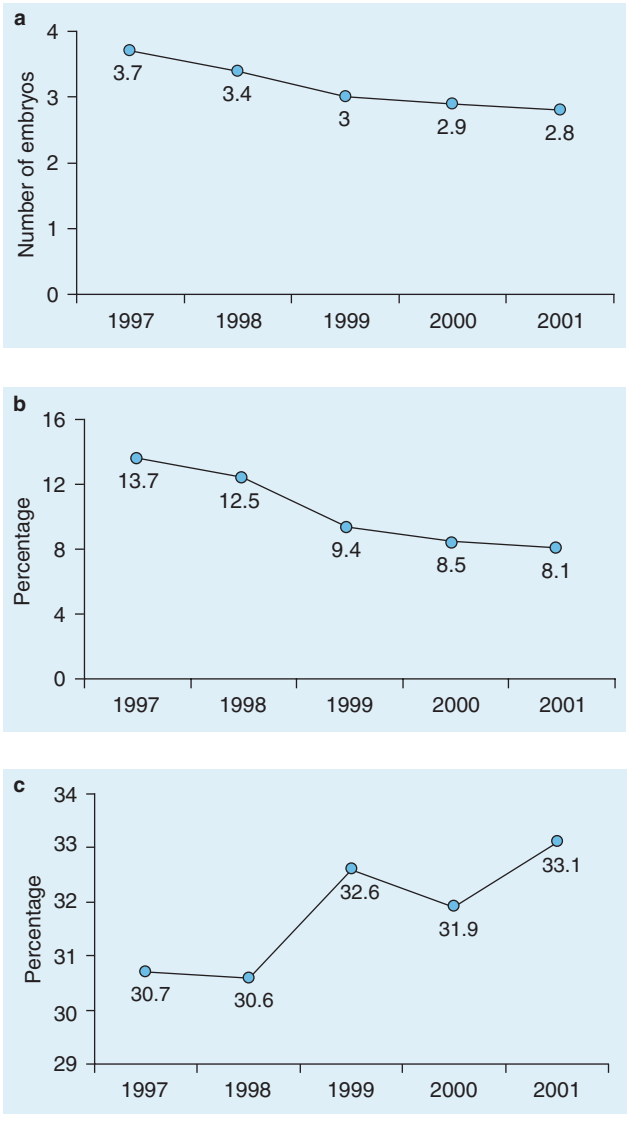


**Figure 10.6** (a) Average number of embryos transferred, maternal age < 35 years; (b) percentage of pregnancies with triplets or more, maternal age < 35 years; (c) percentage of pregnancies with twins, maternal age < 35 years

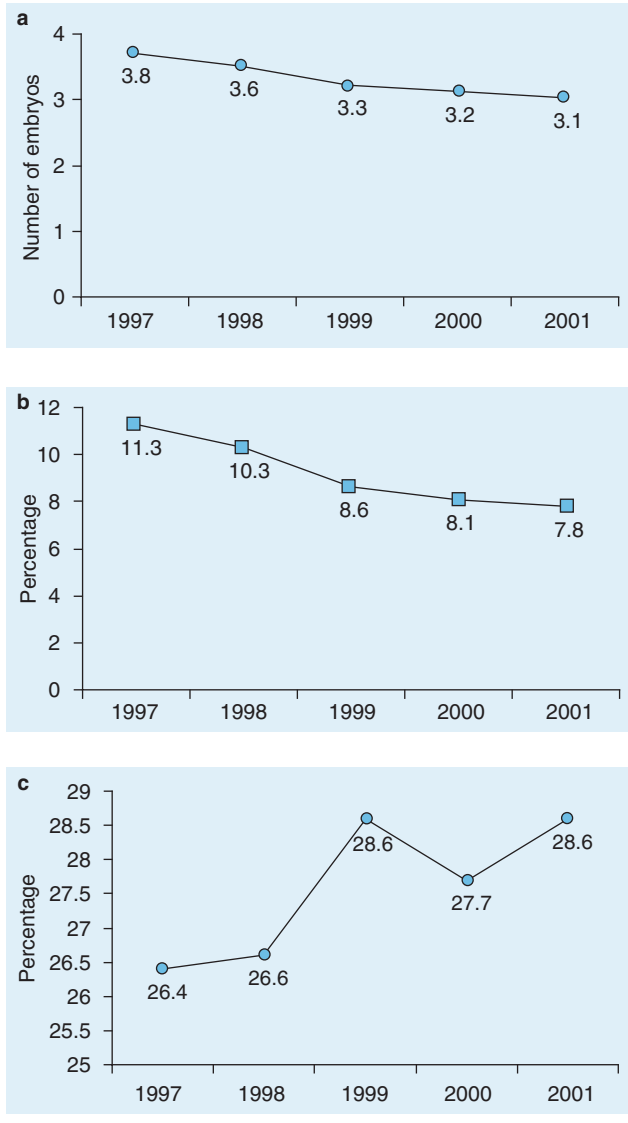


**Figure 10.7** (a) Average number of embryos transferred, maternal age 35–37 years; (b) percentage of pregnancies with triplets or more, maternal age 35–37 years; (c) percentage of pregnancies with twins, maternal age 35–37 years

As dismal as this last statement sounds, this chapter also heralds some good news. Efforts to contain the epidemic have begun; but the change cannot be achieved overnight. Instead, what is apparent is an unplanned, stepwise resolution. By this we mean that slow, yet steady, decline in the delivery of multiple infants occurred between the years 1997 and 2001. This pattern is more apparent in women younger than 38. The first, albeit far from total, success lies in the drop in the delivery rate of triplets/+ for all age groups below 40. The major explanation for this decline is the lower number of embryos transferred. The most significant impact on the delivery rates of multiples of higher order was on the younger group of mothers, where the average number of embryos transferred in 2001 was almost one embryo less compared with 1997. In older patient groups, however, where ART programs were less daring in reducing the number of embryos transferred, a less dramatic drop in high multiples was achieved, until a full halt was noted at age 40.

This leads us to suggest that there exists a certain *threshold* change in the number of embryos transferred, below which a drop in the number of triplets and higher-order multiples cannot be affected. For example, this rate dropped by 18% when the embryo number was 31% lower for 35–37-year-old patients. The rate dropped by 13% when the embryo number

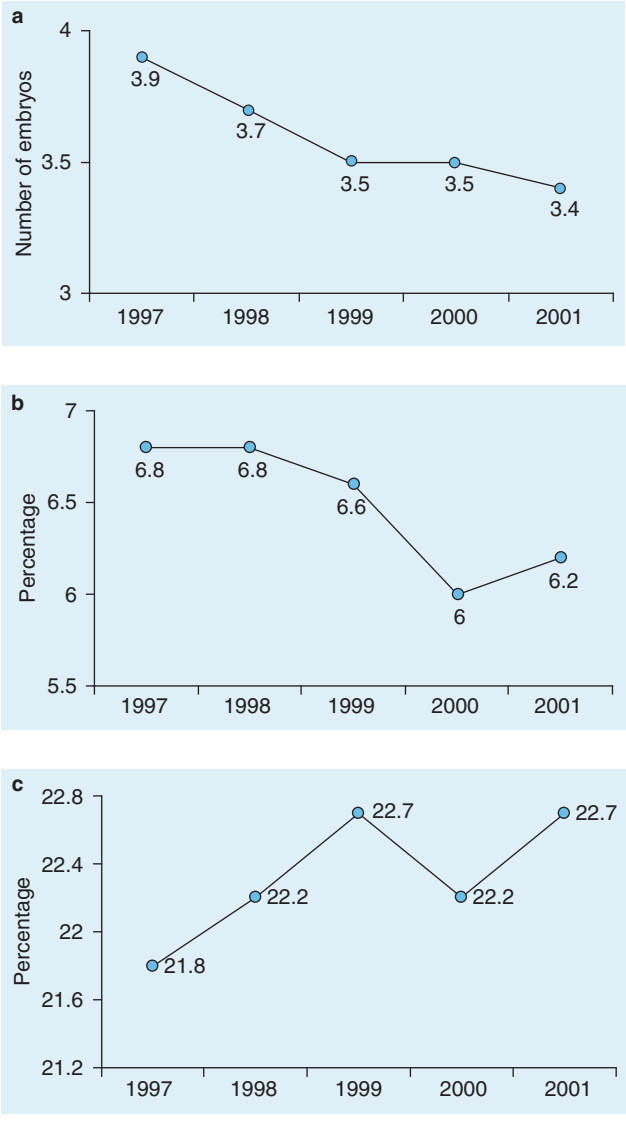


**Figure 10.8** (a) Average number of embryos transferred, maternal age 38–40 years; (b) percentage of pregnancies with triplets or more, maternal age 38–40 years; (c) percentage of pregnancies with twins, maternal age 38–40 years

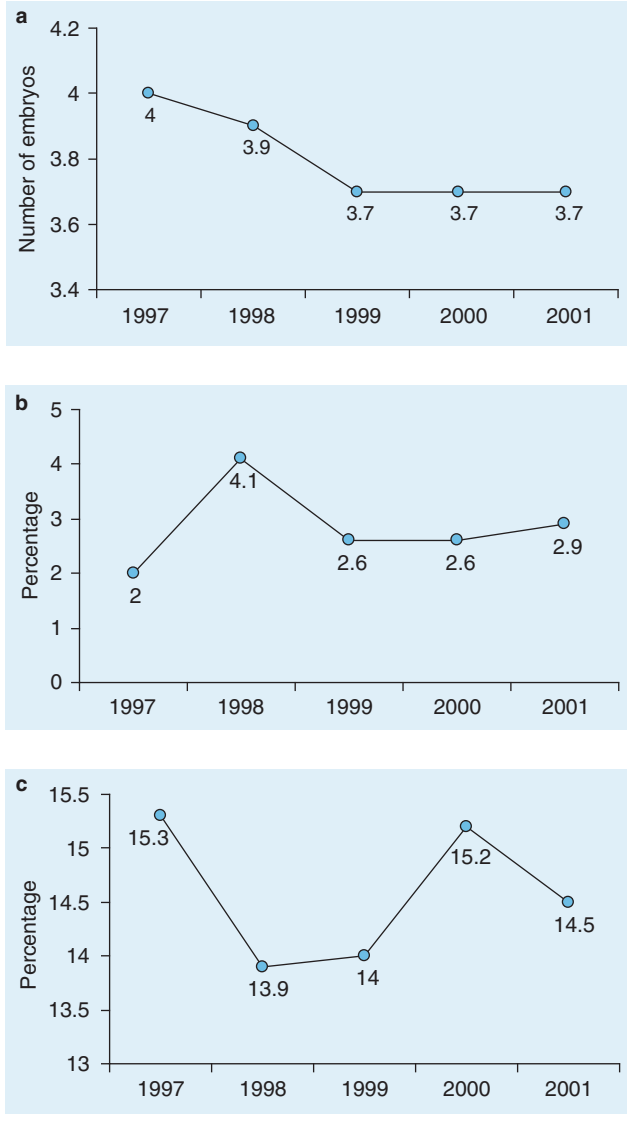


**Figure 10.9** (a) Average number of embryos transferred, maternal age 41–42 years; (b) percentage of pregnancies with triplets or more, maternal age 41–42 years; (c) percentage of pregnancies with twins, maternal age 41–42 years

was only 9% lower for the 38–40-year-old age group, and not at all when the embryo number was only 7% lower for 40 and above. Thus, the threshold can be a 7–9% decrease.

Obviously, this is only the first effort in the work required to reduce the number of iatrogenic multiples. As more programs embrace similar practice changes, the experience described here should drive practitioners to take bolder strides in order to make an impact. We recommend that practitioners have a transfer strategy clearly aimed at producing a singleton-at-a-time, and follow it, not giving in to irrational pressures from patients and staffers alike. One cannot be timid in this business. What may seem like an easy and sometimes rapidly made decision to add one more embryo for 'good luck' may come back to haunt that couple now facing the hardships of multiple gestation (with or without handicaps) for a lifetime.

To date, there has been no success in reduction of twin gestations. In fact, in younger patients for whom the rate of higher-order multiples declined, the twinning rate went up. When we deal with these rates at the time of delivery, triplets/+ that undergo selective reduction will end up as twins, thereby increasing the twin side of the equation.

The reason that twinning has not been reduced to date is because of the trickle down effect from

triplets/+. We believe bolder reforms in embryo transfer strategy are mandatory to see iatrogenic triplets and higher-order gestations practically disappear and for the twinning rate to drop dramatically.

## Improving the trends

Several measures are currently being explored in the United States in an attempt to reduce the number of higher-order multiple deliveries. At the forefront of this effort is the limitation of the number of embryos transferred. Additional measures aimed at supporting this primary strategy without compromising pregnancy rates include embryo scoring, blastocyst transfer, cryopreservation and preimplantation genetic diagnosis. Additionally, natural-cycle IVF may be getting a second chance. Fortunately, changes in insurance coverage should help to facilitate the processes.

## Limiting the number of embryos transferred to one or two

With the highly improved implantation rates, the main strategy being used to reduce the number of babies coming out is to reduce the number of embryos going in[4]. The average number of embryos transferred in 2001 is still too high, but the available data represent only a snapshot in a rapidly declining curve that has hopefully gained momentum in the last, as yet unreported, years. This stepwise, gradual process is easier to implement once programs realize that in their own environment, rather than based on the literature, a drop to one embryo transferred across the board should not reduce the total viable pregnancy rate. A parallel drop in multiples is an extra bonus. As triplets and above gradually disappear from delivery rooms and NICUs, attention will be directed to the next frontier – twins.

A recent study suggests that with proper patient and embryo selection, single embryo transfer can halve the twinning rate without compromising the overall pregnancy rate[5]. Various complex selection models have been devised to determine optimal conditions for single embryo transfer. These include looking at such variables as maternal age, day of transfer and embryo scoring[6].

## Embryo scoring

Before transferring embryos into the patient, many IVF programs assign each embryo a score. Several scoring systems have been introduced, based on embryo morphology and rate of development, to help predict the likelihood of implantation. For example, the Mean Cumulative Embryo Score (MCES) considers both the quality and number of embryos transferred[7]. First, each embryo is given an embryo score, which is assigned based on number of cells, blastomere size and presence of cytoplasmic fragments. Multiplying the embryo score by the number of blastomeres derives a cumulative embryo score. The total cumulative embryo score divided by the number of embryos transferred yields the MCES. Studies conclude that higher embryo scores are required to maintain similar pregnancy outcomes for older patients as compared with the younger study group.

The Graduated Embryo Score (GES) is another example of embryo scoring[8]. After three unique evaluations at separate stages of development, embryos are given a cumulative score, based upon the presence of nucleoli aligned along the pronuclear axis 16–18 h post-insemination, the symmetry of cleavage and fragmentation at 25–27 h and the cell number and grade at 64–67 h. The GES is a total of all three of the above scores, and helps to predict which cleaved embryos will form blastocysts.

## Blastocyst transfer

For about two decades, embryos were transferred 2–3 days after fertilization. ART practitioners felt an urgency to rush these extracorporeal embryos back into the body in order to cut to the minimum the potentially adverse effects of laboratory variables such as temperature, humidity, $CO_2$ concentration and culture media on embryo development[9]. From a physiologic standpoint, in a normal reproductive cycle, an embryo reaches the uterus after 5 days of migration, corresponding to the time that the endometrium is just about prepared for implantation. On day 3, an embryo is typically found in the Fallopian tube while the uterus is several days from preparation for implantation. It is therefore evident that blastocyst transfer more closely approximates natural reproduction. Greatly improved laboratory conditions allow extended embryo culture and the clinical utilization of blastocysts. Not only has blastocyst transfer not compromised results, but rather, many programs have witnessed an increase in their pregnancy rate, along with a significant drop in the rate of high multiples[10,11]. With reported pregnancy rates greater than 60% when transferring one high-scoring blastocyst[12], some programs have ventured into single blastocyst transfers in select cases, thus reducing twinning as well. More recently, some programs have chosen to return to day 3 transfers. Equipped with the new understanding of which embryos develop into blastocysts, transfer of a lower number of embryos on day 3 is possible without compromising pregnancy rates.

## Preimplantation genetic diagnosis

The embryo's genome corresponds to the maternal genome until its activation at the 8-cell stage. Prior to this period, sampling of the embryo will reflect the parent oocyte. Preimplantation genetic diagnosis (PGD) is therefore accurate in determining the activity of the developing embryo only *after* the 8-cell stage. Additionally, a cell can be removed from the differentiated trophectoderm during the biopsy of a blastocyst, enabling the embryo to remain unharmed. As women age, the number and quality of eggs available for ovulation decreases. The resultant embryos of these women are at increased risk for aneuploidy, most notably trisomies, but monosomies as well[13]. These chromosomal abnormalities are primarily of maternal origin. Additionally, the association between aneuploidy and impaired implantation has been well established.

PGD has been explored as a means of improving pregnancy rates in women of advanced maternal age. Other patients postulated to benefit from PGD include those with recurrent pregnancy loss and patients with repeated, failed IVF cycles[14].

In order to analyze an embryo's genome it is necessary to remove one or two cells, typically beyond the 4-cell stage. These embryos are evaluated by fluorescence *in situ* hybridization (FISH), which identifies those with chromosomal abnormalities. The most commonly probed chromosomes, X, Y, 13, 16, 18 and 21, are probed for trisomy. Aneuploidy, polyploidy, haploidy and the fraction of mosaic embryos can also be determined. Embryos found to be chromosomally abnormal are excluded from transfer.

Two potential benefits have been reported in IVF cycles that have incorporated PGD into their embryo selection process: reduced embryo loss after implantation, and an increase in ongoing pregnancy and delivery rates[13]. Therefore, it has been suggested that PGD has four prospective advantages: prevention of trisomic offspring; reduction of spontaneous abortions; improvement of implantation rates; and finally, reduction of multiple births by minimizing the number of embryos required to achieve acceptable pregnancy rates[14,15].

## Cryopreservation

With recent improvement in cryobiology, normal embryos should suffer little damage in the freezing and thawing process. The reason that frozen–thawed embryo transfer success rates still lag behind is that the initial quality of the embryo was inferior to that of the freshly transferred sibling. With curtailment of the number of embryos transferred, embryos of excellent quality should be available for freezing, and should result in similar pregnancy rates to those of fresh cycles. Cryopreservation makes medical, as well as economical, sense.

A recent study developed a theoretical model limiting the number of embryos transferred to two, with cryopreservation and subsequent transfer of the remaining embryos, yielding a cumulative pregnancy rate of 77%. According to the authors of this model, a twin rate of less than 20%, and no triplet or higher-order pregnancies, can be expected[16].

In the competitive ART market fueled by public access to clinic-specific SART data, a change in reporting pregnancies as the *combined delivery rate from fresh and frozen* should more fairly represent the true success of an ART program as well as energize the campaign to increase singleton deliveries.

## Natural cycle IVF

The first successful IVF pregnancy was the result of a natural, unstimulated menstrual cycle[17]. For over a year, the attempts by the Joneses in Norfolk, Virginia, to duplicate the success achieved in England in a natural cycle failed to produce a single pregnancy. It was only after they started to use gonadotropins that the first pregnancy was achieved. Subsequently, a variety of drugs have been incorporated into IVF cycles in an effort to recruit more oocytes for retrieval. These drugs, however, are not without side-effects. The most commonly used drugs, gonadotropins, may lead to ovarian hyperstimulation syndrome (OHSS). OHSS is a potentially life-threatening complication where symptoms range from abdominal distention and weight gain to pleural effusion, electrolyte imbalance, hypovolemia and hypotension. Natural-cycle IVF eliminates the risk of OHSS.

Other advantages of natural-cycle IVF include low cost resulting from the absence of drugs (except for human chorionic gonadotropin (hCG)) and the much reduced need for monitoring, thus making this form of IVF available for patients who cannot afford ART or who choose not to go through treatment for fear of hyperstimulation.

One recent study calculated that natural-cycle IVF could be offered at approximately 23% of the cost of a stimulated cycle[17]. But a return to natural-cycle IVF will require more than that. As results of the limited experience with natural-cycle IVF have been disappointing, only a study from good centers demonstrating high pregnancy rates can bring ART back to where it started.

## Monozygotic twinning

Monozygotic twinning is apparently more frequent in ART cycles, and is responsible for many recent

cases in which the number of fetuses/babies is higher than the number of embryos transferred. As monozygotic multiples are at a higher risk than multizygotic pregnancies, a new and urgent challenge for ART appears. Currently it is unclear whether monozygosity is the result of a specific laboratory technique[18,19] or a phenomenon associated with extended culture, such as in blastocysts[20].

## An important message to health-care providers

One important piece of statistics is absent from this monograph, namely, the rate of multiple gestations resulting from the non-IVF use of gonadotropins. This is the so-called 'controlled ovarian hyperstimulation' (COH). No law currently mandates centers to report statistics on COH outcomes. Clearly, a large proportion of multiples and multiples of high order are the result of COH.

For years, ART programs have boasted the limitation of multiple births as one of the reasons to prefer IVF to ART. However, this was not translated into action, and ART continued only to contribute multiples in droves to already overpopulated NICUs. Now that the age of reason has dawned on us, there is real hope that ART, unlike COH, will prove true as advertised: a fertility treatment aimed at singleton births. The huge potential for ART to make a real impact and effect a significant drop in high-order multiples should finally convince insurance carriers to recognize this important change, increase coverage for ART and not mandate that patients undergo COH prior to ART[21]. With time and continued effort, ART in the USA will likely resolve the iatrogenic epidemic it has largely been responsible for initiating.

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# Multiple Births and Infertility Treatments in France: Results from the FIVNAT Registry

*E. Papiernik, J. de Mouzon and B. Blondel*

11



## INTRODUCTION

In France, as in many other developed countries, ovulation induction and assisted reproductive technologies (ART) have resulted in an increase in multiple births after human menopausal gonadotropin, follicle stimulating hormone and clomiphene citrate became available in 1967, and the first child conceived by *in vitro* fertilization (IVF) was born in 1982. At present, it is possible to assess the effect of ART in France because all the clinics performing it have to be authorized by the Ministry of Health, according to French law, and because those clinics must provide an annual report to the health authorities describing procedures and births. This includes numbers of IVF, intracytoplasmic sperm injection (ICSI) and artificial insemination with spouse or donor semen procedures. At the same time, it is difficult to measure the effects of ovulation induction outside ART, because there is no national reporting of these treatments and data on pregnancy initiation (including infertility treatments) are not collected routinely for all French births[1].

Multiple pregnancies have numerous consequences for both the children's health and the families[2]. For example, the recent increase in the rate of preterm delivery in many countries is partly explained by the increase in twin births and by the increase in preterm deliveries among twin pregnancies[3,4].

The objective of this chapter is to describe the impact of fertility treatments on multiple pregnancies and deliveries in France. First, we describe briefly the current increase in multiple births. We then estimate the respective roles of ART and ovulation induction in multiple deliveries. Finally, we focus on ART using the FIVNAT registry. With this data set, our aim was to study the risk of multiple deliveries according to medical policies of embryo transfer.

## RATES OF MULTIPLE DELIVERIES

The number of multiple deliveries rose in France over the past 30 years, as shown by data derived from vital statistics (INSEE, National Institute for Statistics and Economic Studies)[5]. The rate of twin deliveries was at a minimum in 1972 at 9.0 per 1000, and increased afterwards continuously to 15.0 per 1000 in the year 2000. Trends for triplet deliveries were different. The rate rose steeply from 0.8 per 10 000 deliveries in 1971 to 4.5 per 10 000 in 1989 and then fell; recent data suggest a leveling off.

In the years 1998–2000, the overall number of deliveries increased (Table 11.1, +4.9%), but the increase in the number of twin deliveries was larger (+8.8%), whereas the number of triplet deliveries decreased substantially (−12.1%).

## IMPACT OF ALL FERTILITY TREATMENTS ON MULTIPLE DELIVERIES

Infertility treatments play a major role in the increase of multiple pregnancies in the overall population. When ovulation induction alone is used, the risk of multiple pregnancies is reported to be 6–8% with clomiphene citrate[6]. It is much higher with gonadotropins, and may reach 20–30%[7]. When insemination is carried out with ovulation stimulation, the percentage of multiple pregnancies can reach 20%[8,9]. The risk is also very high with ART. In 1999, in European countries, 26% of deliveries after IVF or ICSI with fresh embryos were multiples[10].

**Table 11.1** Rates of twin, triplet and quadruplet deliveries in France in 1998, 1999 and 2000. Data from reference 5

| | *1998* | | *1999* | | *2000* | | *Difference 2000–1998* | |
|---|---|---|---|---|---|---|---|---|
| | *n* | *Rate* | *n* | *Rate* | *n* | *Rate* | *n* | *%* |
| Twins (/1000) | 10 553 | 14.4 | 10 967 | 14.9 | 11 483 | 15.0 | + 930 | + 8.8 |
| Triplets (/10 000) | 240 | 3.3 | 209 | 2.9 | 211 | 2.8 | –29 | –12.1 |
| Quadruplets and more | 6* | | 6 | | 5 | | –1 | |
| Multiples, total (/1000) | 10 799 | 14.8 | 11 182 | 15.2 | 11 699 | 15.3 | + 900 | + 8.3 |
| Total deliveries | 730 717 | | 736 830 | | 766 421 | | + 35 704 | + 4.9 |

*One set of quintuplets

**Table 11.2** Proportions of twin and triplet deliveries after fertility treatment in France in 1998, 1999 and 2000. Data from FIVNAT, 1998–2000, and references 3 and 5

| | *1998* | | *1999* | | *2000* | |
|---|---|---|---|---|---|---|
| | *n* | *%* | *n* | *%* | *n* | *%* |
| *Twins* | 10 553 | | 10 967 | | 11 483 | |
| IVF* | 1 820 | 17.2 | 1 843 | 16.8 | 1 867 | 16.2 |
| Insemination | 372 | 3.5 | 372 | 3.4 | 429 | 3.7 |
| Ovulation induction† | | ~ 10.7 | | NA | | NA |
| *Triplets* | 240 | | 209 | | 211 | |
| IVF* | 103 | 42.9 | 107 | 51.2 | 94 | 44.5 |
| Insemination | 15 | 6.3 | 14 | 3.7 | 17 | 8.0 |
| Ovulation induction‡ | 44 | 18.3 | 9 | 4.3 | 18 | 8.5 |

*Including intracytoplasmic sperm injection (ICSI) and frozen embryo replacement; †in the 1998 national perinatal survey, 30.9% of twins were born after fertility treatment[14]; consequently, data from FIVNAT and the 1998 survey suggest that about 10% of twin deliveries occurred after ovulation induction alone; ‡estimation based on the hypothesis that the increase in the number of triplets since 1972 was explained only by fertility treatments and increasing maternal age (see calculations in text); IVF, *in vitro* fertilization; NA, not available

This figure reached 30% in a world collaborative report on ART in 1998[11].

In France, data on the role of ART in multiple deliveries are derived from the FIVNAT registry (French IVF national registry)[12,13]. This registry produces statistics for most of the 95 centers that are allowed to provide ART. Data are collected for every treated cycle and for every clinical pregnancy, and then are analyzed at national level (scientific co-ordinator J. de Mouzon). Information is given for IVF, ICSI and fresh or frozen embryo replacements. This voluntary contribution is complemented by a compulsory report from each center to the French IVF regulation authority that includes data on artificial insemination.

In the years 1998–2000, we estimated the proportion of multiple deliveries attributable to ART by dividing the total number of ART multiple deliveries by the total number of multiple deliveries derived from vital statistics. In 1998, 17.2% of the French twin deliveries resulted from IVF or related techniques, and 3.5% resulted from insemination (Table 11.2). The rate for IVF was 16.2% in 2000. The proportion of triplets resulting from IVF and related techniques was 42.9% in 1998 and 44.5% in 2000, and that resulting from artificial insemination was 6.3% in 1998 and 8.0% in 2000.

What remains unknown is the number of multiple deliveries after ovulation stimulation alone. In 1998, data were available from a national perinatal survey based on a representative sample of 13 000 births[3]. Women were interviewed after delivery about previous fertility treatments. It was found that 30.9% of all twin deliveries resulted from such treatments[14]. It is thus possible to infer from these data and the FIVNAT registry that about 10% of twin deliveries resulted from ovulation stimulation alone.

Such an estimation was not possible for triplet deliveries because the sample in the national perinatal survey was too small. However, we estimated the proportion of triplet deliveries after ovulation induction using other available statistics. We calculated the expected number of triplet deliveries in 1998, using the hypothesis that the triplet delivery rate in each maternal age group had not changed since 1972, i.e. before the diffusion of fertility treatments. A figure was obtained by applying 1972 age-specific triplet rates to the distribution of maternal age in 1998. Using the hypothesis that the difference between the observed number and the expected number of triplet deliveries was explained only by fertility treatments, 44 of 240 triplet deliveries (18.3%) would be attributable to ovulation induction in 1998. This rate would be 4.3% in 1999 and 8.5% in 2000.

The impact of ART on multiple deliveries is known for several countries. The proportion of deliveries resulting from ART among all twin deliveries was 12% in the USA in 1997–2000[15], 17% in Sweden in 1994–95[16], 24% in Flanders in 1992–97[17] and 26% in Finland in 1998–99[18]. The proportion of deliveries resulting from ART among triplet deliveries was similar in France to that observed in the USA: 42% in 2000[15]. This lack of difference, although the proportion of triplets among ART babies was far higher in the USA, was due to a smaller number of ART cycles in the population in this country.

Knowledge of the proportion of multiple births resulting from ovulation induction alone is lacking. In 1989, a survey of all triplet births in the UK showed that 31% of them were born after ovarian stimulation alone and 35% by ART[19]. The East Flanders Prospective Twin Survey provides statistics on all twins born in this area since 1985[20]. In 1985–89, 18% of twin deliveries occurred after ovulation induction alone and 4% after ART (Derom, personal communication). In 2000–02, these proportions were, respectively, 17% and 27%. The results from these two countries suggest that, in Western countries, ovulation induction has a substantial impact on twin as well as triplet deliveries.

## ROLE OF TRANSFER POLICIES ON MULTIPLE DELIVERIES IN IVF AND ICSI

The risk of multiple pregnancy and birth is mainly related to the number of embryos replaced at each attempt, and to the woman's age. Moreover, in a case of multiple pregnancy, when the number of developing fetuses is equal to or greater than three, multifetal reduction (MFR) is usually offered to the couple, according to the French good practice guide on *in vitro* fertilization (JO 28/02/99, pp. 3061–3069 arrêté du 12/01/99).

If the woman's age is a factor, the number of embryos to be transferred is usually a medical decision. This decision generally relies on the number of embryos produced and on an *a priori* estimation of the woman's chance of becoming pregnant, which is strongly related to her age and to the apparent quality of her embryos. Thus, when more than one embryo is produced, the physician has the choice to the transfer all the embryos or only some of them.

The results of these policies are shown in Table 11.3, which relies on all transfers included in the FIVNAT registry during the years 1998, 1999 and 2000. The table is divided into two parts, according to women's age (≤ 37 years and ≥ 38 years), since the policies differ. The results are reported according to the number of transferred embryos and the presence of extra embryos (not transferred). This presence means that a choice was possible among the cohort of embryos produced and that some of them were not replaced in the uterus. The usual policy is to choose the best-quality embryos to be transferred, but there are no data on embryo quality as such in FIVNAT.

The studied parameters were the per-transfer clinical pregnancy and delivery rates, the per-delivery twin and triplet rates, the per-ongoing pregnancy multifetal reduction (MFR) rate and the per-newborn rates of very preterm delivery (< 33 weeks) and of very low birth weight (< 1500 g). A pregnancy was defined as clinical if at least one gestational sac was seen at ultrasound examination. A delivery was defined as a pregnancy ending at 22 weeks of gestation or more. The preterm birth rates and the proportions of low-birth-weight newborns were computed for all the babies, whether they were singletons, twins or triplets, to appreciate better the impact of treatment on all ART babies. The pregnancy and delivery rates can be viewed as efficacy markers for IVF, whereas preterm deliveries, low-birth-weight babies and multifetal reductions can be considered as adverse outcome measures.

For women of 37 years and less (Table 11.3), the two most frequent situations were elective transfers of two (29.5%) and of three (26.6%) embryos, an elective transfer being defined as a transfer with extra embryos. These were associated with the highest per-transfer clinical pregnancy rates (32.8% and 31.9%, respectively) and delivery rates (26.0% and 24.3%). It is also interesting to observe that 3.1% of the transfers were elective transfers of a single embryo, and that less than 1% involved five embryos or more. The choice of not transferring all the embryos produced was always associated with a higher pregnancy rate. It can also be noted that transfers of three, four or five embryos were associated with lower pregnancy rates compared with the elective transfer of two embryos, which means that

**Table 11.3** Distribution of transfers and of treatment outcomes according to number of transferred embryos, presence of extra embryos and women's age. Data from FIVNAT, 1998–2000

| *Transfer distribution* | | | *Clinical pregnancies*† | *Deliveries* | | | | *Babies* | | |
|---|---|---|---|---|---|---|---|---|---|---|
| *Transferred embryos* | *Extra embryos** | *Transfers (%)* | *(%)* | *All*† *(%)* | *Twins*‡ *(%)* | *Triplets*‡ *(%)* | *MFR*§ *(%)* | *Total (n)* | *<33 weeks*¶ *(%)* | *<1500 g*¶ *(%)* |
| *≤37 years* | | | | | | | | | | |
| 1 | no | 11.0 | 10.9 | 7.6 | 1.2 | 0.0 | 0.2 | 433 | 0.7 | 0.2 |
| | yes | 3.1 | 17.8 | 12.7 | 2.5 | 0.0 | 0.0 | 170 | 2.9 | 2.4 |
| 2 | no | 13.3 | 19.4 | 14.5 | 15.6 | 0.2 | 0.1 | 1222 | 3.6 | 2.3 |
| | yes | 29.5 | 32.8 | 26.0 | 26.3 | 0.3 | 0.6 | 5061 | 5.2 | 3.4 |
| 3 | no | 9.8 | 24.4 | 17.9 | 23.6 | 1.9 | 1.4 | 1218 | 5.8 | 4.2 |
| | yes | 26.6 | 31.9 | 24.3 | 30.1 | 2.7 | 3.1 | 4975 | 8.0 | 6.3 |
| 4 | no | 2.1 | 25.1 | 17.0 | 27.2 | 4.2 | 3.2 | 286 | 8.0 | 4.8 |
| | yes | 3.7 | 28.2 | 21.8 | 34.2 | 2.8 | 5.9 | 682 | 8.5 | 6.7 |
| 5 | no | 0.4 | 26.9 | 19.0 | 27.1 | 2.1 | 2.0 | 55 | 3.6 | 4.0 |
| | yes | 0.5 | 26.6 | 19.4 | 30.7 | 0.0 | 7.8 | 68 | 7.4 | 6.5 |
| Total | — | 100.0 | | | | | | | | |
| *≥38 years* | | | | | | | | | | |
| 1 | no | 16.3 | 8.6 | 4.8 | 1.0 | 0.0 | 0.0 | 79 | 0.0 | 0.0 |
| | yes | 3.3 | 10.7 | 7.0 | 11.1 | 0.0 | 0.0 | 24 | 4.2 | 0.0 |
| 2 | no | 16.0 | 14.6 | 9.3 | 10.0 | 0.0 | 0.5 | 183 | 2.7 | 2.8 |
| | yes | 13.5 | 24.0 | 16.4 | 16.9 | 0.7 | 0.0 | 273 | 3.3 | 3.4 |
| 3 | no | 13.2 | 19.8 | 12.3 | 13.8 | 0.9 | 0.9 | 202 | 1.5 | 2.1 |
| | yes | 24.5 | 26.5 | 17.1 | 18.6 | 1.2 | 2.2 | 620 | 6.0 | 5.1 |
| 4 | no | 4.2 | 21.3 | 11.4 | 19.7 | 0.0 | 1.4 | 70 | 11.4 | 5.9 |
| | yes | 7.0 | 24.0 | 17.6 | 25.1 | 1.6 | 3.6 | 228 | 7.5 | 4.8 |
| 5 | no | 0.9 | 25.9 | 17.5 | 13.0 | 4.3 | 0.0 | 24 | 0.0 | 0.0 |
| | yes | 1.1 | 23.2 | 14.9 | 24.0 | 0.0 | 0.0 | 26 | 0.0 | 0.0 |
| Total | — | 100.0 | | | | | | | | |

*Embryos remaining after transfer (frozen or discarded); †rate per 100 transfers; ‡rate per 100 deliveries; §rate of multiple fetal reductions (MFRs) per 100 ongoing pregnancies; ¶rate per 100 newborns

they were probably assigned to couples with a poorer chance of becoming pregnant.

On the other hand, the twin, triplet and MFR rates increased with the number of transferred embryos. We summed the triplet and the MFR rates, since a multifetal reduction generally aims to reduce the number of developing embryos to two or to one. This multiple rate increased from 0.3% or 0.9% (depending on the absence or presence of extra embryos) when two embryos were transferred, to 3.3% and 5.8%, respectively, for three embryos, 7.4% and 8.7% for four and 4.1% and 7.8% for five. Again, the multiple risk was always higher in the case of presence of extra embryos than in the opposite situation. The trends were similar for twin deliveries.

For elective transfers of two embryos, the percentage of babies born at less than 33 weeks of gestation was 5.2% and the percentage of those weighing less than 1500 g was 3.4%. These two rates were increased by around 60% if three or more embryos were transferred, whether there were extra embryos or not.

Finally, with two embryos replaced by choice, the proportion of triplets was only 3 per 1000 pregnancies, whereas the pregnancy rate was maximized. The replacement of three embryos or more did not result in a higher percentage of pregnancies, but did result in higher proportions of triplet deliveries, of very-preterm and of very-low-birth-weight babies. [*Editor's Note*: the same is found in other programs.]

For women 38 years and more (Table 11.3), there were some differences compared with the younger group. The most frequent decision was to replace three embryos by choice (24.5%), and this subgroup was associated with the highest clinical pregnancy rate (26.5%). If only two embryos were replaced by choice, the pregnancy rate was close to this (24.0%), but in the subgroups of two or three embryos with no extra embryo, rates were much lower. When

**Table 11.4** Odds ratios for clinical pregnancy occurrence and their 95% confidence intervals (CIs): results from multivariate logistic regression analyses. Data from FIVNAT, 1998–2000

| | *All women 87 612 transfers* | | *Age ≤ 37 years 68 576 transfers* | | *Age ≥ 38 years 19 036 transfers* | |
|---|---|---|---|---|---|---|
| | *Estimate* | *95% CI* | *Estimate* | *95% CI* | *Estimate* | *95% CI* |
| *Transferred embryos* | | | | | | |
| 1 | 0.46 | 0.43–0.49 | 0.46 | 0.43–0.49 | 0.48 | 0.42–0.54 |
| 2 | 1 | — | 1 | — | 1 | — |
| 3 | 1.06 | 1.03–1.10 | 1.03 | 0.99–1.06 | 1.27 | 1.16–1.38 |
| 4 | 1.03 | 0.96–1.10 | 1.00 | 0.92–1.08 | 1.20 | 1.06–1.35 |
| ≥5 | 1.08 | 0.92–1.27 | 0.98 | 0.79–1.22 | 1.34 | 1.05–1.71 |
| *Extra embryos* | | | | | | |
| No | 1 | — | 1 | — | 1 | — |
| Yes | 1.63 | 1.57–1.69 | 1.65 | 1.59–1.72 | 1.50 | 1.38–1.52 |
| *Age (years)* | | | | | | |
| ≤37 | 1 | — | — | — | — | — |
| ≥38 | 0.67 | 0.64–0.70 | — | — | — | — |

combining triplet and MFR rates, the multiple rates also increased with an increasing number of transferred embryos from 0.5% and 0.7% for two embryos (respectively, if there were no extra embryos or if there were some), to 1.8% and 3.4% for three embryos and 1.4% and 5.2% for four. However, these proportions were lower compared with those in women of 37 years and less, taking into account the number of transferred embryos. The same was true for the twin deliveries, which increased slowly between two and three transferred embryos and only increased more for elective transfers of four and five embryos. However, the proportions of very-preterm and very-low-birth-weight babies were much higher if three or four embryos were replaced instead of two, at a similar level as for younger women.

When a multivariate analysis (logistic regression) was conducted on the pregnancy chances (Table 11.4), it was concluded that the transfer of three embryos was associated with only a very small increase in odds ratio (OR 1.06, 95% confidence interval (CI) 1.03–1.10), and the odds ratios were not significantly increased for four embryos (OR 1.03, 0.96–1.10) or for five (OR 1.08, 0.92–1.27). The main factors were the existence of extra embryos (OR 1.63, 1.57–1.69) and woman's age of 38 or more (OR 0.67, 0.64–0.70). However, when the logistic model was applied to the two subgroups of women aged 37 years or less and 38 years or more, the conclusion was modified in the older group, where the transfers of three, four and five embryos were associated with significantly higher odds ratios for pregnancy occurence compared with two embryos (around 1.30). There was no significant OR in the younger group.

On the other hand, the number of transferred embryos was associated with a very strong effect on multiple pregnancies and on multifetal reduction (Table 11.5). Thus, if a two-embryo transfer was considered as the reference category, the odds ratios for twin deliveries increased to 1.3 (95% CI 1.2–1.5) for three, to 1.9 (1.6–2.2) for four and 1.6 (1.0–2.5) for five. ORs were dramatically increased for triplet delivery (respectively, 11.1, 6.8–17.9; 18.4, 10.1–33.6; 5.1, 0.7–38.8) and for MFR (5.8, 3.7–8.5; 12.5, 7.8–20.1; 14.5, 5.9–35.7). The existence of extra embryos was associated with an increased risk and age of 38 years or more with a substantial decrease.

Clearly, these results come from an observational study, and not from a randomized protocol. However, published studies comparing the transfers of two and three or more embryos are generally observational. Only recently, a few controlled trials comparing single- and double-embryo transfers have appeared. The reasons for the very small number of randomized studies are related to the fear that reducing the number of transferred embryos decreases the chances to become pregnant, and also to the complexity of success factors related to pregnancy rates: woman's age, previous failures, oocyte number, and quality and number of available embryos for transfer. For example, in a cohort of 327 patients, with 545 cycles, Gerris and colleagues[21] were able to select only 53 patients who fulfilled the inclusion criteria (first cycle, age < 34 years, ≥ 2 high-quality embryos and couple's consent).

Most of the published observational studies come to the same conclusion, that is, reducing the number of embryos transferred from three to two does not

**Table 11.5** Odds ratios for twin and triplet deliveries and for multifetal reduction and their 95% confidence intervals (CIs): results from multivariate logistic regression analyses*. Data from FIVNAT, 1998–2000

| | *Twin deliveries* | | *Triplet deliveries* | | *Fetal reductions* | |
|---|---|---|---|---|---|---|
| | *Estimate* | *95% CI* | *Estimate* | *95% CI* | *Estimate* | *95% CI* |
| *Transferred embryos* | | | | | | |
| 1 | 0.06 | 0.03–0.11 | — | — | 0.4 | 0.05–2.75 |
| 2 | 1 | — | 1 | — | 1 | — |
| 3 | 1.3 | 1.2–1.5 | 11.1 | 6.8–17.9 | 5.8 | 3.7–8.5 |
| 4 | 1.9 | 1.6–2.2 | 18.4 | 10.1–33.6 | 12.5 | 7.8–20.1 |
| ≥ 5 | 1.6 | 1.0–2.5 | 5.1 | 0.7–38.8 | 14.5 | 5.9–35.7 |
| *Extra embryos* | | | | | | |
| No | 1 | — | 1 | — | 1 | — |
| Yes | 1.6 | 1.4–1.7 | 1.3 | 0.9–1.9 | 2.15 | 1.5–3.2 |
| *Age (years)* | | | | | | |
| ≤ 37 | 1 | — | 1 | — | 1 | — |
| ≥ 38 | 0.5 | 0.4–0.6 | 0.3 | 0.2–0.6 | 0.5 | 0.3–0.8 |

*Calculations were made on 12 828 pregnancies for twin risk (9536 singletons and 3292 twins), 9719 pregnancies for triplet risk (9536 singletons and 183 triplets) and 16 475 ongoing pregnancies for multifetal reduction (MFR) risk (16 244 without MFR and 231 MFR)

jeopardize the pregnancy rate. Thus, in a German, retrospective analysis[22], the elective transfers of two and three embryos were associated with a pregnancy rate of, respectively, 22.0% and 22.5%. Also, in a historic study comparing two periods when three embryos were systematically transferred (when possible) and when only two were transferred at the first attempt[23], the overall pregnancy rates were similar. This is probably not the case for single-embryo transfer. Thus, in the reported clinical trial[21], single-embryo transfers ($n = 26$) were associated with a decreased pregnancy rate, compared with dual-embryo transfers (38.5% vs. 74.1%, $p < 0.05$), and also with a decreased multiple pregnancy rate (10% vs. 30%, not significant).

One of the limitations of most studies of the transfer policies is the lack of data on embryo quality, obviously a very important implantation factor. This comes from the difficulty in its assessment, since it is generally based upon morphologic criteria, upon which there is not universal agreement, and also from the association of different-quality embryos in the same transfer. An indirect means of judging its impact is to compare the elective transfers of two embryos (transfers in which a choice was made among embryos produced) with the transfers of two embryos where no choice was possible, since only two were produced. The same can be done with the transfers of three or more embryos. In effect, the pregnancy rates associated with elective transfers of a given number of embryos are always higher than those associated with non-elective transfer of the same embryo number. However, this will be better understood when embryo quality is available for all transfers.

It appears clearly that the number of transferred embryos is directly related to the multiple pregnancy risk, whereas it does not play an important role in pregnancy rate when at least three embryos are available for transfer. However, some other factors must be taken into account, particularly women's age, since at 38 years or more, pregnancy rate decreases and the multiple pregnancy rate is much lower than for younger women. The number of transferred embryos has a direct influence on the percentage of preterm and of low-birth-weight babies, because of the multiple pregnancy rate.

## INTERNATIONAL COMPARISONS OF THE IMPACT OF TRANSFER POLICIES

There are huge differences in embryo transfer policies between countries, as shown by the last world report on ART. This report is published approximately every other year, with data coming from countries where a national registration of ART is in place. It includes data collected at a national or a supranational level on the various ART procedures, and their results. The last report concerned all of America, almost all of Europe and some Asian countries, in total 44 countries. Table 11.6 summarizes the results from 28 countries (Latin America included 11 countries)

**Table 11.6** Number of transferred embryos and multiple pregnancies in selected countries, classified by percentages of transfers with three or more embryos. Data from reference 11

| | *Clinics reporting* (%) | *Total transfers* (*n*) | *Number of transferred embryos* | | | *Deliveries* | | |
|---|---|---|---|---|---|---|---|---|
| | | | *3* (%) | *≥4* (%) | *Average* (*mean*) | *Per OPU** (%) | *Twin*† (%) | *Triplet*† (%) |
| Sweden‡ | 100 | 2 921 | 3.2 | 0.0 | 1.92 | 23.9 | 22.9 | 0.5 |
| Finland‡ | 100 | 2 503 | 8.2 | 0.1 | 1.90 | 20.5 | 25.0 | 0.2 |
| Australia‡ | 100 | 5 337 | 26.9 | 2.1 | 2.15 | 13.3 | 22.0 | 0.7 |
| Switzerland‡ | 100 | 778 | 29.0 | 2.8 | 2.22 | 11.0 | 21.8 | 1.0 |
| New Zealand‡ | 100 | 485 | 36.1 | 1.6 | 2.33 | 21.9 | 21.8 | 1.7 |
| United Kingdom‡ | 100 | 13 929 | 43.9 | 0.0 | 2.35 | 19.9 | 26.5 | 3.2 |
| France‡ | 100 | 17 639 | 39.5 | 8.6 | 2.41 | 16.5 | 25.2 | 1.6 |
| Germany | 84.5 | 13 701 | 56.1 | 0.0 | 2.44 | 13.7 | 21.4 | 4.0 |
| Russia | 62.5 | 3 094 | 17.2 | 45.4 | 2.64 | 14.3 | 25.1 | 5.3 |
| Italy | 54.0 | 4 564 | 46.4 | 16.8 | 2.69 | 16.3 | 20.2 | 4.6 |
| Hong Kong‡ | 100 | 618 | 48.9 | 18.1 | 2.72 | 13.1 | 26.3 | 0.0 |
| Greece | 44.4 | 2 807 | 37.5 | 33.1 | 2.94 | 17.6 | 37.3 | 1.6 |
| Singapore‡ | 100 | 1 498 | 68.4 | 2.5 | 2.63 | NA | 22.6 | 3.8 |
| Latin America‡ | 100 | 3 501 | 23.0 | 48.2 | 3.33 | 19.3 | 22.2 | 7.0 |
| Czech Republic‡ | 93.3 | 3 204 | 38.5 | 34.6 | 2.97 | 19.2 | 36.7 | 5.1 |
| Hungary | 75.0 | 757 | 48.6 | 24.7 | 2.91 | 17.6 | 25.5 | 5.4 |
| Spain | 37.9 | 2 059 | 42.2 | 31.2 | 2.94 | 17.4 | 27.7 | 4.7 |
| USA‡ | 100 | 25 339 | 33.8 | 45.8 | 3.46 | 30.0 | 33.2 | 6.9 |

*Rate of pregnancy per oocyte pick-up (OPU); †rate per delivery; ‡complete or almost complete coverage; NA, not available

where the percentage of reporting clinics was *greater than* 75% (with the exception of Greece, Italy, Russia and Spain), and where information on the number of transferred embryos and on multiple pregnancies was available. Countries are ordered according to the percentage of transfers with three embryos or more. From this Table, one sees that the mean pregnancy rate is not strongly related to the percentage of transfers with three or more embryos, except for the USA, where almost 80% of the transfers involved three embryos or more and the pregnancy rate was 30%. On the other hand, the percentage of triplet pregnancies increased very much according to the number of embryos transferred. It reached approximately 7% in Latin America, where the percentage of transfers of three or more embryos was in excess of 70%, compared with less than 1% in countries where fewer than 30% of transfers involved three embryos or more.

## CONCLUSION

Infertility treatments play a major role in the high multiple pregnancy rate observed in France, as in many developed countries. If, during the period 1998–2000, triplet deliveries seem to decrease (−12.1%), this is not the case for twin deliveries, which are still increasing (+ 8.8%). In ART, the major risk factor is the number of transferred embryos. ART still plays a major role even if transfer policies are changing, as is the case in many countries, by decreasing the number of transferred embryos; other treatments (including artificial insemination) are involved in approximately the same number of twins and many fewer triplets, compared with ART. Large efforts still need to be made to decrease the total number of multiple pregnancies. More and more articles favor single-embryo transfer, as the associated multiple pregnancy rate is very low. However, these procedures appear to be more favored in a small percentage of couples, young, with a high embryo quality, in order not to decrease the pregnancy chance too much. Efforts also need to be made to reduce the multiples risk in other infertility treatments, in which the number of embryos cannot really be controlled.

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# Errors in Gestational Age: Implications in Studies of Perinatal Epidemiology

*C. V. Ananth and R. W. Platt*

12



## INTRODUCTION

In epidemiologic and clinical risk assessment studies of adverse pregnancy outcomes, gestational age is clearly one of, if not the most important, factor in assessing perinatal risk. Estimation of gestational age in large, population-based studies relies heavily on the timing of the last normal menstrual period as reported by the patient. Unfortunately, the menstrual estimate of gestational dating is fraught with errors – both systematic and random. Inaccurate recall of the date of the last normal menstrual period is one of the chief biases in the process of over- and underestimation of gestational age[1]. In contrast, bleeding very early in pregnancy – often mistaken for menstrual bleeding[2] – frequently also leads to underestimation of gestational duration. Irregular or delayed menstrual cycles lead to an overestimation of gestational duration, as these women may not exhibit the presumed 15-day interval between ovulation and menstrual bleeding[3–5].

In general, errors in gestational age based on menstrual dating not only affect studies of perinatal outcome, but also may seriously bias temporal comparisons of such outcomes. Although sonographically estimated gestational age is considered superior to estimations based on menstrual dating, using early ultrasound is biased as well[6], as the last menstrual period (LMP) forms the basis for the sonographically estimated gestational age. Thus, in the absence of a true gold standard for the estimation of gestational age, several algorithms (discussed below) have been proposed to flag erroneous gestational ages. These algorithms are chiefly designed to identify implausible gestational age (in relation to birth weight) in singletons, and the ability of these rules to distinguish random error from true pathology – the two likely sources of extreme birthweight-for-gestational age[7] – in twin gestations remains unknown.

Several recent studies applied these rules to identify erroneous gestational ages in singleton gestations and evaluated the implications of such errors on an array of adverse pregnancy outcomes[7–9]. However, some of these algorithms[10,11] are based on clinical interpretations of birth weight and gestational age, developed specifically for singleton gestations. As such, these algorithms are designed to exclude implausible birth-weight/gestational age combinations in singleton gestations. Whether these rules apply equally to the exclusion of implausible birth weight/gestational age combinations in twin gestations remains largely unknown. If these algorithms perform differently among twins compared with singletons, then their resulting impact on adverse perinatal outcomes remains equally unassessed. Other methods for identifying erroneous gestational ages based solely on statistical properties of observed distributions[8,12,13] have also been shown to be effective among singleton gestations.

In this chapter, we apply three algorithms for 'cleaning' birth-weight/gestational age data among twin live-borns in the United States. We also compare the overall birth weight and gestational age distributions of observations identified for exclusion under each of these three algorithms, as well as the impact of such exclusions on twin infant mortality. The algorithms considered include the median ± 4 standard deviations rule, Tukey's rule[12] and Alexander's algorithm[11]. Other rules based on clinical opinions[14] and statistical algorithms[8,13] are not considered here.

## THE UNITED STATES TWIN BIRTHS COHORT COMPOSITION

The United States linked period natality and infant mortality data files for the years 1998 through 2000 were used[15]. These data were assembled by the National Center for Health Statistics of the United States Centers for Disease Control and Prevention and correspond to data abstracted from live birth and infant death certificates[16].

Gestational age was based on an algorithm used by the National Center for Health Statistics, in turn based primarily on the LMP. Approximately 1% of records did not contain gestational age information and these records were excluded. In a small fraction of records, a valid year and month of LMP was available but not the day. In such instances, the missing day of LMP was imputed by the National Center for Health Statistics[17]. Finally, if the LMP was missing or the birth weight was incompatible with LMP-based gestational age, a clinical estimate of gestational age, also contained on the birth and infant death data files, was used by the National Center for Health Statistics instead[16].

## GESTATIONAL AGE 'CLEANING' ALGORITHMS

We applied three algorithms for identifying and cleaning gestational age (relative to birth weight) in twin births. These algorithms include: a birth weight cut-off of ± 4 standard deviations from the median birth-weight-for-gestational age; a rule based on expert opinion[11]; and a modification of Tukey's rule[12]. The expert opinion rule is based on specifying birth-weight ranges for a given gestational age that can be considered plausible. The modified Tukey's rule classifies as implausible those birth weight/gestational age combinations for births with a weight over twice the interquartile range over (or under) the 75th centile (or 25th centile) of birth weight for gestational age[12].

## FREQUENCY OF GESTATIONAL AGE 'ERRORS' IN TWINS

In the United States, 344 852 twin live births were delivered at ≥ 22 weeks of gestation (1998–2000). Of these, 1030 (0.3%) were identified for exclusion based on the median ± 4 standard deviations criteria; 4044 (1.2%) under Tukey's rule; and 1303 (0.4%) under Alexander's expert clinical opinion algorithm (Figure 12.1). Tukey's rule flagged the most records with implausible birth weight/gestational age for exclusion, whereas Alexander's and the median ± 4 standard deviations algorithms identified the least.

The median ± 4 standard deviations and Tukey's algorithms identified more twin live births at higher birth weights (Table 12.1). For instance, at ≥ 3000 g birth weight, 28.2% and 25.5% of live births based on these two algorithms, respectively, were identified for exclusion, whereas Alexander's criteria identified 17.8% for exclusion. For analysis relating to gestational age, these algorithms consistently identified 5–6 times more live births for exclusion at lower gestational ages (22–27 and 28–31 weeks).

Table 12.2 shows the distributional characteristics for birth weight at various gestational ages (i.e. at 22, 32 and 42 weeks), including the crude values as well as those pertaining to the excluded birth-weight/gestational age combinations based on the three algorithms. We also present the revised birth-weight distributions after eliminating the implausible birth-weight/gestational age combinations, as identified by the various algorithms. The distributional characteristics for birth weight are different among the excluded records under every algorithm. When implausible birth weight/gestational age records are excluded under any of the algorithms, the summary statistics for birth-weight change little (compared with the corresponding data for the crude estimates) at higher gestational age (i.e. at 42 weeks). At lower gestational ages (i.e. at 22 and, to a lesser extent, at 32 weeks), however, the differences appear more profound. These general findings were also seen in a previous analysis among United States singleton births[8].

The distribution (density) of birth weight at 25 and 40 weeks' gestation is shown in Figures 12.2 and 12.3, respectively. At 25 weeks' gestation, the distribution of birth weight among the crude and among those excluded under the ± 4 standard deviations rule and Alexander's criteria are non-overlapping, whereas the birth-weight distribution for records identified for exclusion based on Tukey's rule has an overlap at low birth weights with that of the crude data. The distributions of birth weight at 40 weeks' gestational age under each of the three exclusion rules have a bimodal distribution for the ± 4 standard deviations and Tukey's rules, with a large proportion of records identified with very low birth weights (< 1500 g). Surprisingly, a few records with high birth weights (≥ 4000 g) were also identified for exclusion, again based on the ± 4 standard deviations and Tukey's rules but not on Alexander's algorithm.

## IMPACT OF GESTATIONAL AGE ERRORS ON TWIN PRETERM BIRTH AND LOW BIRTH WEIGHT

The impact of these various exclusion rules on gestational age-specific mean birth weight (i.e. fetal

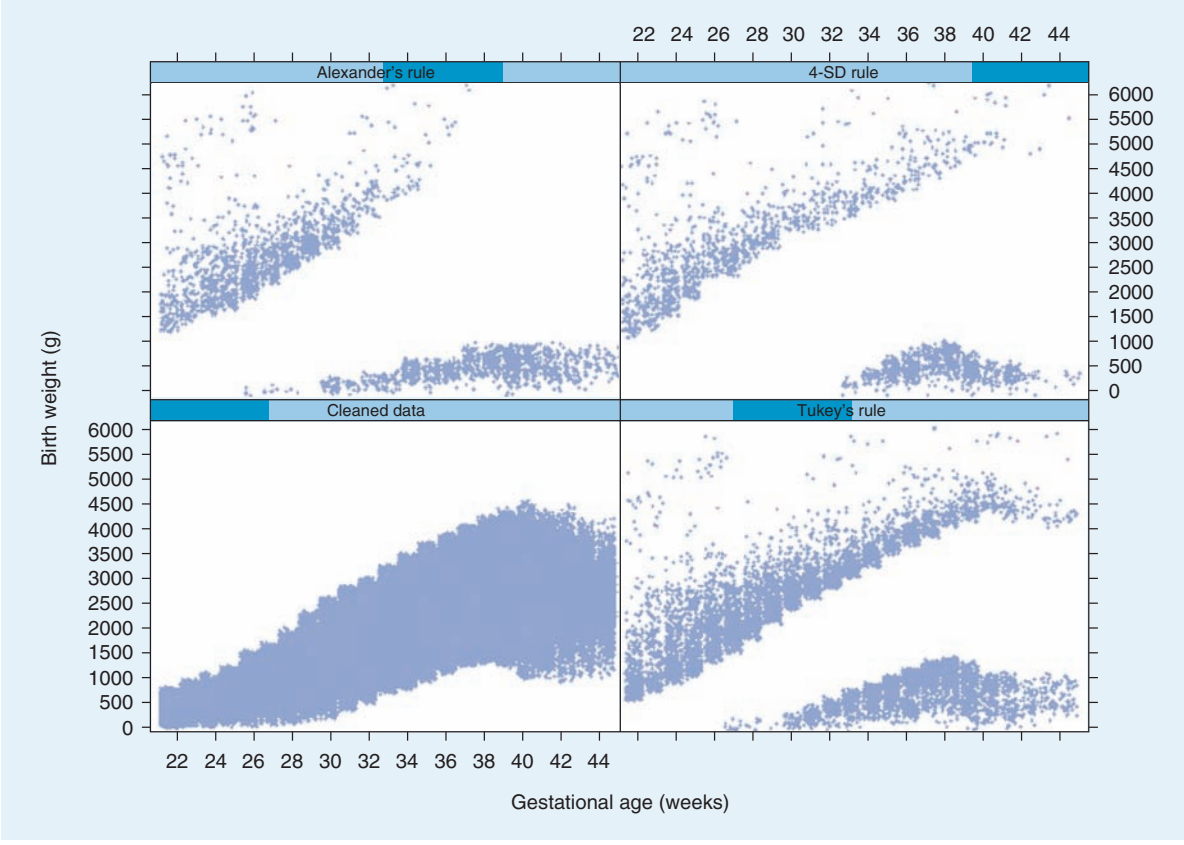


**Figure 12.1** Distribution of birth weight by gestational age among United States twin live births, 1998–2000. Bottom row: left panel refers to all twins, and right panel corresponds to birth weight/gestational ages excluded under Tukey's rule. Top row: left panel refers to birth weight/gestational ages excluded under Alexander's rule, while the right panel shows exclusions under the ± 4 standard deviations (SD) rule

**Table 12.1** Number of live births and among those with implausible birth weight for gestational age before and after applying correction algorithms: United States twin live births, 1998–2000

| | | | *Exclusion of implausible birth weight/gestational age* | | | | | |
|---|---|---|---|---|---|---|---|---|
| | *Crude data* | | *$SD_4$* | | *Tukey* | | *Alexander* | |
| | *n* | *%* | *n* | *%* | *n* | *%* | *n* | *%* |
| *Birth weight* | | | | | | | | |
| < 500 g | 3673 | 1.1 | 109 | 10.6 | 210 | 5.2 | 186 | 14.3 |
| 500–999 g | 15 999 | 4.6 | 253 | 24.6 | 690 | 17.1 | 35 | 26.9 |
| 1000–1499 g | 19 385 | 5.6 | 44 | 4.3 | 762 | 18.8 | 14 | 1.1 |
| 1500–2499 g | 151 065 | 43.8 | 175 | 17.0 | 785 | 19.4 | 299 | 23.0 |
| 2500–2999 g | 107 277 | 31.1 | 159 | 15.4 | 564 | 14.0 | 222 | 17.0 |
| ≥ 3000 g | 47 363 | 13.7 | 290 | 28.2 | 1033 | 25.5 | 232 | 17.8 |
| *Gestational age* | | | | | | | | |
| 22–27 weeks | 18 150 | 5.3 | 331 | 32.1 | 957 | 23.7 | 448 | 34.4 |
| 28–31 weeks | 25 200 | 7.3 | 159 | 15.4 | 908 | 22.5 | 304 | 23.3 |
| 32–36 weeks | 154 297 | 44.7 | 278 | 27.0 | 1249 | 30.9 | 248 | 19.0 |
| 37–41 weeks | 142 308 | 41.3 | 254 | 24.7 | 854 | 21.1 | 251 | 19.3 |
| 42–44 weeks | 4897 | 1.4 | 8 | 0.8 | 76 | 1.9 | 52 | 4.0 |

$SD_4$, ± 4 standard deviations

**Table 12.2** Distributional characteristics for birth weight before and after applying correction algorithms: United States twin live births, 1998–2000

| Gestational age | Method/ algorithm | Number of twin live births | Distributional characteristics of birth weight (g) | | | | |
|---|---|---|---|---|---|---|---|
| | | | Mean | SD | 10th centile | Median | 90th centile |
| 22 weeks | Crude data | 2441 | 503 | 191 | 340 | 478 | 638 |
| | $SD_4$ | 41 | 1558† (485) | 184 (131) | 1361 (340) | 1516 (475) | 1830 (624) |
| | Tukey | 116 | 1163† (470) | 325 (101) | 822 (340) | 1021 (468) | 1645 (595) |
| | Alexander | 36 | 1590† (486) | 173 (137) | 1403 (340) | 1652 (475) | 1870 (624) |
| 32 weeks | Crude data | 12 828 | 1830 | 416 | 1361 | 1809 | 2325 |
| | $SD_4$ | 26 | 4194† (1825) | 785 (401) | 3515 (1361) | 3984 (1805) | 5358 (2325) |
| | Tukey | 232 | 2535† (1817) | 1301 (368) | 509 (1380) | 3033 (1800) | 3515 (2296) |
| | Alexander | 46 | 2397 (1828) | 2042 (397) | 297 (1370) | 3530 (1809) | 4820 (2324) |
| 42 weeks | Crude data | 2522 | 2665 | 549 | 2000 | 2693 | 3305 |
| | $SD_4$ | 7 | 435† (2671) | 64 (537) | 305 (2013) | 454 (2693) | 510 (3305) |
| | Tukey | 34 | 1277† (2683) | 1382 (504) | 454 (2035) | 794 (2693) | 4423 (3300) |
| | Alexander | 26 | 706† (2687) | 187 (511) | 545 (2035) | 737 (2693) | 936 (3309) |

†$p < 0.001$ compared with the crude (mean) birth weight in the corresponding gestational age category; $SD_4$, ± 4 standard deviations; numbers in parentheses indicate the mean and SD for birth weight after excluding implausible birth weight/gestational ages based on the exclusion criteria

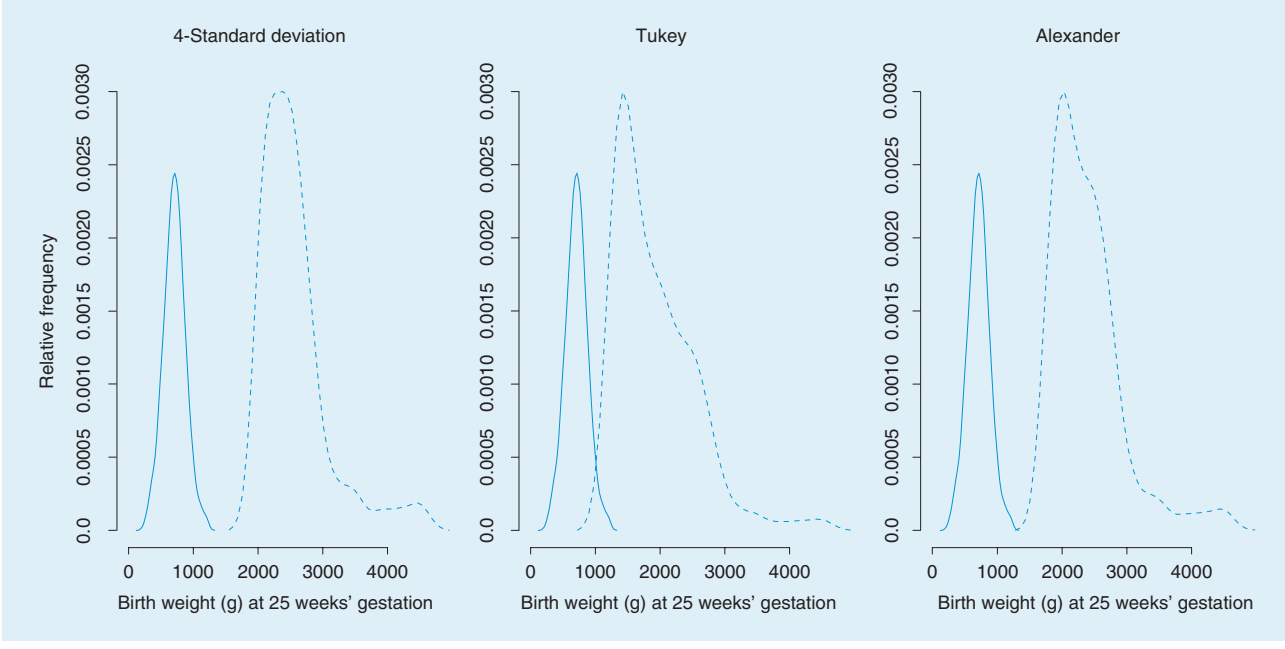


**Figure 12.2** Density of birth weight at 25 weeks' gestation among United States twin live births, 1998–2000. Left panel refers to birth-weight distribution identified for exclusion under the ± 4 standard deviations rule; middle panel refers to distribution identified for exclusion under Tukey's rule; and right panel refers to distribution identified for exclusion under the Alexander's rule. The solid line in each of the panels corresponds to the birth-weight distribution after excluding births under all three rules

growth) is shown in Figure 12.4. The gestational age-specific crude mean birth weight was fairly similar to those after excluding the implausible birth weight/gestational age combinations based on each of the three exclusion algorithms (left panel). Nevertheless, mean birth weights were drastically different between the crude and among those records identified for exclusion (right panel).

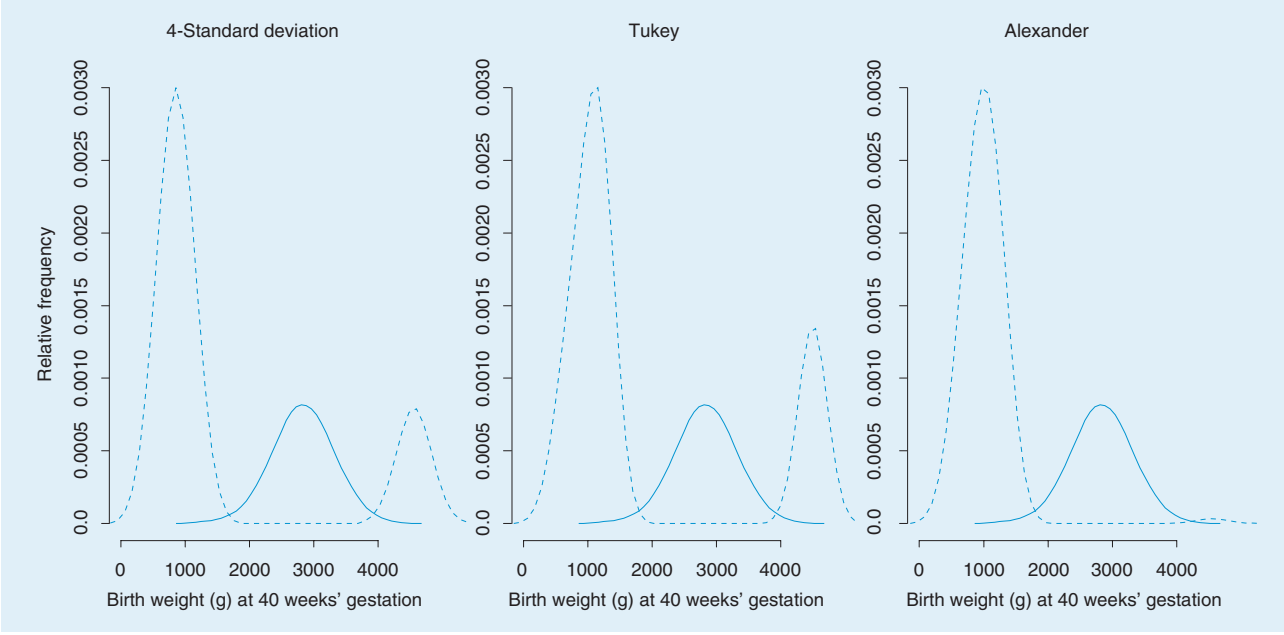


**Figure 12.3** Density of birth weight at 40 weeks' gestation among United States twin live births, 1998–2000. Left panel refers to birth-weight distribution identified for exclusion under the ± 4 standard deviation rule; middle panel refers to distribution identified for exclusion under Tukey's rule; and right panel refers to distribution identified for exclusion under Alexander's rule. The solid line in each of the panels corresponds to the birth-weight distribution after excluding births under all three rules

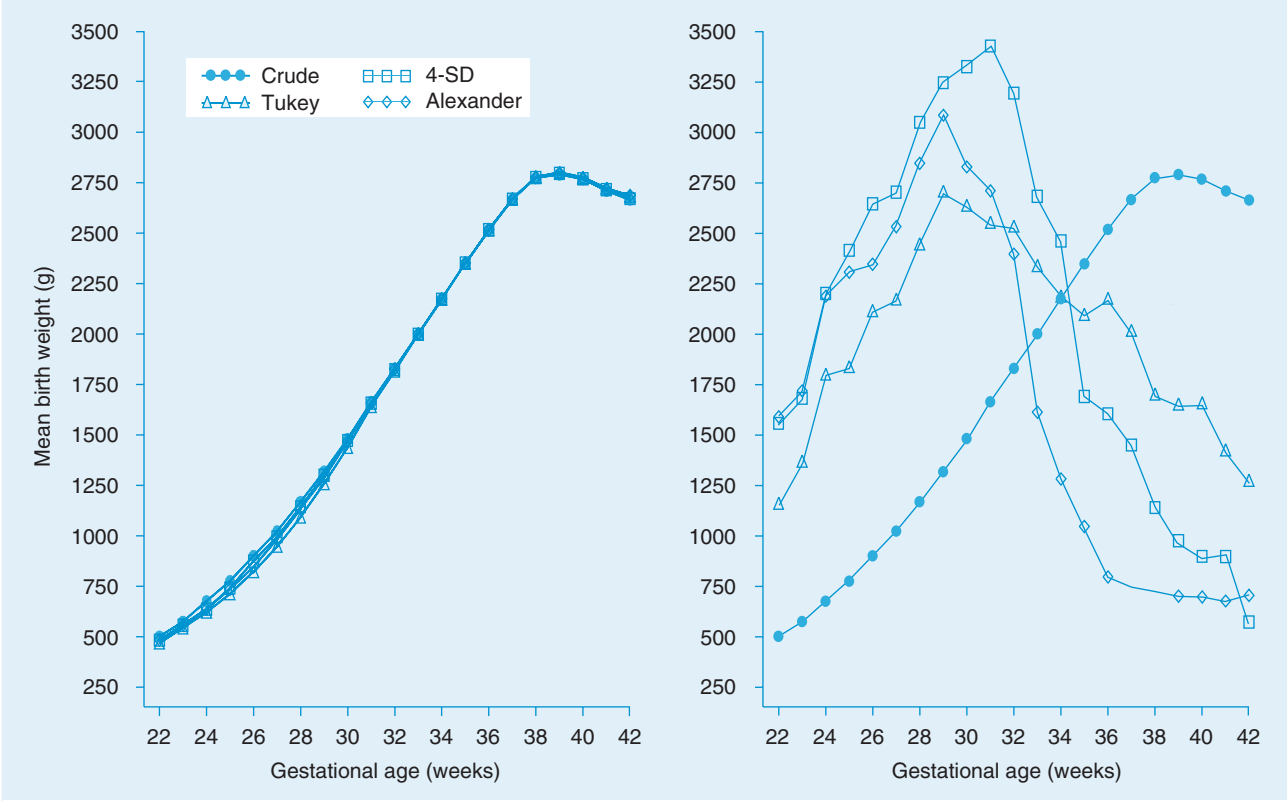


**Figure 12.4** Gestational age-specific mean birth weight among United States twin live births, 1998–2000. The left panel shows crude mean birth weight, and mean birth weight after excluding implausible records based on each of the three algorithms. The right panel shows crude mean birth weight and the mean birth weight of records identified for exclusion based on the three algorithms

**Table 12.3** Implications of excluding implausible birth weight/gestational age based on various algorithms for birth weight and gestational age: United States twin live births, 1998–2000

| | | *Exclusion of implausible birth weight/gestational age*[†] | | |
|---|---|---|---|---|
| | *Crude data* | *$SD_4$* | *Tukey* | *Alexander* |
| *Low birth weight* | | | | |
| < 2500 g (%) | 64.0 | 78.5[†] (63.9) | 81.3[†] (63.8) | 79.3[†] (63.9) |
| < 1500 g (%) | 26.7 | 71.9[†] (26.6) | 74.7[†] (26.0) | 71.2[†] (26.5) |
| < 1000 g (%) | 15.6 | 69.5[†] (15.3) | 61.5[†] (15.0) | 70.7[†] (15.2) |
| *High birth weight* ≥ 3000 g (%) | 30.6 | 64.6[†] (30.5) | 64.7[†] (30.3) | 51.1[†] (30.6) |
| *Preterm birth* | | | | |
| < 37 weeks (%) | 58.1 | 75.2[†] (58.1) | 78.5[†] (57.9) | 79.9[†] (58.1) |
| < 32 weeks (%) | 23.4 | 65.9[†] (23.2) | 68.6[†] (22.7) | 75.0[†] (23.1) |
| < 28 weeks (%) | 11.3 | 56.6[†] (11.2) | 52.8[†] (10.8) | 64.1[†] (11.1) |
| *Post-term birth* ≥ 42 weeks (%) | 3.3 | 3.1 (3.3) | 8.2[†] (3.3) | 17.2[†] (3.3) |

[†]$p < 0.001$ corresponding with rates in the crude data category; $SD_4$, ± 4 standard deviations; numbers in parentheses indicate frequency of the outcome after excluding implausible birth weight/gestational ages based on the exclusion criteria

**Table 12.4** Implications of implausible birth weight/gestational age based on various algorithms infant mortality*: United States twin live births, 1998–2000

| | | *Exclusion of implausible birth weight/gestational age*[†] | | |
|---|---|---|---|---|
| | *Crude data* | *$SD_4$* | *Tukey* | *Alexander* |
| *Birth weight* | | | | |
| < 500 g | 456.8 | 367.0 (459.5) | 395.2 (460.5) | 408.6[†] (459.3) |
| 500–999 g | 230.8 | 213.4 (231.1) | 187.0[‡] (232.8) | 202.9 (231.5) |
| 1000–1499 g | 41.8 | 90.9 (41.7) | 59.1 (41.1) | 214.3[‡] (41.7) |
| 1500–2499 g | 8.1 | 62.9[†] (8.1) | 44.6[†] (8.0) | 43.5[†] (8.1) |
| 2500–2999 g | 3.4 | — (3.4) | 10.6[‡] (3.3) | 9.0 (3.4) |
| ≥ 3000 g | 3.3 | 31.0[†] (3.1) | 16.5[†] (3.0) | 12.9[‡] (3.2) |
| *Gestational age* | | | | |
| 22–27 weeks | 270.0 | 45.3[†] (274.2) | 61.7[†] (275.0) | 40.2[†] (275.8) |
| 28–31 weeks | 44.4 | 6.3[‡] (44.6) | 44.1 (281.6) | 65.8 (44.1) |
| 32–36 weeks | 8.2 | 197.8[†] (7.8) | 107.3[†] (7.4) | 286.3[†] (7.7) |
| 37–41 weeks | 4.5 | 177.2[†] (4.2) | 80.8[†] (4.1) | 187.3[†] (4.2) |
| 42–44 weeks | 9.2 | 250.0[†] (8.8) | 171.1[†] (6.6) | 230.8[†] (6.8) |

*Table entries denote infant mortality rates expressed per 1000 twin live births; [‡]$p < 0.01$, [†]$p < 0.001$ corresponding with infant mortality rates in the crude data category; $SD_4$, ± 4 standard deviations; numbers in parentheses indicate infant mortality rate after excluding implausible birth weight/gestational ages based on the exclusion criteria

The effects of excluding implausible birth weight/gestational ages using each of the three exclusion rules on low birth weight and preterm delivery among twin live births are indicated in Table 12.3. All of these four exclusion algorithms identified a 1.5–2.5-fold increased number of twin live births for exclusion, with the proportions for exclusion being greatest among the very-low-birth-weight (< 1000 g) and the very-preterm (< 28 weeks) births.

## IMPACT OF GESTATIONAL AGE ERRORS ON TWIN INFANT MORTALITY

The effects of implausible birth weight for gestational age on twin infant mortality based on the various exclusion rules are indicated in Table 12.4. Birth weight- and gestational age-specific infant mortality rates were 2–20 times higher among live-born twins identified for exclusion based on various algorithms,

compared with the corresponding birth weight- and gestational age-specific crude infant mortality rates. For instance, the infant mortality rate among twin live births weighing ≥ 3000 g was 3.3 per 1000 live births, whereas the mortality rate was 31.0 per 1000 live births among births excluded under the median ± 4 standard deviations criteria, 16.5 per 1000 live births using Tukey's rule and 12.9 per 1000 live births based on Alexander's criteria.

## CONCLUSIONS

These findings underscore the extent to which errors in gestational age among twins can affect mortality statistics, as well as indicators of adverse twin perinatal outcomes (such as low birth weight or fetal growth restriction). These errors appear to be more common at early (i.e. 22–24 weeks) and late (i.e. ≥ 42 weeks) ages, especially among infants of high birth weight (i.e. ≥ 3000 g). Our analysis also indicates that Tukey's rule identifies the greatest proportion of records of implausible birth weight/gestational age combinations for exclusions. For population-based studies that involve large amounts of data such as the one examined here, Tukey's rule may be the most appropriate for excluding the implausible birth weight/gestational ages in twin gestations. Having said this, in the final analysis, the choice of an algorithm must also be based on careful consideration of the goal and objectives of the intended analysis. Studies that involve temporal comparisons of perinatal indicators (such as trends in preterm delivery or infant mortality) should be aware of the extent to which gestational age errors can erroneously attenuate temporal comparisons.

## ACKNOWLEDGMENTS

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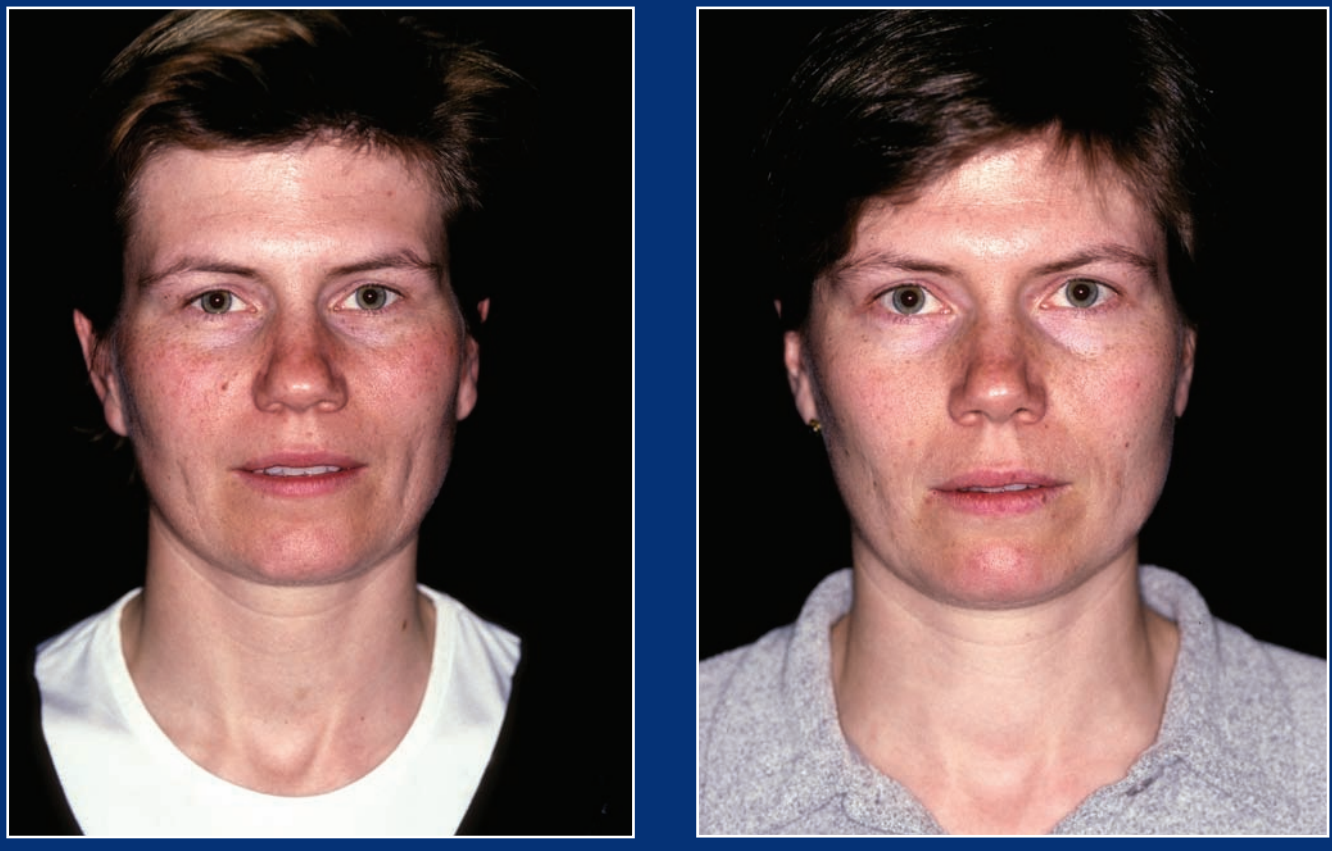
# SECTION II
# BIOLOGICAL CONSIDERATIONS



**33-year-old female monozygotic, monochorionic, non-mirror twins, Belgium, 2004.**

Participants since birth in the East Flanders Prospective Twin Study. Twin A left, Twin B right.

Progress in understanding the biology of twinning is slow but continuing. As an example, ancient theories suggested that twins were monsters resulting from divine punishment and were only replaced during recent times with the appreciation of different placentation and the recognition of zygosity. Further, current racial and genetic explanations for the generation of dizygotic twins are not different from what was known almost 50 years ago. Only very recently, the poorly understood etiology for spontaneous zygotic splitting has been clarified to some degree by observations from assisted reproductive technologies. Similarly, the underlying physiological processes for twin transfusion syndrome and reversed perfusion sequence were revealed by sophisticated imaging and other techniques.

This section, therefore, reiterates the fact that our current understanding of the twinning phenomenon is limited and far from being complete. Despite our intention to focus on anatomical and physiological issues, some chapters inevitably contain a clinical approach. Conversely, biological aspects of pathological twinning are often discussed in the more clinical sections of the book.

*I.B. and L.G.K.*

# Contents of Section II

# Definition of Multiple Pregnancy


*I. Blickstein*

It is told (by Cicero, one of the greatest Roman orators and statesmen) that Hippocrates (a renowned physician of ancient Greece) suspected a pair of brothers to be twins[1]. Hippocrates reached this conclusion because they both became ill at the same time, and their disease progressed to a crisis and subsided in the same length of time for each of them. The astrologer Posidonius the Stoic challenged this diagnosis of twinning, and explained this coincidence by the fact that the two brothers were conceived and born under the same constellation (Figure 13.1).

Centuries later, in the first edition of his book *Inquiries into Human Faculty and its Development* (Figure 13.2), Francis Galton (1883) commented[2]:

> *'The reader will easily understand that the word "twins" is a vague expression, which covers two very dissimilar events – the one corresponding to the progeny of animals that usually bear more than one at a birth, each of the progeny being derived from a separate ovum, while the other event is due to the development of two germinal spots in the same ovum. In the latter case they are enveloped in the same membrane, and all such twins are found invariably to be of the same sex.'*

This definition is a considerable part of the foundation for modern medical thinking, and remained in use, albeit in a refined nature, until the end of the 20th century.

The definition of twinning, as conceptualized by these early writers, has changed radically with the implementation of infertility treatment over the past two decades. To appreciate this change, one may imagine how these early scholars would consider the so-called 'Angela' case[3]. This Italian woman was concomitantly a surrogate mother for two unrelated couples and delivered unlike-sexed twins. Postnatal blood typing (confirmed by DNA fingerprinting) allowed identification of each baby's genetic parents. This is presumably the first case in which the twins were not genetically related to each other, nor was there any genetic relationship to the mother.

It follows that at the present time, simple definitions of twinning are unsuitable to encompass the whole spectrum of multiple gestation as seen by modern, technologically astute clinicians. In order to formulate the most appropriate definition of twinning, it is necessary to consider the following[4]:

(1) The *definition should include multiple gestations that do not end with more than one fetus/neonate*. Thus, cases of singletons following embryonic or fetal demise, following spontaneous or iatrogenic reduction, should be considered as a multiple gestation. This definition should also include combinations of a fetus and a complete hydatidiform mole.

(2) A pregnancy should be defined as *intracorporeal* rather than intrauterine to include multiple gestations of the heterotopic type. These are encountered much more frequently following assisted reproduction. The definition should exclude twins produced by cloning, but may include monozygotic (MZ) twins in whom zygotic splitting occurred *in vitro*.

(3) The *number of zygotes* at the beginning of gestation should be considered in the definition in order to include cases of conjoined twins, and

**Figure 13.1** Debate between Hippocrates, the medical man (on the right, examining a beaker) and the astrologer Posidonius the Stoic (on the left, gazing at the stars), whether the two diseased brothers (center) are twins. Dutch medieval iconography, artist unknown

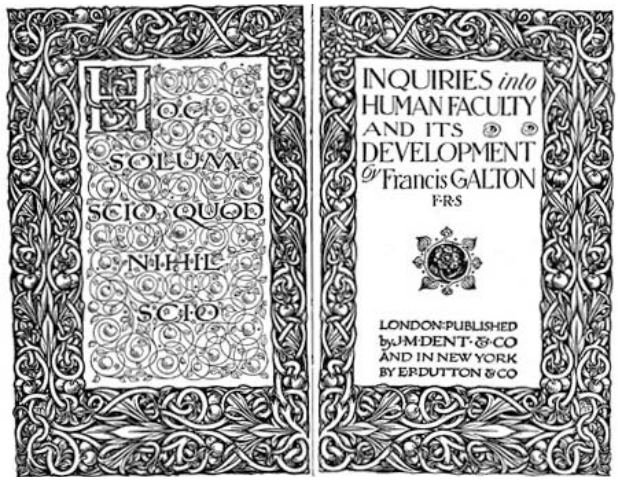



**Figure 13.2** Cover of the re-issue of *Inquiries into Human Faculty and its Development* by Francis Galton. Dent & Dutton (Everyman), 1907

inclusion of a set of MZ twins among a higher-order multiple pregnancy.

(4) The *production time* of the zygote(s) should be incorporated in the definition to include cases of *superfecundation*, which may occur during ovulation induction and assisted reproductive technologies (ART). The definition should enable consideration of two embryos produced in the same ovulatory cycle but transferred on different occasions as *biological twins* that develop as singletons in different pregnancies. As an exception to the definition, and due to the advent of cryopreservation, it may also include thawed embryos produced in different cycles but transferred simultaneously in one cycle.

(5) The definition disregards the source of zygote(s) in order to include multiple pregnancies resulting from transferred fertilized donor eggs, or multiples developing in a surrogate womb.

Bearing in mind these points, the following definition of multiple pregnancy is proposed. *Irrespective of the final number of fetuses/neonates, a multiple pregnancy is the result of intracorporeal development of more than one zygote and/or the intracorporeal development of a split zygote, which was produced in the same or in a different ovulatory cycle*. Only the future will reveal whether the definition is sufficiently comprehensive for all types of spontaneous and iatrogenic multiple pregnancies.

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# Natural Factors Influencing Multiple Gestation: Perspectives from Long-term Observations in Scotland

*D. M. Campbell*

14



## INTRODUCTION

Unlike the increases in twinning reported from developed and developing countries[1–5] in which no accepted manner is known to disentangle the contribution of increasing maternal age *per se* and the increase in maternal age associated with decreasing fecundity and thus more fertility treatment, the twinning rate in the Grampian region of Scotland (Figure 14.1) has not only increased similarly. However, linkage to the infertility registers has enabled identification of those multiple pregnancies resulting from the management of infertility. To our knowledge, this is unique because it is simultaneously possible to examine the natural twinning rate, which has also increased over recent years, albeit less markedly.

Unfortunately, recording the presence of a multiple pregnancy is inconsistent at different centers throughout the world. Regardless, considerable evidence indicates that twin or higher multiple conceptions are more common than originally thought (see Chapter 36). Part of the problem relates to the fact that ultrasound examination in the first trimester is not routinely carried out in many spontaneous pregnancies in which there has been no clinical problem. In contrast, ultrasound scanning in the first trimester is common after assisted reproduction or when there is a clinical suspicion of a problem as a result of vaginal bleeding. In addition, ultrasound is common in many countries in which patients and their families know of its availability. The United States is a prime example of 'patient-requested' ultrasound examination. Where possible, noting a twin pregnancy from ultrasound evidence, provided it is sufficiently good and not artifactual, is of importance not only to the mother but also for the subsequent development of the offspring (see Chapters 39 and 40).

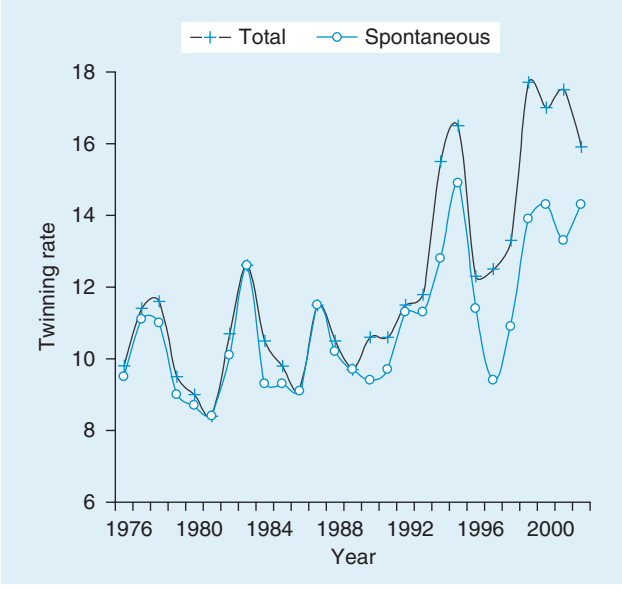


**Figure 14.1** Total and spontaneous twinning rate (per 1000 births), 1975–2002, the Grampian region of Scotland

Ultrasound is particularly useful to record fetal demise. A twin fetus may die at any stage of pregnancy. If this is early in the first trimester the resultant empty sac will be completely reabsorbed, and the prognosis of the remaining fetus is excellent (see Chapter 17). On the other hand, if the fetus dies later in gestation in the second trimester, a fetus papyraceous may be identified at delivery. Whether

**Table 14.1** Factors that may influence spontaneous twinning

| |
|---|
| *Environmental* |
| Geography |
| Clustering |
| Ethnicity |
| Seasonality |
| *Genetic* |
| *Maternal* |
| Parity |
| Age |
| Height |
| Weight and nutrition |
| Cigarette smoking |
| Blood group |
| Socioeconomic status |
| Fecundity |
| *Iatrogenic* |
| Oral contraception |
| Folic acid |

this should be registered as a stillbirth or not is debatable, and will vary from country to country. Spastic forms of cerebral palsy are increased in multiple pregnancy, in particular if one twin dies *in utero*[6], and might be related to single fetal demise at any stage of pregnancy (see Chapter 97).

Legal requirements of birth registration should not prevent obstetricians from recording multiple pregnancies detected early in gestation in case notes even if a normal singleton birth is the outcome. However, it is useful to record the number of twin maternities per 1000 total maternities, bearing in mind that the rate of twin births will be double the amount of maternities. Of the two types of twinning, monozygotic (MZ) and dizygotic (DZ), the DZ rate reached a nadir in the mid-1970s in many Western European countries[7]. The massive increase reported recently is likely DZ twinning associated with assisted reproduction, although MZ twins occur at a higher than expected rate following ovulation-induction agents[8] and *in vitro* fertilization (see Chapters 29 and 30).

When considering the natural factors affecting twinning, it is the DZ twinning rate that is generally most heavily influenced. Such factors are considered under four distinct headings, i.e. environmental, genetic, maternal and iatrogenic (Table 14.1).

## ENVIRONMENTAL FACTORS

### Geography

Large regional differences with up to 15-fold variation in the prevalence of twinning at birth have been noted for many years. Countries are classified into three main groups, low, intermediate and high prevalence[7]. Low prevalence (2–7 per 1000 maternities) is found in Hawaii, Japan and Taiwan. Intermediate prevalence (8–20 per 1000) is found in all countries of Europe, Australia, the USA and Argentina. A high prevalence of twinning (>20 per 1000 maternities) occurs in Nigeria, the Seychelles, Zimbabwe, Bahamas and Jamaica. This large regional variation is primarily due to differences in the DZ twinning rate. MZ rates, in contrast, are remarkably constant throughout the world at around 3.5 per 1000 maternities.

### Clustering

Localized high twinning rates have been noted in Norwegian mountain villages, in Finnish islands, in a single Romanian village and in Colonsay in the Inner Hebrides islands over highly specified time periods[7] and, more recently, in a small village in Brazil[9]. Such clusters are not explained by a high proportion of older women. However, a high familial recurrence from excessive inbreeding in such communities could lead to an increase in the frequency of a genetic recessive trait. None of the studies cited in references 7 and 9 can exclude localized environmental effects, however. A more recent study from Sweden[10] tested the hypothesis that atmospheric pollution from refuse incinerators increased the incidence of twin deliveries, but found no evidence of spatial clustering of twin births in Sweden between 1973 and 1990, when incidences of twin delivery among parishes and areas near incinerators were studied.

### Ethnicity

Whether the geographic variation in twinning is due to climatic conditions or to a factor inherent in different racial groups could be studied by considering twinning rates in immigrants from areas of high incidence to areas of low incidence and vice versa. Japanese immigrants to California, Canada and Hawaii have low twinning rates, similar to those occurring in Japan. In Canada no significant differences could be found between twinning rates of Canadian-born women whose families came from different countries in Europe. This contrasts with a difference in twinning rates between European countries, suggesting that rates are modified by migration[7]. Rates in American Blacks tend to be higher than in Whites, but are very much lower than the twinning rates of West Africa. A recent report from the USA[11] found the lowest twinning rate in the group denoted as non-Hispanic Whites and the highest among non-Hispanic Blacks. Twinning rates within various groups representing Hispanics *per se*

were intermediate. The authors concluded that race/ethnicity studies can be useful in maximizing health outcomes in twins in a racially diverse population. A previous report[12] comparing the twinning rates of 14 ethnic groups in California, USA, suggested that after standardization for maternal age, twinning rates per 1000 maternities were 13.2 for Blacks, 10.05 for Whites and 7.18 for Asians. Differences were also found within the Asian group, with very low rates in Koreans, Thais and Vietnamese. Twinning rates have recently been investigated in Ghana[13]. However, the incidence of 33.4 twin births per 1000 live births in Accra and 26.6 twin births per 1000 live births in Kumasi are not as high as those reported from south-west Nigeria, but still rank among the highest in the world. The results of all studies provide support for the concept that both migration and interethnic mixing modify twinning rates. On the other hand, environmental influence such as dietary factors could lead to differential secretion rates of gonadotropins from the pituitary gland as people adapt their native diet to that of their chosen country.

### Seasonality

The possibility that climatic-related factors might be involved in the etiology of twinning has long been considered as one potential explanation for varying worldwide rates. Problems related to the assessment of seasonality in twinning have been discussed in terms of rates in north-east Scotland and Northern Ireland[14]. At that time, the authors concluded that the available evidence failed to support the existence of seasonal variation in total, DZ or MZ spontaneous twinning in either of the two communities over the time period studied. In Denmark, between 1936 and 1984, a simple harmonic sinusoidal model provided no evidence for seasonality but sequential polynomial analysis detected a peak in twin birth rates in May, June and December, with a low in February and September[15]. Sharma[16] reported a clear bimodal distribution for the twinning rate in south-east India with peaks in April and September. No evidence of seasonality was detected recently for the overall rate of DZ twinning in Brazil[17]. In contrast, significant variations in the seasonal index for overall DZ and MZ twinning rates were reported in Japan[18], with peak months being July and October to December for DZ twins, and April and June for MZ twins. Not all years, however, showed these typical seasonalities.

## GENETIC FACTORS

The tendency for twinning in specific families is well known, and these twins are DZ in particular. It is debatable whether a genetic component is present in MZ twinning[19]. A recent review of the epidemiology of multiple births, however, suggested that the constant frequency of MZ twin pregnancies over time and different geographic areas suggests that they may be partly genetic, whereas the time and geographic trends observed in DZ twinning suggest that environmental factors may play a role[20].

Some authors believe that DZ twinning is inherited only via the maternal line. Extensive reviews of records of the Church of Jesus Christ of Latter Day Saints in Salt Lake City, Utah, demonstrate a twinning rate in the offspring of women who were themselves DZ twins of 17.1 per 1000 maternities, compared with 11.6 per 1000 maternities for the general population. In contrast, the twinning rate of the offspring of males who were themselves DZ twins was only 7.9 per 1000[20]. In west Nigeria, where a high incidence of DZ twinning and polygamy coexist, women whose husbands are themselves twins have similar twinning rates to women whose husbands are not[20]. Women whose husbands have had sets of twins by other wives have similar twinning rates to women whose husbands have not. Women whose fathers are twins have a twinning rate not significantly higher than for women whose fathers are not, and women whose fathers have had twins by other wives have similar rates to women whose fathers have not. Such findings[19] do not suggest a paternal contribution to DZ twinning. On the other hand, extensive studies from the Mendel Institute, Rome, Italy, suggest that the propensity to DZ twinning could be inherited from the paternal side as well as the maternal side. In both the Italian and Nigerian twin groups, zygosity was determined in individuals, either by direct observation and examination of various anthropologic biologic markers or by placentation and blood group markers, whereas in Salt Lake City, zygosity would have been presumed according to the sex of the infants.

The Swedish Twin Registry[21] confirms that women who themselves are DZ twins are at moderately increased risk of having twins (relative risk 1.3). In a mother who is an MZ twin, the risk of having twins is not increased significantly, although MZ mothers have significantly more same-sex twin births. Zygosity in this study was presumed using Weinberg's rule. The Swedish work also suggests a familial component to MZ twinning as well as to DZ twinning, but suggests that the effects might be independent. Not surprisingly, mothers of DZ twins are much more likely to have twins again compared with women who have not had twins. Mothers of MZ twins, however, do not appear to have any greater frequency of twinning in later life than women who have not had twins.

In view of the fact that women who had previous multiple pregnancies have higher pituitary gonadotropin levels than women who had singletons[22], and follicle stimulating hormone (FSH) release is controlled by the feedback of inhibin peptides from the ovary, the inhibin α-subunit was considered a candidate gene for mutations that might increase the frequency of dizygotic twinning[23]. This study[23] concluded that DZ twinning was not linked to variation of the α-inhibin locus on human chromosome 2.

In view of the recent interest in the potential association between preconception folic acid, possible increase in multiple pregnancies and the genetic tendency of multiple pregnancy, a German group[24] investigated the dual mutations of the gene affecting methyl tetrahydrofolate reductase (MTHFR). They found that the T allele frequency was significantly different in singleton and twin mothers. Mothers with the 677C→T mutation had a 2.28 times lower risk of having a twin pregnancy. The investigators postulate that in women with this mutation there is interference with brood size by influencing the proliferation of rapidly dividing embryonic and maternal cells[24].

## MATERNAL FACTORS

### Parity

Matthews Duncan first recognized that twinning was more likely in higher-parity women. These observations have been confirmed repeatedly, although later workers found that the increase in twinning rates with increasing parity applies only to DZ twinning, MZ twinning rates being similar and fairly constant[19].

### Maternal age

Matthews Duncan also observed that the highest rate of twinning was in women from 35 to 39 years of age and that the tendency to twinning gradually diminished on either side of this age[19]. Here again, these observations have been repeatedly confirmed, most recently by Japanese[25], and Argentinian researchers[26].

### Maternal height

Tall women are more likely to produce twins than are short women. Data from Zimbabwe, Nigeria and Aberdeen in north-east Scotland all show that the gradient of twinning persists after standardization for age and parity and is mainly due to the variations in DZ twinning (Figure 14.2). The relative risk for tall women having twins is 1.5–2 compared with short- stature women[19].

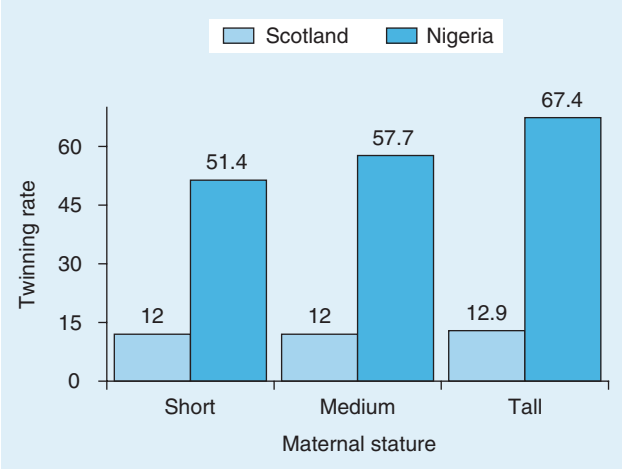


**Figure 14.2** Twinning rate (twins/1000 births) in Scotland and Nigeria, by maternal height. Adapted from the studies of Nylander, as cited in reference 20

### Weight and nutrition

Although height was recognized for a long time as having relevance on twinning, it was not until 1974 that the body build of the mother was also shown to be important, when a significantly low incidence of twinning in primigravidae who were thin compared with those who were of normal body size or fat was shown[27]. This observation has subsequently been confirmed by others and supports the view that twins occur less often in undernourished women. Data from animals suggest that the higher the level of nutrition, the greater the litter size. Indeed, wartime deprivation, such as occurred in the Second World War, led to a fall in DZ twinning rates[28]. It may be expected, therefore, that the higher twinning rates found in tall and obese women might be related to greater dietary intake. Although this explanation is reasonable, the dietary intake of a group of women having twin pregnancies was not significantly different from women expecting singleton pregnancies, at least in a Scottish population[29].

### Cigarette smoking

No significant association was demonstrated between twinning and smoking status in Aberdeen[19]. Smokers tend to be shorter than non-smokers and are of lower body weight. Although smokers had slightly higher rates of MZ and DZ twinning, these differences were not significant. The possible link between maternal smoking and twinning was investigated using the Swedish Birth Registry[30]. Women who smoked were at increased risk of having DZ twins, but only among multiparas and not in primaparas.

No association was present between smoking and MZ twinning.

### Maternal blood group

In a complete analysis of the data from the Aberdeen City District, no particular bood group, A, B or O, or rhesus factor predominated in the mothers of MZ or DZ twins when compared with mothers of singletons. Similarly, no significant association between twinning and blood groups was demonstrated in Nigeria[19].

### Socioeconomic status

Reports on variations in twinning rates by socioeconomic status are difficult to interpret, as the methods of defining social status differ throughout the world. Some studies report twinning rates being highest in upper socioeconomic groups, e.g. in the USA, whereas in other parts of the world, e.g. in Japan, no variation in twinning rates is found according to socioeconomic status. In the UK, no statistical association between social class as defined by the Registrar General and twinning could be demonstrated in either Northern Ireland or northeast Scotland[19]. In China, no difference is present in the incidence rate of twins among different parts of the country nor between urban and rural areas[31].

It has been suggested that a woman's own usual occupation may be more discriminating in terms of twinning rates than that of her husband or partner. An association of twinning with the woman's occupation was shown in more recent years in Aberdeen, whereas in the earlier years of data collection twinning was associated with the husband or partner's occupation. This change and other effects may conceal any social class association. It is reported that maternal height decreases and weight for height increases with decreasing social class, and that these factors act as confounders to any association. Based on our studies in Scotland, it seems likely that socioeconomic status has no major effect on twinning rates[19].

### Fecundity

It has been hypothesized that women who produce twins are more fecund than other women, i.e. they may conceive more easily, possibly due to ovulating more regularly and releasing two oocytes as a result of excess pituitary gonadotropins leading to superovulation[32]. This phenomenon would then be expressed in higher fertility affecting twinning rates. To test this hypothesis is difficult, however, because of the widespread voluntary restriction in family size and the differential use of efficient contraception. Nonetheless, twinning rates are higher in women who conceive within 3 months of marriage and higher in illegitimate pregnancies as reported both from Aberdeen and from Scandinavia, in particular Denmark and Finland. These circumstances support the idea that such women are more fecund[19]. This difference is less apparent in more recent times, however, when social practices in the context of legitimacy, sex, marriage and use of contraception have changed. Frequent coitus has also been suggested as possibly being likely to cause DZ twinning, particularly in young women.

Clearly many of these maternal factors do not operate independently, and the relationships between them and twinning should be considered. Indeed, statistical modeling on the Aberdeen data[19] shows that the significance of parity vanishes once the age gradient is added, indicating that the apparent association between parity and twinning is likely to be one of the concealed age effect. On the other hand, maternal height has an independent effect on twinning.

## IATROGENIC FACTORS

### Oral contraception

The decline in DZ twinning rates in developed countries from around 1960 to the mid–late 1970s is postulated to be a result of depression in twin ovulation rates in women who stopped taking the oral contraceptive pill[33]. There are theoretical reasons why prior oral contraceptive use might alter twinning rates, especially in terms of an adverse effect on hypothalamic–pituitary function, and thus on incidence of DZ twinning[34]. Earlier studies relating to multiple pregnancy following oral contraceptive use were confounded by incomplete population data, inadequately determined zygosity and the retrospective collection of data relating to oral contraceptive use, e.g. questionnaires and interviews at some point in time after the birth of the twins. These criticisms particularly apply to a French study which reported a decrease in DZ twinning after oral contraceptive use and an Australian report of an alteration in the ratio of MZ to DZ twinning rates which they attributed to an increase in MZ twinning following the use of oral contraception[35]. In a large study from Aberdeen based on total births of a geographically defined population, zygosity was determined from blood samples and placentation and the data on the use of oral contraception was routinely collected prospectively. Three control groups were used to take account of age, parity and any secular trend.

This study showed no association between the use of oral contraception prior to pregnancy and either MZ or DZ twinning[36].

### Folic acid

In many countries it is now routine practice to prescribe folic acid prior to conception and in early pregnancy for all women, with a view to decreasing the incidence of neural tube defects. Two studies[37,38] report an increase in multiple pregnancy in women using preconception folic acid, and consider the adverse outcome associated with increased rates of multiple pregnancy worse than the adverse outcome from not taking folic acid. A more recent study finds no such association[39]. Clearly, this is an area in which further work is needed, especially as a result of the findings cited earlier with respect to the possible link to the MTHFR gene mutation.

## CONCLUSION

Overall, many factors are implicated in natural twinning rates which generally affect the incidence of DZ twinning. However, better documentation of those twins resulting from assisted reproduction and fertility drugs is needed in order to disentangle the role of natural factors. It is likely that the small increase in natural twinning rates seen in the Grampian region of Scotland is a result of the increase in the age of the population[40] and the increase in height and body weight over the last 20–30 years (W.A. Liston and D.M. Campbell, unpublished).

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# The Phenomenon of Monozygosity: Spontaneous Zygotic Splitting

*O. Bomsel-Helmreich and W. Al Mufti*

15



## INTRODUCTION

Multifetal pregnancies are associated with various ante- and perinatal conditions that justifiably characterize them as high risk (see Chapters 49 and 50); however, it is not generally appreciated that the biological mechanisms underlying twinning are particularly complex and occur for the most part prior to fertilization. This chapter reviews those factors known or believed to influence the early embryonic division process that leads to monozygotic (MZ) twins.

## MONOZYGOTIC TWINNING

MZ twins result from the division of one embryo whereby both halves generally carry the same genetic heritage and are of the same sex. In mammals, the MZ condition is rare; its frequency is about one per 1000. In contrast, the di- or polyzygotic condition is the rule in most species. An exception is the nine-banded armadillo, where the unique embryo splits into four, resulting in MZ quads.

In humans, the frequency of MZ twins ranges from 3.5 to 5.0 per 1000. The figure of four per 1000 is most often quoted, and probably is close to the median in all populations. Regardless, this frequency corresponds to about one-third of the number of dizygotic (DZ) twins and is independent of ethnicity, which is not the case for DZ twins. Rarely, a heritable component of MZ twins appears, and seemingly can be transmitted through maternal or paternal genes (see Chapter 28). Families with very high frequencies of MZ twins have been observed.

The real incidence of twins is difficult to assess, because the conception rate of multiple gestations is greater than the birth rate. The phenomenon of the 'vanishing twin' is a relatively frequent event as shown by ultrasound visualization (see Chapter 17). Boklage[1] suggests that the loss of one member of a twin pair is best explained by the highly imperfect biology of human reproduction, and that this demise is no more mysterious in twins than in singletons. Nonetheless, monochorionic (MC) twins are at greater risk because of their placentation. The number of MZ vanishing twins is difficult to assess with certainty[2]. The disappearance rate between 6 and 7.9 weeks of gestation is 21% for dichorionic (DC) twins (both DZ and MZ) and 50% for MC twins[3]; less than 10% of twin conceptions will result in a total absence of fetuses[2]. During later reductions after the first trimester, 12% of MZ twins disappear versus 2% for DZ twins or singletons. Sixty-one per cent of twin pairs survive[4]. Because of the high incidence of malformations, the probability of antenatal mortality among MZ twins is much higher than it is among either DZ twins or singletons. In addition, major malformations are found in 2.3% of MZ twins compared with 1% of singletons, whereas minor malformations are found in 4.1% of MZ twins compared with 2.5% in singletons[5]. Twenty per cent of MZ twins are left-handed, a rate which is double that in the general population; speech laterality is five times more frequent[6]. The most vulnerable types of MZ twins are MC–monoamniotic (MA); in addition, male–male pairs fare less well than female–female pairs[5]. Besides, the incidence of male twin pairs decreases from the early to the later embryonic separations[7]. The sex ratio is about equal in

DC–diamniotic (DA) twins, whereas males are only 25% in conjoined twins (Figure 15.1). Two-thirds of MZ twins are MC[8]; this could be either because fewer DC twins are formed, or because the conjunction of fewer cells per embryo together with the generally observed lag in early development particular to the male increases the chances of male demise[9].

## DEFINITION

The division of a single embryo into two equal halves must not be considered an accident. In reality it is the consequence of prior events affecting the gamete. Additional factors also enhance postzygotic division. The earlier that the twinning process occurs, the fewer are the common structures between the individual twins, compared with late separation. These differences may concern birth weight, developmental abnormalities or diseases[10].

MC twins are certainly more likely to undergo epigenetic events than DC twins. They (MC) also have more developmental problems because of the numerous vascular anastomoses that might produce twin–twin transfusion syndrome (25% of all twins)

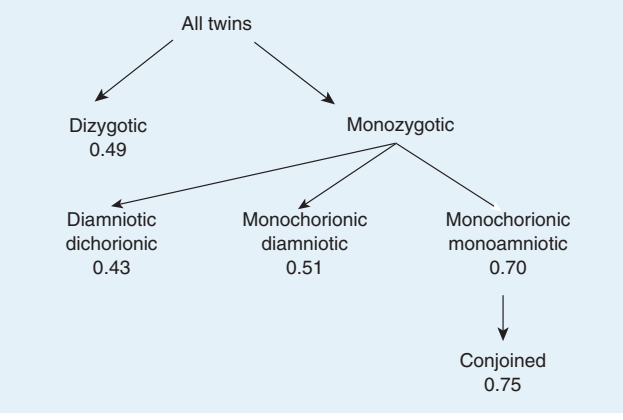


**Figure 15.1** Female sex ratio of twin pregnancies

and subsequent serious deleterious effects on embryogenesis (see Chapter 65).

## DATING AND TYPES OF TWINNING

The actual division of embryos takes place during the first 14 days following fertilization. The moment of twinning separation can be deduced from a later study of the membranes (see Chapter 24).

Four categories can be distinguished (Table 15.1):

(1) Early separation: in 18–36% of cases, separation occurs between the zygote and morula stage, that is up to 72 h post-fertilization. Such embryos are DC–DA. Splitting probably occurs very early, when embryonic cells are totipotent, between the 1-cell and the 8-cell stage.

(2) Later separation: in 60–70% of cases, splitting occurs at the early blastocyst stage, after the formation of the inner cell mass (ICM) which separates from the trophoblast before day 8; the resulting embryos are MC–DA.

(3) Rare separation: 1% occurs after day 8 up to day 12; splitting of the ICM takes place when the amnion has become distinct. The embryos are MC–MA.

(4) The rarest type: conjoined twins result from an even later stage 12–13 days after fertilization. Their frequency is generally one in 200 MZ pairs and about one in 40 000 births, although some geographic variations exist. They are more common in other species probably because a polytocous uterus, predetermined for multiple implantations, or an egg shell, allows safer delivery.

Natural splitting of the ICM has been observed in mammals and photographed in the human.

**Table 15.1** Dating of types of twins

| *Days post-fertilization* | *Amnion* | *Chorion* | *Incidence of MZ twins* |
|---|---|---|---|
| 0–4 | diamniotic | dichorionic | 18–36% |
| 4–8 | diamniotic | monochorionic | 60–70% |
| 8–12 | monoamniotic | monochorionic | 1% |
| 12–13 | monoamniotic | monochorionic | conjoined twins: 1/200 MZ, 1/40 000 total births |

MZ, monozygotic

## ETIOLOGY

The normal development of embryos involves axis formation, patterning and polarization, all of which represent fundamental aspects of development. Like oocyte maturation or fertilization, embryos must follow a well-defined chronologic developmental process to achieve the normal state. This sequence of development can be traced back to the late follicular phase. A disorder in these arrangements can lead to an aberrant development such as twinning, or, even more dramatically, to the death of the embryo.

Axes are initiated very early in development; early perturbation in polarity or patterning in either the oocyte or at fertilization could consequently induce embryo splitting at different stages of embryo development. Inside the follicle, the oocyte is in contact with the granulosa cells around it, which deliver to it essential elements such as STAT3, a protein involved with signal transduction and activation of transcription, and leptin, which is a cytokine product, activator of STAT3[11]. Localization of such molecules could establish gradients inside the cytoplasm of the oocyte. Gonadotropin secretion irregularities during the cycle can influence the process of supplementation; therefore, the normal course of polarization might be disrupted as well as leading to disruption of messages and axis formation. The connection between the granulosa cell and the oocyte is disrupted only following the ovulatory secretion of luteinizing hormone.

Data obtained experimentally as well as after intracytoplasmic sperm injection (ICSI) show that the site of penetration of the sperm affects the rate of fertilization, but not further development (provided that care is taken not to disturb the spindle), so that the process of fertilization *per se* has no disturbing effect on embryo development. Still, the disruption of poles or cytoplasmic micro-organization could well induce a twinning process. For example, introducing a needle at ICSI with consequent cytoplasmic disorganization increases the percentage of MZ twins to a rate which is higher than after *in vitro* fertilization (IVF). Cytoplasmic localization of specifying axes is present in the oocyte or the zygote. Consequently, perturbation of the cytoskeleton occurring *in vitro* is thought to be related to the increase of incidence of MZ twinning.

The first cleavage division is always non-random[12]. The first mitotic cleavage plane is dictated by the position of the second polar body (PB) and the pronucleus, which forms the axis of separation. Leptin or STAT3 is not necessarily equally distributed between the two cells. This early difference may be linked to the formation of two different cell lines due to the existence of two distinct areas in the embryo. The difference may continue during the cleavage state either as two sets of blastomeres or leading to duplication of the inner cell mass.

With close observation and strictly non-invasive techniques, regularities in the axial relationship between blastocyst and zygote become apparent. The position of the second PB is highly non-random in two-thirds of early blastocysts. Yet, the persistent localization of injected oil drops into the zona pellucida (ZP) at the 2-cell stage shows a constant topographic relation up to the blastocyst. Gardner[13], however, carried out this experiment on mice, where development is somewhat different from that observed in the human. These results demonstrate that patterning actually begins before cleavage. Even so, the preimplantation mammalian embryo can develop normally following addition, loss or rearrangement of cells. This suggests that patterning cannot depend exclusively on information already present in the zygote.

Until recently, it was believed that abnormal unequal inactivation of the X chromosome might trigger MZ twinning, as this process could form two distinct cell clusters with contrasting non-random inactivation. Experimental data suggest that commitment to X-inactivation occurs when the embryo consists of 10–20 cells. Splitting after commitment to X-inactivation indicates that MC–MZ twinning takes place 3–4 mitotic divisions after X-inactivation, whereas DC–MZ twinning events occur earlier, before or about the time of X-inactivation. In fact, DC–MZ twins frequently differ in their inactivation pattern, whereas MC–MZ twins display highly similar patterns of X-inactivation. Despite these observations, the overall degree of skewing in MZ twinning is not significantly different from that observed in singletons, showing that X-inactivation does not play a direct role in the twinning process[14].

## EXPERIMENTAL PRODUCTION OF MONOZYGOTIC TWINS

Experiments in mammals highlight blastomeric potentiality during early development. Prior to the 8-cell stage, every embryonic cell is totipotent. Stated another way, each embryonic cell retains its ability to form a normal individual. This stage thus represents the optimal time for blastomeric separation.

Once the compaction or morula stage is reached, however, the cells, by virtue of their topographic position, differentiate into external or internal cells that eventually become trophectoderm and the ICM, respectively. Compensatory crossing from external into internal cells (or vice versa) is possible until the 32-cell stage. In other words, embryonic cell differentiation is not fixed until blastocyst formation[15]. This

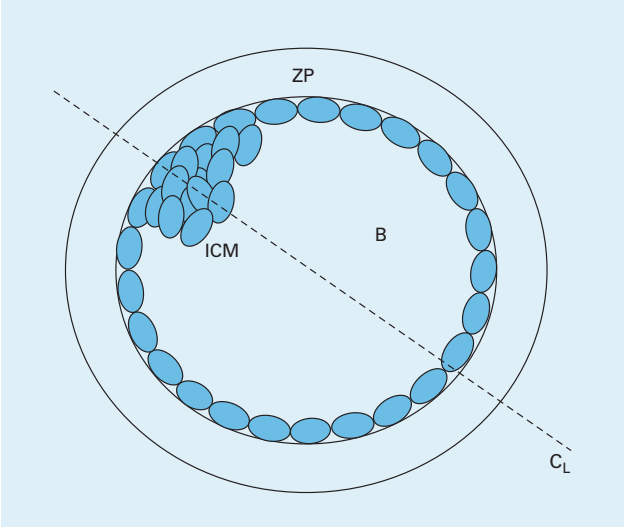


**Figure 15.2** Early blastocyst marking a possible line of cleavage producing monozygotic–monochorionic twins. ZP, zona pellucida; B, blastocele; ICM, inner cell mass; $C_L$, cleavage line

long duration of equipotentiality explains the late division of some twins at the ICM stage as well as the possibility of more or less equal divisions because of compensatory mechanisms.

Surgical embryo splitting at an early stage appears relatively easy. As early as 1952, totipotency of each blastomere from the 2-cell stage to the 8-cell stage was proven in mammals by transferring a unique rabbit blastomere to a host which developed as a normal embryo. Successful embryo splitting has been accomplished in a rhesus monkey, when one out of four blastomeres, after transfer, led to birth of a female. In the human, totipotency exists until the 4-cell stage.

The process of artificial twinning has been extensively used in the cattle and sheep industry. Since 1994[16], thousands of healthy calves born this way have shown neither abnormalities nor health problems. Here, however, the success of embryo bisection is greatest at the blastocyst stage, probably due to a higher number of cells in the ICM (Figure 15.2). Transfer of whole cattle embryos results in a pregnancy rate of 70%, whereas the percentage rate of bisected embryos is 50–55%, resulting in a 100% pregnancy rate for the original whole embryo. Embryos may be cryopreserved as blastocysts, even devoid of their ZP, with a high survival rate. At the same time, this procedure allows the multiplication of high-quality offspring for industrial purposes. MZ twins are the closest approach to perfect clones, including humans.

The success of this process raises the possibility of applying similar techniques to infertile couples who otherwise would choose procedures known to have a lower success rate[17]. Artificial splitting of embryos in humans in the early stages would be comparable to the production of DC–DA twins corresponding to one-third of natural twins. This process would avoid complications encountered with spontaneous MC twins, namely severe prematurity, twin–twin transfusion or even prenatal death. The same would also apply to surgical splitting at the blastocyst stage. Embryo splitting would be particularly beneficial to older women (> 37 years), who produce fewer good-quality embryos, or patients with hypo-ovulation due to ovarian pathologies. The suggestion of applying embryo splitting to humans raises ethical questions, as was the case after the first success of assisted reproductive technologies (ART), IVF, ICSI and others. Nonetheless, these latter procedures are now accepted parts of infertility therapy.

## DISCORDANCE IN MONOZYGOTIC TWINS

Following the fundamental and widely quoted work of Galton in the second half of the 19th century, scientific studies of MZ twins focused almost entirely on their phenotypic resemblance and how the postnatal milieu could or could not influence their possible psychological discordance. Galton formulated this concept as ‘nature versus nurture’. The classic approach was the study of pairs ‘raised together’ versus pairs ‘raised separately’, and the general assumption was the fascinating prevalence of nature. This opinion still holds in the minds of many authorities in spite of the repeated observations that, in a pair of twins, one generally dominated the other and therefore they were not identical. Not only have different hair and eye colors been described in male MZ twins, but fingerprint differences are invariably observed, a fact which assures that MZ twins cannot commit the ‘perfect crime’ so often presented in fiction[18].

Nevertheless, discordances between MZ twins are well recognized, especially in the past decade when twin research has claimed a broader aim. Genetic advances together with prospects of mammalian cloning have initiated research on epigenetic effects, prenatal diagnosis and the prevention of hereditary diseases. Indeed, the verification of various types of discordance is now a common field of study. The earliest perception of discordance was related to karyotypic differences in which one twin always has a chromosome less than the other, e.g. one is $2n$, the other trisomic 21. The zygote was necessarily trisomic 21. At the first cleavage division which is followed by separation of the two blastomeres, one

chromosome, the supplementary 21, is lost from the mitotic spindle so that it is lacking in one of the blastomeres. The most striking cases are MZ twin pairs with different sex: one a boy XY and the other a girl XO[19]. Phenotypic discordances have been described on numerous occasions, and may be attributed to postzygotic unequal division, unequal sharing of venous return of an MC placenta or mutation of a modifying gene.

The discordance between female MZ twins for X-linked genes has two causes: random X-inactivation or deviation in the process of methylation. It is well known that female MZs can be discordant with respect to differential expression of their maternal versus their paternal X chromosomes, and to the spatial or temporal expression of their X-linked genes. Discordances of MZ twins are described for X-linked diseases such as fragile X syndrome (Fra(X)), Fabry's disease, Rett's syndrome, Duchenne's muscular dystrophy and red–green color blindness[10]. Any disregulation of imprinted genes (genes inherited from either parent do not always behave the same way) potentially affects the phenotype. Discordance of Fra(X) or myotonic dystrophy suggests that the genetic potential of each of the MZ twins is realized independently of each other.

The larger number of female MZ twins discordant for Beckwith–Wiedemann syndrome (BWS) suggested an involvement of the X-inactivation process and revealed skewed inactivation of 80 : 20 instead of the normal distribution of 50 : 50. However, the presence of BWS does not correlate with the presence of non-random X-inactivation[9]. An increase of BWS in MZ twins was noted after ART, possibly implying that manipulation of preimplantation stages can affect BWS incidence through epigenetic programming, with its consequence on developmental anomalies.

Contrary to what is often assumed, two members of an MZ twin pair are not exposed to identical environments. This fact induces caution in the use of twin pairs for estimation of the impact of genes in most multifactorial traits and diseases. Schizophrenia is an interesting example. Concordance of schizophrenia in MZs is only 41–65%. Up to now, no specific gene has been ruled out; the difference is probably induced by postzygotic events, including gene instability[20].

In the case of autoimmune disorders, environmental stressors or viruses can interfere. This explains the high rate (70–75%) of discordance of autoimmune diseases among MZ twins[21]. There is a report of MZ twins who both exhibited trisomy 21 but were discordant for other major anomalies[22]. This is equally true for diabetes or anencephaly, anencephaly being a frequent disorder in MZ twins, but its causality remains unexplained. A case of MZ twins in an MC–MA pregnancy was reported by Benirschke and Masliah[23]; both were male and discordant for anencephaly; there was no cord entanglement.

Given the available evidence, the use of the term identical twins for MZs is irrelevant. Moreover, it is a cause of misunderstanding of their development, as they could never be totally identical, whatever the phase of splitting (see Chapters 28 and 94).

## WHAT CAUSES MONOZYGOTIC TWINNING?

Even if we know that chorionicity and membranes point to the approximate moment of embryo splitting, we remain unclear regarding the real inciting factor. It has been suggested by Jongbloet[24] that the real cause is in the ovum itself. A possible hypothesis is that early twinning is linked to an ovopathy relative to aging of the oocyte and evidenced by heterokaryotypic MZ twins. These embryos separate at the first division and remain in the same ZP until hatching. In experimental models, induced delay of ovulation leads to ovopathy, chromosomal anomalies, congenital malformations and twinning. These results have been obtained repeatedly in the rabbit, when two early blastocysts were observed inside the same intact ZP[25].

In the human, MZ twinning has a higher incidence in older women as well as in teenage mothers, i.e. at the beginning and end of reproductive years. This coincides with the two periods of unstable hormonal secretions and possible ovopathy[26]. MZ twinning has also been described in very young primigravida Yoruba mothers in West Africa[27]. The precise mechanisms of induction of the different types of twinning, early, late or very late, are probably different: early totipotent blastomeres separate at the 2- and 4-cell stage, whereas ICM splitting can be enhanced or not by ZP thickness or brittleness; regardless, all splitting events can be correlated to an abnormal hormonal situation in the prezygotic state. Unfortunately, despite these observations, until now no precise study of the possible high rate of gonadotropin secretion in the cycle pertaining to subsequent MZ twinning has been undertaken. To have a broader view of the hormonal profile, it would be useful to investigate the hormonal preovulatory evolution in patients having given birth to MZ twins, or a history of familial tendencies to spontaneous twinning. As for patients undergoing ART, the hormonal follow-up is part of the process, and as such available for observation; but other factors such as ZP thickness, precise culture conditions or manipulation hazards should equally be considered as they can contribute additional determinants.

## THE INFLUENCE OF INFERTILITY TREATMENTS

The use of ART provides additional information regarding the possible causes of embryo splitting. Indeed, the introduction of IVF provided a unique opportunity to observe very early stages of embryonic development. In 1986, Edwards, Mettler and Walters[28] noted that, among babies born after IVF when several embryos were transferred, the number of MZ twins was abnormally high. Later, when ART became common practice, always starting with ovarian stimulation, MZ twinning was observed more frequently than in spontaneous pregnancies. The reported rate was variable, depending on the technique or the authors. When a single embryo was transferred in a setting of conventional IVF, the incidence of MZ twinning was 5%, higher than the usual rate by a factor of twelve[29]. Many circumstances were suggested as the cause of the twinning: culture of the embryo, its duration or manipulation of the gametes, among others. However, the increase of MZ twinning was constantly noted. More than ten separate studies of different ART micromanipulations such as IVF, ICSI, assisted hatching or gamete intrafallopian transfer showed an increased rate from 0.4 to 5% or more[30]. All techniques were preceded by hormonal stimulation and ovarian induction. Such findings put forward the idea that gonadotropin stimulation is the common element and the principal factor of embryo splitting. Multiple births conceived after hormonal stimulation of follicular growth have been particularly well studied in the East Flanders Prospective Twin Survey[31]. The study sample included more than 2500 multiple births. MZ twins represented 1.2% of total births, instead of 0.4%. Fifty-four per cent of the twins were DC–DA versus 37% in those conceived without the benefit of hormonal induction. Other studies have largely confirmed these data.

Several teams recorded splitting of the ICM in cattle, by cinematographic monitoring. In the same context, while observing human blastocysts in culture, it was noted that at the beginning of hatching, sometimes part of the ICM herniated through a small hole in the ZP, was squeezed by the hatching gap and halved into two separate embryos[32]. This suggests that such an event might explain the separation of twins at the blastocyst stage. Clearly, this procedure cannot apply to the early separation of DC–DA twins.

ZP architecture has been implicated in the phenomenon of spontaneous embryo splitting. The width of the ZP of women in their early 30s is about 15 µm, and with aging it decreases to 1 µm. At the same time, hardening and brittleness increase, so that eventual cracks contribute to MZ twins in older

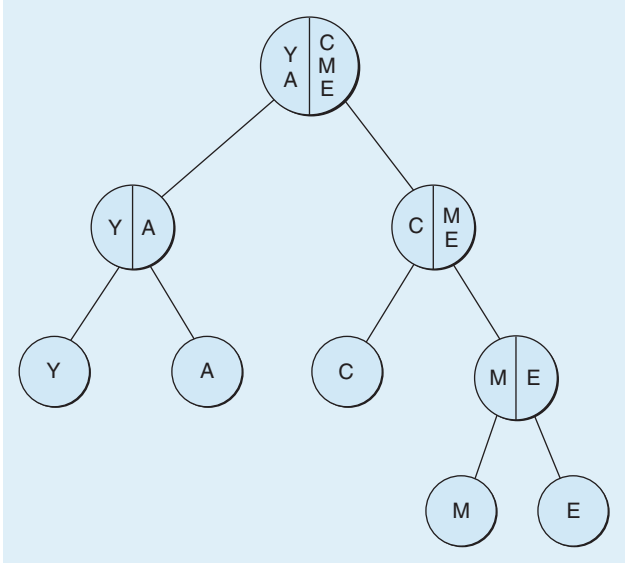


**Figure 15.3** The Dionne quintuplets started as one oocyte which subsequently split at first into two. One half split again (Yvonne (Y) and Annette (A)); the other half split also: one half became Cecile (C), the other half split a third time (Marie (M) and Emilie (E)). The presence of only one placenta, only one chorion and five amnions shows that these divisions occurred very early and in very rapid succession

mothers[33,34]. In another series, 64% of mothers of MZ twins were older than 35 years. All the twins were MC–DA or MA[35]. It was proposed that when treatment with agonists was used on hypogonadic women it could produce alterations of the ZP and possibly the oocyte. Thus, difficulties in hatching could explain the increase of MZ twins after ART. Once again, however, this seems primarily to be a consequence of ovarian stimulation. Nevertheless, there was no higher rate of MZ twinning when the technique of assisted hatching was used, compared with other ART[36].

Instructive information is obtained from the MZ pairs of higher multiples. Some triplets have the same chorion, others have mixed DC and MC placentas. Fifteen sets of spontaneously conceived triplets were analyzed by Machin and Bamforth[37]. In contrast to triplets obtained after IVF, here six sets were MZ (one oocyte), seven were DZ (two oocytes) and only two sets were trizygotic (three oocytes). Other studies showed that most spontaneous triplets contain at least one pair of MZ twins, 24% actually being MC[37]. Another example is that of the famous Canadian Dionne quintuplets (Figure 15.3). They apparently started as MZ twins that underwent three consequent divisions; a sixth embryo was dead *in utero*. The last pair (by division) was the least similar to the others. The co-occurrence in a same

pregnancy of polyovulation, resulting from high gonadotropin levels, followed by splitting more than once, demonstrates again that the hormonal background is relevant.

In addition to the occasional familial tendency to MZ twinning, it is interesting to note that both types of twinning, MZ and DZ, may be found frequently in the same family. These different types of twinning show once more a common susceptibility to a particular hormonal status. It is worth mentioning a certain number of common traits in both types of twins such as left-handedness, hair whorls and dental symmetry.

## CONCLUSION

It is surprising that, over the past 15 years of ART programs, there have been no reports of observing duplication on day 2 or 3 before the transfer of embryos. No two distinct cell masses have been seen at 5 days of culture. However, it is a certainty that MZ twinning eventually resulted after such transfers. Despite handling more than 200 000 embryos, splitting has never been reported. It is true that this demands very careful observation which was not the aim of these procedures, and therefore could have easily been overlooked.

Considering all studies referring to the phenomenon of monozygosity, it is not implausible to suggest that the origin of MZ twins depends mainly on a change in gonadotropin secretion acting on the preovulatory oocyte. Consequently, research should be directed toward more precise knowledge of the hormonal status of mothers with MZ twinning tendencies. This requires closer attention, especially during the late follicular phase.

Many recent studies concerning the contribution of genetic vs. environmental factors to the etiology of certain diseases still use MZ twins as genetic controls for DZ twins. It is surprising that these authors are satisfied that 'identical twins' are more concordant than DZ twins, which is relative, and definitely not 100%.

It is expected that interest in monozygosity will increase. The study of discordance between MZ twins may define the hereditary or the epigenetic cause of certain diseases or anomalies. This will open the way to the understanding and even the treatment of some aspects of human pathology and behavior. Aiming for these two objectives will throw light on hidden possibilities of optimal child development.

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# Superfecundation and Superfetation

*I. Blickstein*

16



## INTRODUCTION

The vast majority of human ovulations result in a monozygotic pregnancy as a consequence of fertilization of a single ovum at mid-cycle. Quite rarely, polyovulation and fertilization of more than one egg may occur, giving rise to a polyzygotic pregnancy. The true frequency of single, in contradistinction to double, ovulations is unknown, but it is accepted that there are many more multiple conceptions than multiple births. Hence, the usually quoted 0.8% of spontaneous polyzygotic multiple births is an underestimation of the frequency of polyovulation in the human female. In addition, this ratio between monozygotic and polyzygotic births is further changed because the frequency of polyovulation is much higher among women receiving ovulation-enhancing medications, and their number is not quantifiable.

Multiple ovulations may occur synchronously (at the same time) or sequentially (on different occasions during the same cycle). It follows that fertilization of more than one egg may occur during one or more inseminations (by coital acts or artificial). As a result, zygotes of different ages are created, a phenomenon known as superfecundation. The subject of superfecundation has been of interest to scholars for more than two millennia. In fact, until quite recently, the explanation of superfecundation has paralleled the theories advanced to explain the twinning process. Unfortunately, the possibility that a woman can conceive from two different coital acts, and thus potentially from two different partners, frequently led to the idea that twins were the consequence of adultery. Indeed, the association between malformations, often of the most bizarre form, and twins was explained as divine punishment for infidelity[1].

Superfecundation, defined as the fertilization of two or more ova released during the same menstrual cycle by sperm from separate acts of coitus, is frequently and erroneously confused with superfetation. In superfetation, which is an entirely different phenomenon, the fertilization and creation of another conceptus is assumed to take place when the female is already pregnant. This chapter discusses why superfetation is considered obsolete, what the evidence is for the occurrence of superfecundation in the human, and the significance of both conditions in their historical and biological context.

## SUPERFETATION

In the human, progesterone, initially produced by a functioning corpus luteum and very soon later by the evolving placenta, potently up-regulates the hypothalamic–pituitary–ovarian axis to such an extent that ovulation is impossible[2]. Spontaneous sequential ovulations are extremely rare, and can be induced by the administration of human chorionic gonadotropin but not with luteinizing hormone (LH), recombinant LH and gonadotropin-releasing hormone agonist flare-up[2]. Moreover, when the uterine cavity is filled by a gestational sac and the cervical mucus changes from estrogenic to progestogenic quality, there is little likelihood that sperm could enter the cervix and begin their upward journey to the oviduct. It follows that sequential ovulations in the human, occurring a few days apart, may explain superfecundation but are unable to produce superfetation.

In spite of evidence (albeit newly appreciated) to the contrary, cases of superfetation in animals and alleged cases in humans are abundant. The earliest reports came from ancient Greece, in the book of

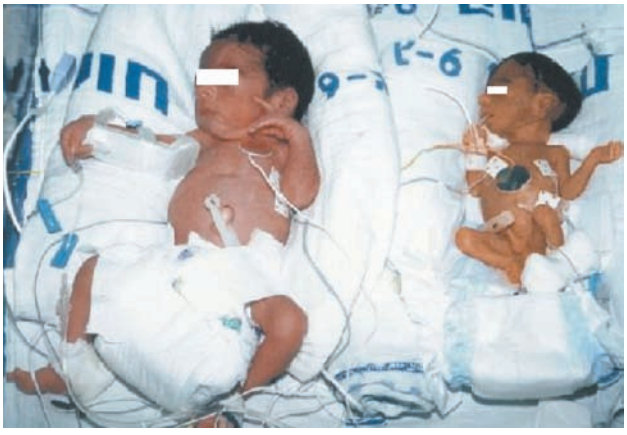

**Figure 16.1** Discordant twins born at 32 weeks. Both had normal intrauterine growth until 20 weeks, when growth of one twin was entirely arrested. The smaller and the larger twins weighed 450 and 1550 g, respectively. Such a case could erroneously be considered as superfetation

Hippocrates entitled *On Superfetation*. Aristotle, in his *Historia Animalium*, suggested that superfetation might occur frequently in hares and mares. His observation that only humans and horses mate during pregnancy led to the assumption that superfetation is also possible in women. An extensive review of alleged superfetation cases can be found in the seminal publication of Gould and Pyle[3] of more than a century ago. These authors cited descriptions by prominent figures such as Parè, Harvey, Mauriceau and Baudeloque. However, not everybody believed in superfetation in ancient times, as is seen in the Talmud (Nidah 27a). This passage concludes that a woman cannot become pregnant and then become pregnant again.

Alleged cases of superfetation through the ages can be explained under several categories.

*Delivery of twins of considerable discordant size (see Chapter 60).* Such cases may frequently be mistaken as being of different gestational ages rather than different sizes. For example, the Talmud describes Yehuda and Hizkiya 'who were twins, the form of one was finished to the end of the ninth, whereas the form of the other was finished to the beginning of the seventh' (Yevamot 6b). Figures 16.1 and 16.2 show a pair of discordant twins born at 32 weeks, and at the age of 2.5 years, respectively. Such twins could easily be confused with superfetation in older times.

Discordant size also occurs in cases with fetal demise when the resulting fetus papyraceus may be considerably smaller than the surviving twin, or fetuses that subsequently died *in utero*. Figure 16.3 shows the eight fetuses of an octuplet pregnancy spontaneously aborted at 19 weeks. This set comprises three fetuses which died spontaneously at 10–11 weeks, two fetuses that were artificially reduced and three fetuses that

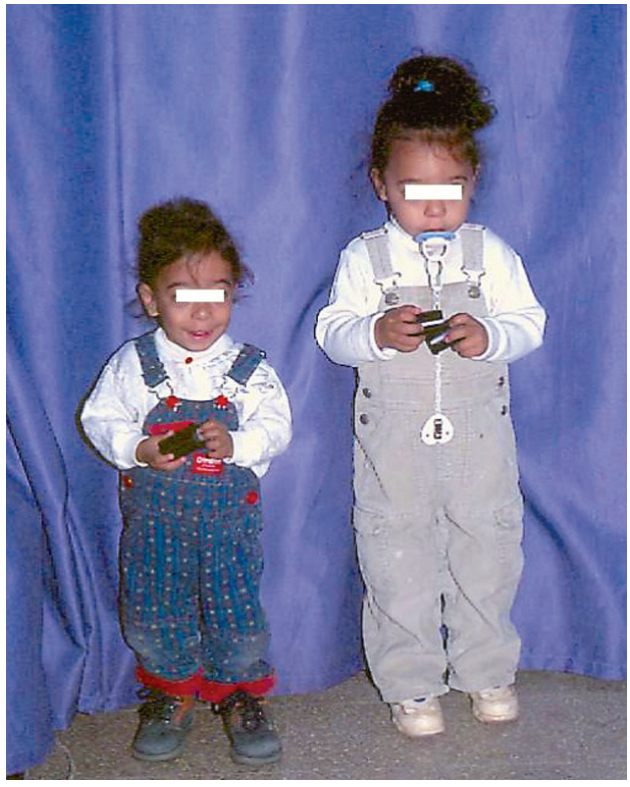

**Figure 16.2** Same twins as in Figure 16.1. Size discrepancy persisted at the age of 2.5 years

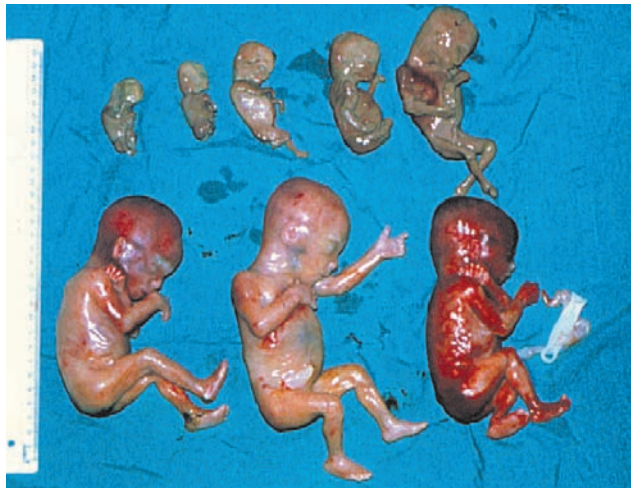

**Figure 16.3** A case of octuplets conceived after human menopausal gonadotropin (hMG) treatment. The three fetuses at the upper left were spontaneously reduced at about 10–11 weeks. The two fetuses at the upper right were intentionally reduced at 12 weeks. The entire pregnancy was spontaneously aborted at 19 weeks. This case could erroneously be considered as superfetation

died during the spontaneous miscarriage at 19 weeks. In older times, the obvious size discrepancy could easily be considered as demonstrating age difference, and thus as a case of superfetation.

Additional cases of early-onset discordance (starting at < 10 weeks) have been asserted to represent superfetation[4–6]. We, however, could show that very early discordance may be seen following double embryo transfer after *in vitro* fertilization.[7] This explanation was not considered by the authors of references 4–6.

*Delayed interval delivery (see Chapter 75)* This refers to multiple birth occurring at different times. The literature is replete with case reports and small series of cases in which one (or more) fetus(es) was (were) aborted or delivered prematurely, whereas the remaining fetus(es) is (are) delivered days, weeks and up to several months later. Although this phenomenon may be considered (*post facto*) to represent superfetation, it clearly is better understood in the context of the complete history of the pregnancy.

*Fraud* As recently as 12 November 2001, the British Broadcasting Corporation reported a 20-year-old Italian woman who had not used any fertility drugs, and claimed that she was going to deliver a singleton that week and then again 3 months later (of triplets). The case became doubtful when the baby was not born in November, and when the would-be father claimed that his wife delivered the first baby, vaginally, sometime in December. Eventually, in January 2002, the woman admitted that she was never pregnant, explaining: 'We tried fertilization treatment that went wrong. But then we invented the story about the double pregnancy, and weren't able to stop it.'

Interested readers may be amused to read the story reported by a prestigious medium[8]. Whereas one may wonder how such a fraud could reach international proportions in the 21st century, one should admit that shams related to twinning are still possible.

*Misdiagnosis of a multiple pregnancy* Before the advent of ultrasonography, twins were frequently diagnosed at birth, following the delivery of twin A. Transabdominal sonography enabled the early diagnosis of twins; however, the rate of missing one sac – especially in high-order multiples – was higher than that noted following the introduction of transvaginal sonography. It is possible that in some cases, in which one sac was initially visualized and a second sac appeared on a subsequent scan, an erroneous impression of superfetation arose.

As noted above, the scientific arguments used to discard the hypothetical occurrence of superfetation are the arrest of further ovulation after the initial ovulation and the inability of sperm to reach the fertilization site in the Fallopian tube. However, modern infertility treatment can theoretically circumvent these obstacles in one of two manners. The first is transfer of sperm directly to the Fallopian tube by a procedure called gamete intrafallopian transfer (GIFT). If this procedure is performed when the patient is already pregnant, and follicles are pushed to ovulate under the influence of hCG, a 'retrograde' fertilization may occur. Obviously, such a gestation is likely to develop in the Fallopian tube because the preceding gestational sac blocks the uterine cavity[9]. A second possibility arises from the fertilization of oocytes *in vitro*, a routine procedure in assisted reproductive technologies. Once created *in vitro*, zygote transfer directly to the Fallopian tube by a procedure called zygote intrafallopian transfer (ZIFT) performed inadvertently during an early gestation may create a heterotopic superfetation[10].

The ovulatory-inhibitory effect of an intrauterine pregnancy might not be the same in the presence of an extrauterine pregnancy. It is speculated that the latter produces less progesterone because of less trophoblastic tissue and a diminished effect on the corpus luteum. It is therefore possible that, in such circumstances, an ovarian follicle might escape the progesterone-induced ovarian suppression. This may be the reason why heterotopic superfetations are repeatedly mentioned in the older[3] as well as in the more recent literature[11,12].

In summary, superfetation should be considered under the following possibilities:

(1) As a misnomer, describing, in fact, superfecundation;

(2) As an erroneous diagnosis of other conditions;

(3) In the circumstance of a heterotopic pregnancy;

(4) In the case of GIFT or ZIFT performed during an ongoing early pregnancy.

## SUPERFECUNDATION

Superfecundation is also known from ancient times. Aristotle discussed this condition in relation to the Greek mythology of Leda, the wife of Tyndareus, King of Sparta. Leda was seduced by Zeus – king of the gods – who disguised himself as a swan. After Zeus impregnated her, her husband impregnated her again. Eventually, she laid two eggs, each producing unlike-sexed twins: Pollux and Helen – the children of Zeus – emerged from one egg, and Castor and Clytemnestra – the children of Tyndareus – from the other.

This erotic mythology provoked the imagination of innumerable artists. My first choice of the two best examples is the 1924 poem describing the mating of Leda and Zeus by William Butler Yeats (Table 16.1). My second best is Leonardo da Vinci's painting of *Leda and the Swan*. The copy shown in Figure 16.4 is one of two done by pupils of the master after the original painting was burned. Of note is the gross mistake showing unlike-sexed twins hatching from a single egg. It

**Table 16.1** *Leda and the Swan* by W. B. Yeats (1924)

A sudden blow: the great wings beating still
Above the staggering girl, her thighs caressed
By the dark webs, her nape caught in his bill,
He holds her helpless breast upon his breast.
How can those terrified vague fingers push
The feathered glory from her loosening thighs?
And how can body, laid in that white rush,
But feel the strange heart beating where it lies?
A shudder in the loins engenders there
The broken wall, the burning roof and tower
And Agamemnon dead.
Being so caught up,
So mastered by the brute blood of the air,
Did she put on his knowledge with his power
Before the indifferent beak could let her drop?

**Figure 16.4** *Leda and the Swan* by Leonardo da Vinci (*c.*1505–10): oil on wood. Reproduced by kind permission of the Earl of Pembroke, Wilton House, Salisbury, UK

could be that Leonardo followed the mythology verbatim, or that zygosity was totally unknown at that time.

The diagnosis of superfetation is often conjectured and speculative. On the other hand, the diagnosis of superfecundation, especially the heteropaternal pregnancy – when the twins are of different color or racial phenotype – is usually unquestionable. Gould and Pyle described the case of a mare that was impregnated sequentially by a stallion and an ass, and eventually delivered at one parturition a horse and a mule[3]. In the human, the best examples are those in which the twins born to the same woman are of different colors. Gould and Pyle cited a long list of prominent medical authorities that described such cases, the earliest of which was from 1714. Interestingly, most cases in the past, but certainly not all of them, described black women (many of whom were servants) who acknowledged that shortly after being with their respective husbands, they had intercourse with a white man[3].

A mix-up at a Leeds *in vitro* fertilization (IVF) clinic in 2002 resulted in the delivery of twins of different colors to an infertile white patient. The blunder could have been at either the fertilization stage (using sperm of a different father, i.e. heteropaternal pregnancy) or the embryo transfer stage (using an embryo from a different couple, i.e. heterologous pregnancy)[13]. DNA fingerprinting confirmed the former possibility. However, in its 'pure' sense, these heteropaternal twins were not a result of superfecundation because they were produced by inseminating retrieved eggs of the same ovulation cohort. Interestingly, England's senior family judge, Dame Elizabeth Butler-Sloss, ruled that the biological father was also the legal father of the twin; however, Dame Elizabeth suggested that the rights of the non-biological father could be protected by court adoption order[13].

Heteropaternal superfecundation seems to be an anecdotal and rare occurrence; however, Wenk and colleagues[14] identified three cases in a parentage-test database of 39 000 records and quoted a frequency of 2.4% heteropaternal superfecundations among dizygotic twins whose parents were involved in paternity suits. James[15] suggested that about one pair in 400 is heteropaternal in the population of dizygotic twins born to married white women in the USA. The incidence of heteropaternal superfecundation, however, clearly depends on rates of infidelity in the population, and may be substantially higher in small selected groups of dizygotic twin maternities, such as women engaged in prostitution. The frequency of twins with different fathers also depends on the extent of efforts in performing elaborate genetic analyses[16–18], leading to the impression that the frequency of heteropaternal superfecundation is underestimated, at least in selected populations[18].

Superfecundation is by no means equivalent to heteropaternity. Estimates from the Galton Institute in London[15] suggest that at least one dizygotic twin maternity in 12 is preceded by superfecundation, with varying frequencies depending on the population's coital rates and rates of double ovulation. Monopaternal superfecundation may also occur in assisted reproduction. Amsalem and colleagues[19]

reported the transfer of two embryos on day 3 and the development of five separate embryonic sacs. Genetic analysis of the twin pregnancy and of the three embryos that were reduced confirmed monopaternal superfecundation. IVF patients with patent Fallopian tubes should be cautioned against intercourse late in their controlled ovarian stimulation, especially if they would decline multifetal reduction[20].

## ETIOLOGY AND BIOLOGICAL SIGNIFICANCE OF SUPERFECUNDATION

There is no convincing explanation of why superfecundation occurs, and if it occurs why it is an exceptional phenomenon. With our current understanding of the ovulatory mechanism, some of the theories offered in the past seem outdated. In general, spontaneous or induced sequential ovulations are unable to produce superfecundation unless met by timely insemination. It follows that sequential fertilizations depend on either the viability of sperm in the female genital tract, or multiple inseminations (natural, artificial or both). Natural multiple inseminations within the time period of potential fertilization means an increased coital frequency at this period. James pioneered the proposition of high coital frequencies at the time of conception related to the birth of dizygotic twins[21]. In simple terms, this means that fertilization of the second egg of a double ovulation is more likely to be achieved by frequent ejaculations. It was estimated that if the coital rate of young women is doubled, their dizygotic twinning probability is increased by roughly 25–30%[22].

This theory was not substantiated by Danish data that found similar coital frequencies in parents of twins and parents of singleton infants[23], but was indirectly supported by Swiss data analyzed by Eriksson and Fellman[24], who deduced that the seasonality of twinning rates paralleled variations of coital rates and multiple ovulation in the early summer months. Another link between superfecundation and coital frequency comes from the alleged increase in gonadotropin levels and thus in double ovulation, which is indirectly mediated by the erotic response to coitus[25].

The biological significance of superfecundation is largely unknown. This is primarily related to the underestimation of its occurrence in fertile monogamous couples. In addition, the interval between two or more sequential fertilizations may be within the range of a few days or less, a time difference that is insufficient to show distinguishable discordance in multiple pregnancies. Regardless, the saga of superfecundation is being revived in recent years, with application of modern technology to understand this phenomenon. It is possible that the very early zygote and its hormonal production may affect in some way the development of a second, younger, zygote. It is unknown, however, whether this effect is beneficial or detrimental to the multiple pregnancy.

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# The Vanishing Fetus

*H. J. Landy and L. G. Keith*

17



## INTRODUCTION

Ultrasonography in early pregnancy confirms the widespread impression that the number of conceived multiple pregnancies exceeds the multiple birth rate. Spontaneous embryonic or fetal loss in the first trimester of multifetal gestations, also known as the 'vanishing twin' phenomenon, is a fairly frequent occurrence[1,2]. Valid and reproducible scientific studies have confirmed spontaneous pregnancy loss in multifetal gestations in animals as well as in humans, these data having been solidified by developments in both sonographic and assisted reproductive technologies[1].

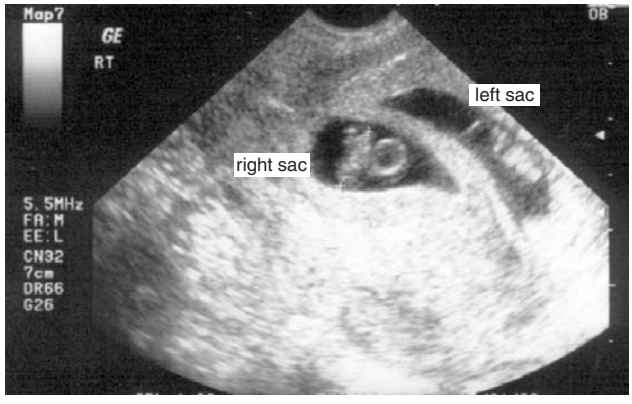


**Figure 17.1** Sonogram demonstrating one viable twin in the right sac and a non-viable twin in the left sac. One week earlier, two viable twins had been seen

## DIAGNOSIS AND FREQUENCY

Although precise mechanisms have yet to be discerned, early pregnancy disappearance most likely involves resorption and/or formation of a blighted ovum. Early reports of the vanishing twin inaccurately suggested a wide range of occurrence, possibly a result of interpretative and/or artifactual error[1,2]. Developments in sonographic technology, however, have helped to refine these numbers. In the past, reports of high rates of multiple gestation probably resulted from sonographic error in the misinterpretation of normal early embryonic structures or of other conditions (e.g. subchorionic hematomas or collections of subchorionic fluid)[1,3]. An educated appreciation of sonographic characteristics can help to identify a true intrauterine gestational sac and minimize interpretive error:

(1) A double contour;

(2) Identification of a yolk sac within the gestational sac;

(3) Recognition of an embryonic heartbeat after 6 weeks of gestation[4].

Transvaginal sonography, available since the late 1980s, provides extraordinarily detailed information regarding the process of early resorption in multiple gestations. The largest amount of information exists for pregnancies with twin and triplet sacs and/or embryos, compared with pregnancies with more than three sacs or embryos (Figures 17.1–17.3)[4–14]. Amalgamating these data reveals that approximately 70% of pregnancies with two sacs or embryos continue as twin gestations. In contrast, only about half

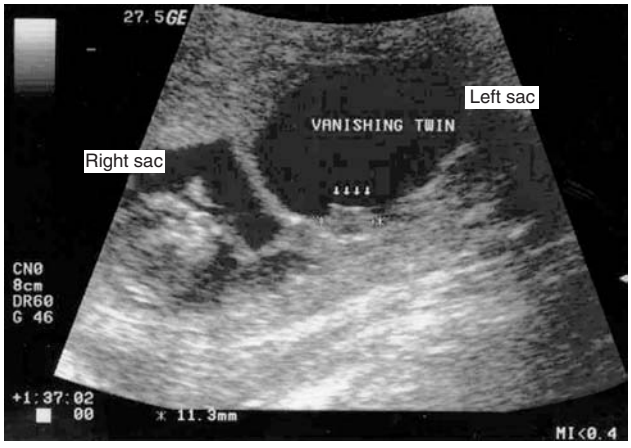


**Figure 17.2a** Sonogram of the same patient as in Figure 17.1 but 4 weeks later, demonstrating one viable twin in the right sac and the resorbing, vanishing twin in the left sac

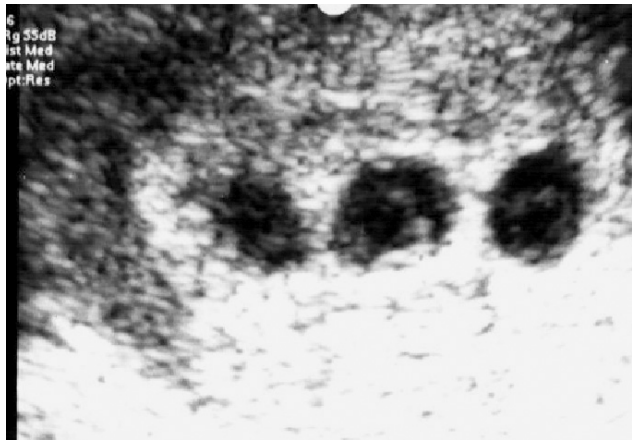

**Figure 17.3** Sonogram demonstrating three gestational sacs at 6–7 weeks. Two sacs contain an embryonic pole with positive heartbeat, whereas the left sac is empty (i.e. blighted ovum). Image courtesy of Yuval Or

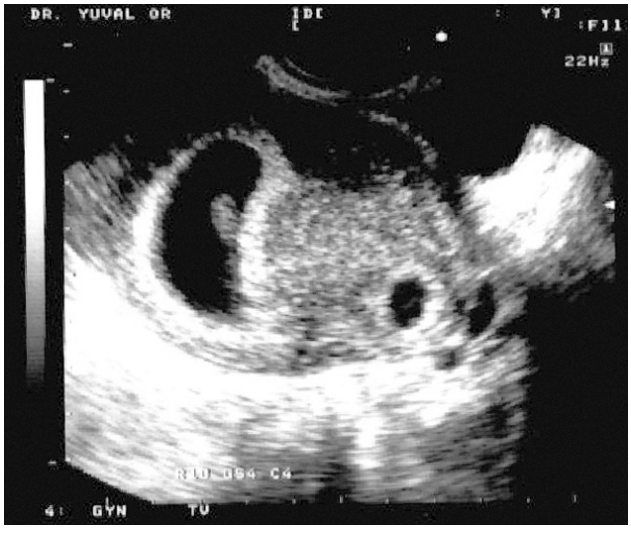


**Figure 17.2b** 'Classical' sonographic scan of the vanishing twin syndrome. The discrepant size of the gestational sacs in early pregnancy is an ominous sign. Image courtesy of Yuval Or

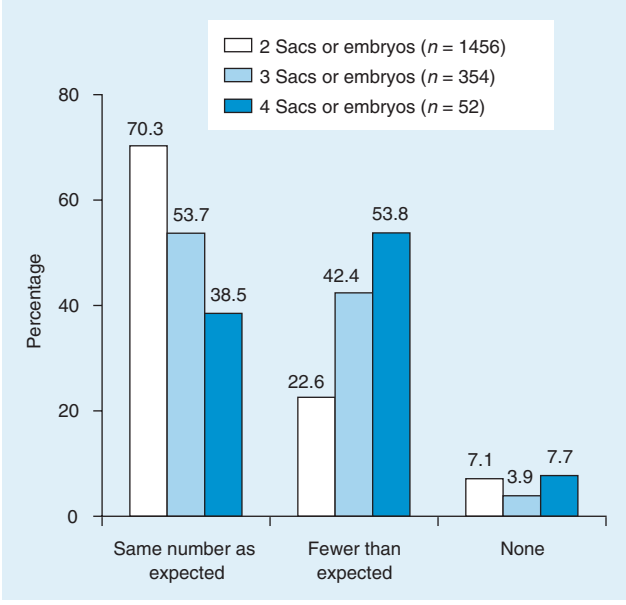


**Figure 17.4** Outcome beyond the first trimester after the sonographic diagnosis of 2–4 gestational sacs and/or embryos. Number of fetuses after the sonographic diagnosis of two sacs or embryos, three sacs or embryos and four sacs or embryos

of pregnancies with three sacs or embryos continue as triplets and, based on a smaller number of reported cases, even fewer (38%) of pregnancies with four sacs or embryos continue as quadruplets. Spontaneous resorption is present in 22.6% of twins and 42.4% of triplet gestations (Figure 17.4)[4–14]. Further stratification of the data for twin or triplet sacs or embryos is seen in Figure 17.5. Meaningful information cannot be calculated from the scant published data describing patients with quadruplets or quintuplets.

Additional analysis of data on twin gestations demonstrates differences in rates of resorption comparing pregnancies conceived spontaneously and those conceived using assisted reproductive technologies (ART). Figures 17.6 and 17.7 demonstrate comparisons of outcomes beyond the first trimester in spontaneous pregnancies and those conceived with *in vitro* fertilization (IVF) and ovulation induction after the early sonographic diagnosis of two sacs (Figure 17.6) and two embryos (Figure 17.7). Higher loss rates are seen with identification of only sacs

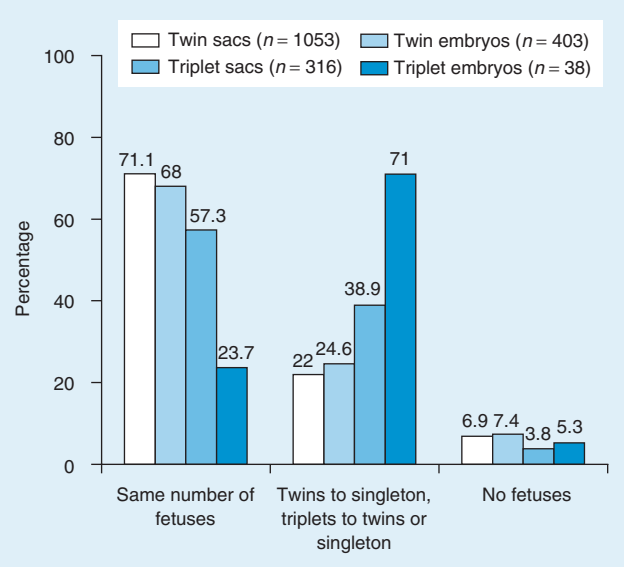


**Figure 17.5** Outcome beyond the first trimester after the early sonographic diagnosis of twin and triplet sacs or embryos. Pregnancy outcome after the sonographic diagnosis of twin sacs or embryos ($n$ = 1456) or triplet sacs or embryos ($n$ = 354)[4–14]

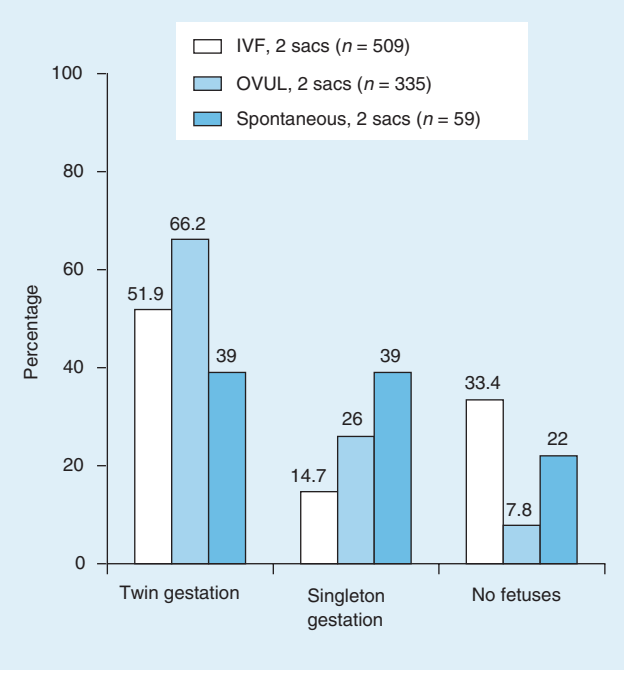


**Figure 17.6** Outcome beyond the first trimester in assisted versus spontaneous conceptions after the early sonographic diagnosis of two sacs ($n$ = 903). Comparison of *in vitro* fertilization (IVF), ovulation induction (OVUL) and spontaneous conceptions[8,9,11,12]

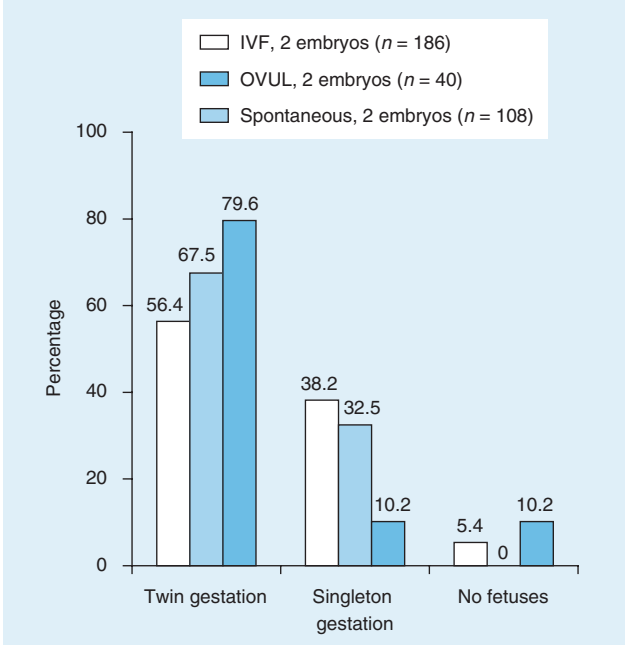


**Figure 17.7** Outcome beyond the first trimester in assisted versus spontaneous conceptions after the sonographic diagnosis of two embryos ($n$ = 344). Comparison of *in vitro* fertilization (IVF), ovulation induction (OVUL) and spontaneous conceptions[4,5,10,13,15]

rather than of embryos. Frequencies displayed in Figures 17.6 and 17.7 have been compiled from different studies and include data from considerably fewer patients with spontaneous conceptions compared with those conceived with ART[4,5,8–13,15]. Moreover, many reported spontaneous pregnancies underwent ultrasound examination only because of complications such as vaginal bleeding. Extrapolation of these data, especially for spontaneously conceived pregnancies, therefore, may not be applicable to the general population.

With sonographic identification of viable twins, the loss of one twin occurs in 38.2% of IVF conceptions, 32.5% of pregnancies conceived with ovulation induction and 10.2% of spontaneous conceptions (Figure 17.7). Sac or embryo disappearance has been described throughout the first trimester, although unconfirmed after 13 weeks[4,5]. Spontaneous reduction rates are higher earlier in gestation, but precise frequencies per given gestational week cannot be extrapolated[4–6,15].

## COMPLICATIONS AND PROGNOSIS

Vaginal bleeding or spotting, a common occurrence in the first trimester among pregnant women, is the

only apparent complication associated with the disappearance of an embryo or a gestational sac. A wide range of appearance of this complication, with rates as high as 76.5%, is described in different patient groups[1]. Clinical bleeding appears to coincide with the vanishing process. Regardless of chorionicity, the prognosis for continuing a pregnancy associated with spontaneous resorption is good[1,15].

Predicting continued fetal viability among sonographically identified twin gestations early in pregnancy may be challenging. More reliable prognoses can be made at later gestational ages and in the absence of an abnormal sonographic finding, such as a subchorionic hematoma. Vanishing rates are more than twice as high in monochorionic compared with dichorionic twin gestations (50% vs. 21%)[15]. Increasing maternal age is associated with higher spontaneous resorption rates[8], although results differ. In one study, no association was seen between twin resorption and maternal age, spontaneous versus induced conception, or indication for sonography[7].

Even the identification of an embryonic heartbeat cannot guarantee continuing fetal viability in multiple gestations. Kelly and colleagues[10] found the rate of increase of serum human chorionic gonadotropin levels to be a more reliable predictor of ongoing viability than embryonic cardiac activity. When sonography demonstrates interfetal crown–rump length variability, possible outcomes include embryo disappearance[13], as well as fetal aneuploidy or congenital anomalies[16].

It has been hypothesized that cerebral palsy of unknown etiology in singletons may be attributable to the early loss of a previously unrecognized monochorionic twin[17]. Accordingly, the survivor's neurological development is impaired throughout pregnancy, with spastic cerebral palsy the resulting clinical manifestation[17]. Although intriguing, data are not consistently supportive of this concept[18]. Furthermore, against such an association is the lack of reported cases following multifetal pregnancy reduction, a procedure that is not unlike the vanishing twin phenomenon[19]. The vanishing twin phenomenon perhaps may underly some isoimmunization cases that develop during gestation in which one rhesus-positive twin disappears in a previously unsensitized rhesus-negative mother[1,2].

## PATHOLOGICAL CONSIDERATIONS

Pathological confirmation of the resorption process is documented by histological findings from the fetal surface of the placenta. These include descriptions of well-defined sacs or cysts; placental nodules or plaques; areas of degenerated chorionic villi; fibrin deposition or fibrinoid degeneration; embryonic remnants; and macerated embryos[1,2,20,21]. The vanishing twin phenomenon has been used to explain discordant chromosome results, including various trisomies, triploidy, tetraploidy and sex chromosome discrepancies[1,2,21].

## CONCLUSIONS

(1) The 'vanishing twin' phenomenon is not an unusual sonographic finding among multiple pregnancies.

(2) The risk of resorption appears to increase with plurality:

  (a) Approximately 22% of conceptions with two sacs or embryos result in singleton gestations;

  (b) Over 40% of gestations with three sacs or embryos result in fewer fetuses than expected;

  (c) The risk of fetal resorption rises to more than 50% in quadruplet pregnancies.

(3) Disappearance rates vary, depending on whether pregnancies are conceived spontaneously versus with ART.

(4) Better outcomes are seen with dichorionic rather than with monochorionic twin gestations.

(5) Disappearance is more frequent earlier in gestation.

(6) The main complication associated with vanishing embryos is vaginal bleeding.

(7) Detailed sonographic evaluation is recommended to follow the progression of the resorption process as well as to assess viability and evaluate growth in the remaining fetus(es).

(8) Careful examination of the placenta and membranes may confirm earlier sonographic findings after delivery.

With continued technological advances, sonography of early pregnancy enables us to have a more complete understanding of fetal development and the relationship of early pregnancy loss in multiple gestations.

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# Uncommon Causes of Twinning: Complete Hydatidiform Mole with Coexistent Twin

*E. Vaisbuch and A. Ben-Arie*

**18**



## INTRODUCTION

A hydatidiform mole with a coexisting live fetus is a rare entity. Suspicion may arise when an ultrasound scan identifies a fetal pole along an abnormal placenta. The main issue is to differentiate between two diagnoses: a singleton pregnancy consisting of a partial hydatidiform mole with an abnormal triploid fetus which usually dies *in utero* during the first half of pregnancy; and a twin gestation consisting of a complete hydatidiform mole along with a coexisting live fetus (CMCF). The latter is extremely rare[1–4], and management is challenging because the fetus may be viable. Information about this entity is scant. Moreover, only a few case reports of a twin gestation with a coexisting hydatidiform mole have accurately distinguished between a partial mole with a live fetus and CMCF. Although CMCF is associated with fetal survival, it carries a significant risk of severe complications such as pre-eclampsia, preterm delivery and development of persistent gestational trophoblastic tumor (GTT).

This chapter discusses the diagnosis, clinical considerations and the controversial management of complete hydatidiform mole with a coexisting fetus (Figure 18.1).

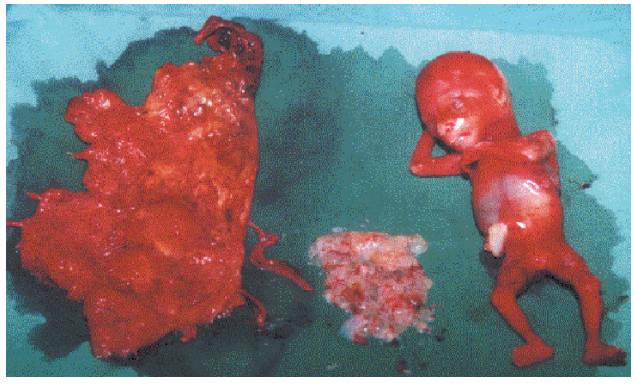

**Figure 18.1** Complete hydatidiform mole (left) with a male co-twin (right) and a normal placenta (center). Pregnancy was terminated at 18 weeks because of severe pre-eclampsia and life-threatening thyrotoxicosis

## CYTOGENETICS AND MOLECULAR BASIS OF PARTIAL AND COMPLETE HYDATIDIFORM MOLE

Gestational trophoblastic diseases are heterogeneous conditions derived from the products of pregnancy. These conditions, including hydatidiform mole, invasive mole, choriocarcinoma and placental-site trophoblastic tumors, are characterized by abnormal growth of the chorionic tissue with varying propensities for local invasion and metastasis. In all these conditions the presence of paternal genes is a prerequisite, as well as a distinguishing feature that separates it from other non-gestational tumors.

Hydatidiform mole is associated with an abnormal placenta with enlarged and edematous chorionic villi, accompanied by hyperplasia of the trophoblast. In the late 1970s, Vassilakos and colleagues[5] first described two distinct pathological entities: partial and complete hydatidiform mole (CHM) with different mechanisms of origin based on cytogenetic analysis. Partial moles derive from dispermic fertilization of a haploid normal oocyte, and produce a

triploid set of chromosomes. In the majority of cases, the extra set is of paternal origin, and fetal parts can be recognized. The incidence of persistent GTT following partial moles is as low as 4%[3].

In contrast, a CHM contains a diploid set of 46 chromosomes, all of paternal origin (androgenic). Sex chromosomes are almost always XX, which are most probably derived from the fertilization of an anuclear ovum by a haploid (23X) spermatozoon, and subsequent duplication of its own chromosomes. No fetal parts can be identified, and the risk of developing persistent GTT is higher (12–20%) than in partial mole[3,6]. It is believed that the higher is the ratio of paternal/maternal chromosomes, the greater is the molar change, as is the case with CHM (2 : 0 paternal/maternal ratio) compared with partial mole (2 : 1).

Differential diagnosis of the combination of a live fetus and a molar-appearing placenta includes three possibilities. The first is a singleton pregnancy consisting of a partial hydatidiform mole and a live fetus. The second consists of a twin pregnancy with one placenta exhibiting a complete mole (no fetus) and the other placenta (sometimes in close approximation with the other) sustaining a normal twin (CMCF). The third possibility is a combination of partial mole and a twin in one sac and a normal twin in the other. In the last possibility, the option of CHM is easily excluded by the presence of two fetuses. The real challenge is to distinguish between the first two possibilities, because of the chance of survival in the instances which include a CMCF. Another very rare possibility is a diploid mole of biparental origin (a partial mole) and a coexistent fetus[7]. The prognosis and risk of persistent GTT of this obscure entity are currently unknown.

Complete and partial moles are associated with distinct fetal and maternal complications. In the combination of a partial hydatidiform mole, the fetus is almost always triploid, and the indication for a termination of pregnancy is clear. In contrast, although the fetus may be normal in a twin pregnancy with a CMCF, continuation of the pregnancy is frequently associated with severe maternal complications, giving rise to a clear mother versus fetus clinical dilemma. The management of such pregnancies can be either immediate termination of the pregnancy to avoid the potential maternal complications, or expectant management to save the fetus but endangering the mother with pregnancy complications or with a potentially persistent trophoblastic tumor.

## INCIDENCE

The incidence of hydatidiform moles varies in different populations, and is much higher in Japan than in Europe or America[8]. The incidence of complete and partial hydatidiform moles is about 1 in 1000 and 3 in 1000, respectively[9]. The coexistence of a hydatidiform mole and a live fetus is a relatively uncommon event, with a quoted range of incidence from 1 in 10 000 to 1 in 100 000 pregnancies. This estimate is based on old series before the era of distinguishing between partial and complete mole. Bowles reported in 1943 one case in 9501 pregnancies. Beischer (1961) reported ten cases in 110 477 pregnancies and Jones and Lauersen (1975) reported eight cases in 175 990 pregnancies[10]. Most of these cases either aborted or resulted in *in utero* fetal death. Cases of molar pregnancy with a coexisting viable fetus are extremely rare, with only 16 cases with a living newborn reported before 1980[10]. In all instances except one, the diagnosis was made after delivery, and without differentiation between the partial and complete molar entities. More recently, accurately diagnosed complete hydatidiform moles were reported with a coexisting fetus[9,11], but only a few with a living newborn. The true incidence of this rare entity is difficult to establish, and some authors suggest that the increased incidence of iatrogenic multiple gestations will cause a higher incidence of CMCF[11]. A final interesting observation, albeit without later confirmation, is that of De George, who reported in 1970 a significant increased frequency (1 : 225) of molar pregnancies before or after a twin pregnancy[12].

## DIAGNOSTIC TOOLS

Most cases of molar pregnancies are diagnosed during the first trimester by ultrasonography. Twin pregnancies, consisting of CHM with a coexisting fetus, are usually diagnosed later in pregnancy. In these circumstances, the initial scan is not easy to interpret, and many cases present in the second trimester with the classical signs and symptoms of gestational trophoblastic disease. Ultrasound, the diagnostic tool of choice, allows determination of the number of gestational sacs and assessment of normal fetal development. In CHM, the sonographic image shows the characteristic vesicular pattern known as the 'snowstorm' (Figure 18.2). When a partial mole is present, focal cystic changes in the placenta, an aberrant gestational sac and congenital anomalies may be seen. When a molar-appearing placenta is recognized, high-resolution sonographic equipment is useful to differentiate between a partial mole and a twin pregnancy with a complete mole and a coexisting normal fetus. Interestingly, Steller and colleagues reported that only 68% of patients with hydatidiform mole and coexisting fetus were diagnosed correctly by abdominal ultrasound[3]. This detection rate is even worse in the first trimester

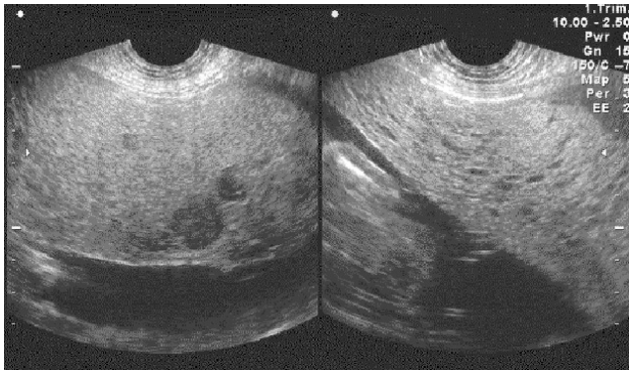

**Figure 18.2** Ultrasound image showing a molar placenta in the right panel with part of the normal fetus (nourished by a second placenta). The left panel shows molar cavitations in the placenta. Image courtesy of B. Caspi

before fetal anomalies associated with a partial mole are visualized.

A markedly elevated human chorionic gonadotropin (hCG) value may suggest CHM, but this determination is not reliable for the diagnosis, especially in twin pregnancies in which hCG levels can be significantly, but normally, elevated. It follows that whenever the diagnosis of a molar placenta/coexisting fetus combination is suspected, the diagnosis can be reached by invasive methods. The histological appearance of villi as well as standard chromosomal analysis may also be inconclusive. Although chromosomal triploidy is diagnostic of a partial mole, a diploid karyotype – typical of a complete mole – has been described in partial moles as well[7,13,14]. Thus, the final diagnosis of a complete mole requires elaborate cytogenetic studies to prove the androgenic origin of the chromosomes[13].

## CLINICAL FEATURES AND NATURAL HISTORY

In the past, most CMCF gestations were terminated immediately following diagnosis, resulting in scant information concerning clinical features and natural history. This circumstance has changed in recent years. Patients can present with vaginal bleeding, hyperemesis gravidarum, early-onset pregnancy-induced hypertension, hyperthyroidism and a uterus that is large for gestational age. Stellar and colleagues[3] compared the clinical characteristics of CMCF with those of singleton complete moles, finding that CMCF are diagnosed later (at 20.1 vs. 13 gestational weeks), have a higher pre-evacuation serum hCG level and have a greater tendency to develop persistent GTT (55% vs. 14%). Bristow and associates[6] compared 26 cases of CMCF that ended either in a previable or in a viable newborn. The groups were significantly different regarding gestational age at diagnosis (17.4 vs. 29.4 weeks), difference between uterine sizes and gestational age at evacuation (8.1 weeks vs. 1.0 week) and pre-evacuation serum hCG level (>1 000 000 vs. 170 000 mIU/l). Previable cases were associated with higher frequencies of pre-eclampsia (31.6% vs. 14.3) and persistent gestational trophoblastic disease (68.4 vs. 28.6%, $p = 0.09$), when compared with the viable cases.

### Vaginal bleeding

The presenting sign in more than 90% of cases is vaginal bleeding, ranging from spotting to heavy bleeding requiring immediate termination of pregnancy[6]. However, in a review of partial moles with non-malformed fetuses and of twin gestations with complete mole and normal conceptus, Vejerslev found that 46.4% of patients experienced no bleeding prior to delivery[2].

### Early-onset pre-eclampsia

This is more frequent (25–35% of cases) in twin pregnancies consisting of CMCF than in normal pregnancies[2,6,11,15]. Severe pre-eclampsia is reported in about 6% of cases, and its occurrence often determines the destiny of the pregnancy.

### Hyperemesis gravidarum

This is found in about 19% of cases[2], but is not the main reason for pregnancy termination. Hyperemesis, however, lasts longer compared with singleton non-molar pregnancies, and may continue far beyond the first trimester.

### Persistent mole

The reported incidence of persistent GTT for a singleton pregnancy with a complete mole is much higher than with a partial mole (12–20% vs. 1–5%). This potential risk is the most problematic factor in counseling couples with CMCF. Most reports concerning CMCF find a very high risk (50–57%) for persistent GTT (Table 18.1). However, the total number of cases collected for this table is small. Sebire and colleagues[9] reported the largest series of 77 cases, and found only a 19% risk for developing persistent GTT, similar to the risk that is found following singleton pregnancies with complete mole.

It is uncertain whether the reported increased risk of persistent GTT following CMCF is due to the delay in evacuation of the pregnancy or to the more aggressive biological behavior of the abnormal trophoblastic tissue in these twin gestations[16]. However, advanced gestational age does not appear to be an independent risk factor for developing persistent GTT[11]. Steller and

**Table 18.1** Complete hydatidiform mole and coexistent fetus

| Reference | n | Intended previable TOP | TOP due to SA, maternal complications or IUFD | Live neonate | Pre-eclampsia | Persistent GTT | Metastatic GTT |
|---|---|---|---|---|---|---|---|
| 6 | 26 | 19 | NA | 7 (27%) | 7 (27%) | 15 (57%) | 5/22 (lung, vagina) |
| 1 | 7 | 5 | NA | 2 (28%) | NA | 4 (57%) | 0 |
| 11 | 18 | 5 | 10 | 3 (17%) | 5 (28%) | 9 (50%) | 6 (lung) |
| 9 | 77 | 24 | 32 | 20 (26%) | NA | 15 (19%) | NA |
| Total | 128 | 53 | | 32 (25%) | | 43 (34%) | |

TOP, termination of pregnancy; SA, spontaneous abortion; IUFD, intrauterine fetal death; GTT, gestational trophoblastic tumor; NA, not available

colleagues found that persistent GTT developed in only one of the five cases in which the fetus survived[3]. Bristow and co-workers[6] found that 68.4% of pregnancies terminated before viability developed persistent GTT, compared with only 28.6% in the group with a surviving infant (difference not significant). Theoretically, this may be due to a more benign trophoblast in pregnancies that reach an advanced gestational age, or due to selection bias because fetal viability cannot be excluded in cases interrupted immediately upon diagnosis[6]. Bruchim and colleagues found that eight of 15 (53.3%) pregnancies with CMCF that ended with a normal fetus developed persistent GTT, including four with lung metastasis[17]. However, the quantity of molar tissue and the time of diagnosis were not reliable indicators of the malignant potential of the mole. Fishman and associates found that serum hCG levels were not predictive for the need of future chemotherapy for persistent GTT[1]. The incidence of maternal complications such as pre-eclampsia and massive vaginal bleeding was significantly higher in patients with than without persistent GTT[11]. In addition, there was a greater propensity for metastasis in CMCF among patients who developed persistent disease, compared with singleton complete mole[15].

## OUTCOME OF PREGNANCIES WITH COMPLETE HYDATIDIFORM MOLE AND COEXISTENT TWIN

Most of the available data come from sporadic case reports, many without an accurate distinction between a partial mole and a CMCF, and some which present duplicate data. Bruchim and colleagues in 2000[17] reviewed the literature, as hydatidiform mole was subdivided into complete and partial mole, and reported a total of 15 CMCF cases with a live neonate delivered at a mean age of 34.3 ± 5.3 weeks. Since that review, reports of 23 additional pregnancies that ended with a live neonate have been published[9,11]. Sebire and colleagues[9] described 126 twin pregnancies with hydatidiform mole and healthy co-twin, including 77 pregnancies that were histologically confirmed as CMCF. Forty-nine cases failed to reach 24 weeks: 24 (31%) elected to terminate the pregnancy, and 25 who elected to continue their pregnancy had either a spontaneous abortion and fetal demise ($n = 23$) or a termination of pregnancy due to severe pre-eclampsia ($n = 2$). Only 20 of the 28 pregnancies that continued past 24 weeks' gestation delivered a live infant at a median gestational age of 35 weeks. Seven had a stillbirth and one a neonatal death. In summary, nearly 60% of CMCF pregnancies which were not electively terminated resulted in either stillbirth of the co-twin or spontaneous pregnancy loss before fetal viability. Nearly 40% of patients who chose to continue their pregnancies had a live birth, frequently beyond 32 weeks' gestation[9]. The potential life-threatening maternal complications included thromboembolic events and severe pre-eclampsia (6%, slightly higher than in a normal twin pregnancy). Persistent GTT developed in 15 cases (19%). This risk was not different in women undergoing elective first-trimester termination of pregnancy and in those who continued their pregnancies, and was similar to that after a singleton CHM (16%). All the women were successfully treated with chemotherapy, and there were no maternal deaths[9].

After the exclusion of duplicate publications, we summarized data from cases with accurately diagnosed complete hydatidiform mole and coexistent fetus (Table 18.1). Of a total of 128 cases, only 32 (25%) resulted in a live neonate, and the overall risk of developing persistent GTT was 34%.

## PROGNOSTIC SIGNS OF PREGNANCY OUTCOME

Estimation of the likelihood of a pregnancy progressing beyond viability without major risks is based on

three prognostic signs. First, twin molar gestations resulting in a liveborn infant tend to have a smaller discrepancy between the actual uterine size and that expected by gestational age[3,6]. Second, the pre-evacuation serum hCG levels of viable gestations are significantly lower than those of the previable group[2,6], a factor that may be related to the suggestion that declining serial serum hCG levels during pregnancy reflect a less active molar growth[16]. Finally, absence of the above-mentioned maternal complications improves the chance of fetal survival.

## MANAGEMENT

It is difficult to recommend an optimal management for CMCF pregnancies because of the scant information available. In the past, the suggested management for a hydatidiform mole with coexistent live fetus diagnosed in early pregnancy was immediate termination of pregnancy[4,15]. This approach was advocated because of the potential risks of fetal anomalies, severe maternal complications and developing a persistent trophoblastic tumor. However, recent advances in ultrasonography and fetal karyotyping enable early and accurate diagnosis of a CMCF. Regardless, an optimal management is still difficult to formulate, as complete cytogenetic information of both mole and fetus is rarely available. Despite these difficulties, with some degree of caution, the literature seems to support continuation of a CMCF pregnancy[2,6,18], albeit not without the ongoing risk of severe maternal complications and development of persistent trophoblastic tumor. Bristow and colleagues[6] and Matsui and associates[11] suggested that the pregnancy may be allowed to continue when fetal anomalies and abnormal karyotype are excluded, and in the absence of pre-eclampsia. Declining serum levels of hCG have also been suggested as a requirement for expectant management[6].

When the diagnosis of a CMCF pregnancy is suspected by ultrasonography, the karyotype of the coexistent fetus should be obtained. As triploid fetuses are likely to die before mid-pregnancy, termination of the pregnancy is recommended as soon as this diagnosis is made. When a normal diploid karyotype is found, excluding the diagnosis of a triploid partial mole, the most probable diagnosis is a dizygotic twin pregnancy with a complete mole. In such a circumstance, it remains controversial whether to continue the pregnancy or to terminate it, because complete molar tissue carries a higher risk of developing a persistent trophoblastic tumor.

If the diagnosis is made near the age of fetal viability, continuation of the pregnancy is an acceptable option, but this should be done only after detailed discussion with the couple (and informed consent), and only when close surveillance to detect early signs of maternal complications can be guaranteed. During counseling, the couple should be informed that the actual risk of pregnancy continuation remains uncertain, as large series of CMCF pregnancies are not likely to be forthcoming owing to the rarity of CMCF. The couple should also know that only about 25% of such pregnancies end with a live birth, some of which have serious consequences of a premature delivery. The potential risk of severe maternal complications should also be explained. The increased risk of developing persistent GTT requiring chemotherapy should be discussed, although it is unclear whether the risk is lower or higher after an elective termination of pregnancy than after birth.

## FOLLOW-UP

The purpose of follow-up after evacuation of a CMCF pregnancy is early diagnosis and treatment of persistent GTT. Follow-up should be as for complete moles. Weekly to bimonthly measurements of serum hCG are recommended. This protocol should be followed until hCG levels are undetectable for three consecutive measurements, and then monthly assessments are carried out for a period of 6–12 months[2]. Contraception during the follow-up period is necessary.

The risk of a recurrent mole in a subsequent pregnancy is reported to be 0.6–2%[2]. No data exist concerning this risk following a CMCF gestation. However, it is not expected to be different.

## HIGH-ORDER MULTIPLE PREGNANCIES AND COEXISTENT COMPLETE MOLE

The first case of a high-order multiple pregnancy coexistent with hydatidiform mole was reported in 1980. Sauerbrei and colleagues reported a triplet pregnancy with a complete hydatidiform mole and two fetuses[19]. Since then, more cases have been reported, but do not significantly expand the limited information about the natural history of such pregnancies. High-order multiple gestations carry an increased risk of preterm labor and pre-eclampsia. When accompanied by a mole, this risk might be even higher. Chao and associates described six cases of CHM coexisting with either a twin or a triplet pregnancy, with the longest reported gestation of 25 weeks, and no surviving infants[20]. The management of these rare pregnancies must be individualized utilizing, where possible, available precepts from the treatment of twin gestations.

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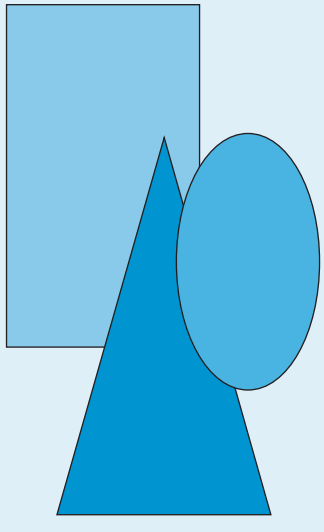
## COMMENT



In the Middle Ages, a molar pregnancy was itself considered as a multiple pregnancy. Reports of women giving birth to tens and even hundreds of offspring at one time are well known[1]. For example, the etching attributed to Ambroise Paré shows a woman carrying 20 babies. Modern scholars suggest that these reports, in fact, represent careful counting of molar vesicles[2]. Sometimes, as reported in a case from 1276, the 365 'infants' were identified by sex and properly baptized[2].

*Isaac Blickstein*

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# The Impact of Ovulation Induction and *In Vitro* Fertilization on the Incidence of Multiple Gestations

*R. P. Dickey and B. M. Sartor*

**19**



## INTRODUCTION

Infertility treatment is estimated to be responsible for more than 224 000 excess multiple births between 1980 and 1997[1]. In 2000, the latest year for which national statistics are available, 118 997 babies were born as twins and 7328 were born as triplets, quadruplets and higher orders[2]. In the USA, assisted reproductive technologies (ART), *in vitro* fertilization (IVF) and related procedures produced 11% of twin births and 45% of triplet and higher-order births[3]. Ovulation induction (OI) without ART is estimated to be responsible for 20% of twin births and 38% of triplet and higher-order births[3] (Figure 19.1). Similar relationships are reported in Britain, where OI exclusive of IVF and related procedures is responsible for 67% of quadruplet and higher-order births[4].

The two principal classes of OI drugs are anti-estrogens, of which clomiphene citrate (CC) is the prototype, and gonadotropins, of which human menopausal gonadotropin (hMG) is the prototype. Human menopausal gonadotropin is a 1 : 1 mixture of follicle stimulating hormone (FSH) and luteinizing hormone (LH), extracted from the urine of menopausal women. Newer refinements of hMG include highly purified urinary FSH, and recombinant FSH produced in tissue culture.

Clomiphene was developed in the USA in 1956, became available for clinical trials in 1959 and was approved for sale in 1967[5] (Table 19.1). Human

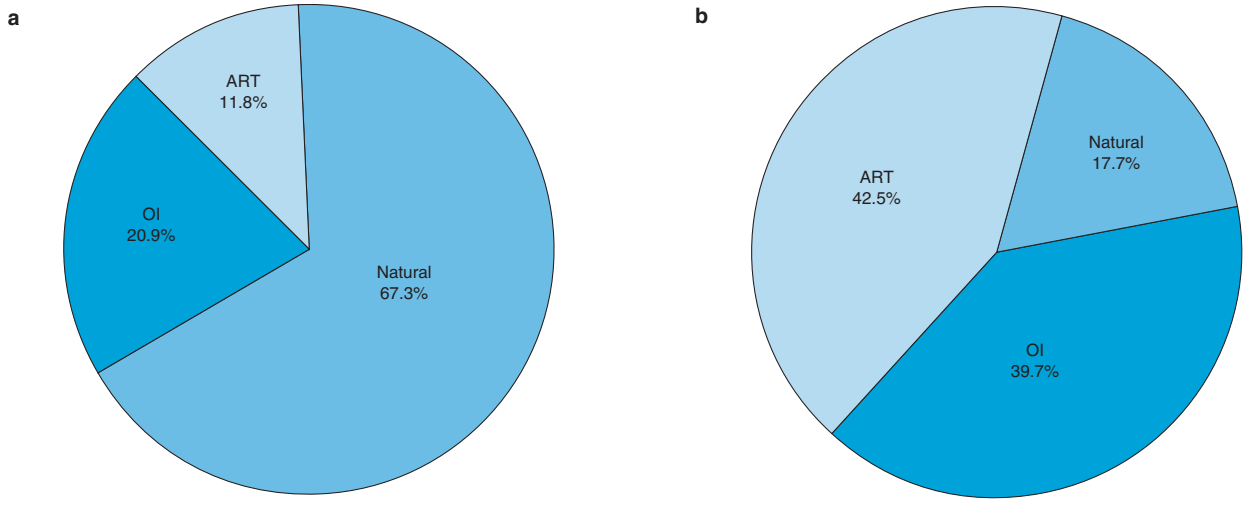


**Figure 19.1** (a) Source of twin births, 2000; (b) source of triplet and higher-order births, 2000. ART, assisted reproductive technologies; OI, ovulation induction. Adapted from reference 3

**Table 19.1** Significant dates for the introduction of ovulation-induction drugs and assisted reproductive technologies

| | |
|---|---|
| 1956 | Clomiphene citrate synthesized by scientists at Merrell Laboratories[5] (MRL-41) |
| 1959 | Human menopausal gonadotropin used for ovulation induction[6] |
| 1959 | Clinical testing of clomiphene citrate/MRL-41 initiated for ovulation induction[5] |
| 1961 | First report of pregnancies with clomiphene citrate published in *J Am Med Assoc*[5] |
| 1962–66 | Clomiphene citrate used in research setting at numerous US university clinics[6] |
| 1963 | Human menopausal gonadotropin (hMG) approved for testing in United States[7] |
| 1967 | Clomiphene citrate (CC) approved by Food and Drug Administration; released for use in United States[5] **(CC)** |
| 1969 | Mid-year hMG approved for use in ovulation induction in United States **(hMG)** |
| 1978 | First *in vitro* fertilization (IVF) birth in England |
| 1982 | 28 December, first IVF birth in United States **(IVF)** |
| 1984 | First description in United States of use of controlled ovarian hyperstimulation (COH) with intrauterine insemination as alternative to IVF[8] **(COH I)** |
| 1987 | Publication in *Fertil Steril*, official journal of the Americian Fertility Society, of article advocating controlled ovarian hyperstimulation with intrauterine insemination as alternative to IVF; 21 pregnancies including five sets of twins (23.8%) and one triplet pregnancy (4.8%)[9] **(COH II)** |
| 1998 | 360 US IVF clinics report 15 367 deliveries including 4917 (32.0%) sets of twins (9834 twin births) and 922 (6.0%) triplet and higher-order deliveries (2766 triplet or higher births)[15] |
| 2000 | 383 US IVF clinics report 19 042 deliveries including 5846 (30.7%) sets of twins (11 692 twin births) and 819 (4.3%) triplet deliveries and higher-order deliveries (2457 triplet or higher births)[16] |
| 2000 | Report on superovulation with intrauterine insemination in *N Engl J Med*; 441 pregnancies including 88 sets of twins (20.0%)* and 39 triplet and higher-order pregnancies (8.8%)*; authors advocate IVF in place of ovulation induction with hMG[10] |

*Multiple pregnancies diagnosed by early ultrasound; 50% of triplet and 75% of quadruplet and higher-order pregnancies will spontaneously reduce to a lower number by birth due to embryo and fetal demise. Abbreviations in bold type keyed to Figure 19.2

**Table 19.2** Results of ovulation induction (July 1983–July 1998). Adapted from reference 11

| | *Clomiphene* | *hMG* | *Clomiphene + hMG* |
|---|---|---|---|
| Follicles ≥ 12 mm | 2.7 | 5.4 | 4.4 |
| Pregnancy rate/cycle | 12% | 19% | 17% |
| Twin conceptions | 9% | 12% | 20% |
| ≥ Triplet conceptions | 0.02% | 7% | 7% |

hMG, human menopausal gonadotropin

menopausal gonadotropin for use in OI was developed in Europe in 1960[6], became available for clinical trials in the United States in 1963[7] and was approved for sale in 1969. CC is taken by patients for 5 days beginning on cycle days 3–5. It causes the hypothalamic–pituitary complex to produce increased amounts of endogenous FSH. The amount of FSH released is regulated through a negative feedback loop and, as a result, CC only infrequently results in the development of two follicles or more than twin births (Table 19.2). By contrast, hMG and related drugs are not modulated by negative feedback, and can cause the development of multiple follicles and triplet or higher-order pregnancies.

The incidence of triplet and higher-order births in the United States has risen dramatically, from 1244 in 1960 to 7328 in 2000, coincident with the introduction of OI drugs in the late 1960s and of IVF in the mid-1980s (Figure 19.2). The greatest increase occurred between 1984 and 1998. This increase was due in part to an increase in the number of clinics performing IVF from approximately 12 in 1984 to 383 in 2000[12–16], and to improved laboratory methods. Another reason for this increase was a change in the manner in which gonadotropins were administered for OI, from employing the lowest dose consistent with follicular development to employing high doses intended to cause multiple follicular development so as to maximize the opportunity for pregnancy during a single cycle. This latter technique, now termed controlled ovarian hyperstimulation (COH), was introduced by Sher and colleagues in 1984[8], but was not widely used until after publication of a study in the journal *Fertility and Sterility* in 1987[9], which advocated COH with intrauterine insemination (IUI) as an alternative to gamete intrafallopian transfer (GIFT) and

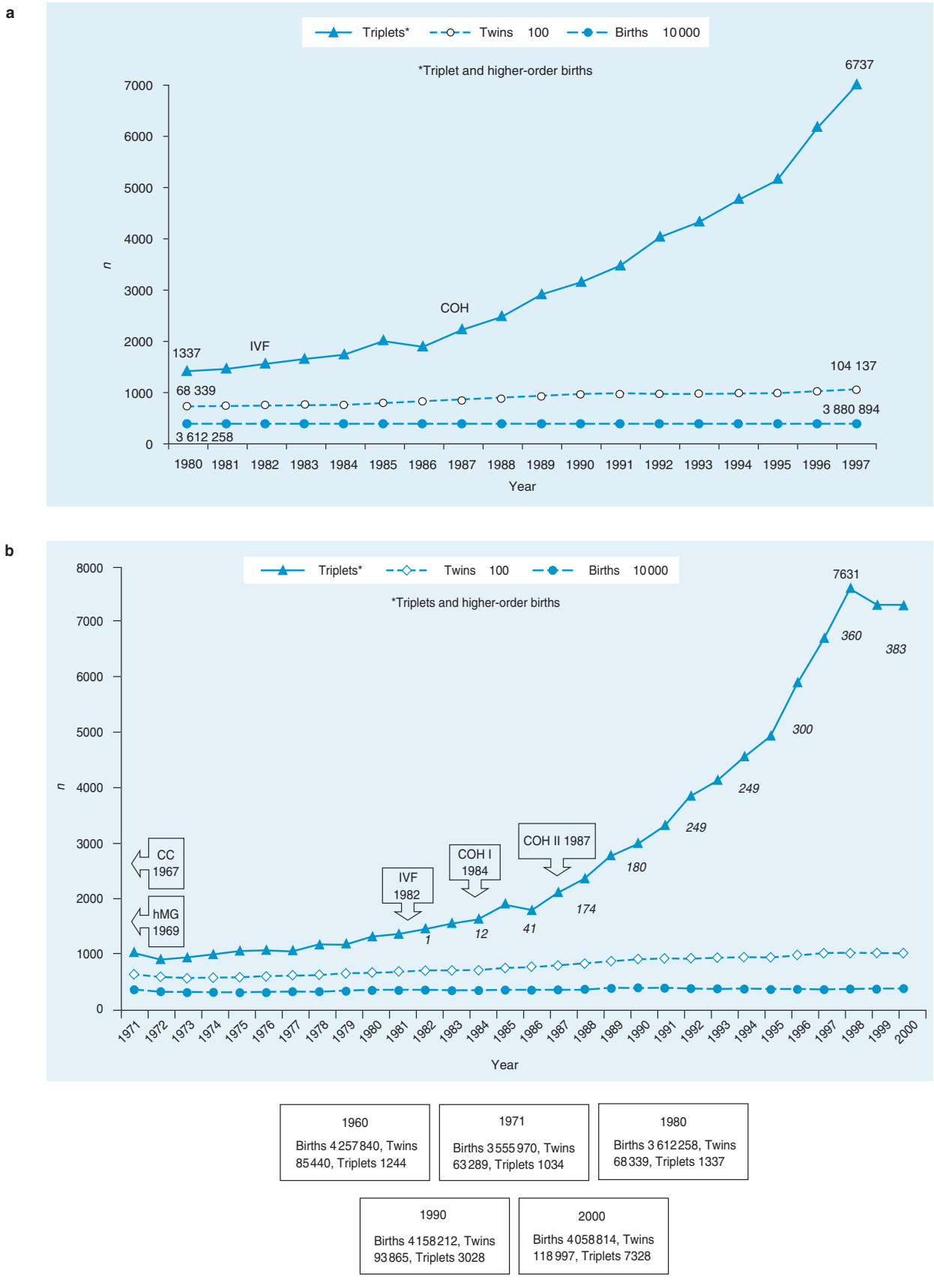


**Figure 19.2** (a) Total, twin and triplet births, USA 1980–1997. Data show individual live births. (b) Total, twin and triplet or higher-order births, USA 1971–2000. Data show individual live births. Italic numbers indicate number of *in vitro* fertilization (IVF) clinics. CC, Clomiphene citrate; hMG, human menopausal gonadotropin; COH, controlled ovarian hyperstimulation

IVF. In 1987, COH–IUI was controversial[17]; by 2000, some were questioning whether COH should not be abandoned entirely and replaced by IVF, because of the increased incidence of triplet and higher-order pregnancies associated with its use[10].

It is commonly believed that triplet and higher-order births were exceedingly rare in the United States before the introduction of OI drugs and IVF, but this is not entirely accurate. As shown in Figure 19.2, 1244 babies were born as a result of triplet and higher-order pregnancies in 1960. This number included 34 sets of quadruplets and 12 sets of quintuplets. The number of twin births actually decreased from 85 440 in 1960 to a low of 56 777 in 1973, 6 years after the approval of clomiphene for infertility treatment, and 4 years after the approval of hMG. The number of twin births did not reach 85 000 again until 1988, and reached 118 997 in 2000, the last year for which information is available at the time of this writing. The latter (2000) number represents an increase of 39% since 1960. The ratio of twin births to total births was 0.0201 in 1960, 0.0181 in 1973 and 0.0293 in 2000, an increase of 46% from 1960 and of 62% from 1973. The number of triplet and higher-order births decreased from 1244 in 1960 to a low of 907 in 1973. Triplet and higher-order births increased to 7631 in 1998, a 513% increase since 1960, and subsequently fell to 7328 in 2000. The ratio of triplet and higher-order births to total births increased from 0.000 292 in 1960 to 0.000 301 in 1973 and to 0.001 936 in 1998, an increase of 563% from 1960 and of 543% since 1973.

The decrease of 303 triplet and higher-order births between 1998 and 2000, and the 6.7% decrease in the ratio of triplet and higher-order to total births, were due in no small part to efforts by the American Society of Reproductive Medicine (ASRM) and the Society of Assisted Reproductive Technology (SART) to convince IVF clinics in the United States to transfer fewer embryos into women aged less than 35 years. This effort was only partially successful. The average number of embryos transferred to women aged less than 35, in all US IVF clinics, was 3.2 in 1998 and 2.9 in 2000[15,16]. In 2000, the average number of embryos transferred into women aged less than 35 was still 3.0 or more in 55% of US IVF clinics, and was 4.0 or more in 8% of US IVF clinics[16]. The number of triplet and higher-order births due to ART decreased by 593, from 48.6% of all triplet and higher-order births in 1998 to 42.5% in 2000[3]. The reason why the decrease in all US triplet and higher-order births was only 303 between 1998 and 2000 is that natural triplet and higher-order births, and triplet and higher-order births due to OI outside of ART, increased. Triplet and higher-order births from OI outside of ART are estimated to have increased by 246 births, from 34.9% in 1998 to 39.7% in 2000[3]. Naturally occurring triplet and higher-order births were estimated to have increased by 38 additional births, from 16.5% in 1998 to 17.7% in 2000.

Some of the decrease in triplet and higher-order births due to ART between 1998 and 2000 might have been due to the increased use of selective reduction. However, if increased use of selective reduction had been responsible for a significant part of the decrease in high-order multiple births due to ART between 1998 and 2000 there should also have been a decrease in high-order multiple births due to OI outside of ART, whereas these increased by 5%. There is an impression among maternal–fetal medicine physicians who perform most selective reduction procedures that the number of such procedures increased between 1998 and 2000 (personal communication, M. I. Evans and R. Carpenter), but the extent of the increase, if indeed it occurred, cannot be determined because of the absence of any requirement that selective reduction procedures be reported (see Chapter 63).

Twin births due to IVF increased between 1998 and 2000 by 2463 births or 21%, from 11 580 in 1998 to 14 043 in 2000, at the same time that triplet and higher-order births from IVF were falling. Twin births due to OI outside of IVF were estimated also to have increased between 1998 and 2000 by 3245 births or 15%, from approximately 21 595 in 1998 to 24 840 in 2000. Twin births occurring naturally were estimated to have increased between 1998 and 2000 by 2565 births or 3%, from approximately 77 520 in 1998 to 80 085 in 2000, but decreased as a percentage of all twin births from 70.0% in 1998 to 67.3% in 2000. In 2003, the proportional and real contribution of IVF to triplet and higher-order pregnancies is falling, and has the possibility of being almost eliminated entirely, while the contribution of OI outside IVF is rising and has become the more imperative problem. Meanwhile, the proportional and real contributions to twin births of IVF and OI outside IVF have increased.

## IMPORTANCE OF PREOVULATORY FOLLICLE NUMBER IN OVULATION-INDUCTION MULTIPLE PREGNANCIES

Pregnancy rates and the incidence of multiple pregnancies in OI cycles intuitively should be related to the number of preovulatory follicles on the day of LH surge or human chorionic gonadotropin (hCG) injection. The relationship of the number of preovulatory follicles to the outcome of IVF is universally acknowledged[18]. Attempts to relate the number of preovulatory follicles to pregnancy rates and multiple pregnancies in hMG cycles in which intrauterine

insemination (IUI) is performed (hMG–IUI) have met with mixed success. A majority of studies find that the number of preovulatory follicles is related to pregnancy rates[19–27] and multiple pregnancy rates[20,22,25,27–31]. Four studies, however, fail to find a relationship between follicular numbers and single[32] or multiple[32–35] pregnancies. Similarly, some studies find an association between estradiol levels and pregnancy rates[20,21] or multiple pregnancy rates[20,26] in hMG–IUI cycles, whereas other studies do not[27,29,30]. (A comprehensive review of these studies is found in reference 11.)

Recommendations to prevent multiple pregnancies and multiple births include withholding hCG administration and IUI when more than six follicles are ≥ 12 mm[28], when more than three follicles are ≥ 14 mm[23,36] or ≥ 16 mm[37], when more than two[38] or three[24,39] follicles are ≥ 18 mm and when estradiol levels exceed 400 pg/ml[40], 600 pg/ml[20], 1000 pg/ml[28,39] or 2000 pg/ml[32,41], respectively.

It is logical to ask: why have so many different guidelines to reduce multiple pregnancies been proposed over the years? The answers are to be found in two key facts. First, some oocytes ovulate in response to hCG when the follicle size reaches 10 mm. As a result, all follicles ≥ 10 to 12 mm must be counted in order to predict the risk of high-order multiple pregnancy. Second, highly sensitive abdominal and pelvic ultrasound techniques were not available in earlier years. Indeed, most early ultrasound studies did not measure follicles smaller than 14 mm. Among those that did, Haning and colleagues[27] concluded that the number of follicles ≥ 10 mm on abdominal ultrasound scan was a better predictor of pregnancy and multiple pregnancy than serum estradiol level in 133 hMG cycles. However, their study did not investigate follicle sizes larger than 10 mm. In contrast, Valbuena and associates[28], using vaginal ultrasound, found that the highest risk of multiple conception occurred in women less than 30 years old who developed more than six follicles ≥ 12 mm and who had estradiol levels ≥ 1000 pg/ml. Furthermore, Navot and colleagues[30] found that patients with multiple pregnancies following hMG had significantly more follicles 12–14 mm and also more follicles 15–17 mm, but no difference in the number of follicles ≥ 18 mm, compared with patients with singleton pregnancies. However, Dodson and co-workers[34] found no relationship between multiple births in hMG cycles and estradiol levels or number of follicles ≥ 10 mm or ≥ 15 mm on abdominal ultrasound, but did not include in their analysis multiple pregnancies that resulted in single births.

Before 2000 only one study, which critically examined the relationship between follicle number and multiple pregnancy in hMG–IUI cycles, analyzed more than 1000 cycles, and follicles smaller than 18 mm were not measured in that study[25]. Since 2000, three studies[10,11,42] including more than 1000 cycles have established that follicles smaller than 14 mm must be counted in order to predict triplet and higher-order multiple pregnancies (HOMPs). Gleicher and colleagues[10] in a 2000 study of 3347 hMG–IUI cycles found that both the pregnancy rate and the incidence of HOMPs were significantly increased in women with seven or more total follicles on the day of hCG administration, but that the number of follicles ≥ 16 mm could not define a group of women at risk for high-order multiples. These authors also found that the incidence of pregnancy and HOMPs was increased when serum estradiol concentration was ≥ 1385 pg/ml by chemiluminescence assay. In the study of Gleicher and colleagues, when fewer than ten total follicles were present, or more than ten total follicles were present but estradiol levels were < 405 pg/ml, the low-order (singleton and twin) pregnancy rate was 26% per cycle, and no HOMPs occurred. Tur and associates[42], in a 2001 multivariate analysis of 1878 hMG–IUI pregnancies, found that predictive variables for HOMPs included: age, peak estradiol levels > 862 pg/ml by radioimmunoassay (RIA) and number of follicles ≥ 10 mm. They concluded that all follicles ≥ 10 mm must be counted in order to predict a HOMP. Tur and associates did not, however, analyze the relationship of follicle numbers to pregnancy rate. Neither Gleicher nor Tur analyzed the relationship of follicle numbers to twin pregnancy separately from singleton pregnancy.

Dickey and colleagues[11] evaluated the relationship of follicle number, as well as estradiol level and age, to twin pregnancy and pregnancy rate per cycle in addition to HOMPs in 3608 CC–IUI and hMG–IUI cycles. In CC–IUI cycles, multiple implantation was more closely related to the number of follicles ≥ 12 mm than to follicles ≥ 15 mm or follicles ≥ 18 mm, and was unrelated to estradiol levels or age. Pregnancy was more closely related to the number of follicles ≥ 15 mm than to follicles ≥ 18 mm or ≥ 12 mm, and was unrelated to estradiol level, estradiol levels per follicle or age. In hMG–IUI cycles, multiple implantation was more closely related to the number of follicles ≥ 12 mm than to follicles ≥ 15 mm or ≥ 18 mm. Multiple pregnancy in hMG–IUI cycles was additionally related to estradiol levels, and was negatively related to age. Pregnancy was more closely related to the number of follicles ≥ 12 mm than to follicles ≥ 15 mm or ≥ 18 mm, and was additionally related to estradiol levels, but not to estradiol levels per follicle, and was negatively related to age.

The relationship between follicle number, pregnancy and multiple pregnancy, in patients without tubal factor and aged less than 43 years, for follicles ≥ 12 mm on the day of hCG (administered to induce

**Table 19.3** Relationship of number of follicles ≥ 12 mm to pregnancy and multiple implantations. Adapted from reference 11

| | *Clomiphene citrate (CC)* | | | | | *Human menopausal gonadotropin (hMG)* | | | | | *CC + hMG* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | *Multiple implants‡* | | | | | *Multiple implants* | | | | | *Multiple implants* | |
| *Number of follicles* | *Cycles (n)* | *Pregnancies* (n (%))* | *Implantation rate† (%)* | *2 (n (%))* | *≥ 3 (n (%))* | *Cycles (n)* | *Pregnancies (n (%))* | *Implantation rate† (%)* | *2 (n (%))* | *≥ 3 (n (%))* | *Cycles (n)* | *Pregnancies (n(%))* | *Implantation rate (%)* | *2 (n (%))* | *≥ 3 (n (%))* |
| 1 | 281 | 20 (7.1) | 7.1 | 0 (0.0) | 0 (0.0) | 61 | 6 (9.8) | 9.8 | 0 (0.0) | 0 (0.0) | 67 | 3 (4.5) | 4.5 | 0 (0.0) | 0 (0.0) |
| 2 | 424 | 49 (11.6) | 6.2 | 2 (4.1) | 1 (2.0) | 97 | 7 (7.2) | 4.1 | 1 (14.2) | 0 (0.0) | 100 | 14 (14.0) | 10.5 | 5 (35.7) | 1 (7.1) |
| 3 | 301 | 41 (13.6) | 5.5 | 9 (22.0) | 0 (0.0) | 116 | 18 (15.5) | 6.6 | 3 (16.7) | 1 (5.6) | 118 | 16 (13.6) | 5.9 | 3 (18.8) | 1 (6.2) |
| 4 | 182 | 22 (12.1) | 3.2 | 2 (9.1) | 0 (0.0) | 111 | 26 (23.4) | 7.4 | 5 (19.2) | 1 (3.8) | 97 | 16 (16.5) | 6.4 | 6 (37.5) | 1 (6.2) |
| 5 | 74 | 8 (10.8) | 2.4 | 1 (12.5) | 0 (0.0) | 112 | 24 (21.4) | 4.5 | 1 (4.2) | 0 (0.0) | 53 | 12 (22.6) | 5.7 | 0 (0.0) | 1 (8.3) |
| 6 | 31 | 7 (22.6) | 4.8 | 0 (0.0) | 1 (14.3) | 63 | 14 (22.2) | 5.0 | 1 (7.1) | 2 (14.3) | 43 | 12 (27.9) | 5.0 | 1 (8.3) | 0 (0.0) |
| 7–8 | 24 | 4 (16.7) | 2.2 | 0 (0.0) | 0 (0.0) | 95 | 20 (21.0) | 4.3 | 3 (15.0) | 2 (10.0) | 51 | 10 (19.6) | 4.2 | 1 (10.0) | 2 (20.0) |
| 9–10 | 10 | 3 (30.0) | 5.3 | 0 (0.0) | 1 (33.3) | 58 | 15 (25.9) | 4.2 | 1 (6.7) | 3 (20.0) | 30 | 8 (26.7) | 3.9 | 1 (12.5) | 1 (12.5) |
| > 10 | 4 | 2 (50.0) | 4.2 | 0 (0.0) | 0 (0.0) | 90 | 24 (26.7) | 2.3 | 3 (12.5) | 2 (8.3) | 35 | 8 (22.8) | 2.2 | 3 (37.5) | 0 (0.0) |
| Total | 1331 | 156 (11.6) | 4.8 | 14 (9.0) | 3 (1.9) | 803 | 154 (19.2) | 4.3 | 18 (11.7) | 11 (7.1) | 594 | 99 (16.7) | 5.0 | 20 (20.2) | 7 (7.1) |

*Percentage per cycle; †per follicle; ‡percentage of pregnancies

**Table 19.4** Critical values for pregnancy and multiple implantation. Adapted from reference 11

| | *Age < 35 years* | | | | | *Age 35–42 years* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | *Multiple implantation* | | | | | *Multiple implantation* | | | |
| | | *2 Sacs* | | *≥ 3 Sacs* | | | *2 Sacs* | | *≥3 Sacs* | |
| | *Pregnancies per cycle* | *Per pregnancy* | *Per cycle* | *Per pregnancy* | *Per cycle* | *Pregnancies per cycle* | *Per pregnancy* | *Per cycle* | *Per pregnancy* | *Per cycle* |
| Estradiol | | | | | | | | | | |
| < 1000 pg/ml | 19.8% | 14.6% | 2.9% | 4.5% | 0.9% | 11.6% | 15.0% | 1.7% | 0.0% | 0.0% |
| ≥ 1000 pg/ml | 23.8% | 16.9% | 4.0% | 11.7%* | 2.8%* | 20.5%‡ | 13.2% | 2.7% | 10.5%† | |
| 2.2%† | | | | | | | | | | |
| Follicles ≥ 12 mm | | | | | | | | | | |
| < 6 | 19.0% | 17.0% | 3.2% | 4.0% | 0.8% | 10.3% | 16.7% | 1.7% | 4.8% | 0.5% |
| ≥ 6 | 23.7% | 13.7% | 3.2% | 13.7%‡ | 3.2%‡ | 24.2%§ | 10.5% | 2.6% | 5.3% | 1.3% |

Fisher's exact test: *$p < 0.05$, †$p < 0.02$, ‡$p < 0.01$, §$p < 0.001$

ovulation), is indicated in Table 19.3. Two types of hMG–IUI cycle were analyzed: hMG started either on day 3, or after 5 days of CC on day 8 or later (CC + hMG). Pregnancy rates did not increase significantly when there were more than four follicles ≥ 12 mm for hMG–IUI or when there were more than five follicles ≥ 12 mm for CC–IUI or CC + hMG–IUI. Two follicles ≥ 12 mm were present in all twin pregnancies, and three follicles ≥ 12 mm were present in 90% of triplet and higher-order pregnancies. When follicles ≥ 10 mm were counted, there were at least three follicles ≥ 10 mm present in all triplet pregnancies. On the day of hCG administration, there were fewer than two follicles ≥ 15 mm in 23% of twin pregnancies, and fewer than three follicles ≥ 15 mm present in 29% of triplet pregnancies. There were fewer than two follicles ≥ 18 mm in 48% of twin pregnancies, and fewer than three follicles ≥ 18 mm in 57% of triplet gestations. These results explain why older studies that only measured preovulatory follicles ≥ 14 mm in hMG–IUI cycles and follicles ≥ 18 mm in CC–IUI cycles failed to find a relationship between follicle number and multiple pregnancies.

Critical values for pregnancy and for multiple pregnancy observed in this study are summarized in Table 19.4 for hMG–IUI and CC + hMG–IUI patients without tubal factor. For patients less than 35 years of age, the incidence of pregnancy and twin implantation was not significantly increased, but the incidence of three or more implantations was tripled when six or more follicles were ≥ 12 mm or estradiol was ≥ 1000 pg/ml. For patients aged 35–42 years, pregnancy rates were doubled when six or more follicles were ≥ 12 mm, but the incidence of twin and three or more implantations was not significantly increased unless also estradiol was ≥ 1000 pg/ml. The incidence of three or more implantations was the same in CC–IUI pregnancies and hMG–IUI or CC + hMG–IUI pregnancies when six or more follicles were ≥ 12 mm. However, six or more follicles of ≥ 12 mm occurred in only 5% of CC cycles compared with 38% of hMG–IUI cycles and 27% of CC + hMG–IUI cycles. The implantation rates per follicle were the same for hMG–IUI, CC + hMG–IUI and CC–IUI, when stratified by diagnosis and age. It is possible, therefore, to conclude that the higher pregnancy rates and incidence of multiple implantations reported for hMG–IUI cycles, compared with CC–IUI cycles, are entirely due to the greater number of preovulatory follicles induced by hMG, and are not the result of better oocyte quality or a better endometrial environment for implantation.

## REDUCING MULTIPLE PREGNANCY FROM OVULATION INDUCTION

Initially, hMG was used exclusively for the treatment of pituitary or hypothalamic amenorrhea and anovulation refractory to treatment with CC. Doses used were relatively low, and the incidence of HOMPs was less than 5%[43]. Subsequently, CC began to be used to increase progesterone levels in patients diagnosed with 'luteal insufficiency'[44], and both CC and hMG were used in patients with normal ovulatory cycles for treatment of 'unexplained infertility'[45,46], as well as in patients who required IUI in an effort to increase per-cycle pregnancy rates[47–49].

The manufacturer's package insert for Perganol® (Serono Laboratories Inc., Norwell, MA), the first hMG preparation sold in the United States (1969), recommended an initial dose of 75 IU of FSH/LH per day, and if there was evidence of ovulation but no pregnancy, repeating the same dose for at least two more courses before increasing the dose to 150 IU FSH/LH. The manufacturer's instructions for the use of subsequent hMG preparations made the same recommendation (Humegon®; Organon Inc., West Orange, NJ), with the exception that if patients had received gonadotropin-releasing hormone agonist the initial dose should be 150 IU FSH/LH (Repronex®; Ferring Pharmaceuticals Inc., Tarrytown, NY). Initially, the package inserts for CC stated either that: 'The majority of patients who respond do so during the first course of therapy, and three courses constitute an adequate therapeutic trial' or that: 'If pregnancy has not been achieved after three ovulatory responses, further treatment is generally not recommended'.

Techniques to reduce multiple pregnancies due to the use of OI outside IVF are listed in Table 19.5. The first is to use the lowest doses of CC or hMG to induce ovulation that result in the development of at

**Table 19.5** Techniques used to reduce multiple pregnancies due to ovulation induction

| |
|---|
| Use lowest doses that result in development of at least one follicle |
| Employ a trial of clomiphene–IUI before using gonadotropins |
| Administer hCG earlier when fewer follicles are ready to ovulate |
| Cancel cycles when excessive numbers of follicles develop |
| Aspirate supernumerary follicles before administering hCG |
| Switch to IVF |

IUI, intrauterine insemination; hCG, human chorionic gonadotropin; IVF, *in vitro* fertilization

**Table 19.6** Relationship of number of previous cycles of clomiphene citrate–intrauterine insemination (CC–IUI) to pregnancy and multiple pregnancy rates during the first three cycles of human menopausal gonadotropin/follicle stimulating hormone–intrauterine insemination (hMG/FSH–IUI). Adapted from reference 60

| Number of CC–IUI cycles | Number of hMG/FSH–IUI cycles | Pregnancies per cycle* | | | Multiple gestations per pregnancy | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | 2 | | ≥3 | |
| | | n | % | OR (95% CI) | n | % | n | % |
| 0 | 1459 | 318 | 21.8 | 1.00 — | 61 | 19.2 | 28 | 8.8 |
| 1 | 408 | 80 | 19.6 | 0.88 (0.66–1.15) | 15 | 18.8 | 6 | 7.5 |
| 2 | 268 | 53 | 19.8 | 0.83 (0.60–1.16) | 10 | 18.9 | 3 | 5.7 |
| 3 | 130 | 25 | 19.2 | 0.83 (0.53–1.31) | 5 | 20.0 | 0 | 0.0 |
| 4 | 57 | 11 | 19.3 | 0.84 (0.43–1.64) | 2 | 18.2 | 0 | 0.0 |
| 5 | 23 | 1 | 4.3 | 0.16 (0.02–1.19) | 0 | 0.0 | 0 | 0.0 |
| 6–12 | 32 | 1 | 3.1 | 0.11 (0.02–0.83) | 0 | 0.0 | 0 | 0.0 |

*Pregnancy rate per cycle: cycles 1–4 (19.6%) vs. cycles ≥ 5 (3.6%), $p = 0.006$ ($\chi^2$); OR, odds ratio; CI, confidence interval

least one preovulatory follicle. Only three studies reported the relationship of CC dose to number of preovulatory follicles[50–52], whereas four investigated the relationship of CC dose to multiple pregnancy[44,52–54]. These studies were primarily concerned with the relationship between body weight and the dose of CC necessary to induce ovulation. One study found a relationship between the dose of CC and number of follicles[52], but none found a relationship between CC dose and multiple pregnancies.

Homburg and Insler[55] and Homburg and Howles[56] reported, in a summary of results from published studies of chronic low-dose treatment for women with polycystic ovarian syndrome (PCOS), that if an initial dose of 75 IU FSH/LH is continued for 14 days with no increase and then increased by no more than 37.5 IU, 69% of cycles are uniovulatory, pregnancy rates of 40% are attained over an average of 1.9 cycles, the twining rate is 5% and the HOMP rate is 0.7%. The results presented in Table 19.3 for hMG–IUI cycles do not conform to these observations, because the patients represented in the hMG–IUI column of this table all received at least 150 mIU of hMG or FSH[11], so the only patients who developed one or two follicles were those who were hypo-responders. Results presented in the CC + hMG–IUI column in Table 19.3 offer a better opportunity for comparison with the results reported for chronic low-dose hMG[55,56], because the most common dose of hMG used following CC was 75 mIU. However, the patients included here represent a mixture of diagnoses, whereas patients in the studies summarized by Homburg and co-authors all had PCOS. The pregnancy rate in CC + hMG–IUI cycles averaged 14% per cycle during the first three cycles. Importantly, the use of low-dose hMG following 5 days of CC did not reduce twin and HOMP rates compared with hMG-only regimens.

The second technique to reduce HOMPs is to use CC–IUI for one or more courses before using gonadotropins. For many years, the standard treatment algorithm for infertility due to anovulation in the United States was as follows: three cycles of CC with coitus or IUI, followed by three cycles of hMG with coitus or IUI, followed by one or more cycles of IVF[57,58]. More conservative models comprising up to six cycles of CC before using gonadotropin therapy were proposed in Israel and the UK[55,59]. This approach presented two problems. First, the number of cycles of CC–IUI that should be attempted before switching to hMG–IUI was unknown, and second, with one exception, until recently no attempts existed to confirm that algorithm models actually work when applied to real patients. Karande and colleagues[57] attempted to compare the algorithm of three CC–IUI cycles followed by three COH–IUI cycles followed by four IVF cycles with IVF alone as primary treatment for couples with newly diagnosed infertility in a randomized study, but the results were inconclusive.

Both questions were resolved by a study presented in 2003[60]. The effect of previous CC–IUI on pregnancy rates and the incidence of multiple pregnancies in later cycles of hMG–IUI were analyzed retrospectively in 551 patients and compared with the outcome of hMG–IUI in 908 patients not previously treated with CC. The results are given in Table 19.6. Mean pregnancy and multiple gestation rates during the first three hMG/FSH–IUI cycles, stratified by the number of previous CC–IUI cycles, are presented. Clinical pregnancy rates per cycle during the first three hMG–IUI cycles averaged 21.8% without previous CC–IUI cycles, 19.6% after 1–4 previous cycles of CC–IUI and 3.6% after five or more previous cycles of CC–IUI. The incidence of triplet and higher-order gestations was inversely related to the

number of previous CC–IUI cycles, and decreased from 8.8% for no previous CC–IUI to 7.5% for one CC–IUI cycle and 5.7% for two CC–IUI cycles. There were no HOMPs in 38 hMG–IUI pregnancies preceded by three or more unsuccessful CC–IUI cycles (incidence < 2.6% of pregnancies). The incidence of twin pregnancies was unaffected by the number of previous CC–IUI cycles. These results suggest that triplet and higher-order pregnancies may be reduced by performing three or more cycles of CC–IUI before using COH–IUI. However, such results may apply only to anovulation, because there were insufficient numbers of high-order pregnancies in patients with other diagnoses to be statistically significant.

The third technique to reduce multiple pregnancies in OI cycles is not to administer hCG or perform IUI when more than one or two preovulatory follicles are present. Here again two problems arise. First, pregnancy rates are low in single-follicle cycles, and second, polycystic ovaries are a common cause of anovulatory cycles. Patients with PCOS who require OI in order to ovulate frequently respond to OI by developing multiple follicles. As noted above, follicles as small as 10 mm may ovulate in response to hCG. This means that all follicles ≥ 10 mm must be counted.

Whereas twin and higher-order pregnancies cannot be eliminated without the possibility that no pregnancy will occur, they can be minimized by taking into consideration the following factors: number of follicles, age and estradiol level; and by canceling cycles when the risk of multiple pregnancy is so high as to be unacceptable. Three published tables provide sufficient information to make a decision as to whether to cancel an OI cycle or proceed with hCG administration and IUI[10,11,42]. Each, however, is incomplete in some way, because it does not include patient age[10], estradiol levels[11] or per-cycle pregnancy information[42]. All three elements are included in Table 19.7 from a study of 2387 cycles of hMG–IUI, in patients without tubal factor, presented in 2003[61]. For age < 32 years, pregnancy rates per cycle increased from 14% when there were one or two follicles ≥ 10 mm to 21% when there were three to six follicles, and were only slightly higher (24%) when there were seven or more follicles. Twin rates increased from 14% per pregnancy to 17% when there were three to six follicles and to 22% when there were more than seven follicles. In these same patients, HOMP rates more than tripled from < 6% when there were three to six follicles to 23% when there were seven or more follicles. For ages 32–37, pregnancy rates and HOMP rates were little different from those for age < 32, except that, when seven or more follicles were present, HOMP rates were greater than 6% only if estradiol was greater than 1000 pg/ml as well. For ages 38–43, no HOMP pregnancies occurred, irrespective of follicle numbers, and no twins unless there were three or more preovulatory follicles. The incidence of triplet and higher-order births as opposed to HOMPs may be expected to be only half as great as the incidence of HOMPs reported in Table 19.7, as a result of spontaneous reduction[62]. From this study we learn that little is gained with respect to increased birth rates by having more than six preovulatory follicles, but much is risked with respect to high-order multiple births.

Table 19.7 also shows that withholding hCG or IUI when there were more than six preovulatory follicles and age was less than 32, or age was 32–37 and estradiol was ≥ 1000 pg/ml, would have resulted in canceling 20% of cycles for ages < 38 years but would have reduced the number of HOMPs by 72%. The HOMP rate in the remaining patients aged < 38 years would be 4% and the pregnancy rate would be 18%. The twin rate would be 18%, but could be lower because 16% of twins in OI cycles are the result of spontaneous reduction from higher-order pregnancies[62]. It is reasonable to conclude that hMG–IUI can be used with relative safety in 80% of patients aged < 38 years and in all patients 38 and above, and that the risks of twins and HOMPs are comparable to those with IVF when two embryos are transferred if cycles are cancelled when more than six follicles ≥ 10 mm are present (see below).

In another study in which preovulatory follicles smaller than 14 mm were measured, Tur and colleagues[42] recommended canceling cycles for patients aged ≤ 32 when there were four or more preovulatory follicles ≥ 10 mm and estradiol was ≥ 862 pg/ml. An estradiol value of 862 pg/ml by RIA is equivalent to 1017 pg/ml by chemiluminescence[15]. If this recommendation had been followed for ages ≤ 32 only, there would have been 35% fewer HOMPs, 15% fewer total pregnancies and a 5% HOMP rate in the remaining patients, compared with 7% if no cycles were cancelled. Cycles cancelled for either four follicles ≥ 10 mm or estradiol ≥ 862 pg/ml, at all ages, would have resulted in 80% fewer HOMPs, 54% fewer total pregnancies and a 3% HOMP rate in the remaining patients. Twin pregnancies were not analyzed separately from singleton pregnancies. The pregnancy rate per cycle could not be calculated in this study, because records of only patients who became pregnant were reviewed.

Gleicher and colleagues[10] made no recommendation for canceling hMG–IUI cycles on the basis of follicle numbers or estradiol levels, because these investigators found that follicles ≥ 16 mm and estradiol levels > 2500 pg/ml could not predict a HOMP. However, in their study, seven or more 'total' follicles, and peak estradiol levels ≥ 1385 pg/ml by chemiluminescence, were significantly related to triplet and higher-order pregnancies. If these levels

**Table 19.7** Observed pregnancy rates per cycle and multiple rates per pregnancy in relation to age, follicle number and estradiol pg/ml* ($E_2$) per gonadotropin–intrauterine insemination cycles 1–3†. Adapted from reference 61

| | *1–2 Follicles ≥ 10 mm* | | | | *3–6 Follicles ≥ 10 mm* | | | | | *≥ 7 Follicles ≥ 10 mm* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | *Multiple implants per pregnancy* | | | | *Multiple implants per pregnancy* | | | | | *Multiple implants per pregnancy* | | |
| *Age* (years) | *Cycles* (*n*) | *Pregnancies*‡ (*n* (%)) | *2* (*n* (%)) | *≥ 3* (*n* (%)) | *Cycles* (*n*) | *Pregnancies*‡ (*n* (%)) | *2* (*n* (%)) | *≥ 3* (*n* (%)) | *≥ 4* (*n*) | *Cycles* (*n*) | *Pregnancies*‡ (*n* (%)) | *2* (*n* (%)) | *≥ 3* (*n* (%)) | *≥ 4* (*n*) |
| < 32 | 212 | 29 (13.7) | 4 (13.8) | 0 (0.0) | 435 | 93 (21.4) | 16 (17.2) | 5 (5.4) | 2 | 337 | 81 (24.0) | 18 (22.2) | 19 (23.4) | 8 |
| $E_2$ < 1000 | 175 | 23 (13.1) | 3 (13.0) | 0 (0.0) | 291 | 61 (21.0) | 10 (16.4) | 3 (4.9) | 1 | 140 | 23 (16.4) | 4 (17.4) | 5 (21.7) | 1 |
| $E_2$ ≥ 1000 | 37 | 6 (16.2) | 1 (16.7) | 0 (0.0) | 144 | 32 (22.2) | 6 (18.8) | 2 (6.2) | 1 | 197 | 58 (29.4) | 14 (24.1) | 14 (24.1) | 7 |
| 32–37 | 219 | 26 (11.6) | 4 (15.4) | 0 (0.0) | 474 | 87 (18.4) | 18 (20.7) | 5 (5.7) | 0 | 245 | 68 (27.8) | 16 (23.5) | 10 (14.7) | 3 |
| $E_2$ < 1000 | 186 | 21 (11.3) | 3 (14.2) | 0 (0.0) | 327 | 60 (18.3) | 12 (20.0) | 3 (5.0) | 0 | 97 | 24 (24.7) | 5 (20.8) | 1 (4.2) | 0 |
| $E_2$ ≥ 1000 | 33 | 5 (15.2) | 1 (20.0) | 0 (0.0) | 147 | 27 (18.4) | 6 (22.2) | 2 (7.4) | 0 | 148 | 44 (29.7) | 11 (25.0) | 9 (20.4) | 3 |
| 38–43 | 162 | 9 (5.5) | 0 (0.0) | 0 (0.0) | 227 | 34 (15.0) | 5 (14.7) | 0 (0.0) | 0 | 72 | 12 (16.7) | 0 (0.0) | 0 (0.0) | 0 |
| $E_2$ < 1000 | 148 | 7 (4.7) | 0 (0.0) | 0 (0.0) | 169 | 24 (14.2) | 3 (12.5) | 0 (0.0) | 0 | 24 | 4 (16.7) | 0 (0.0) | 0 (0.0) | 0 |
| $E_2$ ≥ 1000 | 14 | 2 (14.3) | 0 (0.0) | 0 (0.0) | 58 | 10 (17.2) | 2 (20.0) | 0 (0.0) | 0 | 48 | 8 (16.7) | 0 (0.0) | 0 (0.0) | 0 |

*Estradiol measured by chemiluminescence (CHL), 1000 pg/ml by CHL = 820 pg/ml by radioimmunoassay and 1224 pg/ml by monoclonal antibody; †in patients without tubal factor infertility or poor sperm quality; ‡per cycle

had been used as indications for cancellation, there would have been no HOMPs, but 96% fewer total pregnancies. If instead, the combination of ten or more total follicles and estradiol levels ≥ 935 pg/ml had been used as indications for cancellation, 87% fewer HOMPs and 39% fewer total pregnancies would have resulted, and 28% of cycles would have had to be cancelled. In the remaining patients, the pregnancy rate would be 10% per cycle, and the HOMP rate would be 2%. No HOMP occurred in the study of Gleicher and colleagues[10] when less than ten total follicles were present or estradiol levels were < 405 pg/ml. Twin births were not analyzed separately from singleton pregnancies.

The American College of Obstetricians and Gynecologists (ACOG), in a 1994 ACOG Technical Bulletin 'Managing the Anovulatory State: Medical Induction of Ovulation'[63], recommended withholding hCG 'if there are three or more preovulatory follicles', citing six references. The 2002 ACOG Practice Bulletin 'Management of Infertility Caused by Ovulatory Dysfunction'[64] included the statement, 'the risk of multiple gestation with FSH injections can probably be decreased by withholding hCG and prescribing a barrier contraceptive whenever more than three follicles greater than 15 mm in diameter are detected with pelvic ultrasound', but cited no references as the basis for this recommendation. In a 2002 review of practice patterns, 82% of US board-certified reproductive endocrinologists reported that they withheld hCG in ovulation-induction cycles in order to decrease triplet and higher-order pregnancies[65].

A novel technique for reducing multiple pregnancies in OI cycles, and the only method recommended by the ASRM, is aspiration of excess follicles before administering hCG[66]. This technique was proposed by Ingerslev in 1991[67]. In the only study cited by the ASRM, the pregnancy rate was 21% per cycle, the twin rate was 7.6% and the triplet rate was 1.7%, in 571 hMG–IUI cycles, performed after 1992, if excess follicles were aspirated before administering hCG, when more than three follicles were > 14 mm[68]. By comparison, the pregnancy rate was 20%, the twin rate was 13.3% and the triplet and higher-order rate was 6.6% in 225 hMG–IUI cycles performed before 1992, when excess follicles were not aspirated. The cancellation rate due to excess follicles was reduced from 21 to 8% after 1992. The study was retrospective, and had not been duplicated in another clinic as of the end of 2003.

The patient's wishes must be respected in all situations where cycles may have to be cancelled because of an excessive number of follicles, whether two follicles are present in patients who do not want twins, or a larger number in patients who desire twins and have no known health problems that could prevent a successful twin pregnancy. To do this, it is necessary to provide the patient with as much information as possible about her chances of a multiple pregnancy. In some cases patients will state a wish to proceed, despite the risk of multiple pregnancy, with the plan that they would have selective reduction if there were more than two gestational sacs. In this instance, patients need to be additionally counseled about the risk of selective reduction, and even spontaneous reduction to the remaining embryos[62] (see below). All this requires that pelvic ultrasound be performed on more than one occasion, both before ovulation and after the commencement of pregnancy. It is also important that physicians be aware that the risk of multiple pregnancy when multiple preovulatory follicles are present is the same in CC cycles and in gonadotropin cycles[11], and that preovulatory ultrasound is an absolute necessity in the first CC cycle if not in all CC cycles.

## REDUCING MULTIPLE PREGNANCY FROM IVF AND ART

The impact of IVF and related ART procedures was initially small and unappreciated. The first report from the American Fertility Society was published in 1988, and covered US results for 30 clinics performing IVF in 1985 and 41 clinics in 1986. A total of 933 pregnancies resulting from 5253 IVF embryo transfers and 822 GIFT were described, but the authors did not consider it important enough to report the number of multiple pregnancies[12]. By 1987, however, 119 clinics performed IVF or GIFT; of the 1353 pregnancies that resulted in live births, 279 (20.6%) were twins and 59 (4.4%) were triplet and higher-order births. In spite of these results, the possibility that IVF might result in an excess of multiple pregnancies with health and economic consequences was not addressed at the Congressional hearings conducted by Senator Wyden in 1987[69]. Indeed, the ASRM did not provide guidelines regarding the number of embryos that should be transferred until 1999[70] (Table 19.8). This document recommended transferring two to five embryos depending on patient age, embryo quality and whether there are excess embryos for cryopreservation, but the recommendations were qualified by stating that the (then) current technology could not identify embryos with enhanced implantation potential. These guidelines were based primarily on a Centers for Disease Control and Prevention (CDC) analysis of the relationships of patient age and number of embryos transferred to live birth rate and multiple births in US IVF clinics during 1996[71].

The problem of multiple births in IVF is straightforward, compared with the problem of multiple births as a side-effect of OI alone. The number

**Table 19.8** Guidelines on number of embryos transferred. Adapted reference 70

| | |
|---|---|
| Maximum of two embryos | age < 35, at least three *improved*-quality embryos with excess available for cryopreservation |
| Maximum of three embryos | age < 35, no more than three *good*-quality embryos with none available for cryopreservation |
| Maximum of four embryos | age 35–40 |
| Maximum of five embryos | age ≥ 40, or multiple failed cycles |

of embryos transferred determines the maximum number of babies that can be born, with the exception of multiples that result from monozygotic splitting[72]. Initially, it was accepted that it was necessary to transfer three or more embryos in order to achieve high pregnancy rates in IVF cycles, and that triplet pregnancies were inevitable if high pregnancy rates were to be achieved[73]. Subsequently, however, it was recognized that pregnancy rates did not increase when more than two or three embryos were transferred, whereas the number of triplet and higher-order pregnancies increased significantly[74,75].

The ability to achieve acceptable pregnancy rates with fewer embryos was enhanced by the development in the late 1990s of culture media that allowed embryos to grow to the blastocyst stage prior to transfer, so that the one or two embryos with the best quality could be transferred[76]. A recent report of US IVF clinic results for 2000 confirms that birth rates are not increased by the transfer of more than two good-quality embryos in women younger than 35 who use fresh non-donor eggs and have extra embryos cryopreserved for future use[16]. When these conditions are met, the live birth rate is 30% for single embryo transfer (SET), 50% for double embryo transfer (DET) and 45% or less for transfer of three, four or five and more embryos. The multiple birth rate, twins or more, was 3.7% for SET due to monozygotic twinning, 37.7% for DET and greater than 45% for transfer of three or more embryos. The triplet and higher-order birth rate was 1.0% for DET, due to monozygotic twinning, and 8.5% for transfer of three, 10.0% for four and 7.0% for five or more embryos. In the same report, however, the live birth rates for all patients following SET and DET were only 9.9% and 34.7%, respectively, and did not increase further when more than two embryos were transferred. Compared with DET, SET reduced the live birth rate by 70% for all patients and by 40% for patients with the most favorable prognoses. These reports support the ASRM recommendation that a maximum of two embryos be transferred in patients with the most favorable prognosis, but in disagreement with the ASRM recommendations, demonstrate that birth rates are not increased by transferring more than two embryos in patients with a less favorable prognosis[70].

The reason given for transferring more than two embryos in women aged 35 and older is that miscarriage rates increase as women age owing to an increase in the rate of embryonic aneuploidy. This reasoning may not be entirely accurate as it is based almost entirely on experience with natural twinning. The incidence of twin pregnancies conceived as a result of OI or IVF delivering as twins is 67%, compared with 38% for natural twins[62]. Furthermore, age is not a significant factor in the percentage of twin pregnancies that either miscarry or are spontaneously reduced to singletons, until age 40[62]. Preimplantation genetic diagnosis (PGD) offers the possibility that, in the future, all genetically abnormal embryos can be identified so that only entirely normal embryos are transferred. Until this eventually occurs, however, SET will remain the exception at least in the United States. At present, only the most serious genetic defects are diagnosed by PGD, and the procedure is as yet too expensive to use in all IVF cycles[77].

The European Society of Human Reproduction and Embryology (ESHRE) issued a consensus opinion in 2003, stating that the essential aim of IVF is the birth of a single healthy child, with a twin pregnancy being regarded as a complication, and recommending that single embryo transfer be proposed in a first or second IVF cycle in women ≤ 36 years of age[78]. The concern of many US fertility specialists is that implementation of such a policy would multiply the cost and discomfort for couples undergoing IVF who ultimately desire two children and have no physical impediment to successful completion of a twin pregnancy. The finding in US clinics that SET results in a 40% lower birth rate per transfer compared with DET[16] is consistent with results of randomized studies from other countries[79,80].

Couples who desire a family of two or more children will continue to utilize infertility treatments including ART until they complete their desired family size. When economic models are configured with a two-child family as the end result, the differences between the costs of elective SET and DET including neonatal care are substantial. One economic study that compared the cost of SET, DET and elective transfer of three embryos concluded that the data clearly demonstrated the importance of both the two-embryo limit and maintaining DET as

an option, rather than limiting procedures to SET[81]. Using data provided by the Human Fertilisation and Embryology Authority (HFEA), London, for 20 029 patients who underwent at least three IVF cycles in 1994 in the UK, and analyzing both the cost of IVF cycles and the cost of delivery and neonatal care in the UK in 1994, the authors concluded that elective DET would result in a cost saving of £65 million ($104 million) per year when compared with elective SET, and that elective DET would result in a cost saving of £1.3 million ($2.1 million) per year compared with elective transfer of three embryos.

Since IVF with single embryo transfer is the only means to ensure conception of a singleton pregnancy in patients who require OI in order to become pregnant, it is possible that the ESHRE recommendation might be extended to OI outside of IVF. If this were to occur, it would result in denial of pregnancy to many infertile couples who cannot conceive otherwise and who reside in countries where IVF is not paid for by the government or a private health-insurance concern. When advocates of an elective SET policy stress that additional pregnancies result if cryopreserved embryos are transferred in subsequent cycles, they overlook the facts that many embryos do not survive the freeze–thaw process, and that patients have to undergo additional cycles of daily injections that are as lengthy as (although less expensive than) their initial stimulation cycle in which embryos were obtained.

Many patients in countries where IVF is not a free health benefit, and even some in countries where IVF is paid for but waiting lists are long and the number of cycles limited, consider a twin pregnancy as a desirable outcome of infertility treatment. In Nordic countries, where most IVF is free, there are 1000–1500 treatment cycles per million inhabitants, whereas in the United States, where most IVF must be paid for by patients, there are only about 200 treatment cycles per million inhabitants[82].

Limiting the number of embryos transferred to a single embryo would have little impact on overall twin birth rates and on national health-care costs compared with the reduction in costs and decrease in neonatal and developmental morbidity that might be accomplished by earlier diagnosis of twin gestations and better prenatal care. If a maximum of one embryo had been transferred in the United States during 2000, the total number of twin pregnancies would decrease by only 10%, but triplet and higher-order births would decrease by 35%[3]. Rather than limiting transfers to a single embryo, which would increase the cost of completing a family by IVF/intracytoplasmic sperm injection, greater efforts should be made to identify patients at increased risk of prematurity if they become pregnant with twins. Factors in addition to multiparity known to increase the risk of premature delivery include non-white race, chronic disease, previous prematurity, absence of prenatal care[83], nulliparity[84] and height < 165 cm[85].

## EFFECT OF SPONTANEOUS REDUCTION ON MULTIPLE PREGNANCY DUE TO OVULATION INDUCTION AND IVF

Multifetal pregnancy reduction (MFPR) from quadruplet and higher-order gestations to twins significantly decreases the risk of delivery before 28 weeks and associated neonatal and developmental morbidity, as well as the risk to the mother[86–88]. However, twins resulting from the reduction of quadruplet and higher-order gestations may deliver earlier[89–92] and may be more likely to have restricted fetal growth/intrauterine growth restriction (IUGR) than unreduced twins[93,94]. The effect of MFPR on triplet gestations reduced to twins is less certain[86,88,95]. Most triplet pregnancies deliver after 32 weeks[96–98]. The majority of published studies have found that following MFPR, twins reduced from triplets deliver at a later gestational age or at higher birth weights than unreduced triplets[89,90,99–102]. Other reports, however, have found no significant difference in length of gestation[86,88,96].

Until recently, it was not appreciated that spontaneous fetal reduction occurs frequently, exposing singletons and twins that started as triplet and higher-order pregnancies to the same risk at the end of pregnancy as might occur with MFPR. A study reviewing the outcomes of 704 multiple gestations diagnosed by early first-trimester ultrasound clarified this misconception[62]. Spontaneous reduction of one or more gestational sacs occurred before the 12th gestational week in 36% of 549 twin pregnancies, 53% of 132 triplet pregnancies and 65% of 23 quadruplet pregnancies (Table 19.9). In comparison, spontaneous reduction (miscarriage) occurred in 19.2% of 6149 singleton pregnancies. The percentage of multiple pregnancies continuing unreduced at 12 weeks decreased with increasing initial number of gestational sacs and with age. The percentage of twin pregnancies that delivered unreduced decreased from 67% for age < 30, to 63% for age 30–39 and to 38% for age ≥ 40. In a similar fashion, the percentage of triplet pregnancies that continued unreduced decreased from 54% for age < 30, to 48% for age 30–34 and to 36% for age ≥ 35 (Table 19.9).

A higher percentage of twin pregnancies conceived as a result of hMG or IVF/GIFT delivered as twins (67%), compared with twins conceived naturally (38%) (Table 19.10). The percentage of triplet pregnancies conceived as a result of IVF/GIFT delivered as triplets was 64%, compared with 37% conceived as a result of hMG outside of IVF/GIFT, 21% conceived as a result of CC and 10% conceived naturally. The

**Table 19.9** Effect of maternal age on multiple pregnancies continuing at 12 weeks. Adapted from reference 62

| Age (years) | Patients (*n*) | Number of fetuses continuing | | | | | Ratio* |
|---|---|---|---|---|---|---|---|
| | | 0 (%) | 1 (%) | 2 (%) | 3 (%) | 4 (%) | |
| *2 sacs* | | | | | | | |
| < 30 | 235 | 18 (7.7) | 60 (25.5) | 157 (66.8) | — | — | 0.80 |
| 30–34 | 196 | 20 (10.2) | 53 (27.0) | 123 (62.8) | — | — | 0.76 |
| 35–39 | 105 | 10 (9.5) | 29 (27.6) | 66 (62.8) | — | — | 0.77 |
| ≥ 40 | 13 | 3 (23.1) | 5 (38.5) | 5 (38.5) | — | — | 0.58 |
| Total | 549 | 51 (9.3) | 147 (26.8) | 351 (63.9) | — | — | 0.77 |
| *3 sacs* | | | | | | | |
| < 30 | 43 | 2 (4.6) | 6 (14.0) | 12 (27.9) | 23 (53.5) | — | 0.77 |
| 30–34 | 58 | 2 (3.4) | 5 (8.6) | 23 (39.7) | 28 (48.3) | — | 0.78 |
| 35–39 | 28 | 4 (14.3) | 3 (10.7) | 11 (39.3) | 10 (35.7) | — | 0.65 |
| ≥ 40 | 3 | 0 (0.0) | 0 (0.0) | 2 (66.7) | 1 (33.3) | — | 0.78 |
| Total | 132 | 8 (6.1) | 14 (10.6) | 48 (36.4) | 62 (47.0) | — | 0.75 |
| *4 sacs* | | | | | | | |
| < 30 | 8 | 0 (0.0) | 0 (0.0) | 4 (50.0) | 1 (12.5) | 3 (37.5) | 0.72 |
| 34–35 | 11 | 0 (0.0) | 0 (0.0) | 3 (27.3) | 4 (36.4) | 4 (36.4) | 0.77 |
| 35–39 | 4 | 1 (25.0) | 0 (0.0) | 1 (25.0) | 1 (25.0) | 1 (25.0) | 0.58 |
| ≥ 40 | 0 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0.00 |
| Total | 23 | 1 (4.3) | 0 (0.0) | 8 (34.8) | 6 (26.1) | 8 (34.8) | 0.72 |

*Number of embryos continuing at 12 weeks divided by number of initial gestational sacs

**Table 19.10** Effect of ovulation-induction drugs on multiple pregnancies continuing at 12 weeks. Adapted from reference 62

| Treatment | Patients | | Number of fetuses continuing | | | | | Ratio‡ |
|---|---|---|---|---|---|---|---|---|
| | *n* | Age (years) | *0* (%) | *1* (%) | *2* (%) | *3* (%) | *4* (%) | |
| *2 sacs* | | | | | | | | |
| None | 56 | 31.0 | 13 (23.2) | 22 (39.3) | 21 (37.5)† | — | — | 0.57 |
| Clomiphene | 211 | 29.8 | 15 (7.1) | 50 (23.7) | 146 (69.2) | — | — | 0.81 |
| hMG/FSH* | 122 | 30.9 | 11 (9.0) | 35 (28.7) | 76 (62.3) | — | — | 0.77 |
| IVF/GIFT | 160 | 31.8 | 14 (8.8) | 39 (24.4) | 107 (66.9) | — | — | 0.79 |
| *3 sacs* | | | | | | | | |
| None | 5 | 29.6 | 2 (40.0) | 2 (40.0) | 0 (0.0) | 1 (20.0) | — | 0.33 |
| Clomiphene | 24 | 31.1 | 1 (4.2) | 4 (16.7) | 14 (58.3) | 5 (20.8) | — | 0.65 |
| hMG/FSH* | 30 | 31.3 | 3 (10.0) | 3 (10.0) | 13 (43.3) | 11 (36.7) | — | 0.69 |
| IVF/GIFT | 73 | 32.0 | 1 (1.4) | 4 (5.5) | 21 (28.8) | 47 (64.4) | — | 0.85 |
| *4 sacs* | | | | | | | | |
| None | 0 | — | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | — |
| Clomiphene | 2 | 28.0 | 0 (0.0) | 0 (0.0) | 2 (100.0) | 0 (0.0) | 0 (0.0) | 0.50 |
| hMG/FSH* | 7 | 30.0 | 0 (0.0) | 0 (0.0) | 2 (28.6) | 2 (28.6) | 3 (42.8) | 0.78 |
| IVF/GIFT | 14 | 32.5 | 1 (7.1) | 0 (0.0) | 4 (28.6) | 4 (28.6) | 5 (35.7) | 0.71 |

*Not *in vitro* fertilization (IVF) or gamete intrafallopian transfer (GIFT); †none vs. clomiphene citrate $P < 0.0001$, none vs. hMG/FSH $P < 0.01$, none vs. IVF/GIFT $P < 0.001$; ‡number of embryos continuing at 12 weeks divided by number of initial gestational sacs; hMG, human menopausal gonadotropin; FSH, follicle stimulating hormone

percentage of quadruplet pregnancies conceived as a result of either IVF/GIFT or hMG outside of IVF/GIFT delivered as quadruplets was 38%.

The length of gestation in single and twin pregnancies continuing past 24 weeks was inversely related to the initial number of gestational sacs (Table 19.11).

**Table 19.11** Length of gestation according to number of babies born and number of gestational sacs (GS) on initial ultrasound. Adapted from reference 62

| | *n* | *Length of gestation** | | *< 24 weeks* (*n* (%)) | *25–28 weeks* (*n* (%)) | *29–32 weeks* (*n* (%)) | *33–36 weeks* (*n* (%)) | *37–40 weeks* (*n* (%)) | *> 40 weeks* (*n* (%)) |
|---|---|---|---|---|---|---|---|---|---|
| | | *Days* | *Weeks* | | | | | | |
| *Singleton* | | | | | | | | | |
| 1 GS | 4683 | 275 ± 17 | 39.3 | 148 (3.2) | 15 (0.3) | 41 (1.0) | 183 (3.9) | 2155 (46.0) | 2141 (45.7) |
| 2 GS | 140 | 272 ± 17† | 38.9 | 0 (0.0) | 0 (0.0) | 2 (1.4) | 14 (10.0) | 75 (53.6) | 49 (35.0) |
| 3 GS | 14 | 265 ± 33‡ | 37.9 | 0 (0.0) | 1 (7.1) | 1 (7.1) | 0 (0.0) | 7 (50.0) | 5 (35.7) |
| *Twins* | | | | | | | | | |
| 2 GS | 336 | 254 ± 21 | 36.3 | 13 (3.9) | 11 (3.3) | 19 (5.7) | 92 (27.4) | 178 (53.0) | 23 (6.8) |
| 3 GS | 48 | 250 ± 19** | 35.7 | 0 (0.0) | 1 (2.1) | 3 (6.2) | 18 (37.5) | 24 (50.0) | 2 (4.2) |
| 4 GS | 8 | 243 ± 17§ | 34.7 | 1 (12.5) | 0 (0.0) | 2 (25.0) | 3 (37.5) | 2 (25.0) | 0 (0.0) |
| *Triplets* | | | | | | | | | |
| 3 GS | 57 | 230 ± 25 | 32.9 | 2 (3.5) | 10 (17.5) | 8 (14.0) | 25 (43.8) | 12 (21.0) | 0 (0.0) |
| 4 GS | 6 | 225 ± 20 | 32.1 | 0 (0.0) | 0 (0.0) | 2 (33.3) | 4 (66.7) | 0 (0.0) | 0 (0.0) |
| *Quadruplets* | | | | | | | | | |
| 4 GS | 4 | 223 ± 3 | 31.9 | 1 (25.0) | 0 (0.0) | 2 (50.0) | 1 (25.5) | 0 (0.0) | 0 (0.0) |
| 5 GS | 1 | — | — | 1 (100.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| *Quintuplets* | | | | | | | | | |
| 5 GS | 2 | 215 | 30.7 | 1 (50.0) | 0 (0.0) | 1 (50.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

*Length of gestation of mean ± standard deviation for pregnancies delivered after completion of the 24th week; †different from 1 GS, $p < 0.05$; ‡different from 1 GS, $p < 0.01$; **different from 2 GS, $p < 0.01$; §different from 2 GS, $p < 0.001$

Compared with singletons that began as single gestations, the average length of gestation for singleton births was shortened by 10 days when three sacs were present initially and by 3 days when there were two. The average length of gestation for twin births that began as twin gestations was 254 days (36.3 weeks). The average length of twin births was shortened by 4 days, to 250 days (35.7 weeks), when three gestational sacs were present initially, and by 11 days, to 243 days (34.7 weeks), when there were four.

Birth weights of singletons and twins were inversely related to the number of initial gestational sacs (Table 19.12). The trend towards decreased birth weights of singletons and twins that began as higher-order pregnancies, compared with unreduced singleton and twin births, was not significant. There was no consistent relationship between the incidence of restricted fetal growth/IUGR and the initial number of gestational sacs in pregnancies that spontaneously reduced to a lower birth number.

Subsequent analysis limited to multiple gestations resulting from IVF/ART found that 15% of singleton births and 19% of twin births following IVF began as higher-order gestations[103] (Table 19.13). Singleton births following IVF that began as single, twin and triplet or higher-order gestations were born 1.8 days, 5.0 days and 12.4 days earlier, respectively, compared with spontaneous singleton births that began as single gestations. Twin births due to IVF that began as twin, triplet and quadruplet or higher-order gestational sacs were born 2.7 days, 6.2 days and 18 days earlier, respectively, compared with spontaneous twin births that began as twin gestations. The proportion of singletons and twins due to IVF, born before 32 weeks, was not increased compared with spontaneously conceived singletons and twins, in the absence of spontaneous reduction from higher-order gestations.

This was the first study to show that the average length of gestation and weight of twins which had spontaneously reduced from quadruplets and triplets were less than those of unreduced twins. In addition, the average length of gestation and weight of singleton births that had spontaneously reduced from triplets and twins were less than those of unreduced singleton pregnancies. The differences in average birth weight were small and possibly not clinically important, 119 g (4 oz), when twins reduced spontaneously to singleton births, or triplets reduced spontaneously to twin births. However, the differences were larger and potentially clinically important, 228–429 g (8–15 oz), when triplets reduced spontaneously to singletons, or quadruplets reduced spontaneously to twin or triplet births.

The new information regarding spontaneous reduction in IVF/ART pregnancies indicates that the

**Table 19.12** Birth weight and intrauterine growth restriction (IUGR) according to birth number and number of gestational sacs. Adapted from reference 62

| | *Initial number of gestational sacs* | | | |
|---|---|---|---|---|
| *Birth number* | *1* | *2* | *3* | *4* |
| *Singleton* | | | | |
| Patients (*n*) | 4683 | 140 | 14 | 0 |
| Average weight (g) | 3360 ± 599 | 3200 ± 650* | 3132 ± 879* | — |
| RFG (IUGR) infant† (%) | 4.5 | 15.7 | 14.3 | — |
| *Twins* | | | | |
| Patients (*n*) | — | 336 | 48 | 8 |
| Average weight (g) | — | 2453 ± 575 | 2334 ± 577** | 2024 ± 668** |
| RFG (IUGR) infant (%) | — | 14.1 | 11.4 | 6.2 |
| One with RFG (%) | — | 17.3 | 16.7 | 12.5 |
| Two with RFG (%) | — | 5.3 | 6.2 | 0 |
| *Triplets* | | | | |
| Patients (*n*) | — | — | 57 | 6 |
| Average weight (*g*) | — | — | 1816 ± 598 | 1541 ± 276 |
| RFG (IUGR) infant (%) | — | — | 7.0 | 11.1 |
| One with RFG (%) | — | — | 19.3 | 33.3 |
| Two with RFG (%) | — | — | 1.8 | 0 |
| Three with RFG (%) | — | — | 0 | 0 |

*$p = 0.002$, compared with one gestational sac; **$p = 0.003$, compared with two gestational sacs;
†restricted fetal growth (RFG) (IUGR): percentage of babies < 10th centile for gestational age

**Table 19.13** Length of gestation according to number of initial gestational sacs (GS). Adapted from reference 103

| *Treatment* | *n* | *Length of gestation** (days) | *Preterm* (days) | *24–32 weeks* (*n* (%)) | *< 37 weeks†* (*n* (%)) | *≥ 37 weeks* (*n* (%)) |
|---|---|---|---|---|---|---|
| *Single birth* | | | | | | |
| None | | | | | | |
| 1 GS | 2680 | 276.6 | –3.4 | 34 (1.3) | 126 (4.7) | 2554 (95.3) |
| IVF/ART | | | | | | |
| 1 GS | 261 | 274.8 | –5.2 | 3 (1.1) | 19 (7.3) | 242 (92.7) |
| 2 GS | 41 | 271.6 | –8.4 | 1 (2.4) | 5 (12.2) | 36 (87.8) |
| ≥ 3 GS | 5 | 264.1 | –15.8 | 0 — | 1 (20.0) | 4 (80.0) |
| *Twin birth* | | | | | | |
| None | | | | | | |
| 2 GS | 21 | 254.5 | –25.5 | 2 (9.5) | 8 (38.1) | 13 (61.9) |
| IVF/ART | | | | | | |
| 2 GS | 106 | 251.8 | –28.2 | 11 (10.4) | 44 (41.5) | 62 (58.5) |
| 3 GS | 21 | 248.3 | –31.7 | 3 (14.3) | 10 (47.6) | 11 (52.4) |
| ≥ 4 GS | 4 | 236.5 | –43.5 | 1 (25.0) | 3 (75.0) | 1 (25.0) |

*From adjusted onset of menstruation; assumes ovulation, or oocyte retrieval day 14; †< 37 weeks = 24.0–36.6 weeks inclusive; IVF, *in vitro* fertilization; ART, assisted reproductive technologies

increased incidence of premature birth reported for IVF singleton and twin births, compared with spontaneous pregnancies, is due in large part to the initial occurrence of higher-order gestations. Before accepting that twin births due to IVF are at inherently greater risk for prematurity than spontaneous twin births, on the basis of outcome data from IVF procedures performed before 1998 when transfer of three or more embryos was common, it is necessary to evaluate the outcome of only IVF births that follow the transfer of two embryos into patients of similar age, weight and parity.

The data pertaining to spontaneous reduction of twin and triplet pregnancies are limited. In a 1988 review of 11 reports comprising 278 multiple, mostly twin, pregnancies in which ovulation stimulation was not used, 14% of multiple pregnancies ended in abortion, and 58% ended in single births[104]. Smith-Levitin and colleagues[99] reported a spontaneous reduction rate of 18% after the 9th gestational week in 66 expectantly managed triplets. Leondires and associates[95] reported a 13.6% incidence of spontaneous reduction after the 9th week for 81 triplet pregnancies resulting from ART. Lipitz and co-workers[102] reported the miscarriage of all embryos between the 9th and 20th gestational weeks in 13.2% of 106 expectantly managed triplets in a prospective study, but did not report how often spontaneous reduction to twins or singleton pregnancies occurred. The differences in the incidence of spontaneous reduction and complete abortion of all gestational sacs or embryos between Tables 19.9 and 19.10 and earlier reports may be explained by the fact that they derive from referral centers where patients were not seen before the 9th gestational week.

The incidence of restricted fetal growth (IUGR) following spontaneous reduction in Table 19.12 was less than half that reported by Depp and colleagues[93] following MFPR to twins. Also, in agreement with other studies[99,100], no increase was found in restricted fetal growth with increasing numbers of initial gestational sacs. Depp and colleagues[93] were the first to suggest that the differences in outcome between twins resulting from MFPR and unreduced twins were not the result of the MFPR procedure, contrary to the opinions of others[90–92]. The findings in Tables 19.11 and 19.12 support the hypothesis that the impairment of early placental development because of multiple implantation sites is the cause of early delivery following MFPR as well as spontaneous reduction. The finding that the percentage of embryos continuing at 12 weeks is related to the number of initial gestational sacs also indicates that placental crowding is a factor in spontaneous reduction of multiple pregnancies before 12 weeks.

An important result of the findings in the various studies of spontaneous reduction in multiple pregnancies is that the decision to perform MFPR does not need to be finalized until the mid- to late first trimester. Obstetricians managing pregnancies in which there were initially three or more gestational sacs which later reduced spontaneously to singleton or twins need be aware that such pregnancies may deliver 4–10 days earlier, with babies weighing 119 g (4 oz) to 429 g (15 oz) less than unreduced singletons and twins.

## SUMMARY

Multiple pregnancies are an unavoidable but manageable consequence of infertility treatment when the use of ovulation-induction drugs is deemed necessary for patients who desire more than one child, and who are judged (based on currently available criteria) to be capable of carrying a twin pregnancy to at least 36 weeks. The impact of IVF and ovulation induction outside IVF on the number of twin births in the United States is numerically small, less than 10% and 20%, respectively. These procedures are, however, responsible for 83% of triplet and higher-order births. Twins, whether natural or the result of infertility treatment, represent only 12% of all premature births in the USA[105]. Twins due to ART, therefore, account for only 1.4% of total premature births in the USA, and twins due to OI outside of ART account for only 2.5% of total premature births. Furthermore, infants from multiple births have a greater chance of survival than do singleton infants of the same birth weight, gestational age and ethnic origin[106].

The increased incidence of perinatal mortality and morbidity, as well as later developmental abnormalities, of twins compared with singleton births is principally related to a higher incidence of prematurity and low birth weight (see Chapters 1 and 90). The incidence of prematurity and low birth weight, however, can be ameliorated by nutritional supplementation during the first 28 weeks of gestation[107–110], and may also be reduced by progesterone supplementation started between 16 and 20 weeks' gestation[111,112].

The causes of multiple births resulting from infertility treatment are well known: they are the number of preovulatory follicles used for ovulation induction, and the number of embryos transferred for IVF. Techniques to reduce multiple births resulting from infertility treatment are straightforward and not difficult to employ. For IVF, single embryo transfer would eliminate twin births except in rare cases of monozygotic splitting, and would eliminate triplet and higher-order births. Given the present state of IVF technology, if single embryo transfer was employed in all IVF cycles, birth rates per cycle would be reduced by 70% in all patients, and by 40% in patients with the best prognosis due to excess embryos and age less than 35[16]. Limiting the maximum number of embryos transferred to two may be the more reasonable solution.

The solution is more complex for the use of ovulation-induction drugs outside of IVF, but not more difficult to implement. Simply stated, the use of clomiphene citrate for at least three cycles before employing gonadotropins, and the use of low doses of gonadotropins for at least three cycles before proceeding to higher doses, would reduce rates of multiple births. Performing preovulation ultrasound, and canceling cycles or converting to IVF when more than two follicles ≥ 10 mm to 12 mm are present in either gonadotropin or clomiphene citrate cycles, would eliminate triplet and higher-order births, as well as reduce, although not eliminate, twin births. For women aged < 32 years, pregnancy rates would be 14% per cycle and cumulative pregnancy birth rates could reach 70% after five cycles[61]. Whether or not these admittedly conservative approaches to infertility treatment are employed to reduce multiple pregnancy depends on mutual understanding between patients and physicians, and the resolute determination of the latter to do no harm.

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# Micromanipulation and the Risk of Multiple Pregnancy

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**20**



## INTRODUCTION

Micromanipulation has become an important aspect of all human assisted reproduction programs in the past 20 years, with two simple goals: improving fertility treatment results and overcoming male infertility. The commonest micromanipulation techniques used are listed in Table 20.1.

A good micromanipulation system contains five critical elements: an inverted microscope, a micromanipulator, microscopic glass tools, a stereoscopic microscope and appropriate environment control.

## MICROMANIPULATION TECHNIQUES

Of all the micromanipulation techniques, intracytoplasmic sperm injection (ICSI), assisted hatching (AH) and embryo biopsy for preimplantation genetic diagnosis (PGD) are most commonly responsible for the increased incidence in monozygotic (MZ) twins and multiple pregnancies in *in vitro* fertilization (IVF) cycles. All are used in an effort to increase fertilization rates in partners with low sperm counts, to increase rates of endometrial implantation and to provide preimplantation genetic information. Studies in animal models suggest strongly that MZ twinning can be induced through ovum or embryo 'manipulation', either mechanical or chemical. In particular, zona manipulation in placental animals appears to increase monoamniotic twinning[1].

Although the mechanisms by which MZ twins are formed in the human are not completely understood, many investigators postulate that the splitting of the inner cell mass at an early stage of development may cause duplication of the embryo[1]. Splitting of the zygote may occur at any time during the first 2 weeks after fertilization, resulting in various forms of MZ twinning (see Chapter 24). Zygotic splitting probably begins with the protrusion of some trophectoderm cells through a small opening in the zona pellucida. Factors that appear to predispose to splitting include alterations in thickness of

**Table 20.1** Micromanipulation techniques

| *Technique* | *Objective* |
|---|---|
| Intracytoplasmatic sperm injection | overcoming sperm penetration problems |
| Cytoplasmic transfer | investigating embryo development |
| Assisted hatching | facilitating implantation of the embryo |
| Preimplantation genetic diagnosis or blastomere biopsy | for the diagnosis of genetic disease and aneuploidy |
| Pronuclear DNA injection | producing transgenic animals |
| The production of chimeras | investigating cell fate and development |
| Nuclear transfer | investigating nuclear equivalence |

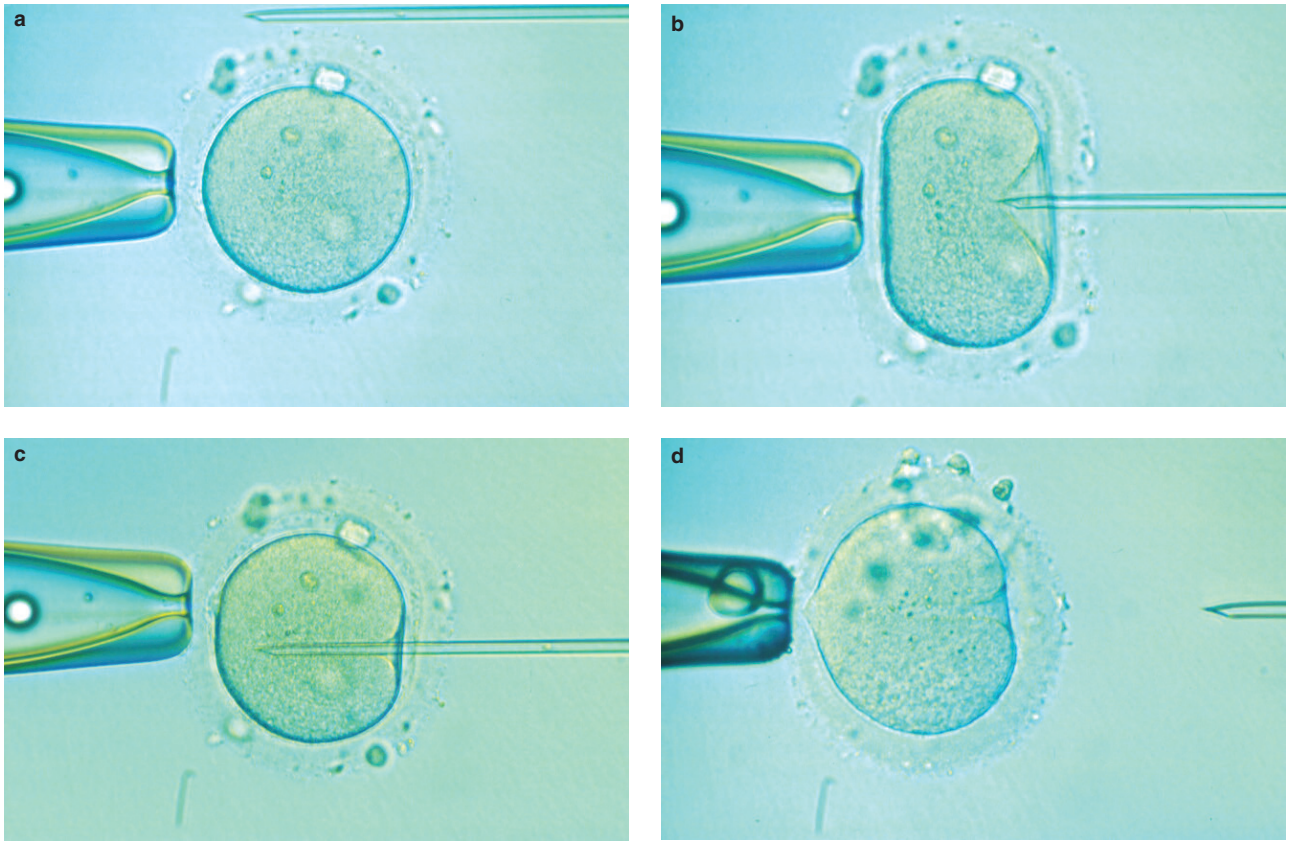


**Figure 20.1** Intracytoplasmic sperm injection (ICSI) procedure: (a) pipette holding the oocyte; (b) while the pipette holds the oocyte in place, the needle containing a single spermatozoon is piercing the oocyte on the other side; (c) the tip of the needle is inside the oocyte, and a single spermatozoon is injected; (d) the needle is withdrawn. ICSI procedure completed

the zona pellucida, time of implantation and assisted reproductive technologies (ART).

## Intracytoplasmic sperm injection

Spermatozoa sometimes fail to fertilize an egg during conventional IVF. Failure is particularly common in the presence of grossly abnormal semen parameters, or when the numbers of spermatozoa are deficient. In the majority of instances, gamete micromanipulation is the only way to overcome this problem. Initially, techniques focused on the obstacles to sperm penetration, by thinning the zona pellucida through exposure to enzymes or creating an opening through localized chemical digestion, mechanical breach or even photoablation. Although associated with a fertilization rate of 20%, these techniques were abandoned owing to their requirements for numerous functional spermatozoa with good progressive motility and complications such as multiple sperm penetration.

ICSI, on the other hand, entails the deposition of a single spermatozoon directly within the cytoplasm of the oocyte, bypassing the zona pellucida and the oolemma (Figure 20.1). The ability of ICSI to achieve higher fertilization and pregnancy rates, regardless of the sperm characteristics, makes it the most effective micromanipulation procedure to treat male infertility. In fact, the therapeutic possibilities of ICSI range from instances in which, after sperm selection, the spermatozoa show poor progressive motility, to application in azoospermic men where spermatozoa are surgically retrieved from the epididymis and the testes. ICSI is also useful when specific oocytes are considered for PGD. As removal of the polar body requires the stripping of cumulus–corona cells, ICSI is the only option to avoid polyspermy.

Historically, three types of micromanipulation procedure were developed to improve fertilization rates. The first involved the creation of an artificial gap in the zona pellucida, either by manually dissecting a hole using needles or by using a chemical agent to 'burn' a hole in the zona. This procedure was described as partial zona drilling (PZD). The second was a more invasive procedure that totally bypassed the zona by placing spermatozoa directly in the

perivitelline space, so-called subzonal insemination (SUZI). The third method was the direct injection of a single spermatozoon into the ooplasm of the oocyte (ICSI)[1]. The first ICSI pregnancy occurred in 1992, when a human spermatozoon was accidentally injected into the ooplasm of a human oocyte during a SUZI procedure. Initially, this technique led to only limited improvement of the fertilization rates compared with SUZI[2]. Despite the external manipulation of essential 'primordial' human tissues, at present, the incidence of congenital malformation in babies born after ICSI is not higher than in the general population; however, patients should be counseled about the higher risk of transmitted chromosomal aberrations and of sex-chromosomal aberrations, and the risk of transmitting fertility problems to the offspring[3].

Much has been written about ICSI and the increased incidence of twins, especially MZ twins. Tarlatzis and colleagues[4] recently compared conventional IVF–blastocyst-transferred cycles with ICSI–blastocyst-transferred cycles. The overall incidence of MZ twinning was 3.3% per cycle in both groups; however, a statistically significant increase was observed in the multiple pregnancy rate (10.8 vs. 2.6%) and moreover, a difference in the MZ twinning rate (5.9 vs. 0%) was observed in the ICSI group, compared with conventional IVF. Abusheikha and colleagues[5] reported an incidence of 8.9% of MZ twins subsequent to ICSI, compared with 0.9% after conventional IVF. The effect of zona pellucida manipulation on MZ twins was also confirmed in another study that showed a significant increase in MZ twins after mechanically assisted hatching (1.2%), compared with non-use of this technique (0%)[6]. These findings are probably due to the artificial opening created by mechanical trauma involved in assisted hatching and ICSI, rather than natural autolysis of the zona which is responsible for splitting of the inner cell mass, as there were no cases of MZ twins when the zona pellucida was not manipulated. da Costa and associates[7] reported that six of 814 (0.7%) MZ pregnancies occurred after ICSI and transfer of 2–8-cell-stage embryos. From the time these investigators introduced day-5 transfers (blastocyst stage), five of 129 (3.9%) pregnancies resulting from ICSI were complicated by MZ twinning, representing a 5.6-fold increased risk of MZ splitting[7]. No differences in age or number of oocytes recovered were observed; however, the mean number of embryos transferred was lower and the implantation rate higher in day-5 transfer.

## Assisted hatching

The zona pellucida of mammalian eggs and embryos is an acellular matrix composed of sulfated glycoproteins, which play different roles during fertilization and embryonic development. The main function of the zona pellucida after fertilization is to protect the embryo. It is postulated that the blastomeric cells are only weakly connected, and that the zona pellucida is needed during the migration of the embryo through the reproductive tract to maintain its physical integrity. Implantation has been observed after the replacement of zona-free morulae or blastocysts, whereas the transfer of zona-free precompacted embryos results in lack of adherence to the walls of the oviduct or to each other. A possible protective role against hostile uterine factors has also been described.

The first report of the use of AH in human embryos was by Cohen and colleagues in 1992[8]. These authors reported an important increase of implantation rates with mechanical AH in embryos from unselected IVF patients. The mechanism by which AH promotes embryo implantation remains unclear. However, as the implantation window represents the critical period when the endometrium reaches its ideal receptive state for implantation, precise synchronization between the embryo and the endometrium is essential. In a randomized study, Liu and co-workers demonstrated that implantation occurred significantly earlier in patients whose embryos were submitted to AH, compared with controls, possibly by allowing earlier contact between the embryo and the endometrium[9]. Furthermore, although most molecules are able to cross the zona pellucida, the rate of molecular transport may be related to the zona thickness. The presence of an artificial gap may alter the two-way transport of metabolites and growth factors across the zona pellucida, permitting earlier exposure of the embryo to vital growth factors. In addition to facilitating embryonic hatching, it has been postulated that AH allows earlier hatching, therefore aiding earlier embryo–endometrium contact. Using human chorionic gonadotropin production as a marker, Liu and co-workers showed that implantation occurred 1 day earlier in hatched embryos compared with unhatched controls[9]. AH may therefore promote successful implantation of embryos with defective hatching by enabling contact with the endometrium within the implantation window. This effect is even more important when one considers that delayed implantation is associated with a higher incidence of miscarriage.

Whatever the underlying cause, the logic of AH is artificially to create a slit or hole through which the blastocyst can escape. This can be achieved mechanically by PZD, chemically using acid tyrode or by using lasers. Hershlag and colleagues[6] studied the incidence of MZ twinning after mechanical AH. The

**Table 20.2** Comparison of non-hatched and hatched *in vitro* fertilization cycles: rates per embryo transfer. Modified from reference 6

| *Outcome* | *Non-hatched (%)* | *Hatched (%)* | *p Value* |
|---|---|---|---|
| Pregnancies | 25.2 (141/559) | 37.1 (250/674) | < 0.0001 |
| Viable pregnancy | 21.8 (122/559) | 33.5 (226/674) | < 0.0001 |
| Multiple pregnancy | 6.8 (38/559) | 13.1 (88/674) | < 0.0003 |
| High-order multiple pregnancy | 3 (17/559) | 4.3 (29/674) | < 0.245 |
| Monozygotic twins | 0 (0/559) | 1.2 (8/674) | < 0.01 |
| Ectopic pregnancy | 0.5 (3/559) | 1.2 (8/674) | < 0.363 |

**Table 20.3** Relationship between assisted hatching and pregnancy, multiple gestation and monozygotic twinning, USA, 1996. Adapted from reference 17

| | *Number of cycles* | *Pregnancy rate per transfer (%)* | *Multiple pregnancy rate (%)* | *Monozygotic multiples (%)* |
|---|---|---|---|---|
| Without assisted hatching | 21 490 | 33.3 | 41.5 | 0.13 |
| Assisted hatching with some transferred embryos | 3 310 | 40.1 | 46.2 | 0.16 |
| Assisted hatching with all transferred embryos | 10 703 | 33.9 | 39.1 | 0.33 |
| Total | 35 503 | 34.1 | 41.3 | 0.20 |

results given in Table 20.2 suggest that pregnancy rate per embryo transfer in the hatched group increased from 25.2 to 37.1%, and the multiple pregnancy rate from 6.8 to 13.1%. In the non-hatched series there were no MZ twins, compared with eight cases in the hatched series (1.2% per embryo transfer).

Schieve and associates[10] reviewed all the IVF–embryo transfer cycles initiated in US clinics in 1996, a total of 35 503 cycles and 11 247 pregnancies, and concluded that the risk of MZ twinning was increased considerably when AH was performed (Table 20.3).

### Preimplantation genetic diagnosis

In the mid-1980s, the development of polymerase chain reaction methods for amplification of specific fragments of DNA from single cells paved the way for PGD of inherited diseases, using one or more cells biopsied from embryos at a preimplantation stage after IVF (Figure 20.2). As the human oocyte and embryo are encased within the zona pellucida until the blastocyst stage, any sampling procedure requires micromanipulation to penetrate this glycoprotein layer. This is followed by the removal of target cells with minimal damage to the embryo, a process that also requires expert micromanipulation. The first PGD cycles were carried out in late 1989 at the Hammersmith Hospital, London, in couples at risk of an X-linked disease.

## MICROMANIPULATION TECHNIQUES AND MULTIPLE PREGNANCIES

Some authors have linked the use of ovulation-induction drugs to MZ twinning[11]. Others have calculated an increased incidence of MZ twins in the setting of IVF, with or without zona manipulation[6,12–18]. One well-accepted hypothesis to explain the higher incidence of monozygosity suggests that manipulation of the zona pellucida, either by chemical changes produced by the ovulation-inducing drugs[12] or by the artificial conditions of *in vitro* media[13], permits herniation of the inner cell mass during hatching. Alikani and associates[14] described an incidence of 0.84% zygotic splitting, twice the expected frequency, and proposed that zona manipulation is the probable cause of these MZ twins. A higher rate of zygotic splitting – 3.49% – was reported by Slotnick and Ortega, a figure

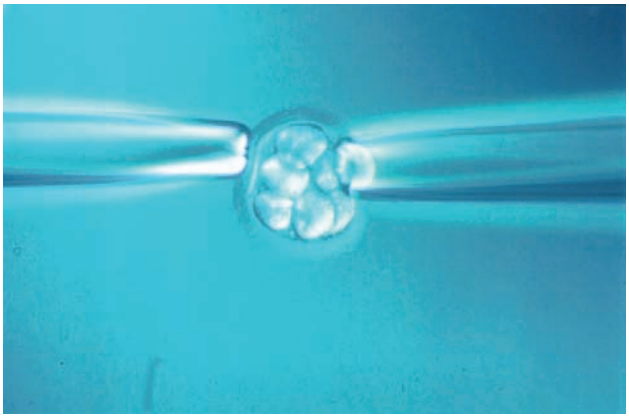

**Figure 20.2** Preimplantation genetic diagnosis biopsy of the embryo. Image courtesy of I. Belil and A. Veiga

seven times higher than the rate of spontaneous twinning[15].

Other studies find contrary evidence. For example, Sills and colleagues[16] reported 23 sets of MZ twins from 1911 assisted reproduction pregnancies (1.2%), with no correlation to manipulative techniques, and concluded that the most likely cause was the increased number of embryos transferred to the uterus. This explanation does not agree with the two studies of Blickstein and co-workers[17,18], who reported the frequencies of MZ splitting following single-embryo transfer. In the most recent study of zygotic splitting[18], the authors evaluated the outcome of 15 644 cycles with single-embryo transfers in 7832 IVF patients in the UK. Overall, there were 1104 live births (7.1% of the cycles, 79.1% of pregnancies), including 22 twin and three triplet sets. The multiple pregnancy rate after single-embryo transfer represents a 2.3% zygotic splitting rate among *in vitro* conceptions, a figure six times higher than the 0.4% rate after spontaneous pregnancies, as quoted in the literature. The interested reader may be referred to a recent summary of the relevant publications related to monozygosity after ART[10].

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# Cloning

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21



## INTRODUCTION

Although human clones had not yet been reported, the scientific as well as the non-scientific community worldwide realized that human clones were just around the corner when Wilmut and colleagues reported: 'The first offspring to develop from a differentiated cell were born after nuclear transfer from an embryo-derived cell line that had been induced to become quiescent'[1]. Undoubtedly, the announcement of the delivery of the celebrity lamb Dolly in February 1997 marked a new era in our appreciation of the biology of twinning.

Monozygotic (MZ) twins are considered to represent natural-form clones and occur in a few mammalian species. MZ twinning is widely thought to result from zygotic splitting at some stage following fertilization (see Chapter 28). One of the procedures used in some species for cloning is embryo splitting. However, although this mechanism resembles the natural twinning process in many ways, the twins that result from bisecting the primordial embryo are not strictly 'clones', in the sense that they started as a product of sexual reproduction. In contrast, clones resulting from nuclear transplantation represent asexual reproduction, whereby the diploid genotype is taken from the individual to be cloned.

Because modern texts on the biology of twinning are unlikely to be considered complete without addressing the issue of cloning, this chapter discusses clones as a new prototype of MZ twins.

## CLONING PROCEDURES

The 'classical' method to produce clones is named after the Roslin Institute (Edinburgh, UK), where

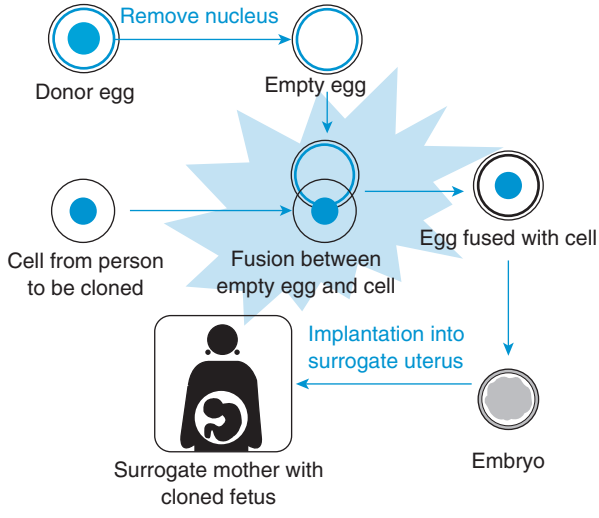


**Figure 21.1** The Roslin method of cloning. A woman is shown only to illustrate the possibility of human cloning

Dolly was conceived. In general, the Roslin method includes four steps (Figure 21.1).

The first removes the nucleus from a donor egg. In this process, nuclear (i.e. haploid set) DNA is removed, but other genetic material (such as mitochondrial DNA) remains within the ooplasm (i.e. the egg's cytoplasm). In practical terms, this means that the clone certainly differs in its cytoplasmic DNA from the parent cell.

The second step involves selection of a somatic (i.e. with a diploid set of DNA) cell from the individual to be cloned. In simple terms, this means transfer of differentiated genetic material from one adult mammal to the empty egg of another mammal of the

same species. In the case of Dolly, a mammary gland cell was chosen.

In the third step, electric current is applied to induce fusion between the somatic cell (containing the diploid nucleus) and the empty egg achieved by enucleation. The key to successful cloning lies in this step, whereby the genes of the somatic cell, which were turned off during the lifetime of the individual to be cloned, must be reactivated. As simple as it may sound, this crucial step was attempted 277 times before the procedure was successful in creating Dolly.

In the last step, the product of fusion (the cloned embryo) is allowed to undergo division *in vitro* until it is transferred into a surrogate uterus. Ultimately, the surrogate mother delivers the cloned infant. One commonly cited negative aspect of the potential for human cloning is the price paid until the first clone is born, as pregnancies of many cloned fetal lambs either miscarried or delivered with serious diseases until Dolly was born.

It is important to distinguish between cloning and natural reproduction on several points. First, the cells of the cloned embryo possess the nuclear genetic material of the individual who was cloned (the so-called cloned adult) and the cytoplasmic genetic material of the egg donor, and thus carry the nuclear genes of the cloned adult only. Second, the cloned embryo is exposed to the influence(s) of the intrauterine milieu of the surrogate mother, and is certainly of different age from the cloned adult. In contrast, naturally occurring MZ twins result from sexual production of a zygote containing one-half of the genes from each parent and sharing the same (cytoplasmic and nuclear) genetic material. Moreover, naturally occurring MZ twins are exposed (to a great extent) to the same influence(s) of the intrauterine milieu of their (usually) genetic mother, and are certainly of the same biological age. Such differences are important, and are often cited when clones are compared with MZ twins.

Finally, it should be emphasized that MZ twins are not truly 'identical' in either phenotype or genotype as a result of post-zygotic genetic changes (see Chapters 32 and 94), alterations associated with intertwin transplacental anastomoses (as in twin–twin transfusion, see Chapter 65), unequal placental sharing and intrauterine crowding (see Chapter 32). Consequently, clones and MZ twins are comparable in intersib diversity[2].

## ADVANTAGE AND DISADVANTAGES OF CLONING

There is general agreement that genetic diversity is a vital characteristic for the survival of species. The disadvantages of inbreeding are well known in humans and other animals in terms of the frequency of genetic diseases, on the one hand, and the natural mechanisms, starting at a subcellular level, that increase genetic variability, on the other. Among mammals, few species produce MZ offspring. The most interesting example is the nine-banded armadillo (Figure 21.2) that only produces MZ quadruplets. In the armadillo, the embryo is implanted, after a long (several months) voyage in the oviduct, in a special niche in the uterus. This location cannot harbor more than one embryo at a time. Subsequently, the implanted embryo undergoes binary fission to two and then to four MZ embryos. It is assumed that MZ twinning in the armadillo is an advantage, because otherwise only singleton offspring would be created.

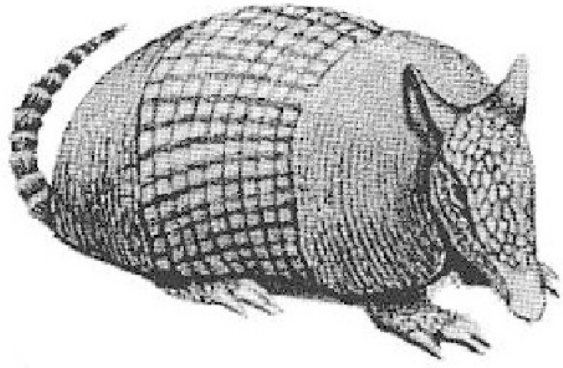

**Figure 21.2** The nine-banded armadillo

In contrast, it may be that MZ twins in the human display no genetic advantage, as they counteract the natural force of genetic diversity. The only exception is that MZ twins might serve as highly suitable candidates for tissue or organ replacement for each other. This 'role' of twins is commonly cited as a potential advantage of human cloning, whereby the early embryonic stages (i.e. blastocyst), containing the so-called multipotent inner cell mass, may be induced to develop into the three primordial germinal layers. These layers contain stem cells that may eventually replace diseased tissues. Examples are given for neural tissue to treat Alzheimer's disease, pancreatic tissue to remedy diabetes and so on. It should be stressed, however, that the great potential of such therapeutic applications is currently under investigation using embryonic stem cells derived from blastocysts that are surplus after *in vitro* fertilization. Despite this potential, the difference between having your own (cloned) stem cells and having heterologous stem cells is quite obvious.

## ETHICAL PROBLEMS OF CLONING

Most ethics-related debates about cloning are associated with the millennia-old definition of the beginning of life. For those who believe that life begins with the unification of sperm and egg, the existence of Dolly, which was created without the unification of sperm and egg, was a genuine philosophical paradox.

Although the disquieting potential consequence of human cloning is currently based on theoretical grounds as opposed to facts, the potential for human cloning raises serious ethical, philosophical, religious, legal and other problems. Further complexity to the debate is the distinction that must be made between human and animal cloning and between cloning and stem cell research. A comprehensive discussion of these issues is certainly beyond the scope of this chapter, but the interested reader will find the literature replete with publications regarding all aspects of cloning[3,4].

## EPILOGUE

In many ways, the debates about human cloning closely resemble the debates that arose about the ethics of *in vitro* fertilization. Such discussion is a natural reaction of society to startling advances in science. However, as it is unthinkable to consider the current practice of reproductive medicine without *in vitro* fertilization, it is likely that in the future it will be inconceivable to consider medicine without cloning. What is needed is a reliable construct (legal or other) to respond to the challenge of human cloning in a realistic manner that will simultaneously protect human rights and permit science to thrive for the best interests of humanity.

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# Natural History of Multiples Conceived by *In Vitro* Fertilization

*G. B. La Sala, A. Gallinelli, G. Nucera and M. T. Villani*

22



## INTRODUCTION

Multiple pregnancies are the most significant, albeit avoidable, complication of *in vitro* fertilization (IVF). With increasing worldwide clinical experience, it became obvious that success rates, in terms of clinical pregnancies and 'take-home' babies, are highly dependent on the quality of oocytes as determined by maternal age. This reality led to the widespread use of controlled ovarian hyperstimulation to increase ovum pick-up rates, which in turn led to improved fertilization rates based upon a higher number of fertilized eggs – now termed embryos. Unfortunately, when more than a reasonable number of embryos are available for transfer, ethical as well as clinical problems may arise. One is then faced with the option of either discarding or freezing surplus embryos in order to avoid excess embryo transfer (ET) (see Chapter 19). Often, when the number of ETs causes a high-order (triplets or more) multiple pregnancy, multifetal pregnancy reduction (MFPR) is offered (see Chapter 63).

Discarding surplus embryos or MFPR is not always welcomed by society, either for social or for religious reasons. For example, in the IVF service at the Arcispedale S. Maria Nuova Hospital in Reggio Emilia, Italy, cryopreservation, disposal of surplus embryos or MFPR is not permitted. By default, all available embryos are transferred, a circumstance that has been somewhat controlled by changes in *in vitro* insemination policies during recent years (Table 22.1). Quite obviously, this policy results in high numbers of multiples and, at the same time, provides a quite unique opportunity to appreciate the natural history of multiple pregnancies following IVF, especially high-order multiples.

## NUMBER OF MULTIPLES

Figure 22.1 shows the distribution of clinical pregnancies according to plurality in the years from February 1987 to 2003. Altogether, there were 787 clinical pregnancies including 316 (40.2%) multiples, of which 112 sets (14.2%) were high-order multiples[1]. In comparison, data from the UK show 25% twin and 5% triplet pregnancies[2], whereas US data show 32% twin and 6% triplet pregnancies[3], differing primarily from the Reggio Emilia data by the high-order multiples rate.

**Table 22.1** Different policies of insemination of retrieved oocytes at Arcispedale S. Maria Nuova Hospital

| *Period* | *Insemination of retrieved oocytes* |
|---|---|
| February 1987–December 1997 | insemination of all retrieved oocytes |
| January 1998–January 2001 | insemination of ≤ 6 for ages < 38 years<br>insemination of all retrieved oocytes for age ≥ 38 years |
| February 2001–present | insemination of ≤ 5 for ages < 38 years<br>insemination of all retrieved oocytes for age ≥ 38 years |

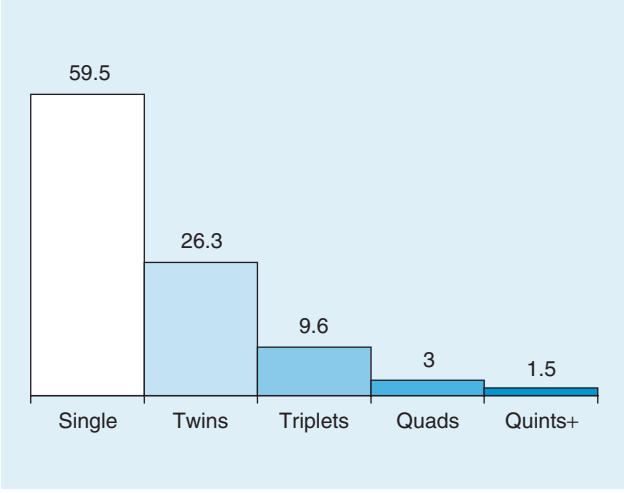



**Figure 22.1** Clinical pregnancies ($n = 790$) according to plurality. Multiple pregnancy constitutes 41% of the *in vitro* fertilization conceptions. Data are shown as percentage

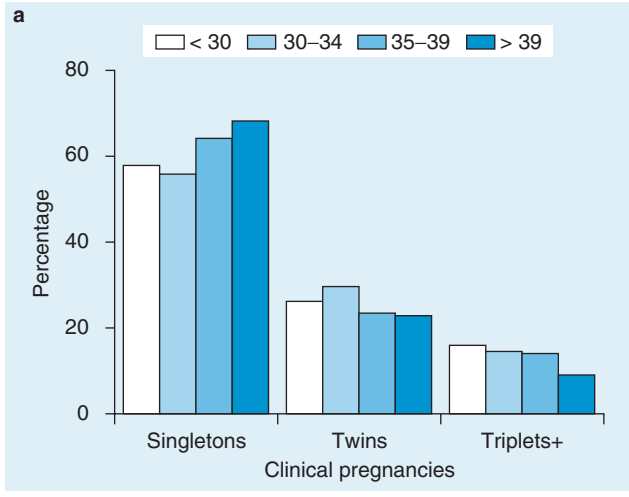
The effect of maternal age on plurality is shown in Figure 22.2a and b. It is clear that the 1998 change of policy (Table 22.1) did not significantly change the overall frequency of multiples among the different age groups (Figure 22.2b), although a decline is noted from 44.2% in patients 30–34 years old to 31.9% in patients aged > 39 years. This is probably because when three or more embryos are transferred, one should not expect higher frequencies of multiples[2].

## SPONTANEOUS ABORTIONS

The unique Reggio Emilia IVF data set enables one to appreciate the spontaneous abortion rates of multiples (loss of the entire pregnancy before 12 weeks). The overall abortion rate in this data set was 20.9%. However, it was significantly higher (27.9%) among singletons compared with multiples (12.8%). Moreover, Figure 22.3 suggests two levels of abortion frequencies: 8.8–9.1% for twins and triplets and 16.6% for quadruplets or more.

## SPONTANEOUS REDUCTION

The natural counterpart of MFPR is spontaneous reduction. The frequency of spontaneous abortions is clearly different between twins (8.8%) and triplets or more (14.1%) (Figure 22.4). However, the frequency of spontaneous reduction proven by ultrasound visualization of at least one fetus is higher among the latter group (46.9%), compared with 25.5% for twins ($p < 0.05$). This observation may be partially explained by the inability of the uterine environment to nurture higher-order multiples, resulting in more frequent resorption of one or more fetuses. The alternative



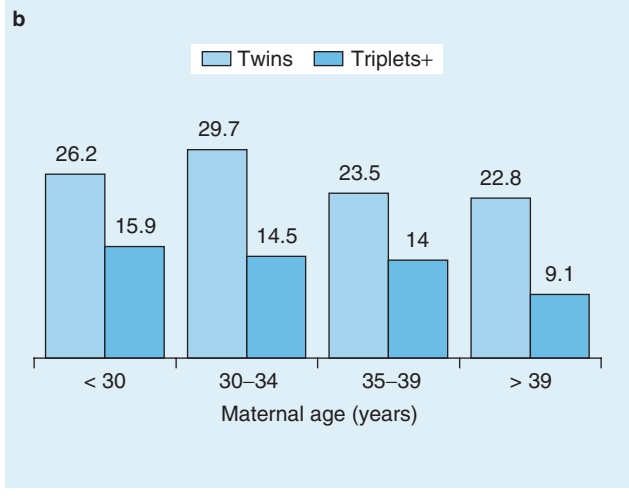




**Figure 22.2** (a) Effect of maternal age (years) on plurality and (b) frequencies (%) of clinical twins and triplets according to maternal age

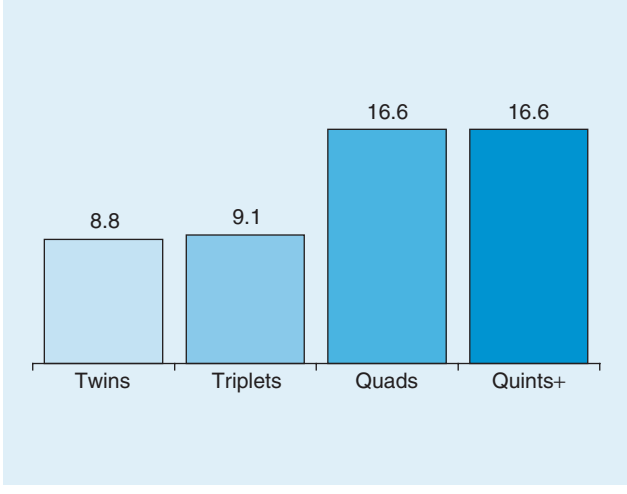



**Figure 22.3** Spontaneous abortion rates (%) according to plurality. Two distinct levels may be seen for twins and triplets and for quadruplets or more, respectively

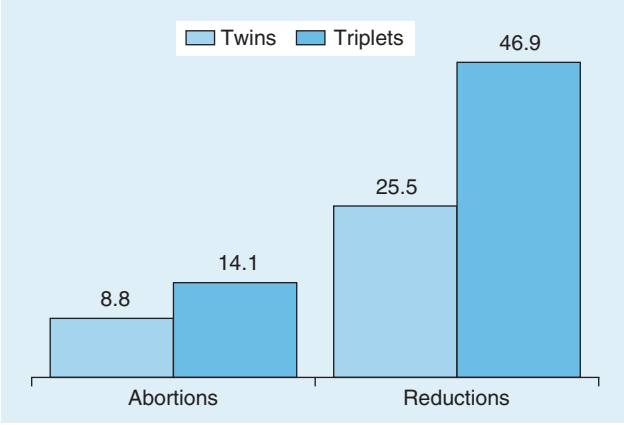



**Figure 22.4** Spontaneous abortion versus spontaneous reduction rates (%) according to plurality

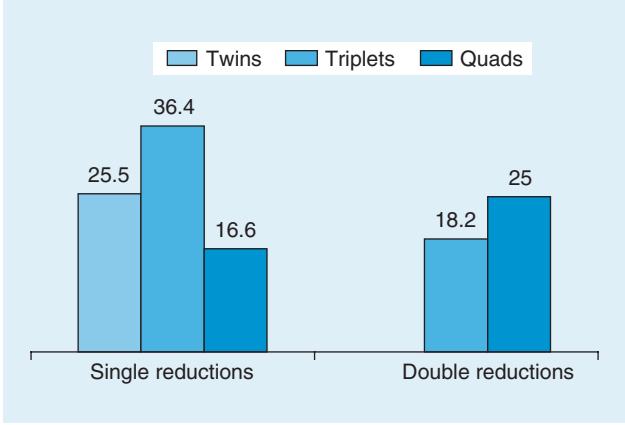



**Figure 22.5** Spontaneous reduction of one or two fetuses according to plurality

hypothesis, namely that higher spontaneous reduction rates result from the fact that more fetuses are present (and can undergo spontaneous reduction), seems less plausible. It is not unreasonable to expect that single and double reductions increase with plurality. As can be seen in Figure 22.5, however, single reductions are least common among quadruplets and more (16.6%), and then increase from 25.5% among twins to 36.4% among triplets. In contrast, spontaneous reductions of two fetuses in triplet and quadruplet and more gestations remain similar (18.2 and 25%, respectively).

## CONCLUSION

The Reggio Emilia IVF data set highlights three important issues. The first is the clear association between IVF and high-order iatrogenic multiple pregnancies. The frequencies of high-order multiples in this service represent approximately a more than 25- and 100-fold increased incidence for iatrogenic twins and high-order multiples, respectively, compared with naturally occurring multiples[4].

The second issue is the association between the patient's age and the risk of multiple pregnancies. The data set suggests that the risk of multiples is not influenced by age, primarily because the number of transferred embryos has not been greatly influenced by the insemination policy. Although this data set is relatively large, the sample size is inadequate to draw conclusive evidence regarding the association between maternal age and the risk of abortion or spontaneous reduction. Finally, the data show that abortions as well as spontaneous reductions increase in non-linear patterns, but these should be confirmed with larger data sets.

Owing to their relative frequency, the most important group of high-order multiples are triplet pregnancies. This database suggests for the first time that triplets do not routinely undergo spontaneous abortion (Figure 22.3) or spontaneous reduction to twins, as do higher-order multiples. In the absence of MFPR, the uterine environment may support such pregnancies until premature birth occurs[5]. Indeed, our outcome data suggest that 66.7% of triplets weigh less than 2000 g, and as many as 21.2% weigh less than 1500 g[1]. These figures compare with 71% and 28% in the findings of Blickstein and Jacques from a US prenatal data set[6].

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# Heterotopic Pregnancy

*Y. Or and A. Barash*

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## INTRODUCTION

Heterotopic pregnancy is the rare simultaneous coexistence of intrauterine and extrauterine gestational sacs. The fact that practitioners do not regularly see this condition elevates its diagnostic and therapeutic challenges. Heterotopic pregnancy is believed to result from the implantation of dizygotic twins at widely separated sites. In the modern era of assisted reproductive technologies (ART), heterotopic pregnancy is more common than was the case in the past. As heterotopic pregnancy may present a life-threatening situation, physicians must have a high index of suspicion in order to reach an early diagnosis and institute treatment.

## HISTORICAL NOTES

The first description of a heterotopic pregnancy, diagnosed at autopsy, was by Duverney in 1708, and cited by Reece and colleagues[1]. The first review was conducted by Gutzweiller in 1873 and reported 276 cases, cited by Gamberdella and Marrs[2]. In 1966, Felbo and Fenger documented a total of 523 cases[3]. Payne and colleagues in 1971 first described a heterotopic pregnancy after ovulation induction with clomiphene citrate and corticosteroids. In this case the patient presented with signs and symptoms of an ectopic pregnancy, and an intrauterine twin pregnancy was noticed as well. The diagnosis was confirmed at laparotomy, and salpingectomy was performed. The intrauterine twin pregnancy was carried to term and delivered by cesarean section (cited by Tal and associates[4]). Robertson and Grant reported in 1972 the first herterotopic pregnancy after gonadotropin treatment, cited by Tal and associates[4]. The first two heterotopic pregnancies resulting from ART were described in 1985 by Yovich and co-workers and Sondheimer and colleagues, cited by Goldman and associates[5]. Both patients underwent *in vitro* fertilization (IVF), and had five embryos transferred. Since then, hundreds of cases have been reported in the literature.

## INCIDENCE

The incidence of spontaneous heterotopic pregnancy is reported variously in the literature. As heterotopic pregnancy is, by definition, a multiple pregnancy with a combination of an intrauterine and an extrauterine pregnancy, its incidence depends on the incidence of each component. De Voe and Pratt calculated a theoretical figure using the incidence of ectopic pregnancy, 0.37%, multiplied by the rate of fraternal multiple pregnancies, 0.8%. The result of this calculation was 0.003%. However, they reported two cases among 13 527 deliveries at the Mayo Clinic in 1947, for an incidence of 0.015%[6]. In 1982, Richards and colleagues[7] performed the same calculation as De Voe and Pratt and determined an incidence of 0.0064%, or 1/15 600 pregnancies, using the incidence of ectopic pregnancies at that time as described by Kitchin and co-workers[8]. In 1990, Molloy and colleagues performed 6204 IVF/gamete intrafallopian transfer (GIFT) cycles which resulted in 1001 pregnancies, ten of which were heterotopic, for an incidence of 1%[9]. In the same year, Dimitry and associates reported 1996 IVF cycles from the period 1984–88 which resulted in 315 clinical pregnancies, nine of which were heterotopic, for an incidence of 2.9%[10]. Shortly thereafter, Dor and co-workers described 4/428 heterotopic pregnancies (0.9%) after 2624 IVF cycles over a period of 9.5 years[11].

In summary, the estimated incidence of heterotopic pregnancy ranges from 1–2/30 000 in the general population to 1/100 with ART.

## RISK FACTORS

The precise cause of heterotopic pregnancy is obscure, but being a multiple pregnancy with a combination of an intrauterine and an extrauterine pregnancy, the risk factors for each entity must be addressed. Ectopic pregnancy is most often associated with tubal damage and altered embryo transport. Documented tubal pathology, commonly resulting from previous surgery, pelvic infections and endometriosis, is the strongest risk factor for ectopic pregnancy.

A history of tubal surgery carries the highest risk for ectopic pregnancy, especially if the surgery was performed for a prior ectopic pregnancy or for sterilization[12]. Smoking, increased incidence of sexually transmitted diseases resulting in salpingitis and the efficacy of antibiotic therapy in preventing total tubal occlusion after an episode of salpingitis are related to the increasing incidence of ectopic pregnancy in general, and heterotopic pregnancy in particular[13].

The risk factors leading to multiple pregnancy are especially important in discussion of the etiology of heterotopic pregnancy. Undoubtedly, the most significant factor is the high incidence of multiple pregnancies after fertility treatments, with rates of 5–10%, 10–30% and 35% following clomiphene citrate, human gonadotropins and IVF, respectively[14]. Glassner and colleagues described two cases of heterotopic pregnancy in patients treated with clomiphene citrate, and concluded that the incidence of heterotopic pregnancy was 1/900 pregnancies after this treatment[15]. Berger and Taymor previously described two cases of heterotopic pregnancy, the first after treatment with clomiphene citrate, and the second after treatment with gonadotropins. Both patients underwent laparotomy and salpingectomy for a ruptured ectopic pregnancy, and both intrauterine pregnancies continued to term, resulting in the delivery of healthy babies. During the 5-year period in which these two cases were observed, 204 pregnancies resulted from the use of clomiphene citrate or gonadotropins, yielding an incidence of 1/100 in this small series[16].

As IVF treatment is a major risk factor for multiple pregnancy as well as ectopic pregnancy, it is conceivable that IVF results in an increased incidence of heterotopic pregnancies, especially considering that IVF was developed to overcome mechanical infertility, whereby tubal pathology is an independent risk factor for ectopic pregnancy. Goldman and colleagues reviewed 34 heterotopic pregnancies following IVF treatments published between the years 1985 and 1991[5]. Several predisposing factors related to the technique of embryo transfer, the number and quality of transferred embryos, the hormonal milieu and the chance for superfecundation are summarized in Table 1 and expanded upon in the following:

**Table 23.1** Factors related to increased rate of heterotopic pregnancy in *in vitro* fertilization patients

| |
|---|
| (1) Transfer of embryos to fundal portion of the uterus |
| (2) Use of human or animal serum in the medium |
| (3) Large volume of transfer medium |
| (4) Large number of embryos transferred to the uterus |
| (5) High level of estadiol before ovum pick-up |
| (6) Superfecundation |

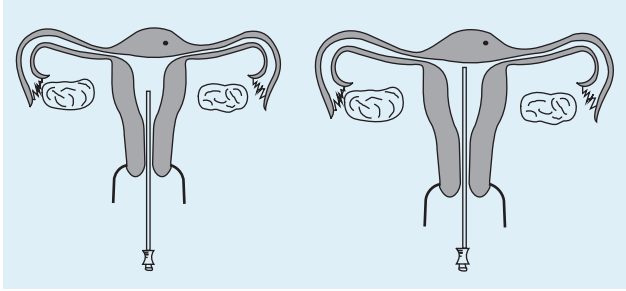

**Figure 23.1** Deep insertion of the transfer catheter (right) may increase the risk for heterotopic pregnancy, whereas transferring the embryos to the mid-portion of the uterus (left) may reduce the risk

(1) Deep insertion of the transfer catheter into the uterine cavity may cause the embryos to migrate from the uterotubal orifice, where they were deposited, into the tubes. Insertion of the transfer catheter into the mid-uterine cavity helps to avoid migration (Figure 23.1). Embryo migration into the tubes may also be facilitated by gravity because of the use of the head-down tilt position (Trendelenburg's position).

(2) A sticky, viscous and heavy medium (high content of human serum) used in some centers for embryo transfer may also contribute to migration of the embryos into the tubes.

(3) A large volume of transfer medium may also facilitate the migration of the embryos into the tubes. Limiting the volume of the transfer medium to 10–20 µl may help to avoid ectopic implantation, although heterotopic pregnancy can occur with volumes less than 10 µl[4,17].

(4) Heterotopic pregnancy occurs after transfer of 2–6 embryos. The pathogenic role of the number of the embryos is not clear. The transfer of one embryo only eliminates the chance for heterotopic pregnancy. Embryo quality may also be a contributing factor, although a heterotopic pregnancy was described after transferring frozen–thawed embryos, suggesting that even such embryos can implant in the Fallopian tubes[5].

(5) The effect of various hormones, including sex steroid hormones, on tubal motility has been studied. Some authors suggest a role for the high estrogen levels just before ovum pick-up in the pathogenesis of ectopic pregnancy. However, reports of heterotopic pregnancies during non-stimulated cycles, when embryos were transferred either after spontaneous ovulation or in synchronized endometrial build-up by controlled estrogen–progesterone replacement therapy, do not support this concept[5].

(6) Superfecundation (see Chapter 16) can happen if a patient with patent tubes is undergoing IVF treatment. Ectopic/heterotopic gestation may result from the spontaneous fertilization of an unrecovered oocyte, if coitus occurs near the time of ovulation[5].

## DIAGNOSIS

The diagnosis of heterotopic pregnancy presents a great clinical challenge, because early diagnosis is undoubtedly difficult but increases the likelihood of salvaging the intrauterine pregnancy. A high index of suspicion for this entity in atypical cases of multiple pregnancy, ectopic pregnancy and abortion is essential for an early diagnosis.

In 1983, Reece and colleagues reviewed 66 cases of heterotopic pregnancy published between 1966 and 1979, including five new cases from their center[1]. The clinical characteristics of these patients represented a highly variable spectrum. The following criteria were helpful in making a diagnosis before ultrasound diagnosis was available:

(1) Uterine fundal height compatible with dates in a patient believed to have an ectopic pregnancy (the absence of a closed cervical os or the presence of vaginal bleeding should not alter the suspicion of heterotopic pregnancy);

(2) Two or more corpora lutea and an enlarged, soft and globular uterus;

(3) The absence of withdrawal bleeding and the presence of pregnancy symptoms following excision of an ectopic pregnancy;

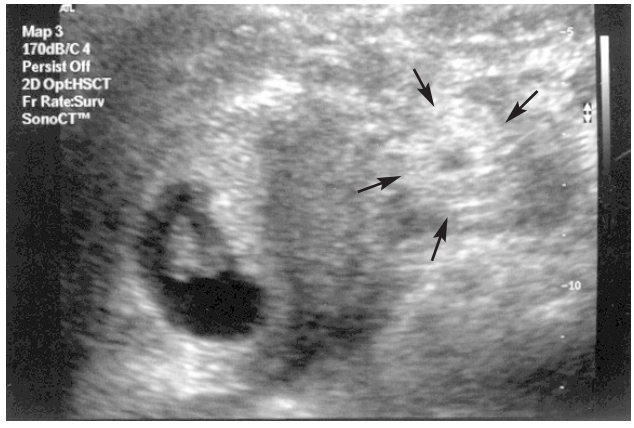


**Figure 23.2** Ultrasound scan showing an intrauterine pregnancy together with a tubal ectopic pregnancy (arrows). Image courtesy of Arie Herman

(4) Hemoperitoneum following the termination of an intrauterine pregnancy;

(5) The combination of abdominal pain, adnexal mass with pain and tenderness, peritoneal irritation and an enlarged uterus;

(6) Higher serum β-human chorionic gonadotropin (hCG) levels than expected in the presence of an intrauterine singleton pregnancy.

Of the 66 cases reviewed, the most common presenting signs and symptoms were: abdominal pain (81.8%), adnexal mass (43.9%), peritoneal irritation (43.9%), enlarged uterus (42.4%) and vaginal spotting (31.8%)[1].

In 1996, Tal and colleagues reviewed 139 cases published from 1971 to 1993[4]. Of these, 111 detailed the clinical course that led to the diagnosis of a heterotopic pregnancy. Diagnosis was made in 59% during emergency laparoscopy or laparotomy. Sonographic detection of an extrauterine gestational sac with or without a fetal pole along with an intrauterine pregnancy was made in another 41%. Nevertheless, sonographic diagnosis was not always made at the first examination, and was frequently delayed. Approximately 70% of the heterotopic pregnancies were diagnosed between 5 and 8 weeks of gestation, almost 20% between 9 and 10 weeks and the remaining 10% after the 11th week. When performing a first-trimester sonographic examination, especially in a patient who has had fertility treatments, it is always advisable to scan both adnexa, to exclude heterotopic pregnancy (Figure 23.2). When the sonographic scan reveals an intrauterine multiple pregnancy, it does not exclude the diagnosis of a heterotopic pregnancy. Zalel and co-workers described an IVF case in which four embryos were

transferred, three of which implanted in the uterus while the fourth was implanted in the left tube. The diagnosis was established in an emergency laparotomy, and salpingectomy was performed. The intrauterine triplets were delivered by cesarean section at 35 weeks[18].

The most frequent location of the ectopic pregnancy in patients with heterotopic pregnancy is the Fallopian tubes. In Tal's review, 89% implanted mostly in the ampullar portion, and the remaining gestations were found in a tubal stump, isthmus, cornua and in the fimbria. The authors also reported the extremely rare instances of two gestational sacs implanted in the same tube alongside the intrauterine pregnancy, and a heterotopic quintuplet pregnancy in which there was an intrauterine triplet pregnancy accompanied by two extrauterine gestational sacs, one in each tube[4]. Unusual locations of the ectopic pregnancy were also described as the uterine cervix, the ovary and the abdominal cavity[4].

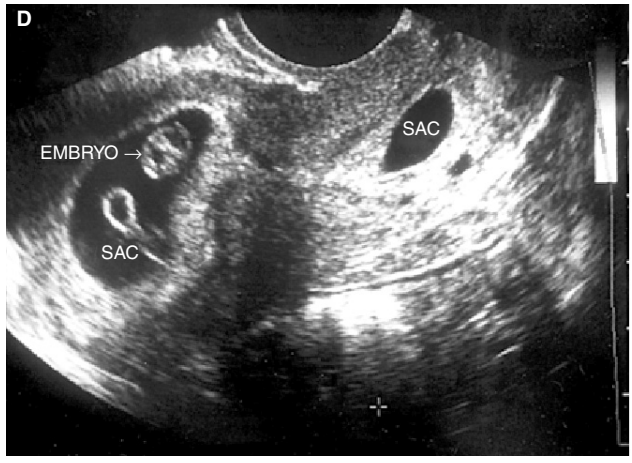


**Figure 23.3** Sagittal view of a heterotopic pregnancy at the age of 8 weeks and 3 days. Note the intracervical gestational sac along with an intrauterine sac containing a viable embryo and a yolk sac. Image courtesy of Yaron Zalel

## THERAPEUTIC OPTIONS

The therapeutic options in a patient with a heterotopic pregnancy are surgical or non-surgical. Counseling about the preferable treatment is mainly influenced by the patient's condition at the time of diagnosis and the location of the ectopic pregnancy. Since most ectopic gestational sacs are located in the Fallopian tube, the most common treatment is salpingectomy, because many patients are diagnosed during an emergency operative procedure to determine the cause of hemoperitoneum. Salpingostomy and 'milking' of the affected tube have also been described[4].

Conservative expectant management with spontaneous resolution of the ectopic pregnancy has been reported sporadically. Rizk and colleagues described 17 patients with heterotopic pregnancy. In one case the extrauterine gestational sac resolved spontaneously[17]. Molloy and associates performed 6204 IVF, GIFT or pronuclei transfer cycles over a period of 4.5 years. Pregnancy was achieved in 995 cycles, of which ten were heterotopic. In one patient conservative management of a provisionally diagnosed ectopic was reported, and the diagnosis was confirmed at cesarean section later in pregnancy[9]. Fernandez and co-workers described 25 heterotopic pregnancies. In three instances, expectant management was justified in the absence of adverse clinical signs. In one other case, laparoscopic salpingectomy was eventually performed owing to persistent hypogastric pain, despite the absence of hemoperitoneum[19].

Selective feticide of the ectopic is performed in some instances of heterotopic gestation. This treatment is suitable, however, only if the diagnosis was made early and the patient is hemodynamically stable. It is more useful when the ectopic is located in places other than the Fallopian tube ampula, such as is the case with an interstitial or cornual pregnancy. Three substances have been used for selective feticide in such circumstances, including potassium chloride, methotrexate and hyperosmolar glucose. Lau and Tulandi reviewed nine cases of heterotopic interstitial pregnancies managed with either conservative medical or surgical techniques[20]. Cardiac activity was encountered in all cases. Six were treated with ultrasonographically guided injection of 0.05–2.0 mmol potassium chloride into the fetal heart or into the gestational sac. One was treated with a combination of potassium chloride and 12.5 mg of methotrexate. Laparoscopic cornual resection was performed in the remaining two patients. All nine cases required no further treatment. Three pregnancies ended in spontaneous abortion of the coexisting intrauterine pregnancy, however, whereas the remaining six cases ended in successful delivery[20]. Systemic administration of methotrexate is contraindicated in these circumstances because it can harm the intrauterine pregnancy owing to its teratogenic potential. Controversy whether local administration of methotrexate to the ectopic pregnancy can damage the intrauterine pregnancy is solved by using potassium chloride or hyperosmolar glucose. Use of hyperosmolar glucose was described by Strohmer and Gjelland and their groups, with successful results[21,22].

A rare case of combined intrauterine pregnancy and cervical pregnancy was described by Mashiach and colleagues (Figure 23.3)[23]. They performed a Shirodkar-type cerclage as the only therapy, with normal vaginal delivery of the intrauterine pregnancy at term.

There are very few instances in which both intrauterine and extrauterine pregnancies have

progressed simultaneously. Reece and colleagues found only 13 such cases; all reached term, and were delivered. Although there is little information available regarding these cases, it is known that the infants survived the neonatal period, but an increased incidence of congenital malformation and mental retardation was observed[1].

## PROGNOSIS

The prognosis for both the mother and the intrauterine pregnancy depends on the time of diagnosis, the patient's condition, the location of the ectopic pregnancy and the chosen treatment. In Tal's review, approximately 66% of the intrauterine pregnancies were born alive and survived[4]. These results are similar to those obtained by Goldman and colleagues, in which 68% of 37 cases reached delivery and survived[5]. The results obtained in Reece's review are even better: 76% of 37 patients who underwent laparotomy for the extrauterine pregnancy delivered at term, 16% delivered prematurely, two had stillbirths and one had a spontaneous abortion[1]. These salutary outcomes are most probably due to the improved diagnosis and therapeutic techniques available today. Nonetheless, fetal wastage is still higher than expected after ovulation induction or ART. Maternal mortality prior to 1935 was 19%. Since 1935, however, more sophisticated and aggressive medical management has reduced the maternal loss to approximately 1%[1,3].

## SUMMARY

Heterotopic pregnancy is a rare complication of multiple pregnancy, but the incidence increases to 1% of pregnancies following ART. Not uncommonly, this circumstance jeopardizes both the mother and her fetuses. It is of great importance that the physician be familiar with this condition, using a high index of suspicion especially in patients who have had fertility treatments. When early diagnosis is made and the patient is stable, more treatment options are available. However, in many instances the diagnosis is reached only after surgical intervention for the investigation of hemoperitoneum. Precautionary measures should be taken to reduce the risk of heterotopic pregnancy during IVF, including reducing the number of embryos transferred into the uterus to one, insertion of the transfer catheter to the mid-uterine cavity instead of the fundal area and minimizing the transfer medium to not more than 10–20 µl. When precautionary steps are considered and careful examination of the patient is conducted, including sonographic scan of both the uterus and the adnexa, an emergency situation can be avoided, and salvage of the intrauterine pregnancy and reduction of maternal risk can be accomplished.

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# Placentation

*R. Derom and C. Derom*



## INTRODUCTION

Placentation in multiple pregnancies is influenced not only by the number of zygotes but also by the number of blastocysts and, before or after implantation, the division of the inner cell mass. If, in the past, the relationship between the number of the zygotes and their divisions and the gross morphology of the placenta was not always clear, this no longer need be the case. With a minimum of instruction, anyone investigating the placenta of a multiple pregnancy should be able to grasp the link between this structure and the origin of the pregnancy.

Single placentas are generally characteristic of monozygotic (MZ) pregnancies and are monochorionic. When they are dichorionic, the single placental mass results from the fusion of two separate placental disks. When two placentas are present, they are almost always dichorionic. Most, but not all, instances of two placentas arise from the dizygotic (DZ) twinning process; some are also present in MZ twinning in which division occurs before implantation (Figure 24.1).

It is not generally appreciated that twin placentation differs widely by race. Table 24.1 documents marked differences in the rates of monochorionic and dichorionic placentation in distinct geographic regions inhabited by different ethnic groups. Considering the extent of these differences, any assessment of zygosity based solely on the number of placental disks is of little value. Rather, it is necessary and crucial to consider the number and structure of the membranes as well as the number of placental disks in order to determine zygosity accurately. Whether placentas are separate or fused may be of crucial importance for fetal growth, as shown later in this chapter and also discussed in Chapter 26.

The principles addressed in the preceding paragraph pertain to triplet and higher-order placentation as well. With regard to triplets, a fused placental mass is more common, regardless of zygosity, simply because of uterine crowding. Figure 24.2 shows the mechanisms of MZ, DZ and trizygotic (TZ) triplets with different types of membranes. It is readily apparent that examination of the membranes alone cannot establish zygosity if the placental mass is trichorionic. Similarly, if the placental mass is dichorionic, the zygosity may be MZ or DZ. Finally, only when the (single) placenta is monochorionic can one truly establish monozygosity, regardless of the number of fetuses. Thus, the principle stated in the preceding paragraph, i.e. that placental examination by itself is insufficient to establish zygosity in all cases, can be extended to the membranes as well. The general rule in triplets is to have a single placental mass, and a single placental mass can result from MZ, DZ or TZ origins. Table 24.2 outlines placental structure in triplets and complements data presented in Figure 24.2.

The relationship between zygosity and placental structure in twins leads to three clinical aphorisms, the last one of which is of paramount importance. As stressed in the preceding commentary, one can conclude from proper examination of the placental membranes (as opposed to the number of placentas) that a twin pair is MZ. The clinical aphorisms are as follows (see Figure 24.1 for visual confirmation):

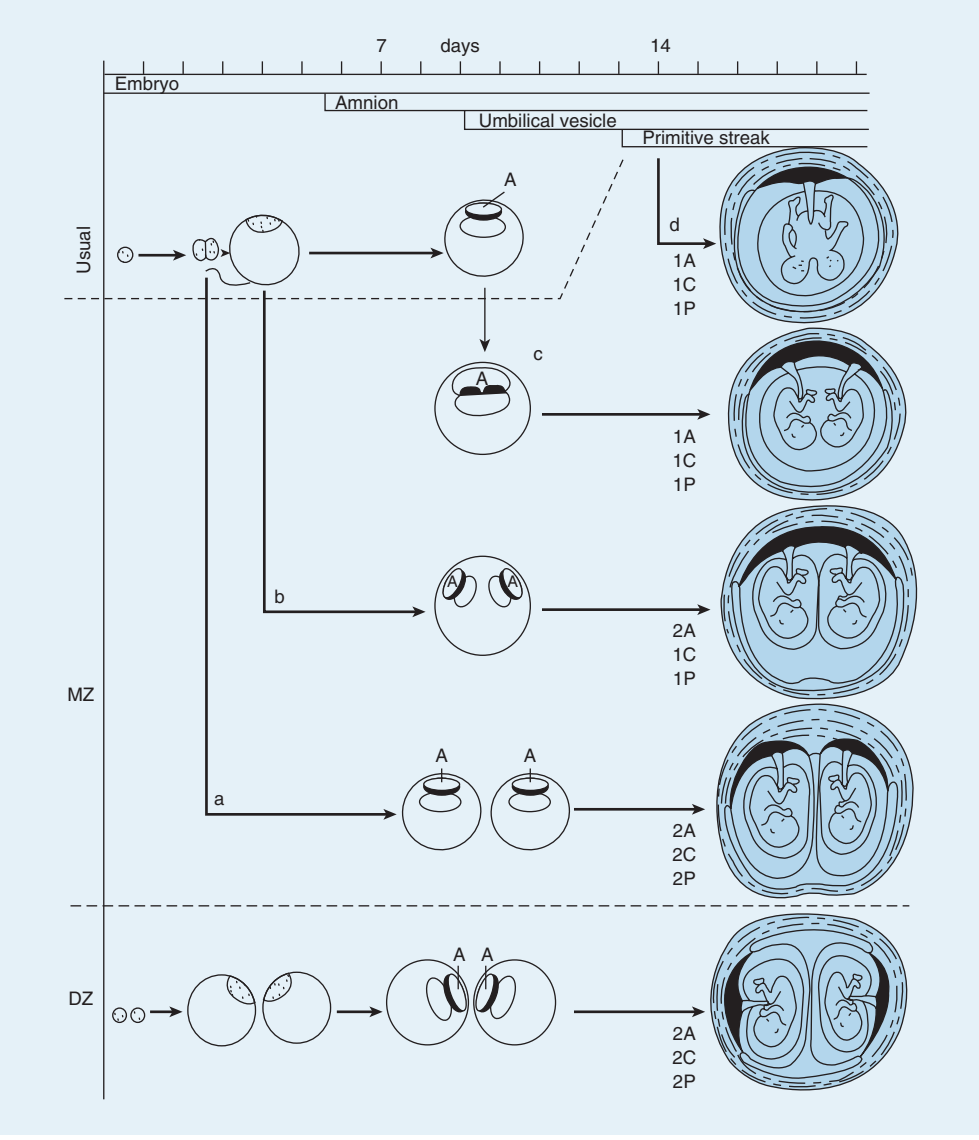


**Figure 24.1** The arrangement of the adnexa (fetal membranes) in twinning. MZ, monozygotic; DZ, dizygotic; A, amnion; C, chorion; P, placenta. Image courtesy of O'Rahilly R, Müller F. *Human Embryology and Teratology*. New York: Wiley-Liss, 1992

**Table 24.1** Geographic distribution of the relative frequencies of placental structures of twins

| | | *Dichorionic* | | |
|---|---|---|---|---|
| | *Monochorionic* | *Single and fused* | *Double or separate* | *Unknown* |
| Ibadan, Nigeria | 5.0 | 51.1 | 41.2 | 2.7 |
| Aberdeen, UK | 18.7 | 34.5 | 41.0 | 5.6 |
| Oxford, UK | 22.5 | 33.0 | 42.5 | 2.0 |
| Birmingham, UK | 19.6 | 80.4 | | — |
| East Flanders, Belgium | 26.3 | 37.2 | 35.3 | 0.1 |
| Japan | 61.8 | 19.7 | 18.5 | — |

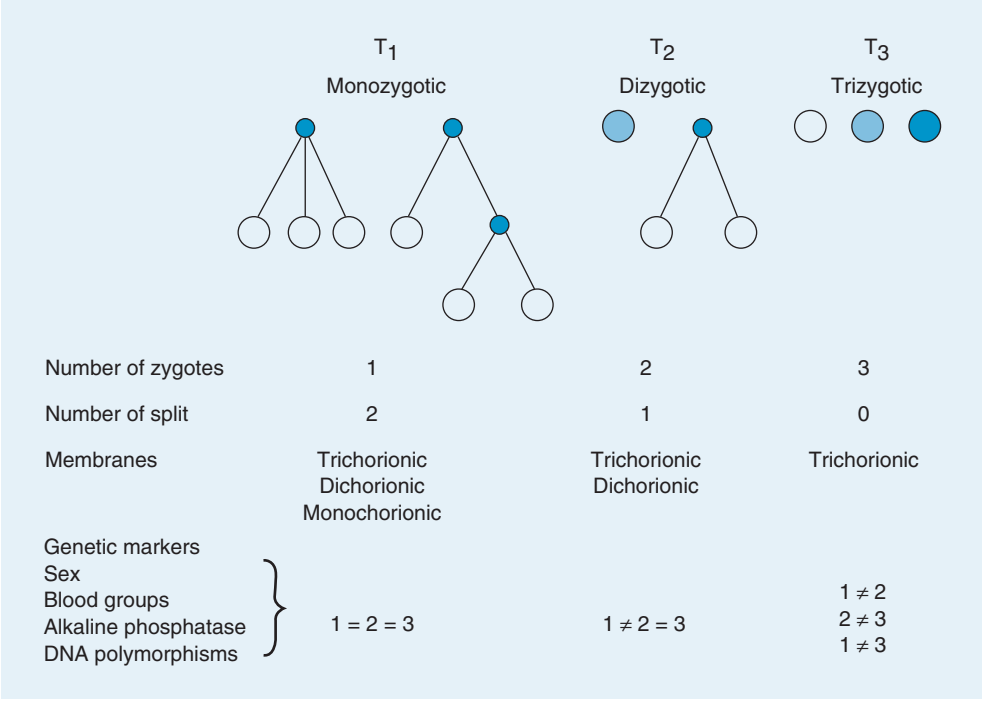


**Figure 24.2** Stylized presentation of zygosity and placentation in triplets (T)

**Table 24.2** Placental structures of triplets

| *Number of chorionic membranes* | *Number of amniotic membranes* | *Denomination* |
|---|---|---|
| 3 | 3 | trichorionic–triamniotic |
| 2 | 3 | dichorionic–triamniotic |
| | 2 | dichorionic–diamniotic |
| 1 | 3 | monochorionic–triamniotic |
| | 2 | monochorionic–diamniotic |
| | 1 | monochorionic–monoamniotic |

(1) DZ twins are dichorionic;

(2) MZ twins are either monochorionic or dichorionic;

(3) A monochorionic placenta is proof of monozygosity.

Only three well-documented exceptions to this third rule have been published[1–3], so that the diagnosis of monozygosity is very close to certainty in monochorionic twins. In a consecutive series of 1438 monochorionic pairs of the East Flanders Prospective Twin Survey (EFPTS), all were of the same sex. Follow-up data are available in a random sample of 491 pairs in which the diagnosis of monozygosity could be confirmed phenotypically and/or according to a similarity questionnaire. In addition, DNA analysis of fetal tissue samples collected on the maternal side of the cotyledons of each member of the pair in 166 random placentas failed to show any discordance of the markers studied.

The aphorisms for triplets (see Figure 24.2 for visual confirmation) are as follows:

(1) TZ triplets are trichorionic;

(2) DZ triplets are either di- or trichorionic;

(3) MZ triplets are tri-, di- or monochorionic;

(4) Dichorionic triplets are either MZ or DZ;

(5) Monochorionic triplets are MZ.

A unique feature of placentation in multiple pregnancy is the high prevalence of marginal and velamentous insertion of one or more umbilical cords. Among singletons, these variations are found in less than 10%, and 2% of cases, respectively, although slightly different rates have been published in various reports[4]. A more complete analysis of velamentous insertion in twins is found later in this chapter along with other data from the EFPTS. In many, but not all instances, marginal insertions are symmetric, i.e. present in both twins, all three triplets or all four quadruplets if the placenta is monochorionic[4,5]. Marginal or velamentous insertion of the cord is associated with preterm birth and low birth weight, and, if present, should always be noted in the delivery record, the operation record or the formal report of the pathologic examination of the placenta.

Most monochorionic placentas show anastomoses between the arteries (A) and the veins (V) at the fetal surface (see Chapter 27). These may be A–A, A–V or V–V. If large enough, A–A and V–V anastomoses are visible to the naked eye. However, injection techniques are usually required to demonstrate small A–A and V–V anastomoses. Arteriovenous anastomoses can only be demonstrated by special techniques (see Chapter 27). The complexity and variety of the anastomotic connections in monochorionic twin placentas are shown in Table 24.3[6] and described more fully in Chapter 27. The only systematic study of placental vascular anastomoses in fused dichorionic twin placentas has been performed by Cameron[7], who found two arterio-arterial anastomoses in a series of 534 dichorionic placental masses. In these instances, the twins were probably MZ. In the EFPTS, we have been unable to demonstrate any vascular communications in a series of 200 dichorionic twins. Undoubtedly, an A–A or V–V anastomosis is a rare event in dichorionic placentation.

The impact of the different types of placental vascular communications is still debated. Clearly, hemodynamic imbalance must result from a one-way fetus-to-fetus passage of blood. We and others are of the opinion that the superficial A–A and/or V–V anastomoses compensate for exchanges in the deep A–V channels, and that the feto-fetal transfusion syndrome mostly or only originates when, during pregnancy, superficial anastomoses are absent, small or few in number (see Chapters 27 and 65).

**Table 24.3** Anastomoses in 39 monochorionic placentas. From reference 6

| | |
|---|---|
| Artery-to-artery only | 4 |
| Artery-to-artery + artery-to-vein | 11****† |
| Artery-to-artery + vein-to-vein | 2† |
| Vein-to-vein only | 0 |
| Artery-to-vein only | 2* |
| Artery-to-vein + vein-to-artery | 3**† |
| Artery-to-vein + vein-to-vein | 2 |
| Artery-to-vein + vein-to-vein + artery-to-artery | 4**† |
| Artery-to-vein + vein-to-artery + artery-to-artery | 4* |
| Artery-to-vein + vein-to-artery + artery-to-artery + vein-to-vein | 3** |
| No anastomoses seen | 4 |

*Case of transfusion syndrome; †probable case of transfusion syndrome

The placentation of monochorionic triplets is entirely comparable to that of monochorionic twins, particularly with regard to vascular anastomoses and the presence or absence of a diamniotic dividing membrane. Monochorionic triplets can have one, two or three amniotic membranes. Published injection studies have yet to demonstrate the presence of vascular anastomoses in monochorionic triplets. However, it can be assumed that they are present, just as they are present in the placentas of monochorionic twins, and in two cases of monochorionic quintuplets[8,9].

Placentation in pregnancies numbering four or more fetuses follows the same pattern as that described for triplets. Theoretically, the placentation of quadruplets can be of 12 types. Tetra-, tri-, di- and monochorionic cases have been described.

## CLINICAL EXAMINATION OF THE PLACENTA(S) AT THE TIME OF DELIVERY

This important issue is described in detail in Chapter 25. In general, four specific features require attention at this time, which should be noted in the delivery room or operation record. These include:

(1) The structure of the fetal membranes;

(2) The unity or division of the placental mass;

(3) The site of insertion of the umbilical cords;

(4) The nature and the extent of the vascular anastomoses in monochorionic placentas.

All features are clinically relevant, but of unequal importance. Clinically, the chorion type is most important, followed by the vascular anastomoses in monochorionic placentas, and finally by placental macroscopic structure and site of the insertions of the cords[10].

Although placental examination is not difficult, it requires some degree of expertise and practice. Errors can occur. For example, a dichorionic placenta with a thin septum can erroneously be classified as monochorionic. Because of such inaccuracies, cases of opposite-sex twins with monochorionic placentas have occasionally been reported. At the Chicago Lying-in Hospital, for example, in a Department of Obstetrics and Gynecology with one of the earliest and most renowned divisions of perinatal pathology, two such cases were mentioned in an early paper[11], but subsequently were retracted when it was determined that the placenta had been investigated in the absence of Edith Potter who headed the division[12].

Antenatal determination of chorionicity by ultrasound is currently a routine procedure worldwide. The diagnosis is correct in 95% of cases, i.e. 91% of monochorionic and 96% of dichorionic pregnancies. If chorionicity is assessed before 14 weeks' gestation, the correct diagnosis is almost always made[13].

Placentas are fused in half of the cases of dichorionic twins. This is of importance to the clinician for several reasons. First, the cords may not both insert in a central location and thus predispose the twins to different intrauterine conditions that may affect growth. Second, the fusion may not be symmetrical, and both halves may comprise a vastly different functional part of placental tissue from which to derive nutrition, apart from any difference based on the site of the cord insertion. According to Corey[14], a comparison of intrapair birth-weight variation of monochorionic– and dichorionic–MZ twins revealed significant differences between monochorionic pairs and dichorionic separate pairs, and no significant differences between monochorionic pairs and dichorionic fused pairs. These findings suggest that placental proximity may have as important an influence on variation in birth weight as the presence or absence of vascular anastomoses. The observations of Corey and her co-workers, based on a sizeable but limited number of cases, should be extended in order to reach sex/zygosity/chorion-type subgroups of 100 or more pairs to warrant firm conclusions with regard to the influence of placental proximity. Such a study has been performed in the EFPTS[15] (see below). Here also, a prenatal ultrasound examination establishes an accurate diagnosis and is now included in the guidelines of the Flemish Society of Obstetrics and Gynecology and probably other societies as well.

The types of insertion of the umbilical cords in twin pregnancies do not differ from those found in singletons, except for the velamentous insertion which can be located either on the dividing or on the peripheral part of the membranes. Because the single umbilical artery syndrome is more frequent in twins and higher-order multiples[4,16], no examination of the cord is complete without recording the number of umbilical arteries. Histologic examination should be performed if one is in doubt about the number of arteries.

Vascular anastomoses are discussed in detail in Chapter 27.

The literature on triplets and higher-order multiple births consists, to a large extent, of case reports and small series, most of which fail to discuss placentation. Examination of the placenta(s) from these gestations should proceed along the same lines as indicated for twins. The dividing membranes between each sac should be dissected, taking into account that, if the placentas are fused, the number of these membranes generally equals the number of fetuses. For example, in a fused trichorionic triplet placental mass, dividing membranes are found between triplets 1 and 2, triplets 2 and 3 and triplets 3 and 1, respectively. The numbers of chorionic and amniotic membranes should always be counted. Figure 24.3 shows a corrosion cast of a

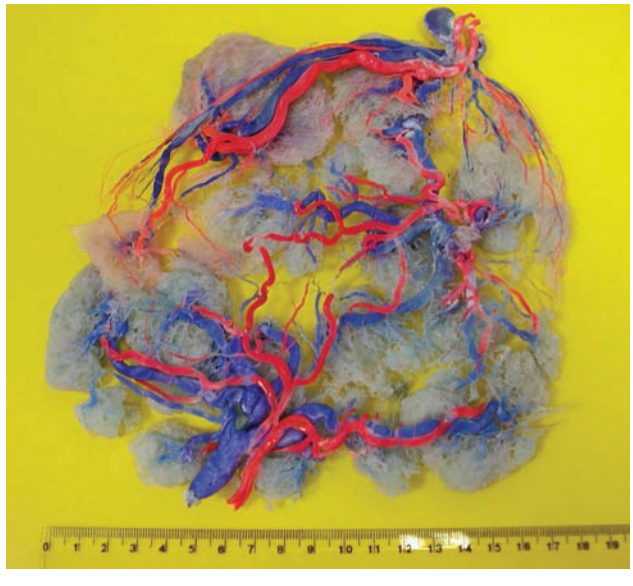

**Figure 24.3** Corrosion cast of a monochorionic–triamniotic triplet placenta. Image courtesy of Drs O. Groutz and Y. Hazan, Lis Maternity Center, Tel Aviv

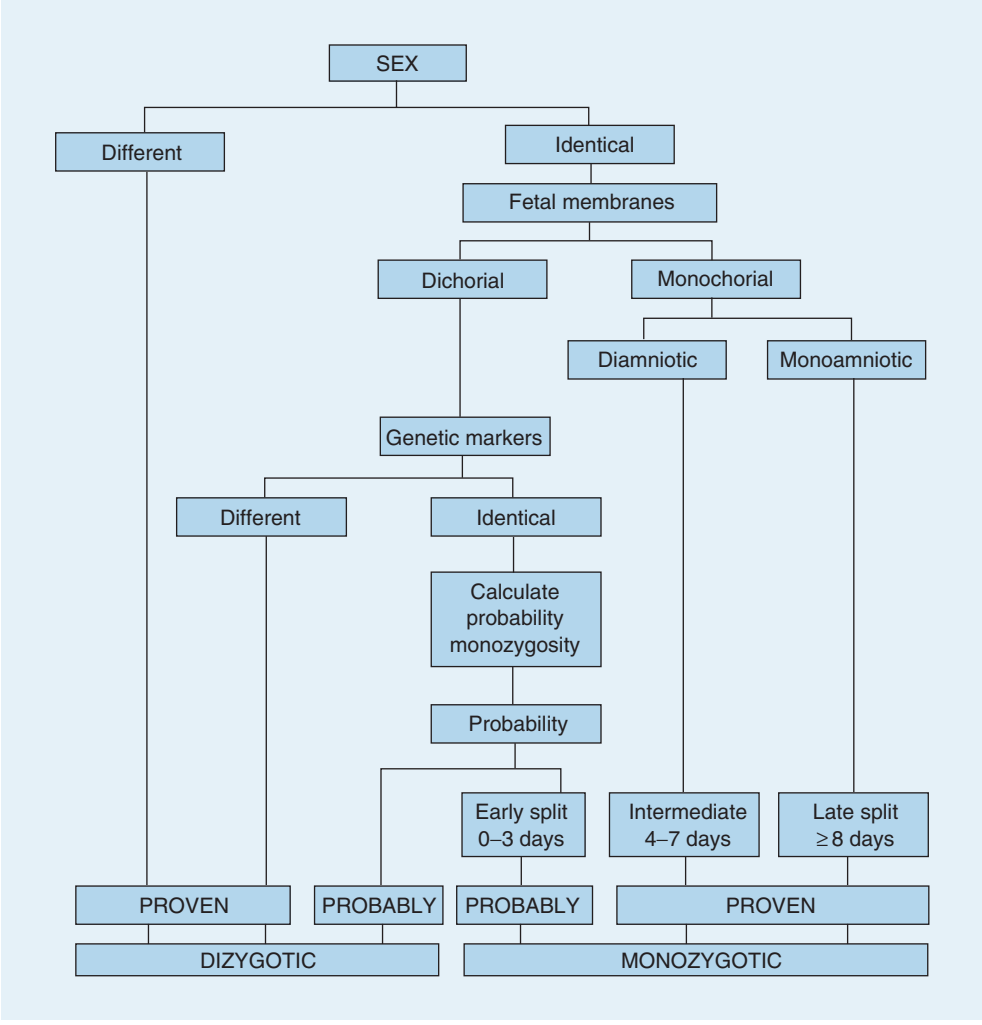


**Figure 24.4** Decision table to determine zygosity and time of splitting. From reference 21

monochorionic triplet placenta. Table 24.2 lists the different placental types encountered in triplets. Extension of this table to quadruplets, quintuplets, etc. should follow the same anatomic principles.

## EXPERIENCE OF THE EAST FLANDERS PROSPECTIVE TWIN SURVEY

Following the plea of Benirschke[17], and being convinced that zygosity determination at birth would be invaluable not only for the multiples and their families but for medical research, we investigated and described fully all placentas from twin and higher-order multiple births in the Province of East Flanders, Belgium since July 15, 1964[18,19]. Twin and triplet placentas were obtained from participating hospitals and examined according to the guidelines described in this chapter. In addition, blood was collected from the umbilical cords of all infants for determination of blood groups, and samples of placental tissue were deep-frozen for later determination of genetic markers if needed. Alkaline phosphatase was the first marker used, but after 1985 the more exact determination of DNA sequences replaced this[15,20,21].

Over the years we developed a flow chart for zygosity determination (Figure 24.4)[19–21]. This chart was of particular value in the population served by physicians practicing in East Flanders. Virtually all multiple births were registered to Caucasian women. In same-sex dichorionic twins or di- and trichorionic triplets with the same blood and placental markers, we calculated the probability of monozygosity[22]. Pairs were classified as monozygotic if the probability was at least 0.95.

## Twins

An overview of the placentation and other basic data obtained in East Flanders is presented in Table 24.4. A total of 5044 twin pairs, 4767 with known zygosity, were available for analysis and these data form the basis of Tables 24.5–8 (see below). In contrast to most studies performed in the first half of the 20th century in Europe and North America, the proportion of monochorionic twins increased, at least during the years 1964–79. This period is the last one during which, but for a few exceptions, all twin pregnancies in East Flanders were spontaneously conceived. In contrast, since 1980, increasing numbers of twin pregnancies have been related to the use of ovulation-inducing drugs. Because, as a rule, most of these iatrogenic pregnancies were DZ and, therefore, dichorionic, the proportion of dichorionic twins increased.

### *Structure of the fetal membranes*

Fetal growth is impaired by monochorionic placentation. The durations of pregnancy being approximately equal, the mean birth weight of twins is highest in DZ twins whose placental mass is dichorionic, and lowest in monochorionic twins (Table 24.5). Note that birth-weight differences are much more influenced by placentation than by zygosity.

Aside from the slightly slower intrauterine growth that characterizes monochorionic twinning, one member of the pair may develop intrauterine growth restriction. Tables 24.6 and 24.7 compare the weight deficits of MZ pairs according to gender and type of placentation. A large deficit, i.e. one of the twins weighs less than 20% of its co-twin, is much more frequent in monochorionic pairs, and more common in females than in males.

**Table 24.4** Number of twin pairs according to sex, zygosity and chorionicity (1964–97). East Flanders Prospective Twin Survey. From reference 10

| | *DZ* | | *MZ–DC* | | *MZ–MC* | | *MZ total* | | *Unknown* | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % |
| Male pairs | 779 | 26 | 238 | 48 | 591 | 48 | 829 | 48 | 145 | 52 |
| Female pairs | 708 | 23 | 256 | 52 | 635 | 52 | 891 | 52 | 132 | 48 |
| Unlike-sexed pairs | 1560 | 51 | — | | — | | — | | — | |
| Total | 3047 | 100 | 494 | 100 | 1226 | 100 | 1720 | 100 | 277 | 100 |
| | | 64 | | 10 | | 26 | | | | |

*n*, number of pairs; DZ, dizygotic; MZ, monozygotic; DC, dichorionic; MC, monochorionic

**Table 24.5** Age of the parents, gestational age, mean birth weight and placental weight. East Flanders Prospective Twin Survey. From reference 10

| | *DZ* | | *MZ–DC* | | *MZ–MC* | | | |
|---|---|---|---|---|---|---|---|---|
| | *Mean* | *SD* | *Mean* | *SD* | *Mean* | *SD* | *Significance (p)* | |
| Age of the mother (years) | 28.4 | 4.6 | 26.6 | 4.6 | 27.1 | 4.7 | < 0.001 | DZ > MZ–DC, MZ–MC |
| *n* | 2998 | | 482 | | 1201 | | | |
| Age of the father (years) | 30.8 | 5.4 | 29.2 | 5.3 | 29.4 | 5.3 | < 0.001 | DZ > MZ–DC, MZ–MC |
| *n* | 2418 | | 408 | | 940 | | | |
| Gestational age (weeks) | 36.5 | 2.8 | 36.2 | 3.0 | 36.1 | 3.4 | < 0.01 | DZ > MZ–MC |
| *n* | 2685 | | 429 | | 1080 | | | |
| Mean birth weight (g) | 2476 | 512 | 2401 | 562 | 2314 | 559 | < 0.001 | DZ > MZ–DC > MZ–MC |
| *n* | 3030 | | 494 | | 1211 | | | |
| Placental weight (g) | 741 | 161 | 720 | 167 | 708 | 164 | < 0.001 | DZ > MZ–DC, MZ–MC |
| *n* | 2639 | | 479 | | 1196 | | | |

*n*, number of pairs; DZ, dizygotic; MZ, monozygotic; DC, dichorionic; MC, monochorionic

**Table 24.6** Asymmetric growth retardation in male monozygotic twin pairs, 1964–91 (percentage weight deficit of smaller twin). East Flanders Prospective Twin Survey

| *Weight deficit (%)* | *Dichorionic (n = 180)* | *Monochorionic (n = 479)* |
|---|---|---|
| 0–10 | 0.64 | 0.51 |
| 11–20 | 0.24 | 0.30 |
| > 20 | 0.12 | 0.19 |
| | $p = 0.02$ | |

**Table 24.7** Asymmetric growth retardation in female monozygotic twin pairs, 1964–91 (percentage weight deficit of smaller twin). East Flanders Prospective Twin Survey

| *Weight deficit (%)* | *Dichorionic (n = 193)* | *Monochorionic (n = 508)* |
|---|---|---|
| 0–10 | 0.61 | 0.46 |
| 11–20 | 0.33 | 0.32 |
| > 20 | 0.06 | 0.22 |
| | $p < 0.001$ | |

**Table 24.8** Percentage of congenital heart disease according to zygosity and type of placentation, 1963–67. East Flanders Prospective Twin Survey. Data from reference 24

| *Zygosity* | *Placental structure* | *No. of infants* | *No. of cases* | *Percentage of malformation* |
|---|---|---|---|---|
| DZ | dichorionic | 1958 | 8 | 0.4 |
| MZ | dichorionic | 264 | 2 | 0.8 |
| MZ | monochorionic | 626 | 8 | 1.2 |

DZ, dizygotic; MZ, monozygotic

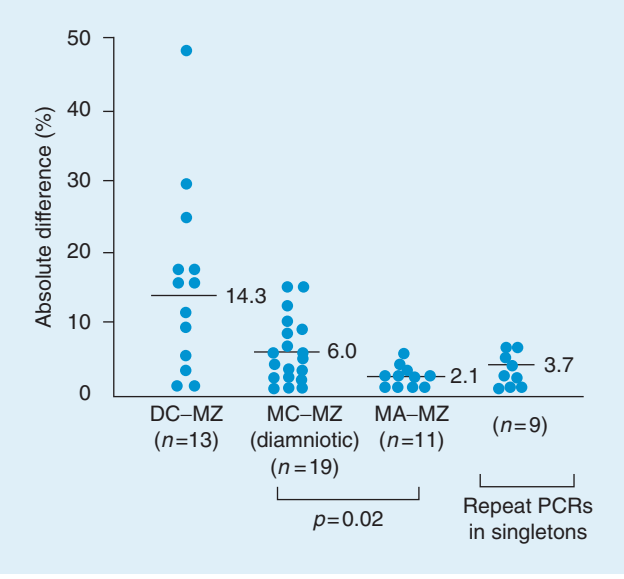


**Figure 24.5** Summary of differences in X-inactivation patterns among various subgroups of monozygotic (MZ) twin pairs and among repeat assays of singletons. DC, dichorionic; MC, monochorionic; MA, monoamniotic; PCR, polymerase chain reaction. From reference 23

The relationship between structure of the fetal membranes and timing of splitting has been confirmed through the study of X chromosome-inactivation patterns of the three subtypes of MZ twinning (Figure 24.5). Clearly, early splitting corresponding to dichorionicity occurs before X-inactivation, allowing each member of the pair to develop its own inactivation pattern. In contrast, when twinning occurs late, leading to monoamniotic anatomy, members of the twin pair have virtually identical patterns of X-inactivation[23].

Preliminary results relating to the prevalence of congenital heart disease in MZ twins point to a possible association with chorion type[24] (Table 24.8). Acardia is not included in this series, because this malformation does not occur in dichorionic twins. We acknowledge that the number of cases is small and the difference in rates is not statistically significant. However, we are of the opinion that additional longitudinal investigations may confirm this trend. The single chorionic membrane with its associated twin-to-twin vascular communications represents the major, if not the only, reason why the perinatal mortality rate is so much higher in MZ twins. Table 24.9 presents mortality rates of MZ twins as related to chorion type. The figures for dichorionic–MZ twins are comparable to those of their DZ counterparts.

Monochorionic–diamniotic twins, on the other hand, and especially monochorionic–monoamniotic twins, show markedly elevated mortality rates. Several aspects of the monochorionic placenta account for its deleterious influence on the viability of fetuses and newborns. Most obvious are the

**Table 24.9** East Flanders Prospective Twin Survey (1964–89). Monozygotic twins. Perinatal mortality according to placentation

| Placentation | Number of pairs | Perinatal mortality (*n* (%)) | |
|---|---|---|---|
| | | Twin 1 | Twin 2 |
| Dichorionic (PMZ ≥ 95%) | 438 | 14 (3.2%) | 26 (5.9%) |
| Monochorionic–diamniotic | 871 | 65 (7.5%) | 84 (9.6%) |
| Monochorionic–monoamniotic | 30 | 9 (30%) | 7 (23%) |

PMZ, probability of monozygosity

**Table 24.10** Sex proportion in monochorionic twin pairs. Data from reference 25

| Placentation | Male pairs | Female pairs | Sex proportion |
|---|---|---|---|
| Diamniotic | 378 | 389 | 0.493 |
| Monoamniotic | 6 | 20 | 0.231 |
| Total | 384 | 409 | 0.484 |

**Table 24.11** Monozygotic–dichorionic twins. Birth weight (g) according to fetal sex in fused and separate placentas. East Flanders Prospective Twin Survey

| | Female pairs | | | Male pairs | | |
|---|---|---|---|---|---|---|
| | Mean | SD | n | Mean | SD | n |
| Fused | 4514 | 1032 | 103 | 4820 | 1135 | 91 |
| Separate | 5009 | 1136 | 91 | 5090 | 1119 | 89 |

**Table 24.12** Frequencies (%) of marginal and velamentous insertion of the cords according to chorion type (*n* = 6935*). East Flanders Prospective Twin Survey

| Cord insertion | Monochorionic placenta | Dichorionic placenta |
|---|---|---|
| Central, paracentral, paramarginal | 69 | 87 |
| Marginal | 22 | 8 |
| Velamentous | 9 | 5 |

*Total number of cases in the study = 7134

hemodynamic imbalances and the growth restriction described previously. Another factor is the excess of marginal and velamentous cord insertions. Besides these three characteristics of the monochorionic placenta, the monoamniotic variety is associated with two additional hazards: intertwining of the umbilical cords and conjoined twinning.

The sex proportion, i.e. the proportion of male/female twins, is lower in MZ than in DZ twins. The figures in the EFPTS are 0.51/0.49, respectively. Within the MZ group, remarkable changes in this proportion are found with respect to the number of amniotic sacs (Table 24.10). Whereas the sex proportion in monochorionic–diamniotic twins does not differ from the dichorionic group, it is lowered to 0.23 in monochorionic–monoamniotic twins.

### *Fusion of the placentas*

As might be expected from the writings of Corey[14], separate placentas should theoretically be more favorable to fetal growth than fused placentas. This was found to be the case in the EFPTS study for MZ pairs (Table 24.11). Here, one witnesses an almost ideal natural experiment in which the location of the placenta is probably the only major variable. The mean weight difference is substantial, and amounts to 239 g in male and 524 g in female pairs. Again, as in intrapair differences in birth weight, the female fetus is more sensitive to changes in intrauterine environment. Changes in the same direction are found in DZ pairs but they are not statistically significant.

### *Cord insertions*

Table 24.12 presents the prevalence rates of marginal and velamentous insertion of the cords according to the structure of the fetal membranes. Marginal insertion is three times and velamentous insertion somewhat less than two times more frequent in monochorionic placentas. These differences are the same for the first- and the second-born twin.

**Table 24.13** Distribution of frequency (%) of type of cord insertion according to perinatal outcome ($n$ = 6949*). East Flanders Prospective Twin Survey

| *Cord insertion* | *Living and well* | *Early neonatal death* | *Stillbirth* |
|---|---|---|---|
| Central, paracentral, paramarginal | 82.7 | 81.0 | 63.1 |
| Marginal and velamentous | 17.3 | 19.0 | 36.9 |

*Total number of cases in the study = 7134

**Table 24.14** Cord insertion and birth weight. Central (c), paracentral (pc) and paramarginal (pm) vs. marginal (m) and velamentous (v). East Flanders Prospective Twin Survey

| | *Twin no.* | *Cord insertion* | *Birth weight (g)* |
|---|---|---|---|
| Monochorionic placenta | 1 | c + pc + pm ($n$ = 645) | 2395 |
| | | m + v ($n$ = 294) | 2227 |
| | 2 | c + pc + pm ($n$ = 649) | 2336 |
| | | m + v ($n$ = 291) | 2154 |
| Dichorionic placenta | 1 | c + pc + pm ($n$ = 2198) | 2522 |
| | | m + v ($n$ = 322) | 2364 |
| | 2 | c + pc + pm ($n$ = 2181) | 2477 |
| | | m + v ($n$ = 314) | 2294 |

Insertion of the cord on the periphery of the placenta is deleterious to fetal well-being. Velamentous insertion is two times more frequent in stillbirths and early neonatal deaths than in live-born twins surviving the early neonatal period (Table 24.13). The higher prevalence rate of marginal insertion in stillbirths is of borderline significance.

The mean birth weight of twins with marginal or velamentous insertion is 160–180 g less than with insertion on the central placental surface, regardless of whether the fetal membranes are mono- or dichorionic (Table 24.14).

## Triplets

Table 24.15 gives the distribution of the placental structure in a series of 165 triplets registered in the EFPTS (Derom and colleagues, unpublished data). The majority of the spontaneous triplets were dichorionic, whereas all but nine induced triplets were trichorionic. The nine induced triplets with dichorionic membranes are proof that not all multiple births originating after ovulation induction are polyzygotic[21].

**Table 24.15** Distribution of chorion type in 165* triplets, from East Flanders Prospective Twin Survey (Derom *et al.*, unpublished data)

| | *Spontaneous* ($n$ = 37) | *Induced* ($n$ = 126) |
|---|---|---|
| Monochorionic | 5 | 0 |
| Dichorionic | 18 | 9 |
| Trichorionic | 14 | 117 |

*One case of unknown chorionicity and one case of unknown origin of pregnancy excluded

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# Placental Examination in the Delivery Room

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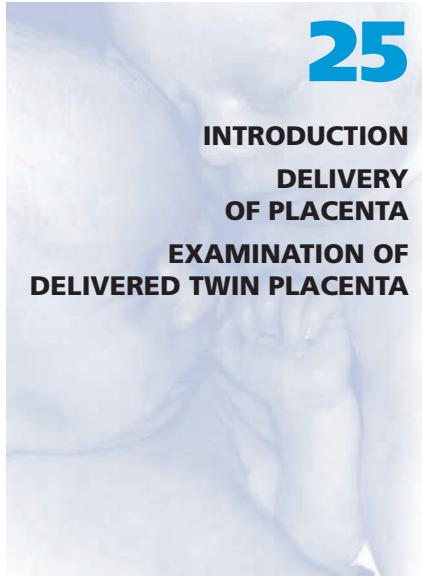


## INTRODUCTION

The importance of the pre- and postnatal determination of chorionicity, amnionicity and zygosity is outlined in numerous studies in the literature and described in detail in Chapter 24 of this book. According to the 'Declaration of rights and statement of needs of twins and higher order multiples', 'every twin and their parents have the right to expect accurate recording of placentation and the diagnosis of zygosity of the same-sex multiple at birth'[1]. In the past, before the advent of ultrasound and DNA-based zygosity studies, the classification of so-called 'fraternal' or 'identical' twins was mainly a postpartum event.

For some decades prior to the 1970s, macro- and microscopic postpartum placental examination and study of phenotypic characteristics remained the primary methods of determining zygosity. More recently, however, widespread use of modern ultrasonographic technology, mainly with high-resolution transvaginal probes in the first trimester, has improved the antepartum prediction of chorionicity and amnionicity to such an extent that this diagnosis is not only possible but of crucial importance for the management of multiple gestations[2]. Ultrasound is currently the best diagnostic technique for antenatal identification of placentation type, with almost 100% accuracy[3,4]. However, when performed in the second and third trimesters, suboptimal sensitivity and specificity are reported[5,6]. This circumstance reflects that ultrasound is not a 100% perfect tool with unlimited capacity for all kinds of prenatal diagnosis. A number of problems hinder it, including advanced gestational age, poor resolution capacity, overlying fetuses, a single placental site, rupture of the dividing membrane by fetal or iatrogenic trauma and the sonographer's experience or lack thereof[7–9].

Ultrasound scanning has become an integral part of prenatal care in industrialized countries, whereas this is not the case in parts of the world where only few women have access to antenatal care. In these instances, histologic examination of the placentas and fetal membranes is also not practical.

The determination of zygosity is important for medical reasons, for scientific research and because parents and their children want to satisfy their curiosity or remove any doubts. As the determination of zygosity in later life is time-consuming and expensive, it is particularly important to point out that the most favorable conditions for determining zygosity are present at birth[10].

Adequate and methodic examination of the placenta at birth by the delivery-room physician can provide the necessary information for zygosity diagnosis and reduce the numbers of sets of twins that require additional research for zygosity determination. Over recent decades, there has been a sharp increase in the incidence of multiple gestations in association with older maternal age of child-bearing and access to modern reproductive technologies. Monochorionic placentation is more common after infertility treatment using assisted reproductive medicine than in naturally conceived twins and higher-order multiple gestations[11]. In this context it is especially important that contemporary obstetricians are aware of the potential advantages of using the placenta for the clinical recognition of zygosity, as it is now clear that monozygous twins are neither phenotypically nor genotypically perfectly identical[12–14].

The remarkable success of using placentation is that it is a paradigm in which, for all practical purposes, monochorionic placentation is equivalent to a monozygotic multiple gestation. Although descriptions of dizygotic–monochorionic twins have been reported recently[15,16], they must be exceptional, and monochorionic placentation remains an excellent predictor of monozygosity. The placenta should be carefully observed by the obstetrician or the midwife immediately after its delivery in all cases of twins and higher-order multiple pregnancies. When needed, pathologic confirmation of the chorion state can be requested, using histologic observation of the interamniotic membrane[17–19] (see Chapter 26). In most instances, placental/membranous examination, along with knowledge of the fetal gender, allows the accurate establishment of zygosity in a sizeable number of cases[20]. Confusion arises only in a small proportion of situations, when concordant-sex pairs have dichorionic placentation, or in those rare instances when chorionicity cannot be accurately determined through examination of the membranes. In such circumstances, the most accurate method for determining zygosity is through DNA analysis using a skin biopsy specimen, umbilical cord tissue or buccal smear[21].

This chapter provides a framework for healthcare providers to examine placentas from multiple gestations. Those who deliver multiple pregnancies will find guidelines for handling the placenta in the delivery room, so that they can gather as much information as possible regarding the diagnosis of chorionicity and zygosity assessment. A number of distinct steps must be clearly and sequentially followed for the best possible results.

## DELIVERY OF THE PLACENTA

### General

In order to obtain the best specimens, delivery of the placenta must be performed carefully, to preserve the anatomic connections between amnions and chorions and the placental masses. To do this, the physiology and clinical management of the third stage of labor must be rigorously respected. The goal is spontaneous delivery of the placenta, that is, one in which little or no external help is necessary.

To begin with, accurate identification of the umbilical cords is important, to ensure that each is properly assigned to the appropriate twin or multiple. The best way to do this is by placing one or more clamps on the terminal part of the umbilical cord of each newborn during delivery. Two clamps are used to label the umbilical cord of the second baby, three clamps for the third and so on.

### Vaginal delivery

In vaginal delivery, the third stage of labor begins as the baby is born, and ends with extrusion of the placenta and fetal membranes. It involves separation of the placenta, its vaginal descent and extrusion. After the birth of each fetus there is a time lag during which the uterine contractions slow down or even disappear. When there is more than one placental disk, premature separation of one of them may take place after delivery of the corresponding fetus and before delivery of the other fetuses. As a rule, the placentas remain inside the uterine cavity, and it is only after the birth of the last child that delivery of the placenta begins to follow the same mechanisms as those of a placenta from a singleton pregnancy. Separation of the placentas begins normally within a few minutes post-delivery, but may take as long as an hour.

*Do not try to remove the placentas manually*. Because of the lesser contractile force of the myometrium, the overdistended uterus and the larger volume of the placental mass, complications are more frequent. When these require some sort of intervention, such as manual placental extraction, manipulations change the anatomy of the organ, making it more difficult afterwards to identify placentation type adequately.

Immediately after the birth of the babies, the consistency and height of the uterine fundus must be assessed. Attempts to accelerate placental expulsion through expression and vigorous massaging may turn out to be dangerous, and are frequently useless. A hand is often placed upon the abdominal wall at the level of the uterine fundus to check whether the uterus is well contracted rather than atonic and filled with blood behind a separated placenta. If the uterus remains well contracted and the amount of vaginal bleeding is normal, placental separation should be allowed to evolve spontaneously.

The initial signs and symptoms of placental separation are clear: the uterus contracts and the fundus becomes hard and globular. This is followed by a gush of blood from the vagina and lengthening of the umbilical cords. Clamps placed on the umbilical cords fall away indicating that the placenta has started to descend. The safest way of knowing that the placenta is in the vagina is by touching it in its inferior portion with a finger introduced into the introitus. Once the placenta is in the vagina, spontaneous delivery is anticipated. At this point the woman usually feels the urge to bear down once again and expels the placenta in the process. Should this not take place, however, the mother should be encouraged to push to increase her intra-abdominal pressure, which might be sufficient to ensure expulsion. If these efforts should fail or spontaneous expulsion is impossible because of epidural anesthesia, after

ensuring the uterus is well-contracted and the placenta is in the vagina, it is then safe to place a hand on the abdomen, pushing and lifting the uterine body in the cephalad direction to propel the separated placenta from the vagina.

When the placenta reaches the introitus, the umbilical cords can be grasped with one hand and elevated under gentle tension, which, in turn, lifts the placenta out of the vagina. However, this maneuver may at times cause rupture of blood vessels near the insertion site of the umbilical cords on the chorionic plate. Moreover, if there are insertional abnormalities, these may tear, causing disruption and damage of the pathologic architecture.

The umbilical cord should never be pulled to draw the placenta out of the uterus. Instead, when the placentas reach the introitus, it is preferable to put an instrument tray near the perineum underneath the placental masses to support them. The woman is then advised to push, and the placenta easily bulges through the vulva and leaves the perineum, sliding towards the instrument tray or the palms of your hands. Next, in a slow and gentle downward movement as the hands move down, the traction exerted by the intrinsic weight of the placentas as the movement is being carried out helps to complete expulsion of the placenta, as well as of the membranes. If the membranes have not loosened completely or are too long, an assistant with a hand placed upon the woman's abdomen should lift the uterine body in the cephalad direction simultaneously with the downward movement of the operator's hands. This maneuver frees the adherent membranes from any thin attachments. When the membranes begin to tear, they must be grasped with a clamp and peeled off with soft traction movements.

### Cesarean delivery

In cesarean sections, the placenta may be removed manually immediately after delivery of the babies by placing a whole hand inside the uterus and gently freeing the placentas from their beds[22]. This may cause hemorrhage, however, if the uterus is not well contracted. Because of this, to preserve the placenta's anatomy and hasten its delivery, I prefer to place my hand inside the abdomen behind the uterine fundus and, with gentle massage, stimulate contraction as soon as the fetuses have been delivered, thus promoting a spontaneous non-traumatic separation of the placenta, which bulges through the uterine incision as the uterus contracts. After placental expulsion, by carrying on massaging the uterus, one also reduces bleeding and the risk of postpartum hemorrhage.

## EXAMINATION OF THE DELIVERED TWIN PLACENTA

The specific techniques and value of placental membrane examination for the determination of zygosity are described by several authors[23,24]. Twins are currently classified according to the structure of their membranes as dichorionic or monochorionic[25]. Ideally, delivery-room examination of the placenta should include identification of the number of placental masses and amniotic cavities, inspection of the membranes, umbilical cords, fetal and maternal surfaces of each placental disk, and cord length measurements, as well as palpation of the villous tissues. This examination also aims at observing the presence and components of each intertwin septum. These procedures enable immediate identification of placental abnormalities, such as discordant variations in the pattern of placentation for each twin, and the presence of vascular anastomoses that may explain clinical features such as discordant twin development or growth. However, the main goal of delivery-room placental examination in a multiple pregnancy is to check whether the placenta is monochorionic or dichorionic, which, along with the gender of the newborns, makes it possible to determine zygosity in more than half of twins.

The best way to proceed is to place the placenta on a table and take a few moments to manipulate it gently under proper illumination, so that the disks, membranes and cords are oriented and the separate amniotic cavities reconstructed as closely as possible to their intrauterine positions in order to define the overall arrangement of the specimen and make the examination easier. Afterwards, it is necessary to separate and dissect the dividing membranes. Anatomically speaking, placentas from twin gestations may consist of two well-separated disks or one disk with several membrane patterns.

In the first instance, there are either twowell-separated disks with one amniotic sac for each, or two distinct disks with sac membranes creating a distinct shared septum, sometimes with overlapping or shared amniochorionic membranes, so-called 'irregular chorionic fusion'. All of these are dichorionic–diamniotic placentations.

In the second instance, the placenta may consist of two fused placental disks with two distinct amniotic sacs (dichorionic–diamniotic fused placenta) or a true single disk with either one (monochorionic–monoamniotic placentation) or two distinct amniotic sacs (monochorionic–diamniotic placentation). Although placentation types are limited to three in twin gestations, in higher-order multifetal pregnancies a combination of monozygotic and dizygotic fetuses is expected, and placentation may be of one

or several varieties. In the examination of twin placentas and, most of all, those from higher-order multifetal pregnancies, numerous membranes need to be identified, oriented, elevated and held. You may choose to do this by yourself, or ask for help from an assistant.

## The dichorionic placenta

The dichorionic–diamniotic twin placenta may consist of two entirely separate disks, each with its own cord and chorioamnionic sac (Figure 25.1). In such cases, the fertilized ova were implanted in very distinct zones of the uterine mucosa, each with its decidua capsularis, which in turn made contact with each other, but are now readily separated. Each placental disk may be examined as if the placenta in question were one of a singleton pregnancy. The fetal surface of the placenta and the free membranes form a continuous layer covered by amnion, with the underlying chorion which had enclosed the umbilical cord and the fetus. With the fetal surface lying up, first identify the opening of the membranes for the exit of the fetus. By grasping them at the border and lifting, the amniotic cavity may be reconstructed (Figure 25.2). Using one's fingers or atraumatic forceps, it is possible to dissect the membranes from the top to the bottom of the amniotic sac and identify the amnion and the chorion of each placenta (Figure 25.3). Normally, the free membranes meet the placental surface at the margin of the vascular or chorionic plate, as in any normal singleton placenta.

When the placental masses are separated but have partially fused or overlapping membranes, the membrane borders can be grasped and elevated to rebuild the amniotic sacs and identify a shared septum, forming the dividing membrane between two amniotic cavities (Figure 25.4). The septum may be attached to the chorionic surfaces across a greater or lesser extension of one or the two placental masses. On overall examination, the meeting plane of the membranous sacs is seen as irregularly positioned, the membranes of one twin overlapping the placental disk of the other, at times significantly. This is not abnormal. Rather, what happened was that during the process of development the chorion of the surface of one or more placentas was stripped off, and the surface was then covered by the membranes of another fetus[26].

Grasp the edges of the dividing membrane with fingers or hemostatic forceps and gently lift it and stretch it. On inspection, this septum is thick and opaque, and four layers are identified by dissection: the amnion and chorion from each twin. Using an atraumatic forceps or other suitable device, carefully identify at the edge of the dividing membrane the amniotic membranes on both sides of the septum and a layer of chorionic tissue that remains in the middle. One of the thin, avascular amnions of one placental side is easily peeled off, followed by

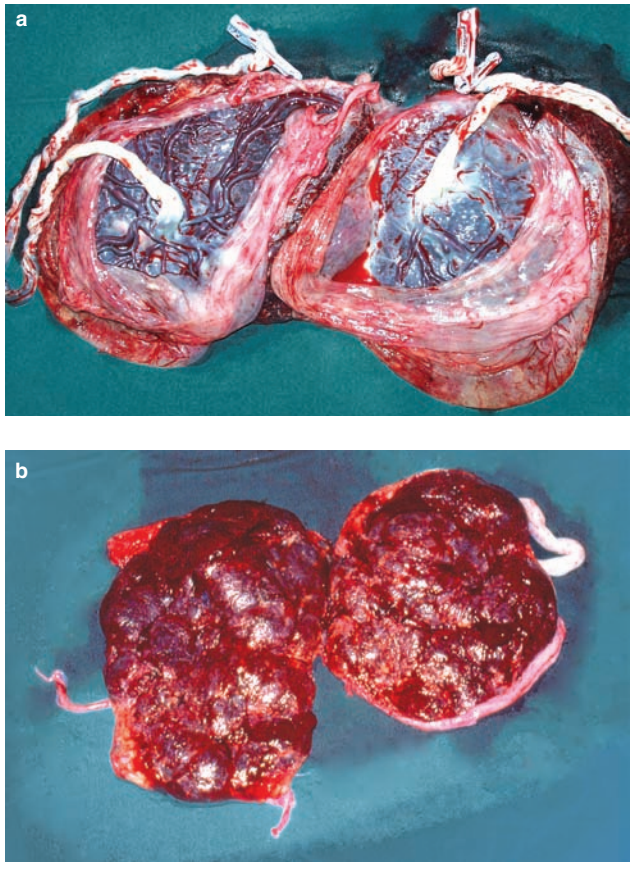


**Figure 25.1** Dichorionic–diamniotic twin placenta. (a) Fetal surfaces of two well-separated placental masses each with its umbilical cord and amniotic cavity. (b) Maternal surfaces. When two distinctly separated placental disks are found, the diagnosis is evident: we are dealing with a dichorionic twin placenta

**Figure 25.2** Reconstruction of the chorioamniotic cavity. Note the opening for the exit of the fetus

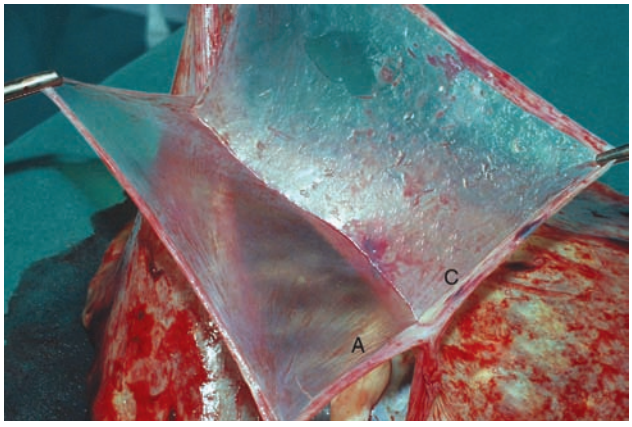


**Figure 25.3** General appearance of the fetal membranes. From the border of the opening of the sac it is easy to strip the amniotic layer from the chorion. The amnion (A) is a thin translucent layer of tissue loosely attached to the chorion (C)

the other. Directly in the middle is the chorionic membrane, composed mainly of two chorions, one from each twin (Figure 25.4). The two chorions that are an extension of the underlying placentas' chorionic tissue may separate to allow the four membranes to be completely isolated. By proceeding with separation of the two layers of chorion one reaches the chorionic plate. Further dissection, however, would disrupt the fetal surface of the placenta, as the villous tissue frees itself from the underside of the chorionic membrane.

When two distinct and separated placental disks are found, the diagnosis is obvious: dichorionic twin placentation. However, in a dichorionic–diamniotic twin placenta the two placental portions (chorion frondosum) may be intimately fused (dichorionic–diamniotic fused). This presents as a single-disk twin placenta with an identifiable thick and opaque septum attached across the chorionic surface, clearly demarcating the two sides of the placental disk and the circulatory areas of each twin (Figure 25.5). It represents two distinct ova implanted side by side, which, because of their great proximity, collided physically during embryonic growth. Accordingly, the insertion line of the dividing membrane also coincides with the border of the fetal surfaces of the two placental masses (Figure 25.5a, b and c). When carefully dissected, three distinct layers of the dividing membrane are clearly observable, corresponding to the two amnions, between which is a third layer corresponding to the two fused chorions. Often these can also be separated with careful dissection, although this may prove difficult if the chorionic layers are thin or fused (Figure 25.5d, e and f).

The chorionic layer of the dividing membrane is an extension of the chorionic tissue of the underlying

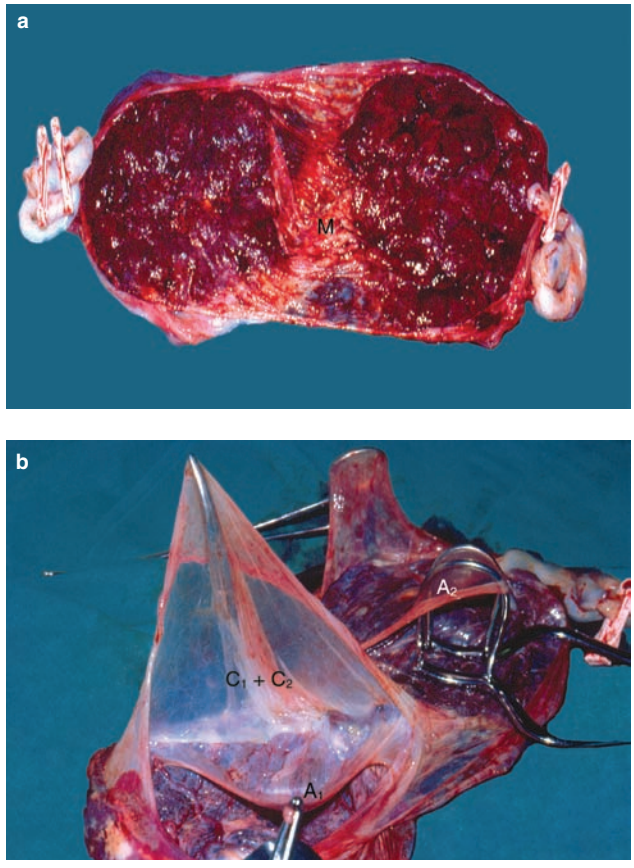


**Figure 25.4** Dichorionic–diamniotic twin placenta. (a) Maternal surfaces of two distinct placental portions with partially overlapped membranes (M). (b) The dividing membrane has four layers (amnion–chorion–chorion–amnion). Notice that the two chorionic layers ($C_1 + C_2$) are adherent and the two amnions ($A_1$ and $A_2$) have been dissected from the chorionic layer

placental components. When one arrives at the chorionic plate by separating the two leaves of the chorionic layer, further dissection is impossible because the septum is firmly anchored to the fetal surface of the placental disk. Indeed, the chorionic membranes cannot be completely stripped off the placental mass without disrupting it because of the extensive ramifications of the chorionic villi from their undersurfaces. If one attempts to cleave them further, the surface of the placenta is disrupted, ultimately proving the existence of the two chorionic membranes (Figure 25.5g and h). In conclusion, same-sex twins with a separate or fused dichorionic placenta may be monozygotic or dizygotic, but opposite-sex twins are dizygotic.

## The monochorionic placenta

In practical terms, the examination of monochorionic–diamniotic placentation is similar to that of a

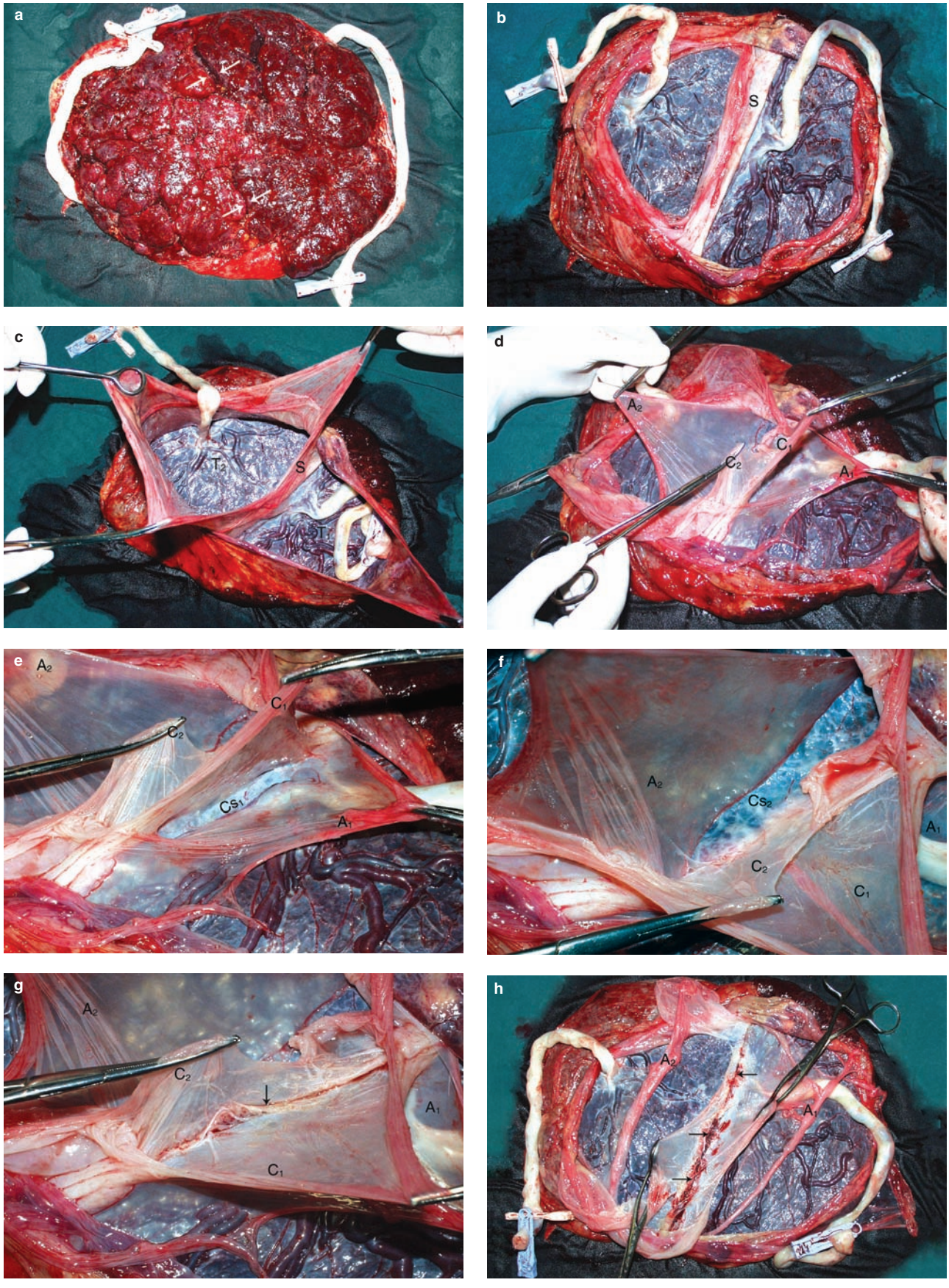


**Figure 25.5** Dichorionic–diamniotic fused single-disk placenta. (a) Maternal surface. Notice the collision zone of the villous tissue (arrows). There are two more or less symmetric placental portions as can be seen from the differential appearances of

dichorionic fused placenta, as a monochorionic placenta presents as a single disk, and must be examined for the presence or absence of a dividing membrane. The nature of the dividing membrane located between twins is an important piece of information based upon the thickness and the insertion place of the membrane. With the fetal surface of the placental disk lying up, lifting the chorioamniotic membrane by its borders restores the two amniotic sacs and identifies the dividing membrane. In such circumstances, a single chorionic sac encloses two juxtaposed amniotic cavities (Figure 25.6a and b). The septum may be whole, contain a gap that allowed for the exit of the second fetus or exist in a completely torn state. It is simple and easy to check in the most general way whether the membrane represents a fused dichorionic single disk or a true monochorionic placentation. In the latter, no interposed chorionic tissue lies between the two amnions, whereby the diamniotic septum is seen to be much more delicate, translucent and thinner than the septum of a dichorionic– diamniotic placenta. Moreover, the septum can easily be elevated from the fetal surface of the placenta because two amnions are not anchored to the chorionic plate, and their attachment point is extremely variable and independent of the vascular pattern of the chorionic plate (Figure 25.6c). It is easy to peel apart the two leaves of amnion from each other (Figure 25.6d and e). When the amniotic membranes arrive at their insertion area on the placental surface, continuing to strip the amnions away clearly leaves a single continuous chorionic plate underneath (Figure 25.6f), demonstrating that the dividing membrane includes only the amniotic layers reflected from the fetal surface of the placenta. Such a maneuver would not be possible unless the placenta was monochorionic and the twins monozygotic.

Monochorionic placentation is linked to the majority of complications in twin pregnancies. Abnormal cord insertions are significantly more common in twin pregnancies, mainly in monochorionic placentations, being almost invariably present among higher-order multiple gestations. Abnormal insertions may take a velamentous form in which the umbilical cord inserts into the fetal membranes. The insertion may be into the intertwin membrane, as is visible in Figure 25.6g, in which the umbilical cord of an acardiac twin is attached to the septum, with vessels passing through the septum to the chorionic plate. In acardiacs the placentas are always monochorionic and may be diamniotic (Figure 25.6g) or monoamniotic.

The examination of a monochorionic–monoamniotic placenta is similar to that of a placenta from a singleton pregnancy, in that, after proper orientation of the placental disk, a single-disk placenta is identified with no dividing membrane and both umbilical cords inside the same cavity. The outer free reflected membranes form a sac, with the wall composed of the amnion juxtaposed with the chorion, that may be examined in the usual fashion (Figure 25.7). The chorioamniotic membrane can be lifted to rebuild the amniotic cavity. Particular attention should be paid to looking for a rupture site, in case a dividing membrane has been torn earlier in the gestation or by an iatrogenic traumatic disturbance, even though this is extremely rare. The umbilical cords may be inserted within a few centimeters of each other or widely separated, and occasionally a single, branched umbilical cord can be observed. If no septal tissue is found along the fetal surface of the placenta and between the umbilical cord insertion sites, and if it is certain that the amnion layer is complete and intact with no signs of a membrane fold, the pattern of placentation is monochorionic–monoamniotic, with both fetuses in the same chorioamniotic cavity, and monozygotic.

### Higher-order multifetal placentas

Placentas of higher-order multifetal pregnancies may be multichorionic and multiamniotic, and are often a mixture of different chorionic types[17].

Figure 25.5 Continued

the maternal surface of the placenta. (b) The septum (S) attached across the chorionic plate between the two umbilical cords and the circulation territories of each fetus. (c) Identification of the fetal membranes. They were stretched slightly to reconstruct the amniotic cavities ($T_1$ and $T_2$). There is a thick and opaque dividing membrane (S) characteristic of the dichorionic variety. (d) Dissection of the dividing membrane. Identify the layers at the top of the septum and grasp them with artery forceps or with your fingers. There are two layers of amnion on either side ($A_1$ and $A_2$), beneath which there are two layers of chorion ($C_1$ and $C_2$). (e) General appearance of the intertwin septal membranes. The amnion ($A_1$) of the first twin is being peeled off the chorion layer ($C_1$) and the chorionic surface ($Cs_1$). Notice the transparency characteristic of the amniotic layer. (f) General appearance of the intertwin septal membranes. Note the amnion layer ($A_2$), chorion layer ($C_2$) and the chorionic surface ($Cs_2$) of the second twin. (g) The two central chorions are being separated; this attempt will be met with success only up to the point of attachment of the membranes on the surface of the placental disk (arrow). (h) Notice the disruption of the placental surface across the line of attachment (arrows) by the attempt to strip further the chorionic membranes from the surface of the placenta. The amniotic membranes ($A_1$ and $A_2$) are rolled to make their location more visible

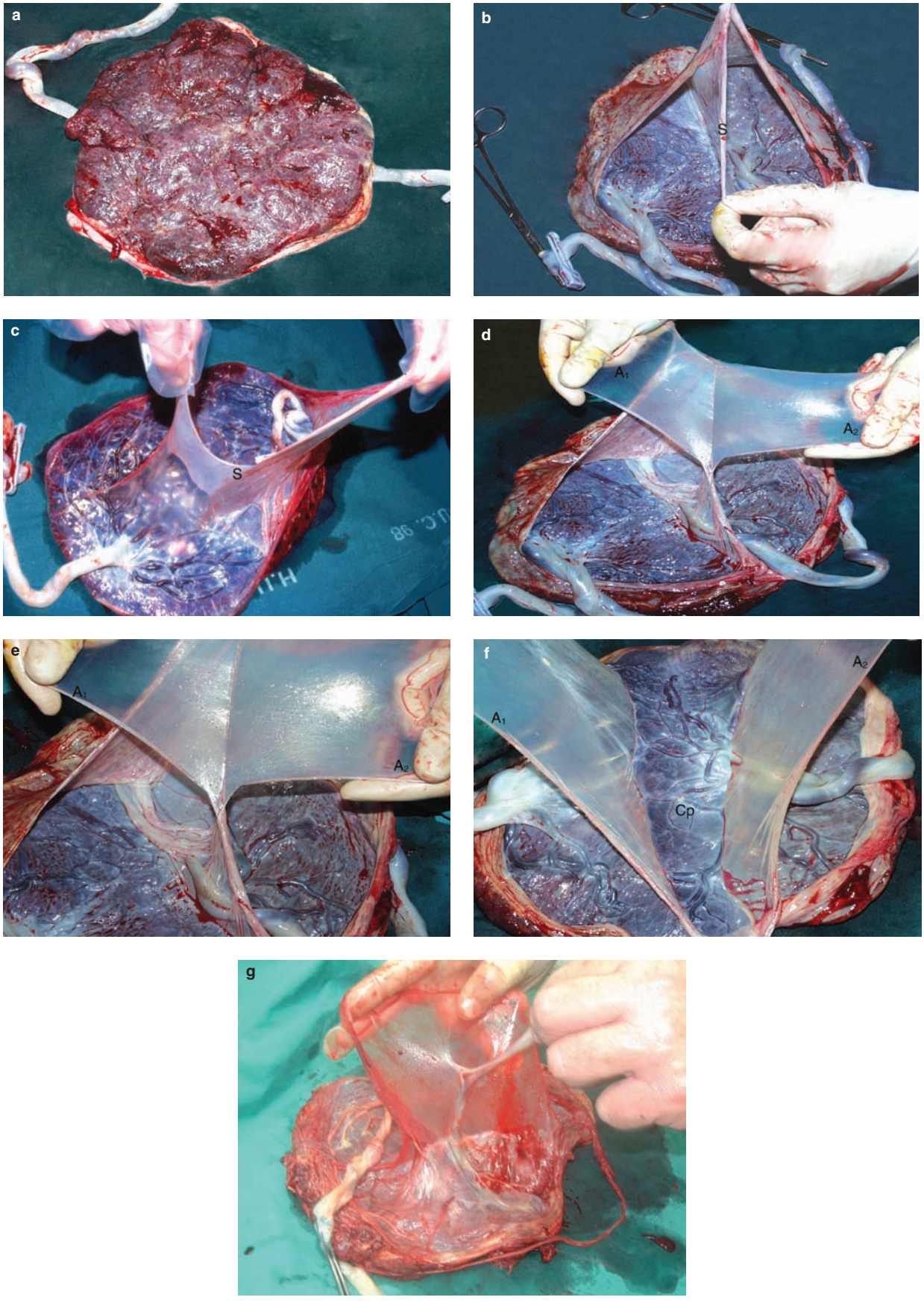


**Figure 25.6** Monochorionic–diamniotic twin placenta. (a) Maternal surface of a true single-disk twin placenta. As can be seen, there is no differential appearance through the maternal surface, and it is not possible to identify a distinct junctional zone.

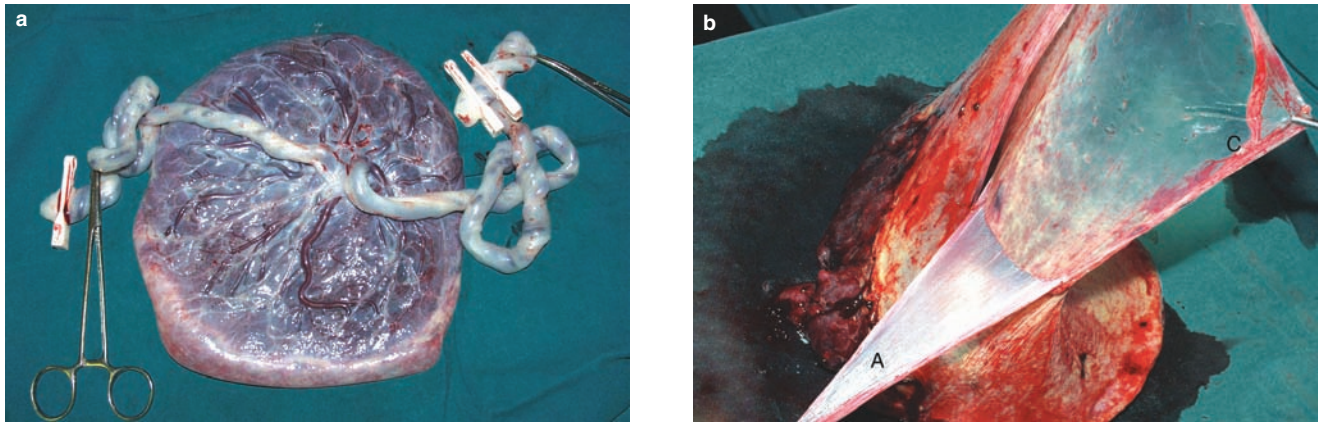


**Figure 25.7** Monochorionic–monoamniotic twin placenta. (a) No septum or any amniotic folds between the umbilical cords inserted closely next to each other. (b) Examination of this pattern of placentation is similar to that of a singleton placenta. A, amnion; C, chorion

Placentas from higher-order multiple gestations are potentially more complex, but here also a number of simple steps can help to identify their particularities. The easiest way is to identify the number of placental disks and sacs for each disk by reconstructing them in a manner that approximates the interior of the uterine cavity, using the hands of an assistant (Figure 25.8a and b). It is easier to handle each separate disk as a singleton placenta and examine the components of each dividing membrane separately, as summarized in the general description of a twin placenta. It may be possible to identify placental portions from the differential appearances of the placental maternal surfaces and the junctional zone of the placental parenchymas (Figure 25.8c and d). As is the case with twins, the nature of the membrane wall separating two cavities that belong to the same placental portion is an essential diagnostic finding for zygosity determination. A thick and opaque dividing membrane that cannot be easily torn apart represents dichorionic placentation, whereas a monochorionic–diamniotic membrane appears more translucent, and its two amnions are juxtaposed with only a sparsely cellular matrix separating them, without the additional presence of chorion. Dissect the first dividing membrane and, if after the removal of the amniotic membrane of each side a layer of tissue remains in the middle, the sac is then separated by a chorion, and placentation is dichorionic. Repeat the same procedure for each of the remaining dividing membranes until all the sacs have been stripped of amnion. When a membrane that separates two cavities is composed solely of amnions, the two cavities will have been transformed into a single one after dissection of the membrane. If at the end, after all the dividing membranes have been stripped of amnion, the two leaves of the adjoining sacs' chorionic membranes do not separate, it is because they are fused and are not easily separable by blunt dissection, the number of cavities being equal to the number of chorionic membranes.

In conclusion, it is possible, important and necessary to identify the pattern of placentation through careful examination of the placenta and fetal membranes after their delivery. In a considerable number of situations, this task provides undeniably good results as far as diagnosis of zygosity is concerned. It is easy to perform a general examination of the placenta immediately after birth in the delivery room. The only thing that is indispensable is proper knowledge of the nature of the two patterns of dividing membranes and the way they present themselves.

Figure 25.6 Continued

(b) Note the placental septum (S), dividing two amniotic sacs. Since there is one placental portion, the main question is whether the placenta is mono- or dichorionic. An overall examination of the membranes of the septum is necessary as they connect to the placental surface. (c) Note the line of 'attachment' of a delicate diamniotic septum (S). The membranes are held up to show their transparency. (d and e) The dividing membranes are being separated in a slow downward movement. There are only two sheets of very thin translucent amniotic tissue ($A_1$ and $A_2$) loosely attached to each other. (f) The two layers of amnion ($A_1$ and $A_2$) may be readily separated, and at their base it is easy to peel them off the underlying chorionic surface leaving a single continuous chorionic plate (Cp). (g) Umbilical cord of the acardiac twin embedded in the intertwin membrane in a case of monochorionic twins with twin-reversed arterial perfusion sequence. (Image courtesy of I. Blickstein)

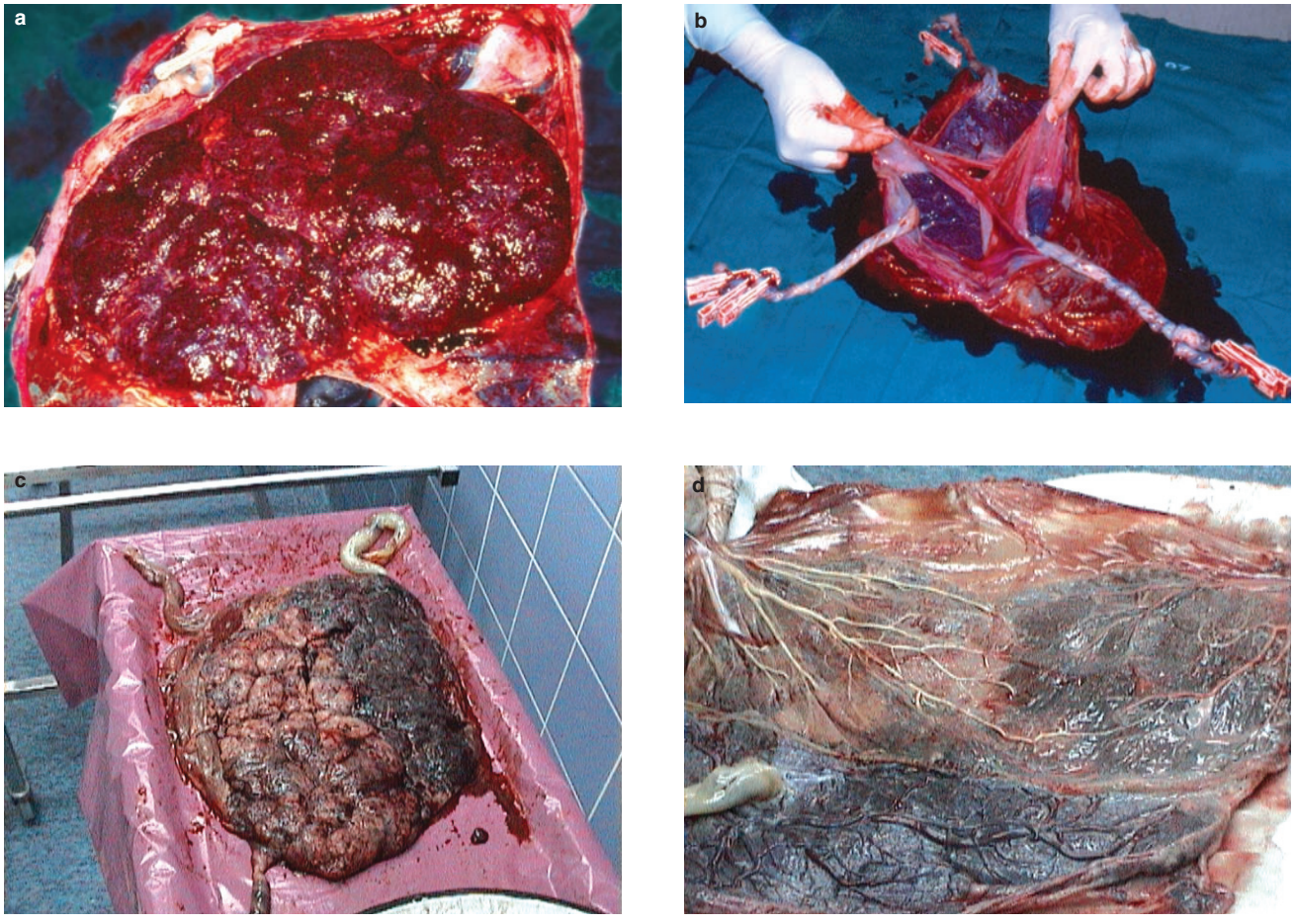


**Figure 25.8** Trichorionic–triamniotic triplet placenta. (a) As can be seen, it is possible to identify three placental portions on the maternal surface. (b) Fetal surfaces. All the dividing membranes have four layers (amnion–chorion–chorion–amnion). (c) Maternal surface of dichorionic triplet placenta. (Image courtesy of M. Ropacka.) (d) Fetal surface of dichorionic triplet placenta. (Image courtesy of M. Ropacka)

The need for sufficient practice in carrying out this task cannot be stressed sufficiently, as only properly trained physicians or midwives have the skills required to ensure reliable results. Until this degree of expertise and practice has been attained, chorionicity should be confirmed histologically. A fragment of the septum and the zone where the septum joins the chorial surface of the placenta, called the T-zone, may be collected for histologic examination, as explained in reference 19 and shown in Chapter 26.

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# Advanced Placental Examination of Twins and Higher-order Multiple Pregnancies

*G. A. Machin*

**26**



## INTRODUCTION

Twin and higher-order multiple pregnancy (HOMP) placentas should be examined routinely because:

(1) Chorionicity is not always determined correctly by prenatal ultrasound, and is relevant to any adverse pregnancy outcomes;

(2) If placentation is proved to be monochorionic (MC) by pathology, twins are monozygotic (MZ) (with very rare exceptions);

(3) Explanations of growth discordance, fetal demise, neurologic injury, extent of chorioamnionitis/fetal inflammation depend on chorionicity;

(4) The usual 'rules' about twin pathology are regularly broken, so that only familiarity with norms allows sophisticated exceptions to be recognized, e.g. 'hybrid' MC/dichorionic (DC) twin placentas, succenturiate lobes in MC placentas masquerading as 'DC' by ultrasound.

The minimal clinical data required for meaningful pathology reporting of twin and HOMP placentas include gestational age, sexes, birth weights and significant clinical complications. It is preferable to know whether conception was spontaneous or assisted, and whether there has been multifetal reduction. The cords should be clearly identified, preferably with one and two clamps for twins A and B, respectively.

## DICHORIONIC TWIN PLACENTATION

DC twin placentas may be separate or fused, as seen by ultrasound or in the pathology laboratory. Viewed from the maternal side, fused DC placentas

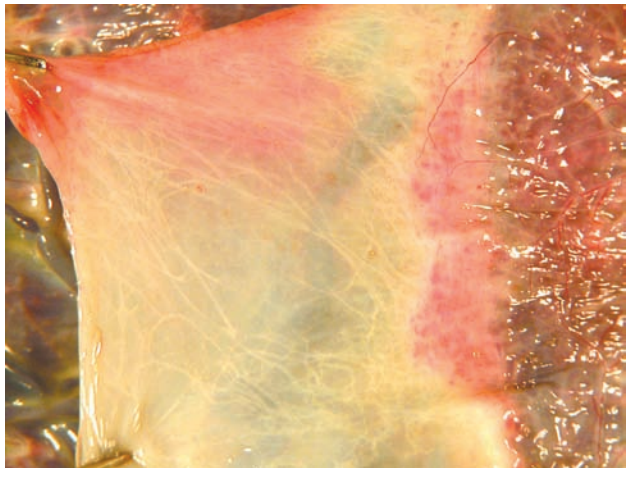


**Figure 26.1** In these fused, dichorionic (DC) placentas, viable parenchymal tissue is seen in the base of the septum. The DC septum has a fine, reticular pattern of sclerosed chorionic vessels

are completely seamless, with what appears to be a continuous parenchymal mass. On the fetal side, however, the membranous septum is palpably thick, sometimes with a ridge of viable residual placental tissue in its base, corresponding with the 'twin peak sign' seen on ultrasound. The septum is translucent but not transparent. Sclerosed chorionic vessels form a fine reticulum (Figure 26.1). There are rarely any interfetal vascular connections, and chorionic vessels running toward the base of the septum from each fetus are deviated from their path to run parallel with the septal base (Figure 26.2). Although instances of interfetal vascular connections have been described in DC twins[1,2], these are exceptionally rare, and the author has never seen a case.

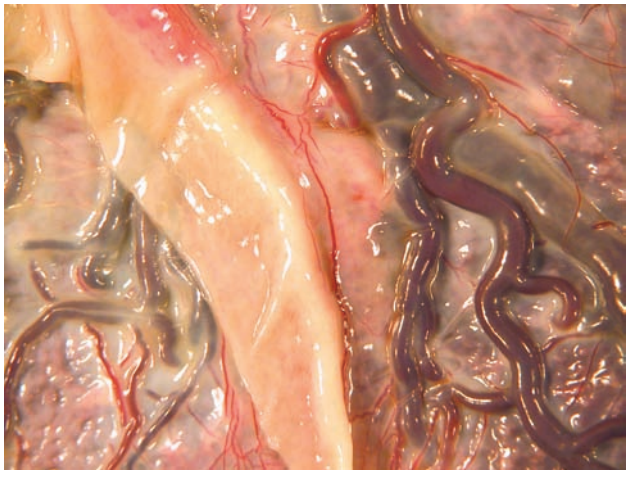
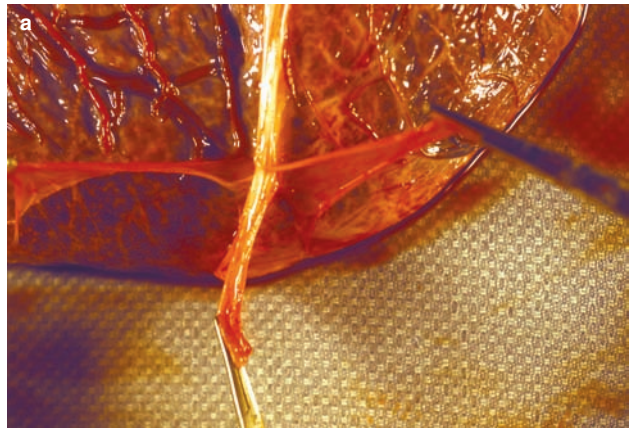


**Figure 26.2** At the dichorionic (DC) septum, chorionic plate vessels turn parallel to the septum, but rarely transgress it

**Figure 26.3** When the cord of the second-born dichorionic (DC) twin inserts into the septal membranes it creates a special kind of vasa previa



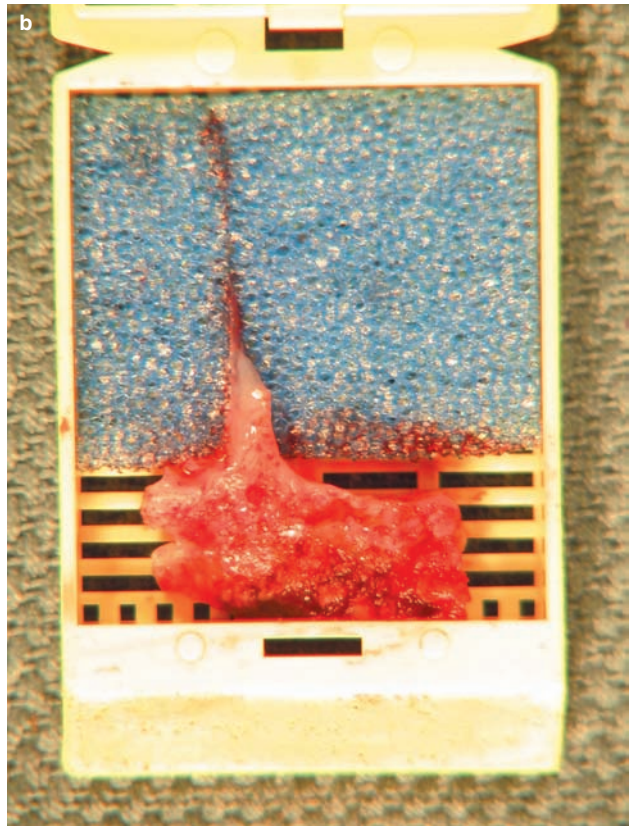




**Figure 26.4** (a) The two amniotic layers of a dichorionic (DC) septum can be peeled apart, leaving the chorionic component, which is firmly attached to the placental disk. (b) Elsewhere in the septum, a block is made of the DC septal T-junction

Velamentous cord insertion is common in DC twins. Sometimes this velamentous insertion is into the septum, creating a special type of vasa previa if it belongs to the 'upper', second-born twin (Figure 26.3).

DC placentation should be recorded permanently by making a 'T-junction' block (Figure 26.4). Separate DC placentas can be weighed separately, allowing the calculation of fetal/placental (F/P) ratios for each twin, especially when there is significant growth discordance. It is also possible to cut fused DC placentas apart along the base of the septum if both F/P ratios are required. Marked growth discordance in DC twins has a different causation and natural history than in MC twins[3]. Growth discordance in DC twins can be caused by placental abnormality of the smaller twin, including: small placental mass, velamentous or marginal cord insertion and parenchymal pathology such as increased perivillous fibrin deposition and/or maternal floor infarction[4]. Differential parenchymal pathology secondary to thrombophilia strongly suggests dizygosity, with differential genetic thrombophilia of one twin but not the other.

DC placentation does not designate zygosity in like-sexed twins, because one-third of MZ twins are DC. Paraffin-processed placental parenchymal blocks

constitute a valuable resource for later DNA extraction and genetic testing, including zygosity studies.

Adverse outcomes in DC twins are caused by factors similar to those in singletons, having no connection with twinning *per se*. There are no special vascular considerations, such as apply to MC twin placentation.

## MONOCHORIONIC TWIN PLACENTATION

The MC twin or HOMP placenta is a single placenta, not two placentas fused together. The difference in structure from DC placentas is highly significant, because the complete absence of chorion in the membranous septum of MC twin placentas allows fetal chorionic plate vessels from both twins to have unrestricted access to the whole placental surface, where they usually form connections of various kinds. In consequence, the cardiovascular systems of MC twins are interdependent, and any deterioration in one twin will inevitably affect the other. In addition, specific patterns of intertwin vascular connections are required for the development of twin–twin transfusion (TTT) and twin reversed arterial perfusion (TRAP). It is important to realize that MC twin gestations are completely surrounded by a seamless single hollow sphere of chorion, both placental and free-membranous. There is no single chorion component in the septum, as is sometimes supposed.

### Examining the septum

A large proportion (95%) of MC twin placentas are diamniotic (DA). However, the MC–DA septum is sometimes difficult to find by ultrasound, so some placentas will arrive in the pathology laboratory with serious questions about monoamniotic (MA) versus DA status. If the amniotic membrane has been completely stripped from the placenta, it is not possible to arrive at a definite diagnosis. However, in my experience, it is rare for the amnion to strip off in MC–MA placentas, largely because cord insertions are close together and anchor the amnion down close to the fetal surface. In contrast, the MC–DA amnion frequently strips. By unraveling the two membrane components from the cord insertions and laying them down again on the placental surface, it is easy to see if there is too much excess of membrane for placentation to have been MA.

Because the septum of MC–DA placentas consists of two layers of amnion only, laid back-to-back, there is no chorionic component. The septum is very thin (like Saran® wrap) and totally transparent. There are no sclerosed chorionic vessels. Cords cannot be velamentously inserted into the septum because there is no chorionic component. The septum meets the placental surface cleanly, without a 'twin peak' or wedge of placental tissue.

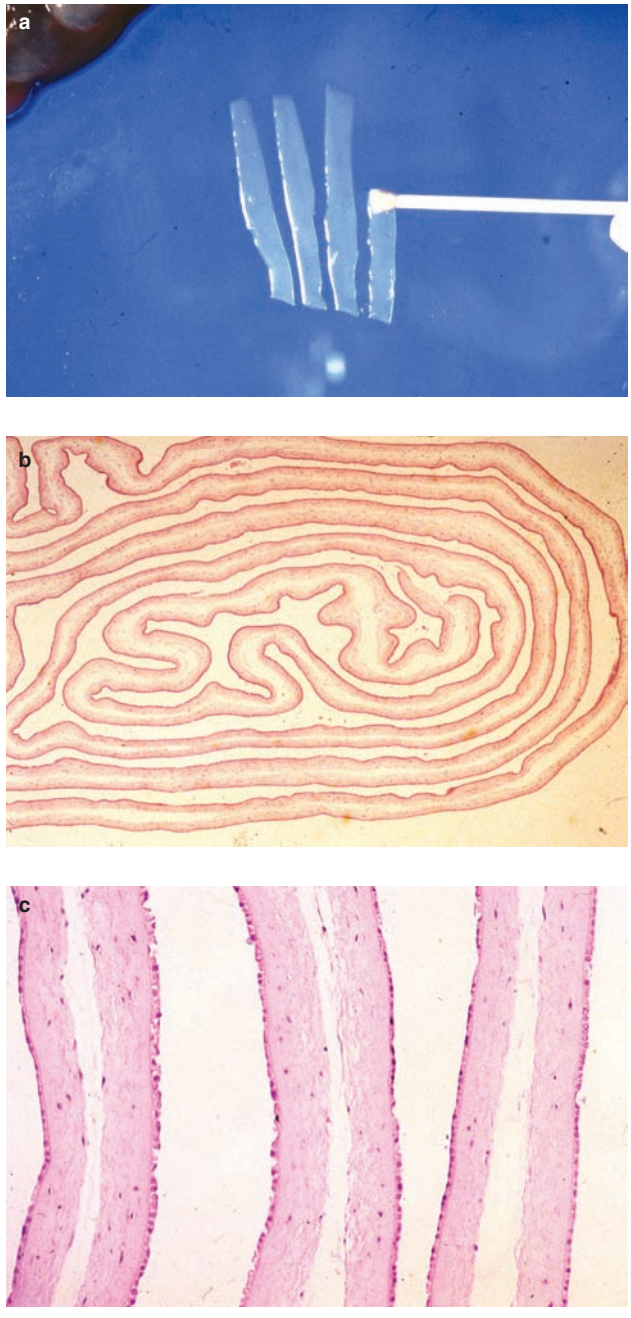



**Figure 26.5** For monochorionic (MC) twins, a membrane roll of the septum leaves the chorionic vessels intact for perfusion studies. With rare exceptions, the MC septal membrane roll is a permanent record that the twins are monozygotic (MZ). (a) Making the membrane roll. (b) Low-power microscopy of the tissue roll. (c) High-power view shows two layers of amnion arranged back-to-back without interposed chorion

By sampling an undisturbed portion of the septum, a membrane roll can be made to confirm MC–DA placentation (Figure 26.5). (This septal membrane roll is also a permanent record of monozygosity.) A T-junction block is not necessary if the placenta is fresh and injection studies are planned.

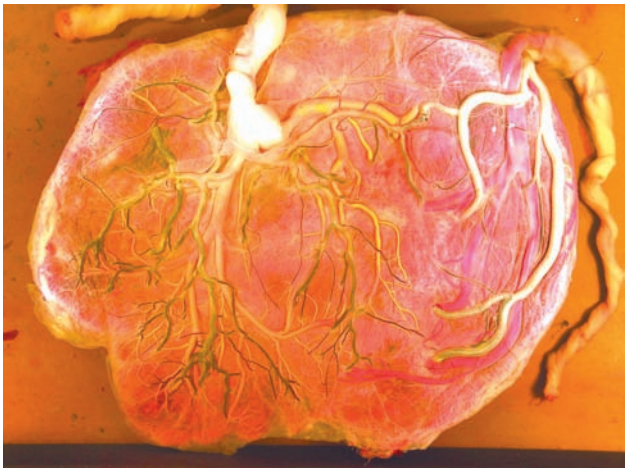


**Figure 26.6** Asymmetric cord insertions in monochorionic (MC) twins cause unequal sharing of the parenchyma, leading to growth discordance. The twin on the right has a thin, marginally inserted cord. Venous return (red dye) constitutes only about 25% of the total parenchyma, the remainder draining to the larger twin on the left

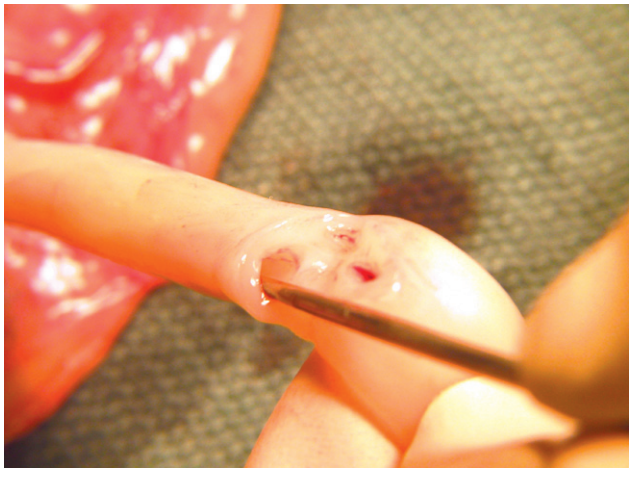


**Figure 26.7** A cautious cut-down into the cord, 3–5 cm from its insertion, allows the venous catheter to be threaded into the chorionic plate veins for perfusion

## Documenting the cord insertions and placental diameters

Cord insertions are documented as central, eccentric, marginal or velamentous. Two placental diameters are measured, the major one lying through both cord insertion points and the other at right angles to those insertions, at a point roughly halfway between the cord insertions – this corresponds with the vascular equator. The major diameter is usually longer than the vascular equator. The vascular equator does not correlate with the base of the membranous septum, and that septum probably moves during gestation, particularly if there are discrepancies in amniotic fluid volumes (see Chapter 27). It is not known whether the ratio of the major diameter to the vascular equator affects the number of equatorial vascular anastomoses.

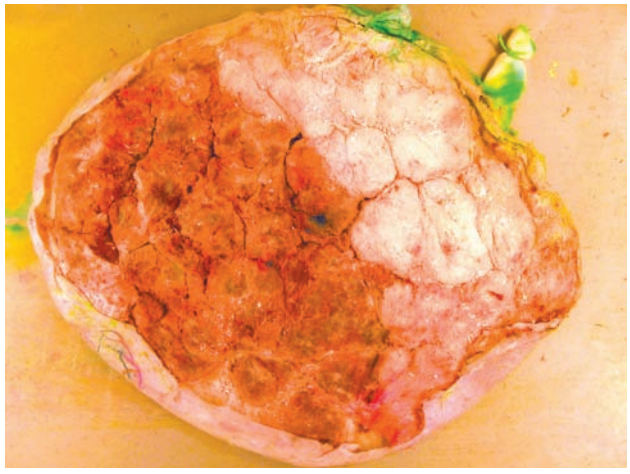


**Figure 26.8** A view of the maternal surface of a monochorionic (MC) twin placenta with fetal demise of one twin. The vascular equator appears as a serrated or 'patchwork quilt' effect, because some cotyledons at the equator have been infarcted by the lack of arterial perfusion from the dead twin. Other cotyledons remain viable because they are perfused by the survivor. Thus the vascular equator is not a smooth line. The pale placental zone on the right corresponds with the dead fetus

Growth discordance in MC twins is almost entirely caused by asymmetric cord insertions, such that the larger twin has a central insertion, whereas the smaller twin has a marginal/velamentous insertion. In this circumstance, the smaller twin perfuses a smaller proportion of the parenchyma and is metabolically challenged (Figure 26.6). A single umbilical artery of the smaller twin can exacerbate the effect of discordant cord insertion. Velamentous cord insertions increase the risks in MC twins[5].

The MC twin placenta should be weighed, although there are no studies of F/P weight ratios in MC twinning.

## Preparing the chorionic plate vessels

It is unusual in clinical practice for pathologists to carry out perfusion studies in MC twin placentas, despite the fact that it is these very vascular structures that are almost entirely responsible for the dire consequences of MC placentation. Perfusion studies are simple and quick to perform on fresh MC placentas, and pathology assistants can be trained to do the work. The presence of the anastomosis of Hyrtl between the umbilical arteries in the cord within 1–2 cm of its insertion makes it necessary to catheterize only one artery in each cord. Size 5 French gauge umbilical vascular-access catheters are used for arteries and veins (Figure 26.7). They are primed with normal saline.

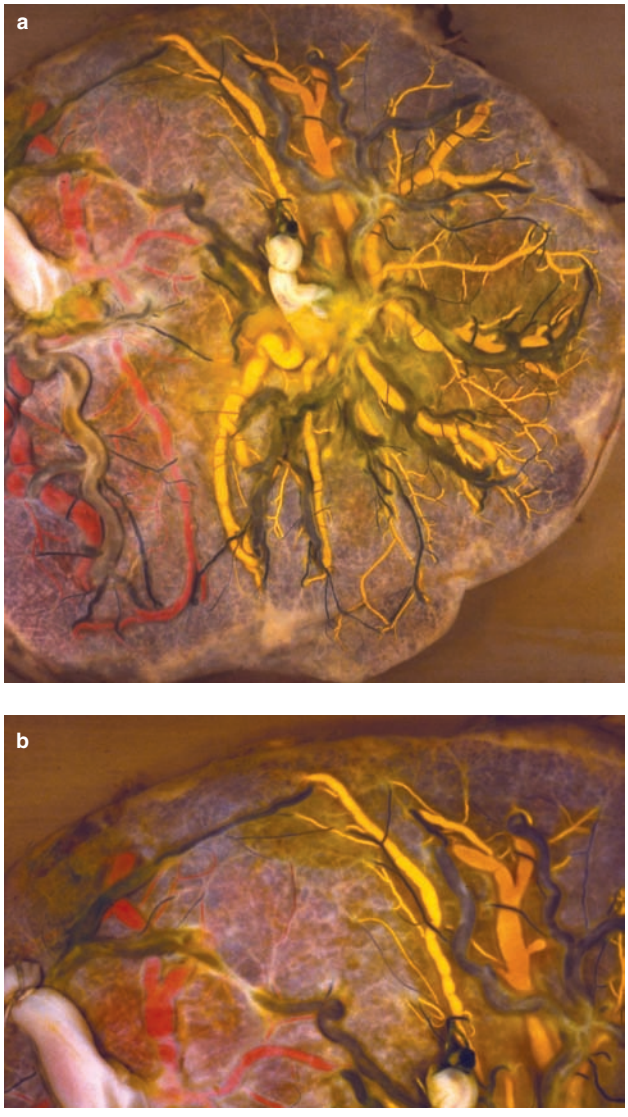



**Figure 26.9** (a) Perfusion study shows an arterioarterial connection and several, bidirectional arteriovenous connections. Arteries in blue, veins of left twin in red, veins of right twin in yellow. (b) Close-up view of upper half of placenta. Near the upper margin of the placenta there is an arteriovenous connection from left to right. The artery (blue) from the left twin perfuses an equatorial cotyledon from which the draining vein (yellow dye) runs to the twin on the right. In the mid-zone there is an arterioarterial connection. Immediately below, there is an arteriovenous connection from right to left; an artery from the twin on the right supplies an equatorial cotyledon from which venous blood (red) drains to the left twin. (c) Line diagram of vascular connections and clinical outcome

A cut-down is made about 3–4 cm away from the cord insertion, and the vessel lumen is dilated with a probe. Several wash-outs may be required, particularly in the vein, for the removal of postpartum clots. The catheter tips may be threaded out into several vascular branches to dislodge clots and clean their distal ends. Blood and clots can be massaged back up the cord and out through the cut-down sites. When the vessels have been thoroughly cleaned out, arterial and venous catheters are tightly tied in with thread or string to prevent back-leakage. It is best to mimic the *in vivo* status by using blue dye for the artery and red for the vein. In the unusual event that there is no arterioarterial (a→←a) connection, a green dye can be used for the arterial tree of the other twin. Venovenous (v↔v) connections are uncommon, so there may be an opportunity to use yellow dye for the second venous dye. The use of several dye colors makes it very clear as to which vessels are present at the vascular equator. In cases where one fetus has died or there has been multifetal or selective termination, the two zones of placental parenchyma are remarkably distinct, and form a mosaic or patchwork serrated effect at the vascular equator (Figure 26.8). This indicates that the equatorial zone of the two twin perfusion zones consists of a series of interdigitating cotyledons of varying sizes, some connected to one twin, some to the other and some to both.

## Types of vascular connections

a→←a and v↔v connections cross the equator on the surface above the chorionic plate and are direct, end-to-end anastomoses. There is usually one a→←a connection per placenta. v↔v connections are found in about 20% of MC placentas, and there may be more than one per placenta. Artery-to-vein (a→v) connections are also common, and there are frequently several, sometimes operating in opposite directions (Figure 26.9). The structure of a→v connections is

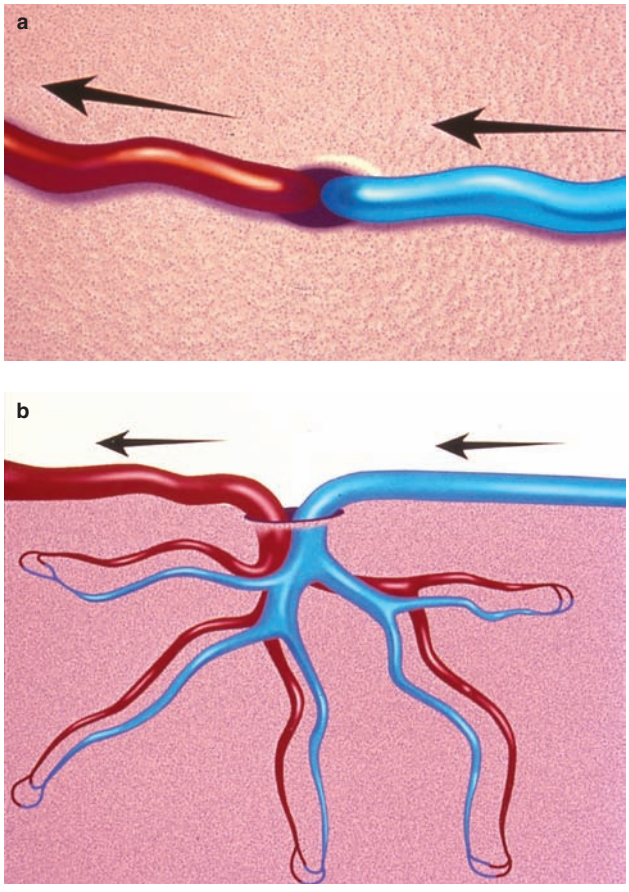



**Figure 26.10** Diagrammatic representation of an arteriovenous connection. (a) Surface view. The feeder artery (from the right) and draining vein (running to the left) meet at the foramen through the chorionic plate, but there is no direct vascular connection on the surface. (b) Side view. The artery and vein penetrate the chorionic plate foramen together. Circulation through the parenchymal capillaries is normal, and net transfusion from donor artery to recipient vein takes place down a pressure gradient. If this were the causative arteriovenous connection in a case of twin-to-twin transfusion, it is only necessary to coagulate the surface vessels, even though the transfusion actually takes place in the underlying parenchyma

frequently misunderstood. These connections represent a 'hybrid' cotyledon at the equator which is perfused by an artery of one twin, but drains to the other twin via the venous end of the connection. The artery of the 'donor' twin perforates the chorionic plate via a foramen to leave the fetal surface and reach the underlying placental parenchyma. The corresponding vein emerges back onto the fetal surface via the same foramen, but proceeds to the cord insertion of the other twin (Figure 26.10). This characteristic surface appearance identifies a→v connections. The diameters of the surface vessels presumably reflect the size of the supplied cotyledons. The structure of a→v connections exactly mimics the feeder vessels of a normal cotyledon

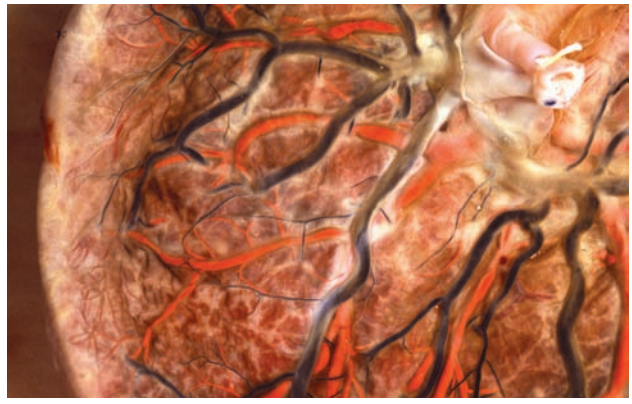


**Figure 26.11** Detail of perfusion of a normal singleton placenta. Note that arterial and venous branches run in pairs in the cotyledonary foramens. This arrangement is exactly replicated in a monochorionic (MC) arteriovenous connection, except that the feeder artery and draining vein are connected to different twins

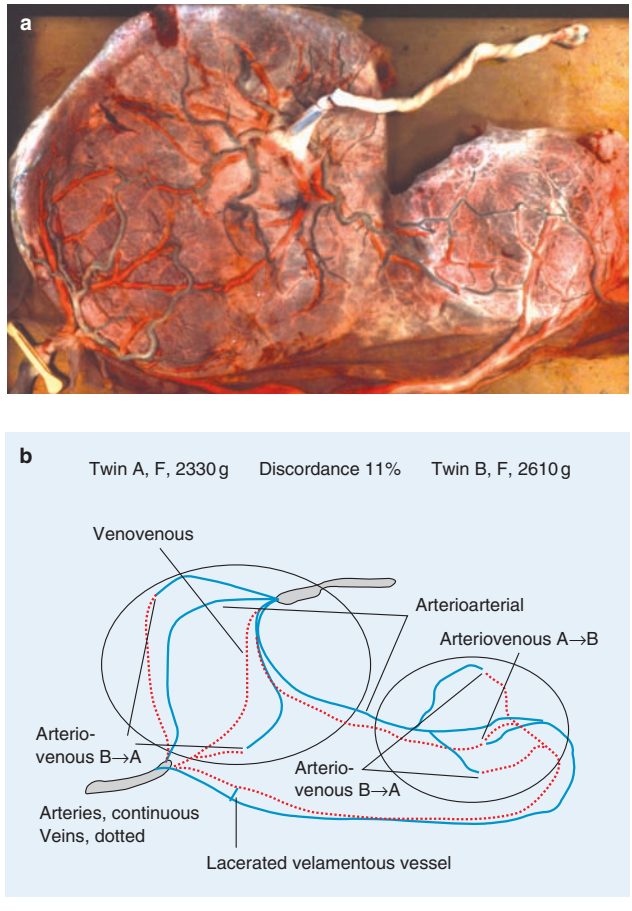
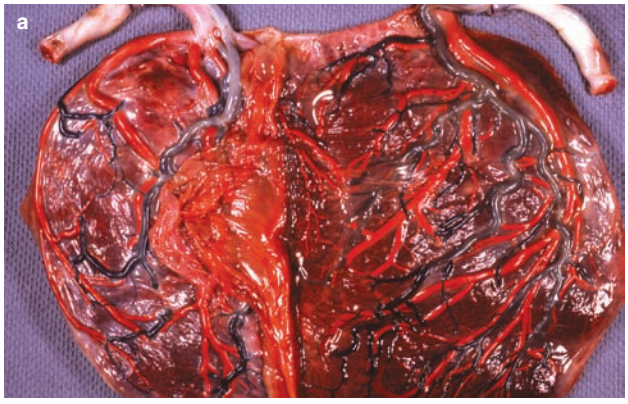
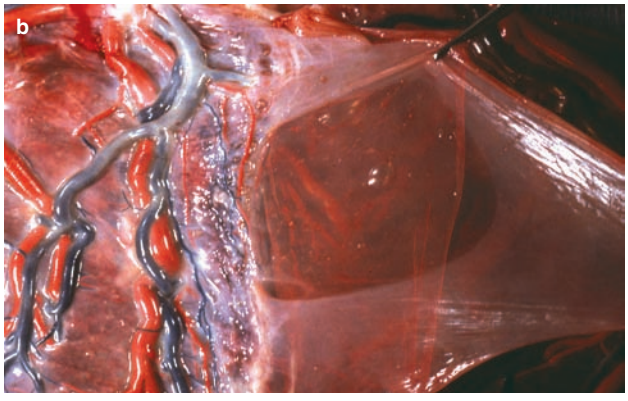



**Figure 26.12** (a) This monochorionic (MC) placenta has a large succenturiate lobe, with vessels running in the free membranes. Because there were 'two distinct placental masses', this placenta was diagnosed by ultrasound as being dichorionic (DC), despite the absence of a twin peak sign. In fact, the septum was very thin and typically MC in appearance. (b) Line drawing



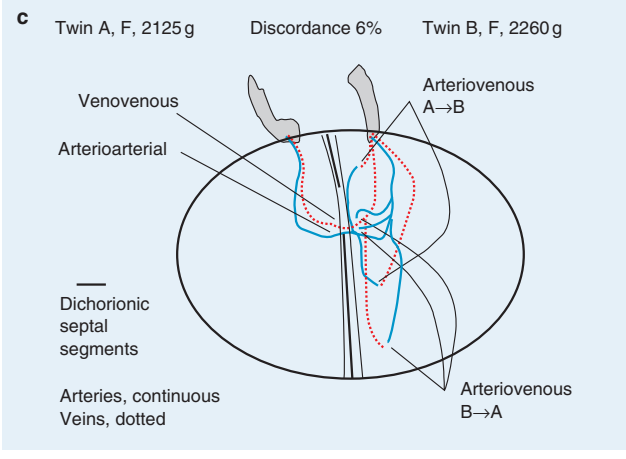




**Figure 26.13** (a) This is a 'hybrid' dichorionic/monochorionic (DC/MC) placenta. It may have arisen just at the moment when the trophoblast was separating from the inner cell mass. This placenta was diagnosed by ultrasound as DC, but most of it was MC, with connecting fetal vessels. (b) Close-up. The transparent window in the septum is the MC component. (c) Line drawing

(twin or singleton) in that the artery and vein traverse a common foramen (Figure 26.11). In the case of an MC a→v connection, the artery is supplied by the donor twin, whereas the vein is connected to the recipient. There is no transfusion directly on the surface. It is not necessary to perfuse dye on the arterial side until

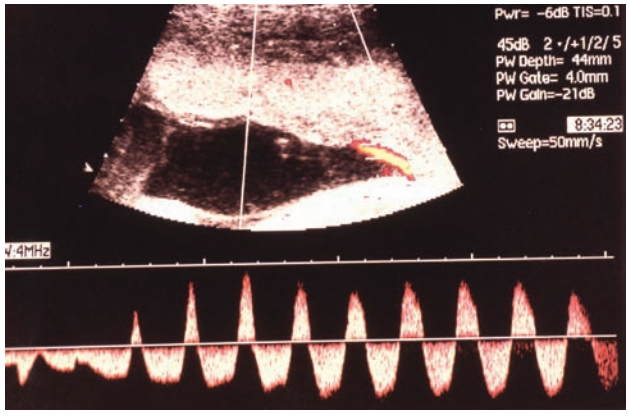



**Figure 26.14** Arterioarterial anastomoses can be diagnosed *in utero* by the typical bidirectional pulsatile flow seen by Doppler study

it is seen emerging up the corresponding vein; the very presence of a feeder artery and draining vein at the mouth of their common foramen is sufficient for the diagnosis of a functional a→v connection. Because of the arteriovenous pressure gradient, there is always net flow from donor to recipient. The numbers and diameters of all three types of connections are recorded. There are usually several connections in uncomplicated MC gestations.

## Defining the vascular equator and assessing parenchymal sharing

In cases of discordant growth and cord insertion, injection studies allow a good estimate of unequal sharing. The vascular equator is a somewhat wavy line defined by the several points where a→v anastomotic feeder and draining vessels abut (head-to-head) on the chorionic plate.

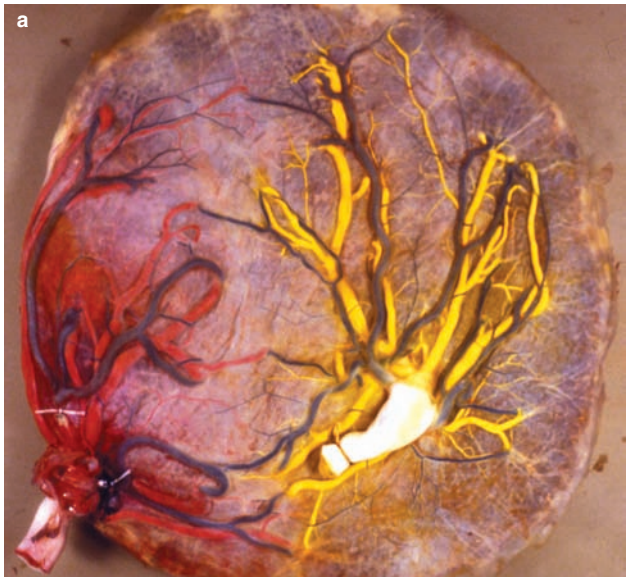
## Uncommon anatomic variants of MC twin placentation

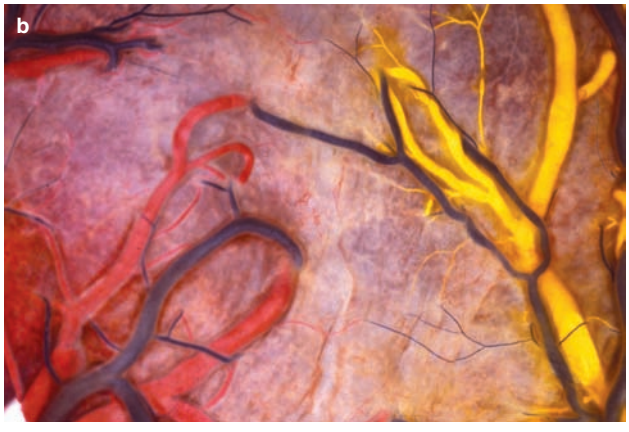
### *Bilobed MC placentas*

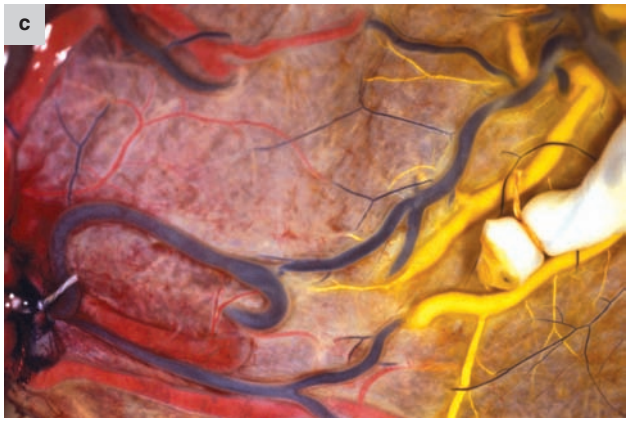
As in singleton placentas, about 1–2% of MC twin placentas are bilobed or have large succenturiate lobes (Figure 26.12). If chorionicity at ultrasound has been designated by the number of 'placental masses' rather than by septal membrane thickness and 'twin peak sign', bilobed MC placentas may have been misdiagnosed as 'DC'. Bilobed MC placentas contain average numbers and patterns of vascular connections, so the development of TTT is possible, a matter for dismay if 'dichorionicity' has been diagnosed on the basis of 'placental masses'.

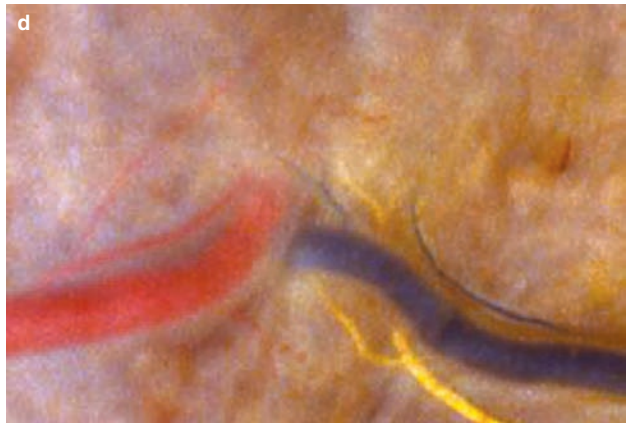
### *Hybrid DC/MC placentas*

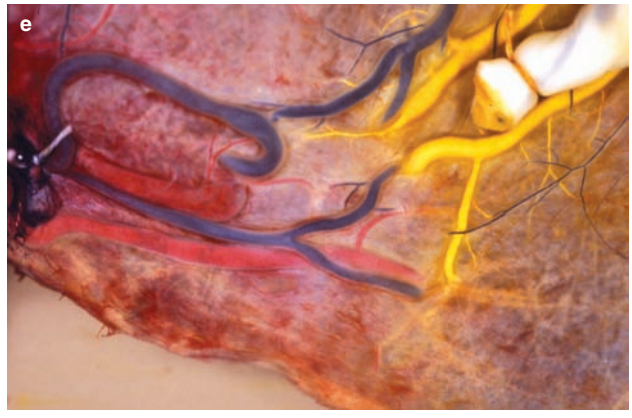
These are very rare. One portion of the membranous septum is DC, whereas the remainder is MC,



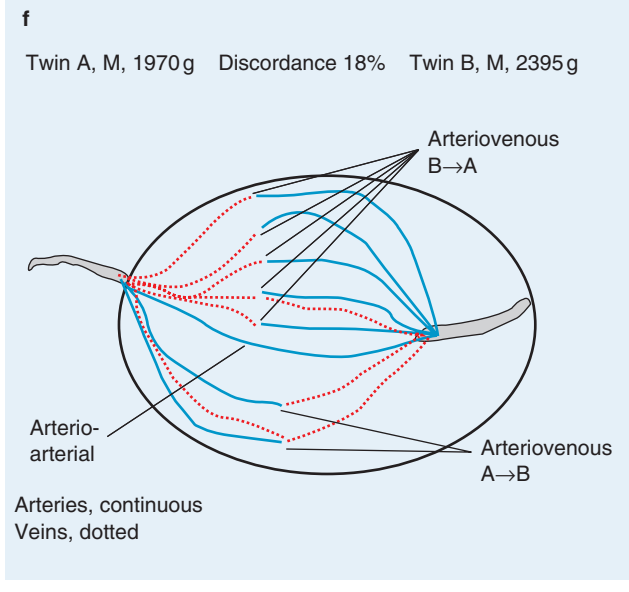
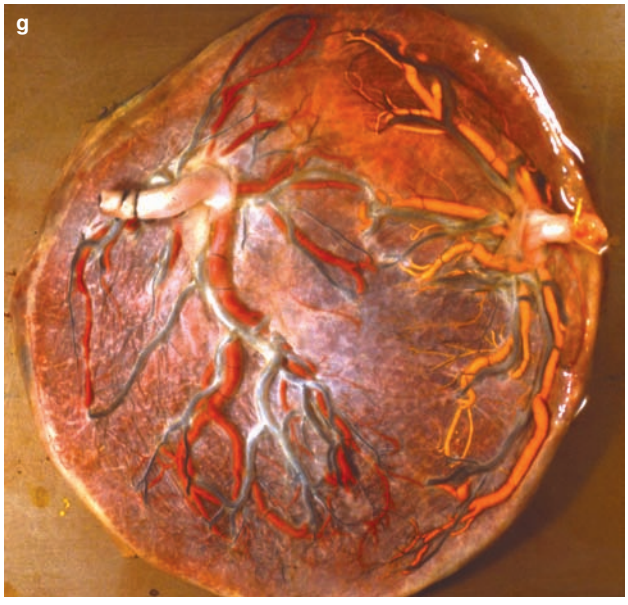
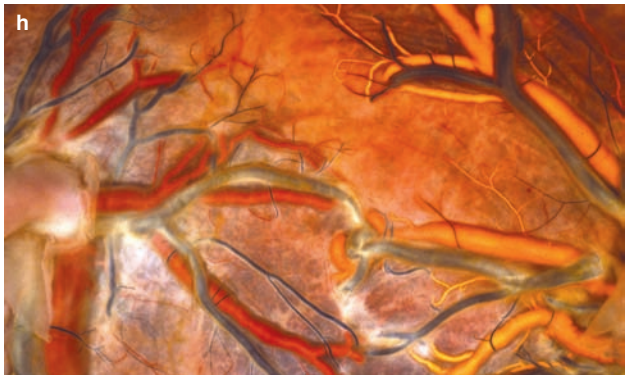




**Figure 26.15** *(Continued)*



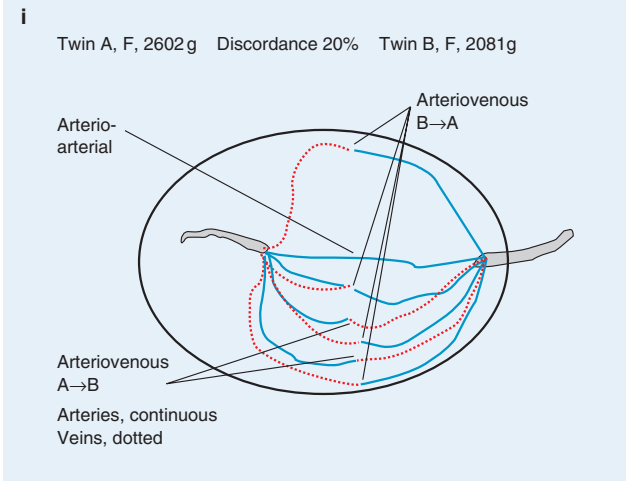




**Figure 26.15** Complex equatorial cotyledons. (a) General view of a placenta with an arterioarterial connection and numerous, bidirectional arteriovenous connections. Veins of left and right twins in red and yellow, respectively. (b) There is a standard arteriovenous connection from right to left (red vein). (c) Close-up view of mid-zone. There is an arterioarterial connection towards the lower edge. At the top edge there is a complex arteriovenous connection primarily draining to the left twin (red vein), but with some drainage back also to the right twin (yellow). (d) Detail of (c), showing the complex cotyledon. (e) Toward the lower edge there is a complex cotyledon supplied by an artery from the left twin, but draining into red and yellow veins. (f) Line diagram of the placenta overall. (g) Overall view of another case with a complex equatorial cotyledon at the mid-zone. (h) This shows an arterioarterial connection within which left (red) and right (yellow) veins drain from a common cotyledon. (i) Line drawing of this case

with usual interfetal vascular connections (Figure 26.13). These cases are likely to have been diagnosed as DC by ultrasound. They probably result from a twinning process at the cusp between 2 and 3 days post-conception (pc), i.e. there is a partial attempt at DC twinning.

### *Uncommon vascular connections at the equator*

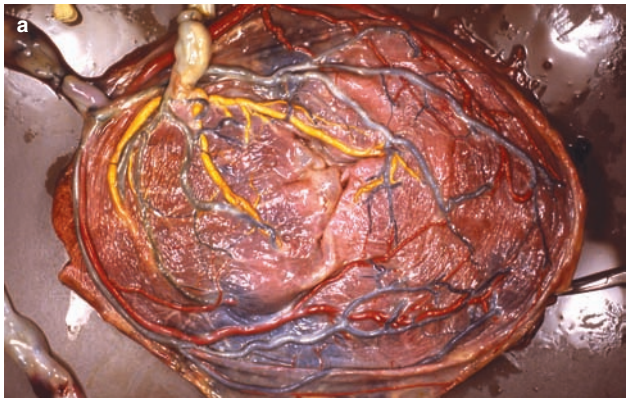
These connections include a→←a connections that dip below the chorionic plate for very short distances (Figure 26.14). These are difficult to diagnose at fetoscopy. Equatorial cotyledons are occasionally perfused by an artery from each twin but drained by veins to both twins. Alternatively, a cotyledon may be supplied by arteries from both twins, but drains venously to one twin only (Figure 26.15). These variants should not affect fetoscopic assessment and management.

### *Concentric placental vascular and parenchymal allocation*

This is very rare and would be difficult to delineate at fetoscopy (Figure 26.16).

## SPECIAL FEATURES OF MONOCHORIONIC–MONOAMNIOTIC PLACENTAS

Cords are usually entwined and/or knotted (Figure 26.17). This can cause fetal brain damage or demise of one or both fetuses. There may be extensive chorionic plate and umbilical vascular thrombosis. Most MC–MA placentas have closely adjacent cord insertions, i.e. less than 4 cm distance, with the result that large a→←a and v↔v connections are usually present between the roots of the cords, preventing the development of TTT. MA twins with TTT usually have cords inserted far apart.



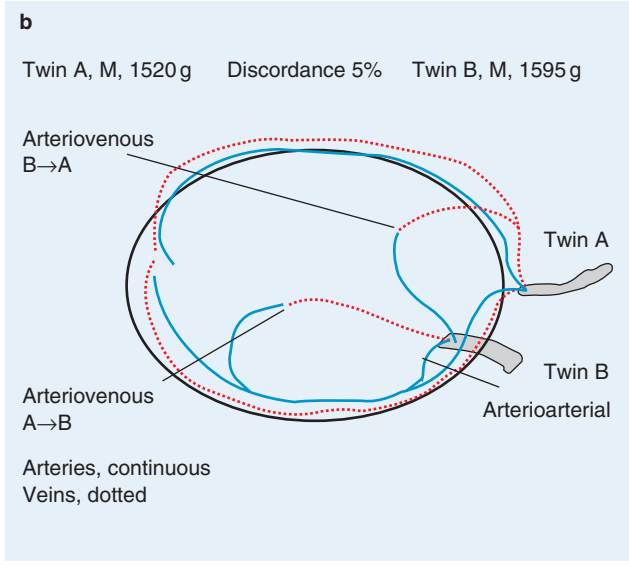
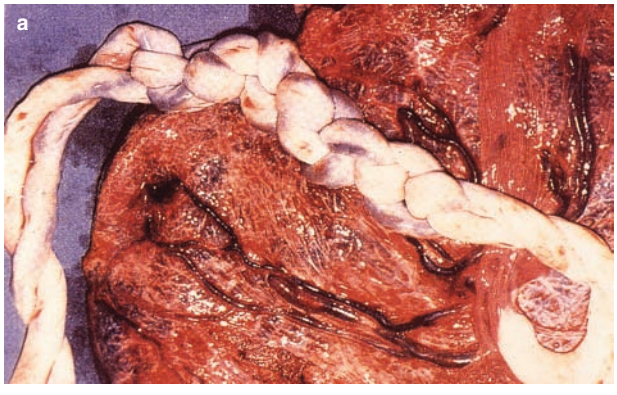
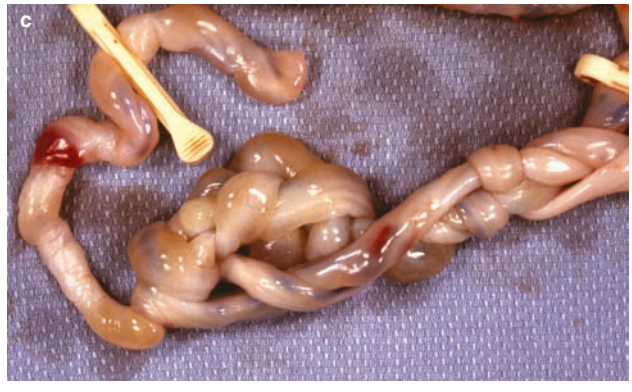
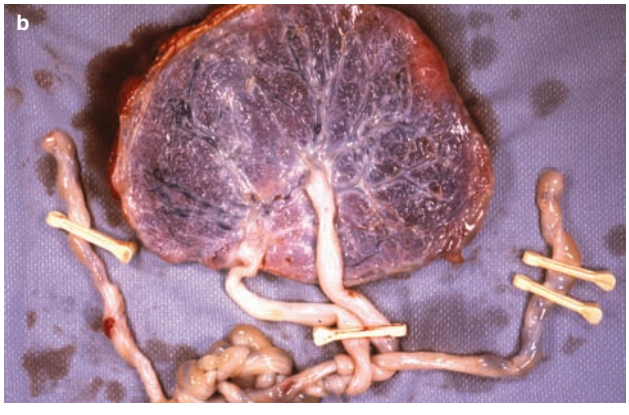




**Figure 26.16** In this case, the parenchymal zone of the smaller twin is enclosed within the zone of the larger twin, creating a concentric arrangement. The vascular anatomy would be very difficult to map by ultrasound or at fetoscopy. (a) Perfusion study. (b) Line drawing



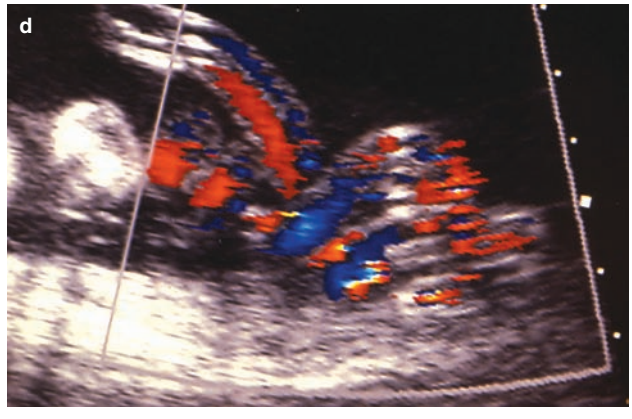
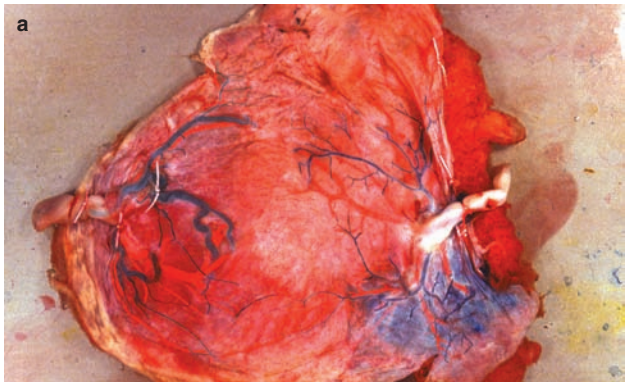




**Figure 26.17** Almost all monochorionic–monoamniotic (MC–MA) twins have entwined, braided and/or knotted cords. (a) These twins survived intact. (b) Both twin fetuses in this case died from cord entwining. (c) Close-up view of complex knotting and braiding. (d) Because braiding occurs in almost all MC–MA pregnancies, it should be looked for in the ultrasound examination, especially in cases where the membranous septum is thin and it is not clear whether the twins are diamniotic (DA) or MA



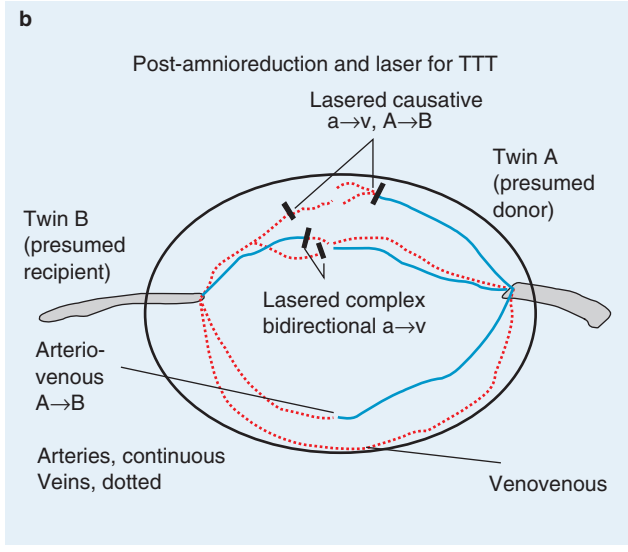
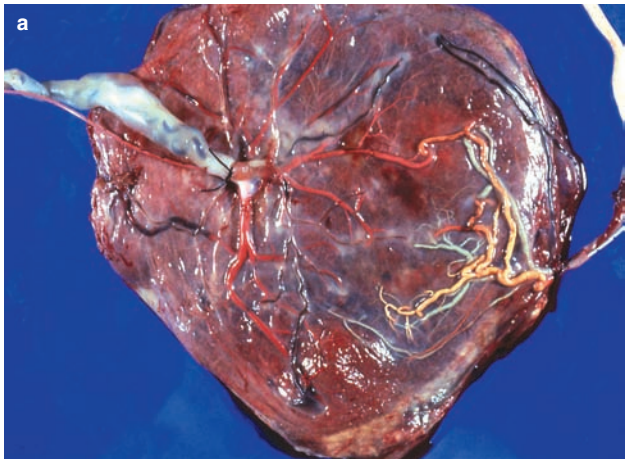




**Figure 26.18** This case had fetoscopic laser coagulation for severe twin-to-twin transfusion (TTT). (a) Perfusion study. A thrombus is seen extending along the vein towards the cord of the recipient from the laser site at the vascular equator. (b) Line drawing



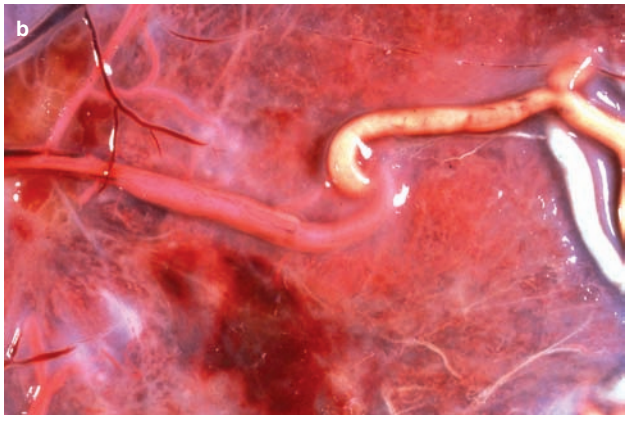




**Figure 26.19** (a) This postpartum perfusion study shows the single, causative arteriovenous connection, upper right. Note that the donor cord is velamentously inserted, with markedly unequal sharing. (b) Detail of the causative anastomosis

## EXAMINATION OF MONOCHORIONIC TWIN PLACENTAS AFTER FETOSCOPIC LASER COAGULATION

Appearances of the laser sites vary according to the time interval since coagulation. Veins are usually more effectively coagulated than arteries, and may show segments of thrombosis extending toward the recipient cord insertion (Figure 26.18). The purpose of perfusion studies is to determine whether there are any persisting interfetal connections. Microscopy of the corresponding cotyledon shows bland villous infarction.

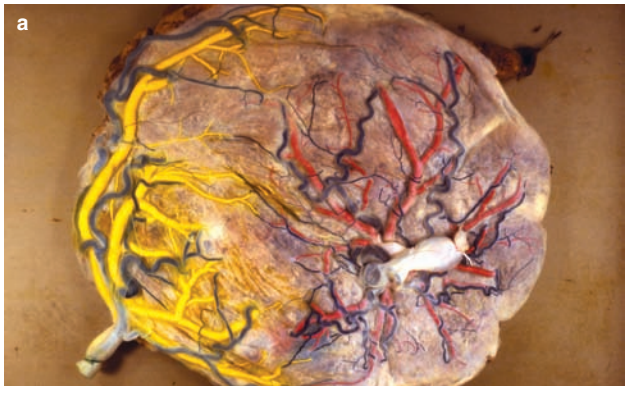
## PATTERNS OF PLACENTAL SHAPE, CORD INSERTIONS AND VASCULAR CONNECTIONS IN SOME SPECIFIC COMPLICATIONS OF MONOCHORIONIC PLACENTATION

### Severe growth discordance

Central and peripheral cord insertions are usually present.

### Twin-to-twin transfusion

In severe cases, there is a dominant, causative a→v connection, which may be the only connection (Figure 26.19). In less severe cases there are other connections that have been unable to compensate effectively for the causative a→v connection. a→v connections in the opposite direction are common, and a→←a connections may also be seen (Figure 26.20).



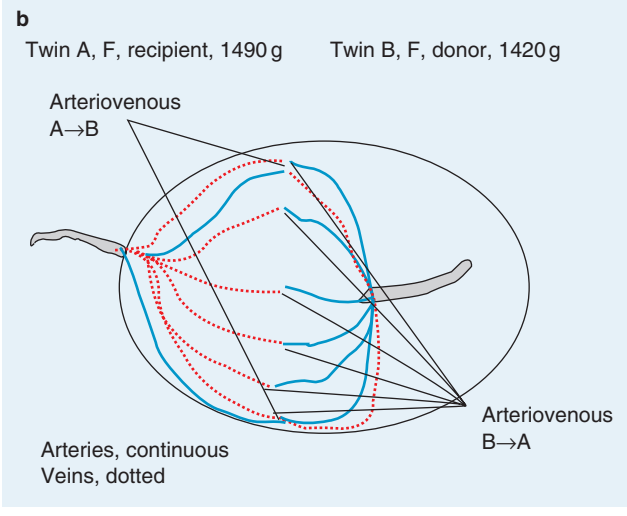




**Figure 26.20** (a) In this case of mild twin-to-twin transfusion, there are several bidirectional arteriovenous connections. These were not quite able to equilibrate, so mild disease developed. (b) Line drawing

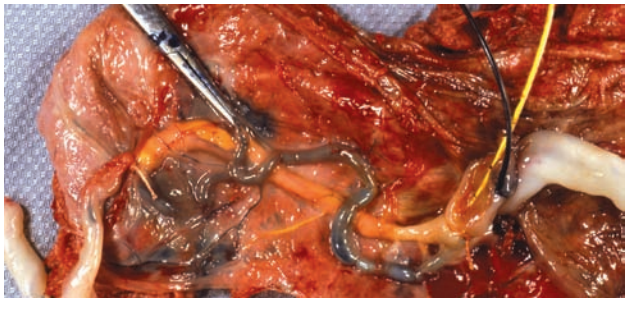


**Figure 26.21** Twin reversed arterial perfusion. The cords are inserted very close together, with large arterioarterial and venovenous connections between their bases. The acardiac cord is to the left

### Twin reversed arterial perfusion

Cord insertions are closely adjacent, such that the circulation of the acardiac fetus is virtually a side-branch of the pump twin umbilical vessels (Figure 26.21). There may be thrombosis in the v→v connection (Figure 26.22).

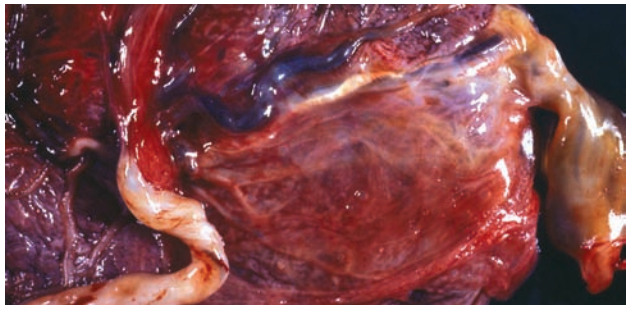


**Figure 26.22** Thrombosis in the venovenous return from the acardiac to the pump twin is caused by sluggish flow. Emboli from the venovenous thrombosis would run immediately to the brain of the pump twin

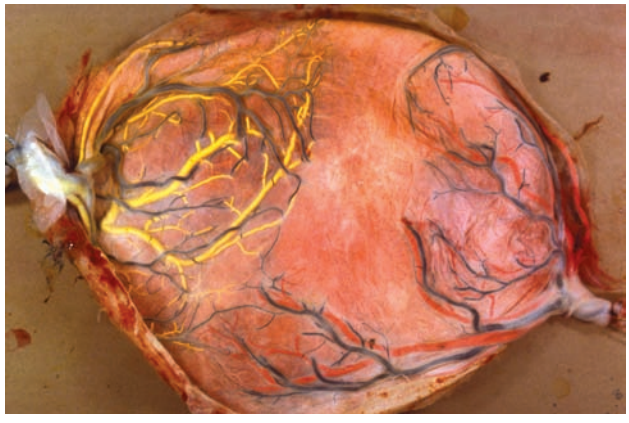


**Figure 26.23** Looking for residual vascular connections after fetal demise of one twin. Success depends on the time interval between death and delivery, but may explain any cerebral pathology in the survivor

### Fetal demise

This may be caused by severe growth discordance, TTT, TRAP and discordant lethal malformation (e.g. cystic hygroma with hydrops). In addition, selective termination for fetal anomaly and multifetal reduction will produce similar placental findings. With the exception of TRAP, the presence of the vascular connections places the surviving co-twin at risk for hemorrhagic hypotension into the placental portion and body of the demised twin. Depending on the interval between fetal demise and delivery, it may be possible to determine the number and type of vascular connections between the dead and surviving fetuses (Figure 26.23).

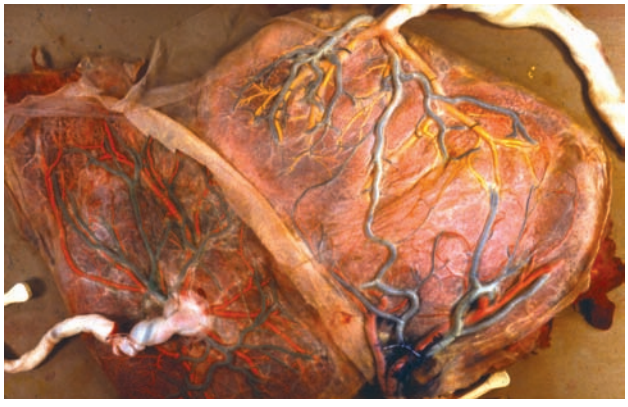
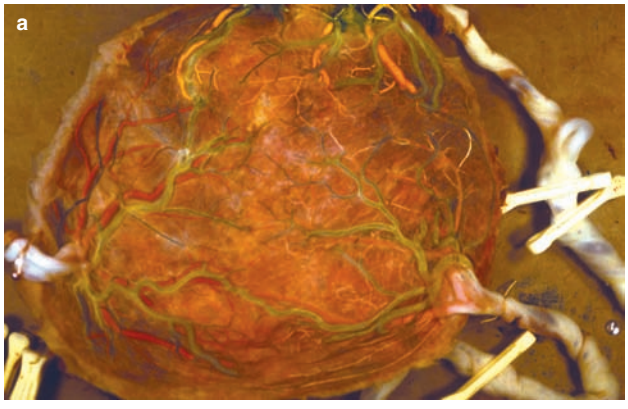


**Figure 26.24** Higher-order multiple gestations usually contain monochorionic (MC) twins or consist of MC triplets. Here there is a dichorionic (DC) triplet with an MC twin pair. There are vascular connections between the MC twins, but none to the DC triplet



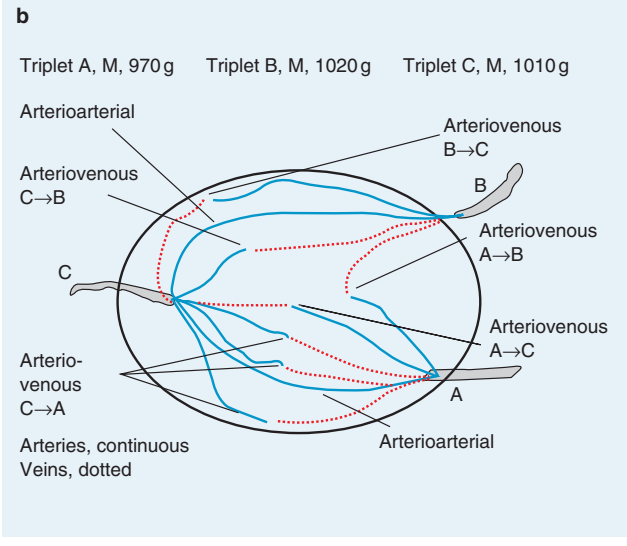




**Figure 26.25** (a) A ring of vessels connects all three fetuses in this monochorionic (MC) triplet placenta. (b) Line drawing

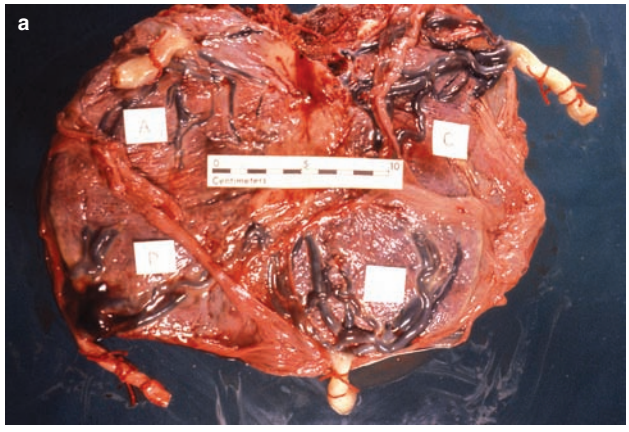




**Figure 26.26** This is a spontaneously conceived monochorionic (MC) quadruplet pregnancy. (a) The placenta was MC, tetra-amniotic. (b) The quadruplets are clearly monozygotic (MZ)

## HIGH-ORDER MULTIPLE PREGNANCY PLACENTAS, INCLUDING THOSE WITH MULTIFETAL REDUCTION

As mentioned in Chapter 31, most naturally conceived triplet placentas either contain MC twins or

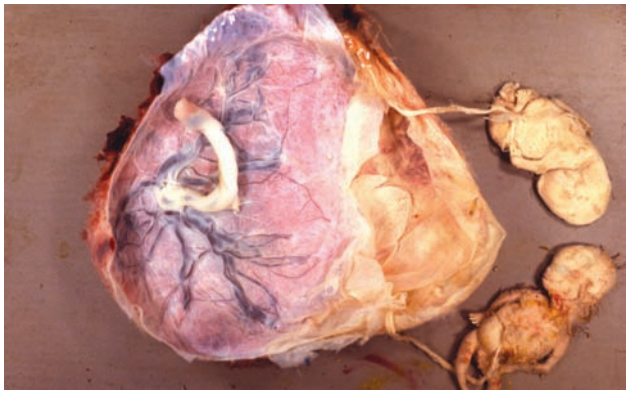


**Figure 26.27** Following multifetal pregnancy reduction, the corresponding papyraceous fetuses are identified. In this case, trichorionic triplets were reduced to a singleton

are entirely MC (Figure 26.24). In the case of DC triplets, and relying on cord identifications by the attending obstetrician, triplet placentas can be thoroughly examined for chorion status, which, in the case of MC twins or triplets, also designates zygosity. Appropriate septal membrane histology is prepared. TTT may occur in DC and MC triplets. In MC triplets with TTT, there is usually one recipient, one primary donor and an accessory donor boosting the primary donor via an a→a connection. MC triplets usually show ring-like connections between all three fetal circulations (Figure 26.25). Quadruplet placentas may contain combinations of DC and MC placentation (Figure 26.26). Careful sampling of septal membranes is necessary.

Following multifetal reduction, papyraceous fetuses are found, usually at the periphery of the surviving placental parenchyma(s) (Figure 26.27). It is rarely possible to delineate chorionic relationships, and this is not necessary, because attempted fetal reduction of one MC fetus usually results in severe injury to the other twin.

## ROUTINE PATHOLOGY

In addition to the special considerations listed above, DC and MC twin placentas should be examined and sampled for pathologic disorders that are also common in singleton placentas: chorioamnionitis and fetal inflammation, cord lesions (e.g. single umbilical artery, hematomas, thromboses, knots, etc.), abruption and marginal hemorrhage, and the full array of standard parenchymal lesions (e.g. fetal and maternal infarcts, intervillous thrombosis, maternal-floor infarction/increased perivillous fibrin deposition, villitis, chorangiomas, thromboses in chorionic and plate and stem villous vessels).

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# Vascular Anatomy of Monochorionic Twin Placentas

*G. A. Machin*



## INTRODUCTION

Compared with dichorionic (DC) twin pregnancies, monochorionic (MC) twin pregnancies (and higher-order multiple pregnancies (HOMPs) that are in part or entirely MC) have increased risks of serious complications, including fetal demise and prenatal injury to the brain, heart and kidneys (Table 27.1)[1–6]. This is the rationale for making the definitive diagnosis of chorionicity by ultrasound no later than 14 weeks into gestation (see Chapters 39 and 40). These increased risks are largely attributable to the fetal vascular structures of MC placentas (see Chapter 65).

The majority of MC twins survive the unusual experience of sharing a truly single placenta that is designed to deliver the metabolic needs for a singleton. However, 15–20% of MC twins develop specific clinical problems that occur exceptionally rarely (if at all) in DC twins. These problems are often fully developed by 18–20 weeks of gestation. The interrelated and overlapping special complications of MC twin placentation include: twin–twin transfusion (TTT) (see Chapter 65); marked growth discordance (see Chapter 60); twin reversed arterial perfusion (TRAP) (see Chapter 71); fetal brain injury to the surviving twin if the co-twin fetus dies, either spontaneously or as the result of selective termination or multifetal reduction without special methodology (see Chapter 64); monoamniotic (MA) twinning (see Chapter 67); and transfusion of cell lines and molecules between MC twins who are discordant for specific malformations and genetic disorders (see Chapters 31 and 32).

All of these conditions may have profound and lifelong effects on surviving twins, for whom MC placentation was the dominant influence on their embryonic–fetal development. This chapter describes the structural elements of MC placentas that result in normal as well as the specific adverse clinical outcomes listed above.

## THE VASCULAR STRUCTURES OF MONOCHORIONIC TWIN PLACENTAS

Two sets of variables are in place at all times of development: first, cord insertions, and second, the number, types, directions and combinations of interfetal vascular connections.

### Cord insertions

#### *Developmental considerations*

The trophoblast first develops as a hollow sphere that completely surrounds the developing embryo and amniotic cavity. Later, the most deeply and advantageously implanted chorionic villi (facing the endometrium) develop into the definitive placental disk. The remaining trophoblast, which faces away and thus out into the uterine cavity, regresses by a process of trophotropism, and is only retained as the outer chorionic layer of the peripheral, non-placental membranes.

The umbilical cord, issuing from the body stalk, may insert at any point into the inner surface of the hollow trophoblastic sphere. In most cases, this cord insertion corresponds with the most deeply implanted (and later central or paracentral) portion of the trophoblast that will become the placenta proper. In singletons, only 9% of cords insert into the placental margin, and only 1% have a velamentous

**Table 27.1** Obstetric/neonatal outcomes measured in monochorionic (MC) and dichorionic (DC) twins

| *Reference** | *Location* | *Study type* | *Outcome measures* | *MC* | *DC* |
|---|---|---|---|---|---|
| 1 | Nova Scotia, Canada | population | PND | 35/588 (5.9%) | 25/1468 (1.7%) |
| | | | mean BWD | 11.7% | 11.0% |
| | | | BWD >25% | 8.6% | 6.5% |
| 2 | Mumbai, India | ?population | PND | 18% | 9% |
| | | | BWD | 35% | 14% |
| 3 | Tochigi, Japan | referral | NND to 1 year | 4/88 (4.5%) | 6/328 (1.8%) |
| | | | neurologic disability | 5.7% | 1.8% |
| 4 | Birmingham, UK | referral | PND | 3/48 (6.2%) | 14/190 (7.4%) |
| 5 | Toronto, Canada | referral | 24–30-week gestation infants surviving 18–24 months death and neurologic disability | 39% | 25% |

*Reference 1: there were more double fetal deaths in MC (2.8%) than DC (0.5%) pregnancies; reference 4: twin–twin transfusion (TTT) was present in 14/44 (32%) MC pregnancies, and was responsible for 7/9 adverse outcomes. All MC infants with adverse outcomes had birth-weight discordance ≥25%, and this was true of 4/12 (33%) DC infants; reference 5: the basis for this anomalous result is not clear; reference 6: adverse outcomes were found in 42% of twins with TTT; PND, perinatal death; BWD, birth-weight discordance; NND, neonatal death

insertion into the free membranes. In contrast, marginal and velamentous cord insertions are far more common in DC twins than in singletons, and it is easy to see the manner in which closely apposed implanted DC placentas could undermine or in other ways distort the intended normal cord insertion of either twin.

Consideration of cord insertions is quite different in MC twins, for whom growth discordance is more frequent and severe than in DC twins[7–9]. Crowding may explain abnormal cord insertions in DC twins, but only one placenta is traversing the Fallopian tube in MC–DA twins. The intercord distance has already been determined prior to implantation. So if one cord insertion site succeeds in being implanted advantageously, it is almost inevitable that the other cord will not do so if there is a significant intercord distance. The cords of MC–MA twins are usually implanted close together, and this implies that large intercord distances are the result of early MC–DA twinning events, just after 2 days post-conception (pc).

### *Combinations of cord insertion sites in MC twin placentas*

Approximately 50% of MC twins have marginal/velamentous cord insertions. The clinical consequences of cord insertions depend on the combination of insertions in any given twin pair. If an MC twin pair has a combination of central and peripheral (especially velamentous) cord insertions, the centrally inserted twin commands a disproportionate amount of placental parenchyma, whereas the velamentous twin may have a very small territory indeed (Figure 27.1) (see also Chapter 26). It is not clear whether interfetal vascular anastomoses influence fetal growth to any degree. It can be argued further that the velamentous twin may have been derived from fewer founder cells than the co-twin, such that the smaller twin is not well equipped for efficient capture of placental parenchyma (see Chapter 31).

## Interfetal vascular connections

About 95% of MC twin placentas have vascular connections between the two fetal circulations. The types, number, directions and combinations of these connections largely determine the increased frequency of adverse outcomes in MC twins (see Chapter 65). These connections are rarely if ever reported in DC twins, and this author has never seen such a case. The small minority of MC twins who totally lack connections have obstetric risks similar to those of DC twins. One of the treatments for twin-to-twin transfusion (TTT) aims to convert MC to DC placentas in terms of vascular connections.

### *Development of fetoplacental circulation*

The primitive vessels of the trophoblast develop independently of the fetal circulation and the two circulations merge as fetal blood vessels grow out of the body stalk at about 8 days pc. The fetal vessels

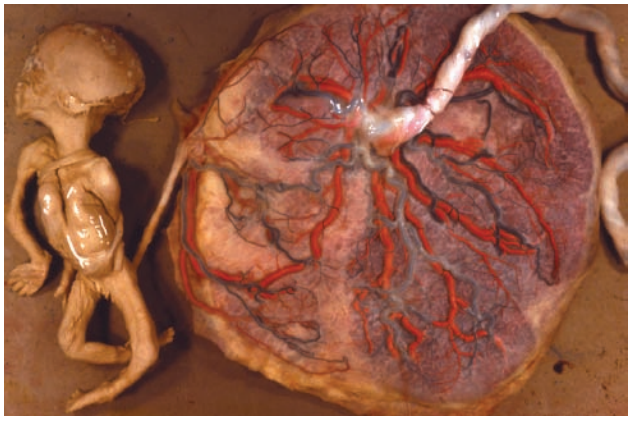

**Figure 27.1** This monochorionic (MC) twin placenta shows markedly unequal parenchymal sharing secondary to asymmetric cord insertions. The smaller fetus eventually stopped growing and died. There was a marginal cord insertion of the dead fetus, and the cord insertion of the surviving twin was central. Arteries are perfused with blue dye, and veins with red dye

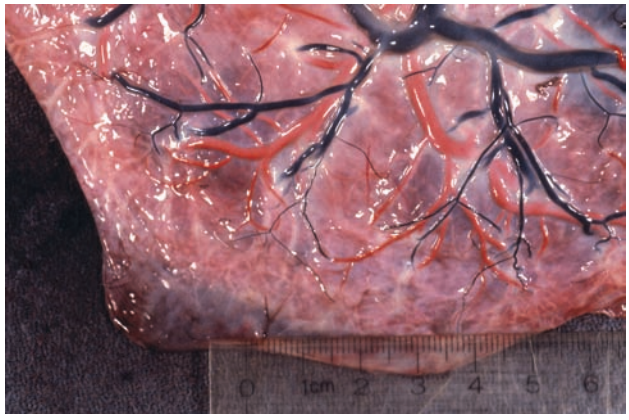

**Figure 27.2** A zone of a normal singleton placenta showing that arteries and veins wander independently on the fetal surface in the chorionic plate. However, when they reach their respective cotyledons, arteries and veins pair up at the foramina leading down to the underlying cotyledonary parenchyma. Arteries and veins are perfused with blue and red dyes, respectively

branch out from the cord insertion over the fetal surface of the chorion. Arteries and veins contact the underlying villi via a limited number of foramina that pierce the chorionic plate. Each foramen supplies one cotyledon. An arterial branch runs through the foramen from the fetal surface to the villi, and the corresponding cotyledonary vein gathers blood from the villi and emerges on to the fetal surface via the same foramen. An artery and vein always traverse the chorionic plate vein foramen as a pair (Figure 27.2).

In MC twins, fetal blood vessels from one twin are connected to cotyledons in the usual way over much of the placenta, where zones belong exclusively to one twin or the other. However, the twins compete to connect to cotyledons at the equatorial zone between the cord insertions. This often results in equatorial cotyledons that are perfused by an artery of one twin (the donor), but whose vein, emerging from the same foramen, has been 'captured' by the co-twin (recipient). This is both the developmental and anatomic basis of the arteriovenous connection (a→vc), a common structure in MC twin placentas that, in certain circumstances, can account for the development of the most common and serious complication of MC twinning, i.e. TTT.

The other types of vascular connections have a simpler structure and function directly on the chorionic plate surface. Arterioarterial (a→←a) and venovenous (v↔v) connections are simple end-to-end structures that do not normally leave the fetal side of the chorionic plate. During development, these vessels presumably meet and connect with each other as they 'search' for cotyledonary foramina.

### *Functional considerations*

Transfusion always occurs along the arteriovenous pressure gradient of each a→vc. Each MC twin placenta may contain more than one a→vc, and these may run in both directions in different equatorial cotyledons. Transfusion occurs at the villous level in the parenchyma, that is to say, the structure of the cotyledonary vessels is entirely normal, but a twin-to-twin transfusion occurs because the feeder artery and draining vein are connected one to each other via the villous capillaries, and via the chorionic plate to each twin. There is no transfusion on the chorionic plate surface.

Provided that the cardiac outputs of both twins are roughly equal, there is no net transfusion in the superficial a→←a and v↔v connections. However, should the blood pressure of one twin drop, blood may rapidly be transfused from the other twin. v→v connections are particularly dangerous, because large blood volumes may be transferred at low pressure and resistance. In placentas with a dominant a→vc in one direction, the presence of a→←ac and/or v↔vc appears to protect against the development of TTT by returning blood from recipient to donor.

a→vc and a↔ac can be mapped *in utero* by Doppler methods[10], but v↔v cannot be detected. In a↔ac, asynchronous fetal hearts send arterial pulses of blood flow across the chorionic plate, causing the typical bidirectional pulsatile flow that is well known.

a→vc can also be detected by Doppler as follows[10]: an apparently single, continuous vascular structure is found running between the roots of the cords and with flow from donor to recipient; when pulsatile

**Table 27.2** Anatomy and function of the three types of interfetal vascular connections

| *Type* | *Arteriovenous* | *Arterioarterial* | *Venovenous* |
|---|---|---|---|
| Frequency in MC placentas | 75% | 80% | 20% |
| Flow | unidirectional, continuous, small volume, down arteriovenous pressure gradient; in a given placenta, several a→vc may flow in opposite directions | bidirectional, pulsatile; moderate volume | bidirectional, non-pulsatile; potentially large volume |
| Clinical significance | causes TTT when inadequately compensated; several a→vc in opposite direction may protect against development of TTT or moderate its severity | protects against TTT; necessary for TRAP; may allow flow from survivor when co-twin fetus dies | may protect against TTT; necessary for TRAP; permits rapid, large volume transfusions when one twin dying or hypotensive |
| Doppler detectable? | yes | yes | no |
| Number per placenta (when present) | 2–3 | 1 | 1–2 |

MC, monochorionic; TTT, twin–twin transfusion; TRAP, twin reversed arterial perfusion; a→vc, arteriovenous connection

characteristics are interrogated, this apparently single vessel is found to be an artery at the donor end and a vein at the recipient end.

The characteristics of these three types of interfetal vascular connections are summarized in Table 27.2.

The number and combination of interfetal vascular connections in a given MC twin placenta determines clinical outcomes (Table 27.3).

## CLINICAL COMPLICATIONS OF INTERFETAL VASCULAR CONNECTIONS

### Chronic prenatal TTT

Prenatal TTT is not a homogeneous disease entity with a simple, single causation. It overlaps somewhat with severe growth discordance, and may have clinical onset at any time in gestation. Characteristically, TTT is diagnosed at about 20–24 weeks of gestation (Figure 27.3). It varies in rapidity of onset and in severity. Staging systems have been proposed[11], but these are unsatisfactory because they imply an inevitable progression to a more advanced stage, whereas some cases resolve spontaneously and simple interventions often reverse the progress of the disease. Mild TTT cases have a vascular anatomy that is only slightly out of equilibrium (see Chapter 26). They have several vascular connections, with slight predominance of the causative a→vc. Loss of equilibrium is presumably caused by polyhydramniotic fluid pressure deforming the placenta and compressing a coexisting vascular connection that should permit downloading of recipient blood back to the donor. Typically, there are a few bidirectional a→v connections as well as an a>–<ac. It is not clear whether this a>–<ac is capable of compensation, as it may merely be a marker for the presence of several a→vc. Fetoscopy with a view to laser coagulation (FLOC) would show a confusing array of vascular connections (see Chapter 26), and it is unlikely that all would be detected. Hence, there is the possibility that FLOC could worsen the clinical condition of mild TTT by creating an unopposed a→vc. In rare cases, amnioreduction causes a reversal of the donor/recipient roles. This proves that amnioreduction affects the physiology of vascular connections, rather than merely prolonging gestation.

By contrast, severe TTT cases have simple vascular anatomy, sometimes with a single causative a→vc and few if any other vascular connections that can compensate for the detrimental effects of the causative a→vc. Removal of polyhydramniotic pressure is not likely to cure these severe cases, whereas FLOC is effective because the vascular anatomy is simple and readily identifiable.

Late onset of prenatal TTT occurs rarely in the third trimester, sometimes in the context of severe

**Table 27.3** Vascular connections and clinical outcomes in monochorionic (MC) twins

| *Clinical setting* | *Connections* |
|---|---|
| No complications | no connections; multiple connections, including bidirectional a→vc, or a→←a plus a few a→vc, with equilibrated bidirectional transfusion |
| TTT | severe: single causative a→vc<br>mild: few, bidirectional a→vc, perhaps with a→←ac |
| TRAP | a→←a plus v↔v |
| Brain-damaged survivor after fetal demise of co-twin | a→←a, v↔v, a→v from survivor to dead fetus |

TTT, twin–twin transfusion; TRAP, twin reversed arterial perfusion; a→vc, arteriovenous connection; a→←a, arterioarterial; v↔v, venovenous

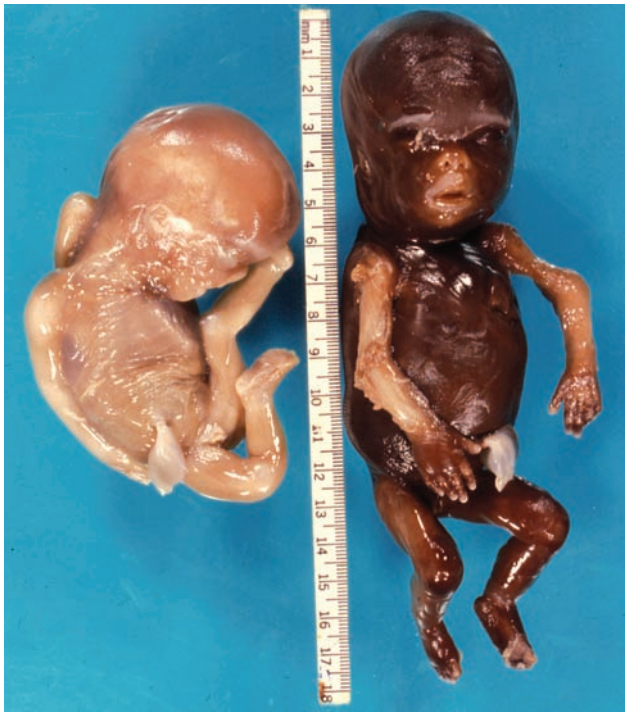

**Figure 27.3** These fetuses both died of twin–twin transfusion (TTT) before any treatment could be offered. The smaller donor twin is pale and shows flexional effects of oligohydramnios. The recipient fetus is larger and plethoric, with incipient hydrops

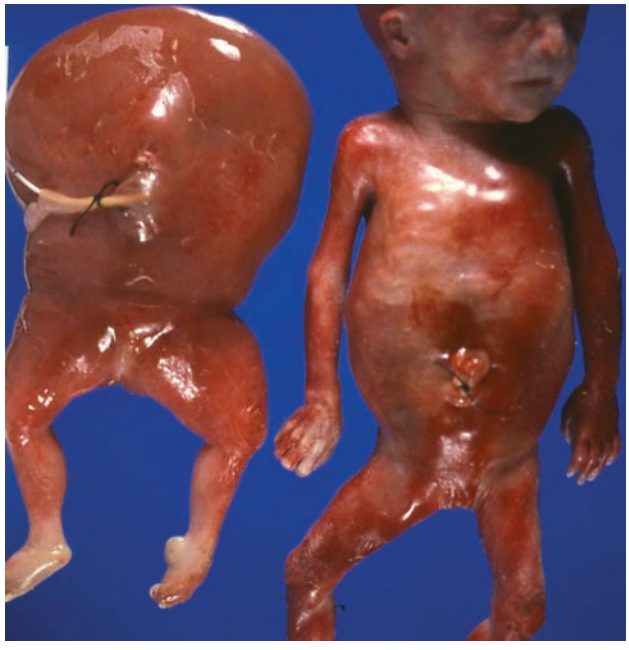

**Figure 27.4** Twin reversed arterial perfusion (TRAP). The acardiac fetus on the left has no head or upper limbs. This is the most common pattern

growth discordance. These cases may be caused by thrombosis in the venous limb of one a→vc, thereby disturbing an equilibrium between bidirectional a→vc[12].

### Acute perinatal TTT

This can occur in previously uncomplicated MC twins in whom the second-born twin is born markedly plethoric, may require blood dilution and usually is hyperbilirubinemic. Acute transfusion occurs in the interval between the cord clamping of the first-born twin and the birth of the second, during which the second-born is attached to the blood-filled placenta. Nothing is known about the optimal intertwin delivery interval in MC twins (see Chapters 78 and 81).

### TRAP

The pathogenesis of TRAP (Figure 27.4) is not known, but at least two mechanisms may operate. First, the acardiac twin may have a major cardiac anomaly (sometimes secondary to chromosomal

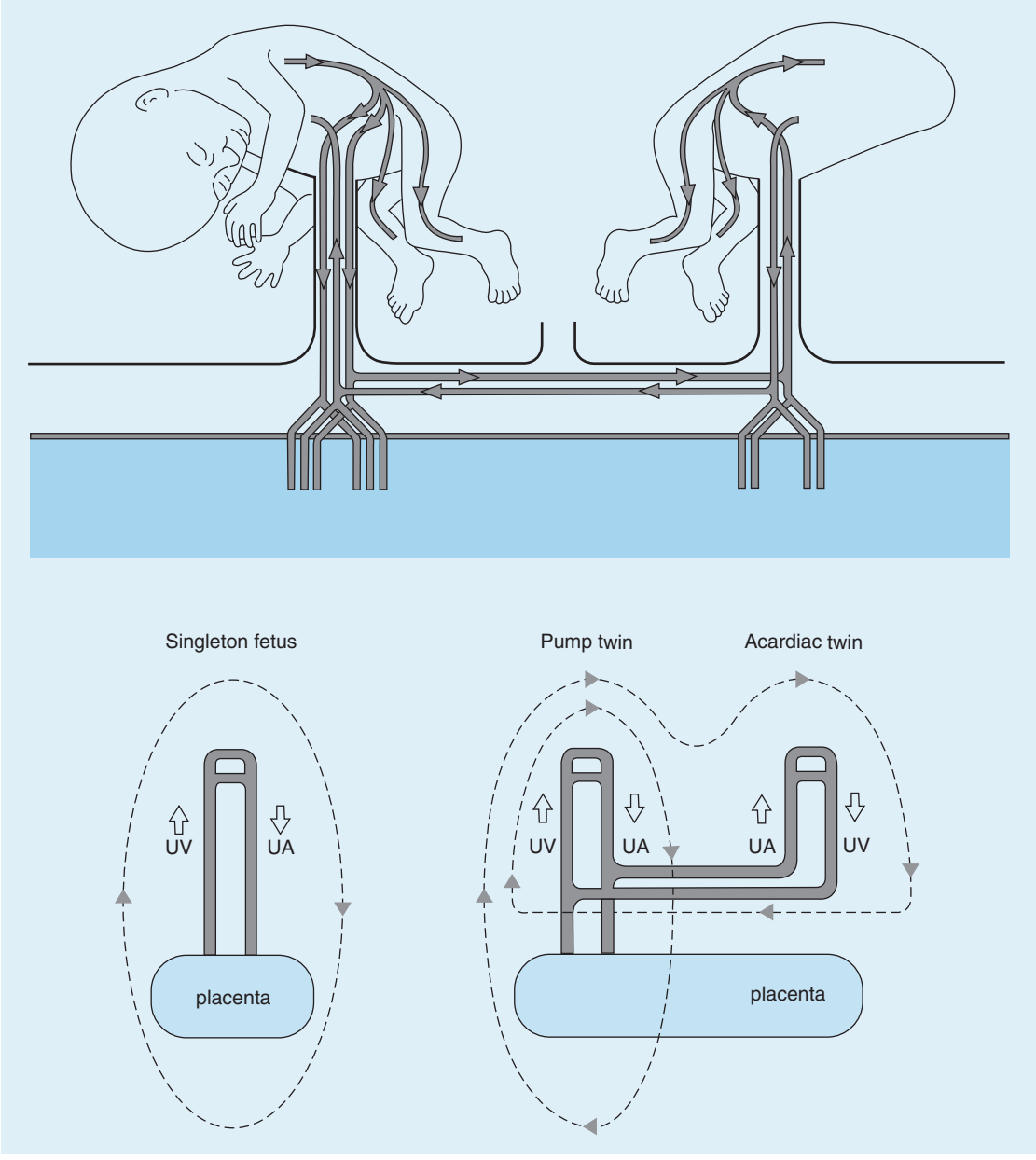


**Figure 27.5** Twin reversed arterial perfusion (TRAP). Because the acardiac fetus has no active circulation, blood returns directly from its body to the pump twin without any passage through the placenta. This blood is therefore 'twice-used', hypoxic, possibly carrying thromboemboli from the venovenous anastomosis and routed directly to the brain of the pump twin

aneuploidy) such that fetal demise and spontaneous miscarriage would be the rule in a singleton fetus. However, the fetus is 'rescued' by the presence of a co-twin and the types of vascular connection that are required for TRAP, namely, close cord insertions and large a→←a and v↔v connections. Second, TRAP may represent a severe form of TTT. In any event, the pump twin perfuses the whole placenta and the acardiac represents a 'side-branch' of the pump twin's circulation. The pump twin may deteriorate because of high-output cardiac failure. Another consideration is that the venous blood returning from the acardiac to the pump twin via the v←→v connection is 'twice-used' (Figure 27.5), having perfused the bodies of both pump and acardiac twins without benefit of a cycle of placental purging. Furthermore, blood flow in the v↔v connection is very slow, thrombosis frequently affects the vessel and thromboembolism is a risk (see Chapter 26). Opinions vary as to whether conservative or interventive management is best[13]. In TRAP, ultrasound-guided ablation of vessels in the cord or body of the acardiac is sufficient,

without harm to the pump twin. However, this management is not appropriate in MC twins with two functional hearts (see below and Chapter 71).

### Impending fetal demise

Causes of fetal demise in one of a pair of MC twins include: severe growth discordance with impending demise of the smaller twin; discordant major malformation, e.g. jugular lymphatic obstruction sequence in MC twins discordant for 45,X chromosome constitution; and TRAP and TTT. The danger to the co-twin is an episode of acute hemorrhage and hypotension as the other fetus dies (theories of transplacental thrombogenesis are nowadays discarded). Brain injury can occur within a few minutes of fetal demise, and hence management is aimed to convert the twins into a non-connected state. More danger exists to the survivor of fetal death in TTT if the recipient rather than the donor dies first[14]. This is because the donor can continue to transfuse into the placenta and body of the recipient via the causative a→vc. Whereas many physicians ablate cord vessels to precipitate the death of the ailing twin, this fails to recognize that the survivor can hemorrhage not only into the body of the dead twin but also into that portion of placental parenchyma that was previously perfused by that twin. In view of this, it seems more logical to use FLOC to separate the two circulations entirely, thus insulating the intended survivor from the placental parenchymal sump of the intended demised twin.

### Selective termination and multifetal reduction

Similar considerations apply as above. Simple cord occlusion may be insufficient to protect the intended survivor from hemorrhagic hypotension after the demise of the selected fetus. The use of digoxin or potassium chloride is contraindicated, because these agents cross via interfetal connections to affect both fetuses. For multifetal reduction, some authors target MC pairs and use standard toxic injection techniques deliberately in order to maximize the survival of the pregnancy by removing both high-risk MC fetuses.

### Vasculogenic pseudoconcordance

As discussed more fully in Chapter 31, interfetal vascular connections can result in unusual and surprising concordance in MC twins. These include:

(1) The 'disguise' of a hypothyroid fetus because normal thyroid hormone is produced by the co-twin and transfused across the connections;

(2) Transfusion of hematopoietic stem cells insures that fetal leukemic oncogenic mutations are present in both fetuses. If one clone of such cells is established in one fetus, both twins will eventually develop leukemia, though not necessarily simultaneously;

(3) The investigation of MC twins for a chromosomal or gene mutational basis when they are discordant for a major malformation must be performed carefully, avoiding the use of blood leukocytes. The reason is that transfusion of mutated stem cells will happen during fetal life, so that the unaffected fetus may give a false-positive result and mask the fact that somatic cells are genetically normal.

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# The Phenomenon of Monozygosity

*G. A. Machin*

**28**

**TIMING OF MZ TWINNING EVENTS**

**ALLOCATION OF FOUNDER CELLS TO MZ TWINS**

**DISCORDANT GENETIC AND EPIGENETIC PHENOMENA**

**OBSTETRIC MANAGEMENT**

**ZYGOSITY AS BASIS FOR 'TWIN STUDIES'**

**IMPORTANCE OF ZYGOSITY AND CHORIONICITY IN POSTNATAL LIFE OF TWINS**

## INTRODUCTION

Monozygotic (MZ) twinning is a form of 'vegetative' reproduction whereby more than one individual results from a single zygote. The event has never been observed directly in humans. MZ twins at birth usually weigh somewhat less than twice the birth weight of singletons of corresponding gestational age, but the discrepancy is usually not great. Hence, a single fertilized egg is capable of producing much more somatic and placental mass than usual, but the mechanisms of overgrowth in MZ twinning are not fully understood. There may be extra mitotic cycles and/or reduced apoptosis, but it is a tribute to the plasticity of early embryogenesis that anatomically normal and well-grown MZ twin, triplet, quadruplet and even quintuplet fetuses can be produced from one fertilized egg. Despite this, profound anatomic anomalies also result from MZ twinning (e.g. conjoined twinning, acardiac twins, twins discordant for regional malformations), and these outcomes have tainted the perception of MZ twinning with the reputation of being a teratologic or 'freakish' event whose mechanism is quite unknown and unknowable.

The prevalence of MZ twinning is fairly constant worldwide by geography and ethnicity. This circumstance suggests that, unlike dizygotic (DZ) twinning, MZ twinning is an intrinsic property of all human zygotes. Familial MZ twinning (Figure 28.1) is currently described with increasing frequency, and there presumably are identifiable molecular mechanisms that cause post-zygotic cells to disaggregate rather more easily than usual, forming two or more inner cell masses. As these are stochastic events, there is no mechanism to ensure that MZ twinning takes place in a way that is either 'tidy' or 'fair'. Indeed, the opposite is often the case.

MZ twins are often presumed to be 'genetically identical' at birth and to have lived their fetal life in a common intrauterine environment, which will have affected them equally. Furthermore, MZ twins are often presumed to have originated from equal numbers of multipotential 'founder cells', and to have enjoyed equal relationships with their sources of placental nutrition and gas exchange. Unfortunately, all of these assumptions are untrue, albeit to varying extents, and more so in some MZ twin pregnancies than in others. The complexity and variety of early MZ twin development lend a degree of sophistication and fascination to the understanding of MZ twinning that also vitiates many 'twin studies' that do not take account of the degree to which MZ twins may be discordant at birth as a result of a variety of environmental, genetic and epigenetic events that take place after conception.

Although striking dissimilarity between MZ twins of a pair is infrequent, it seems likely that all MZ pairs are affected to some degree by the influences described below that cause them to be similar but not absolutely 'identical'. It is misleading to extrapolate from newborn and adult MZ twin phenotypes back to the nature and timing of the twinning event, as even the most simplistic models of MZ twinning events are not universally applicable. This chapter explores recent understandings of events associated with MZ twinning that cast new light on:

(1) Timing of twinning events *per se*;

(2) Allocation of 'founder' cells;

(3) Divergent genetic and epigenetic events in post-conceptional life that cannot be observed in singletons;

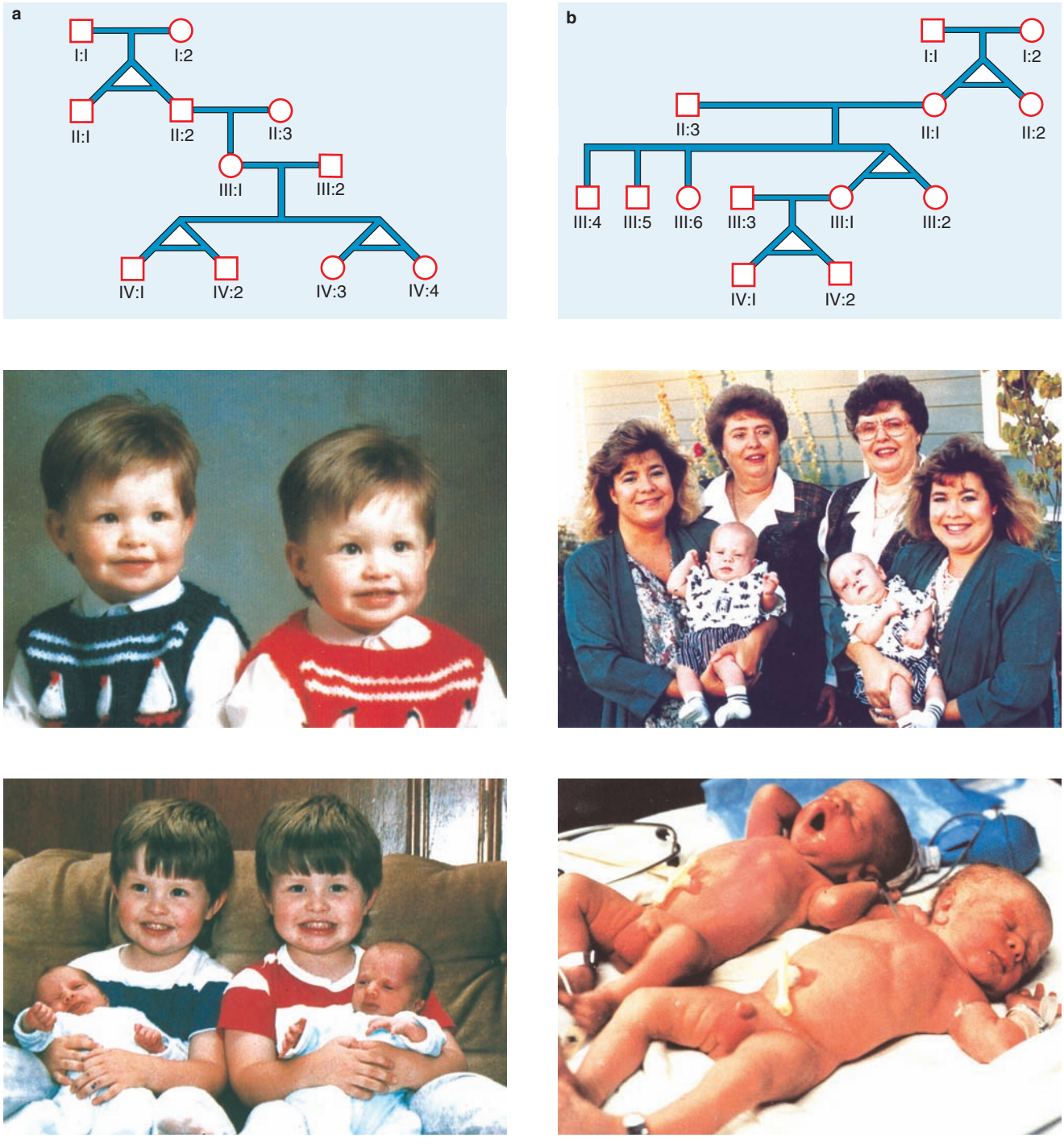


**Figure 28.1** Examples of familial monozygotic (MZ) twinning. (a) Family 1. This mother gave birth to two successive MZ twin pairs. The mother's father was also an MZ twin. (b) Family 2. MZ twinning occurred in three successive generations, suggesting autosomal dominant inheritance

(4) Obstetric management of MZ (mostly monochorionic (MC)) twin pregnancy;

(5) The 'classic twin method' of research;

(6) Zygosity in postnatal life and acceptable methods of twin zygosity testing.

## THE TIMING OF MONOZYGOTIC TWINNING EVENTS

The timing of MZ twinning events can be inferred from: placentation (Tables 28.1 and 28.2); X chromosome-inactivation patterns in female MZ twins (Tables 28.3 and 28.4); asymmetric language

**Table 28.1** Timing of human post-zygotic cell divisions, blastulation, etc., in relation to monozygotic (MZ) twinning

| *Days pc* | *Cell number* | *Comments* |
|---|---|---|
| >1 | 1 | |
| 1 | 2 | |
| 1.5 | 4 | |
| 3 | 8 | morula; zona pellucida dissolves; last opportunity for DC twinning; X-inactivation |
| 4 | | cavitated blastocyst, i.e. only one chorion |
| 7 | | inner cell mass still solid; last opportunity for MC–DA twinning |
| 8 | 128–156 | amniotic cavity forms; twins are now MC–MA with a single primitive yolk sac |
| 12 | | MC–MA twins are conjoined |
| 13 | | primitive streak appears, defining zygote as singleton |

pc, post-conception; DC, dichorionic; MC, monochorionic; DA, diamniotic; MA, monoamniotic

**Table 28.2** Length of windows for monozygotic (MZ) twinning versus placentation frequencies

| | *DC* | *MC–DA* | *MC–MA* |
|---|---|---|---|
| Length of twinning windows (days (%)) | 3 (25) | 5 (42) | 4 (33) |
| Observed proportions of MZ twins by placentation (%) | 33 | 62 | 5 |

DC, dichorionic; MC, monochorionic; DA, diamniotic; MA, monoamniotic

**Table 28.3** Means and ranges (%) for skewed X-inactivation discordance in female singletons, monozygotic–dichorionic (MZ–DC), monochorionic–diamniotic (MC–DA) and monochorionic–monoamniotic (MC–MA) twins[1–3]

| | *Singleton blood* | *Singleton buccal* | *MZ–DC blood* | *MZ–DC buccal* | *MC–DA blood* | *MC–DA buccal* | *MC–MA buccal* |
|---|---|---|---|---|---|---|---|
| *n* | 21 | 21 | 13 | 13 | 20 | 20 | 11 |
| Mean | 18.5 | 11.3 | 15.6 | 11.3 | 17 | 15.1 | — |
| Range | 2.2–43 | 3–27 | 0.02–44 | 3.3–40 | — | 0.6–46.5 | — |
| Mean within-pair discordance | — | — | — | 14.3 | — | 5.9 | 2.1 |

**Table 28.4** Patterns of skewed (sk) X-inactivation in female monozygotic (MZ) twins discordant for phenotypic expression of X-linked recessive disorders[4–7]

| *sk/sk reciprocal* | *sk/sk concordant* | *sk/r* |
|---|---|---|
| FMR1, three cases | factor VIII, one case[4] | DMD, one case |
| DMD, three cases | factor IX, one case[5] | Hunter's, one case |
| Fabry, one case[6] | | |
| CBD, one case | | |

FMR1, X-linked mental retardation; DMD, Duchenne muscular dystrophy; CBD, red–green color blindness, partial deuteran series; r, random

**Table 28.5** Language functional lateralization by handedness in monozygotic (MZ) twin pairs, analyzed by chorionicity[8]

| *Handedness* | *Total* | *MC* | *DC* | *Not known* |
|---|---|---|---|---|
| *RH/RH* (%) | 12 | 5 (42) | 4 (33) | 3 (25) |
| Mean lateralization index, 12 cases | 0.7 | 0.7 | 0.77 | 0.52 |
| Mean within-pair lateralization difference | 0.12 | 0.09 | 0.065 | 0.33 |
| Female (%) | 7 (58) | 4 (80) | 1 (25) | 2 (67) |
| Dominant right hemisphere | 0 | 0 | 0 | 0 |
| *RH/non-RH* (%) | 13 | 8 (62) | 3 (23) | 2 (15) |
| Mean lateralization index, 13 cases | 0.34 | 0.31 | 0.72 | 0.18 |
| Mean within-pair lateralization difference | 0.35 | 0.53 | 0.06 | 0.14 |
| Female (%) | 5 (38) | 2 (25) | 1 (33) | 2 (100) |
| Dominant right hemisphere (%) | 5 (38) | 4 (50) | 0 (0) | 1 (50) |

RH, right-handed; MC, monochorionic; DC, dichorionic

function in the cerebral hemispheres (Table 28.5); and asymmetric dermatoglyphics (see 'Fine tuning').

## Placentation

About one-third of naturally conceived MZ twins have dichorionic (DC) placentas, indicating that each twin received both trophoblastic and somatic stem cells into their cell masses. Therefore, twinning must have happened before the differentiation and physical separation of trophoblastic and somatic cells into the outer and inner cell masses, respectively, of the cavitated blastocyst at about 3 days post-conception. DC–MZ twins are derived from the splitting of about eight blastomeres. Splitting at any time thereafter results in a single MC placenta that continues as such even in the face of subsequent MZ twinning in the inner cell mass. Because the amniotic cavity forms at about 8 days post-conception, twinning between 3 and 8 days results in each twin having an amniotic cavity, i.e. MC–diamniotic (DA) placentation, whereas MC twinning that occurs after 8 days is monoamniotic (MA). Unless twinning occurs before the primitive streak is determined at about 13 days, the zygote remains on course to produce a singleton. Twinning just before 13 days results in various forms of conjoined twins.

In naturally conceived MZ twins, the ratios of DC, MC–DA and MC–MA twins do not correspond with the relative lengths of the windows of opportunity for MZ twinning as defined by placental type (Table 28.2). If MZ twinning events took place at a constant rate during the first 12 days post-conception, proportions of DC, MC–DA and MC–MA twins would vary from those observed. There are indications of high rates of early prenatal loss of MC–MA and conjoined twins[9]. Thus, the under-representation of MA and conjoined twins at birth relative to the frequency of these conditions in earlier gestation is explained by their greater fetal lethality, and the relative excess of DC–MZ twins may be the result of their having no placental complications in contrast with MC twins in general.

## X chromosome-inactivation studies

These studies link inactivation to subtypes and timing of MZ twins, and also indicate that allocation of cells to the twins is not always equal (see below). Despite the female excess in MZ twinning, it is not clear that X-inactivation is a major stimulus to MZ twinning *per se*. Assuming that X-inactivation is a stochastic process in which each female embryonic cell inactivates the maternally or paternally derived X chromosome through an independent, random process (rather than in externally, or mutually, induced patches of cells), inferences can be drawn about the temporal relationship between X-inactivation and the timing of MZ–DC, MC–DA and MC–MA twinning. However, the conclusions thus far reached are only valid if it is accepted that the three-dimensional mutual relationship between embryonic cells in the morula and blastocyst is fixed, and that there is no 'mutual recognition' of similarly X-inactivated cells, with subsequent migration and cloning of similarly inactivated cells during or prior to the twinning event. X-inactivation results are expressed as means and ranges with mean within-pair discordance[1–3] (Table 28.3). Because the window periods for MC–DA and MC–MA twinning are roughly equivalent (4–5 days), the smaller mean discordance for within-pair X-inactivation skewing (sk) in MA than in DA–MC twins suggests that cell allocation is more frequently equal in MA twins, and from a larger population of randomly X-inactivated cells. Very marked within-pair sk was not seen in any twin

pairs in this series. MZ twin X-inactivation studies on blood-derived DNA should be interpreted with caution when the twins are known or suspected to have been MC. Fixed somatic (e.g. buccal) cells are more informative, as in these series.

Details of patterns of within-pair sk discordance were not reported in this series. There are four possible patterns of pair-wise X chromosome inactivation: sk/sk, reciprocal (in opposite directions); sk/sk, concordant (same direction); sk/random (r); and r/r. Degrees of discordant sk might vary within these patterns. Likewise, these patterns could give clues to the mechanisms of allocation of cells to twin embryos before, during and after X-inactivation. For instance, reciprocal sk would suggest some mutual recognition and cloning of previously X-inactivated cells (perhaps stimulating twinning), whereas the sk/r pattern implies likely phenotypic discordance for X-linked traits, as well as unequal allocation of founder cells, with twinning occurring after X-inactivation. It has been suggested that marked sk in singleton females may indicate early loss of a reciprocally sk or r MZ co-twin. By extension, a concordant sk/sk pattern in MZ twins might even suggest the early loss of an MZ co-triplet with reciprocal sk. Combining three reported series of within-pair X chromosome inactivation studies in female MZ pairs without phenotypic discordance for X-linked genetic diseases[1–3], all four sk patterns were seen: sk/sk, concordant: 24 (28%); sk/sk reciprocal: 7 (8%); sk/r: 20 (23%); r/r: 36 (41%). Thus, the majority of female MZ twins do not show detectable discordance for within-pair sk, the most common sk pattern is sk/sk concordant and only 8% have reciprocal sk. X chromosome inactivation patterns have been used to investigate timing of MZ twinning events. It has been shown that X-inactivation precedes the event in MC twins[10], and that X-inactivation patterns confirm MA twinning as a late event in MC twinning[11]. Marked sk has been reported elsewhere as a rare event in the context of investigating discordant within-pair phenotypes for X-linked recessive traits (Table 28.4)[4–7]. All three sk patterns have been seen. In this small series, sk/sk reciprocal is the most common pattern, but it is much less common in non-symptomatic MZ female twin pairs. Concordant sk/sk and sk/r patterns are under-represented in symptomatic twins.

## 'Mirroring' in monozygotic twins

Opposite-handedness is well known within both DZ and MZ twin pairs. For parents of twins, 'mirroring' is one of the most fascinating aspects of their twins' lives. Very few systematic studies have been carried out to explore the extent of 'mirroring' in MZ twins, which certainly does not extend, for instance, to discordant situs inversus[12]. Later MZ twinning (that results in MC–DA and MC–MA twins) could be occurring when the molecular determinants of left/right asymmetry are beginning to be expressed with lateral discordance. In one study of cerebral dominance in genotypically proven MZ twin pairs, functional magnetic resonance imaging (MRI) was used to detect activation of language areas while the twins carried out language tasks[8]. Twelve pairs were concordantly right-handed (RH/RH) and 13 were discordantly handed (RH/non-RH). Chorionicity was known in 20 of the 25 pairs, and was proportionate with the overall frequency of MC and DC twins among MZ twins (Table 28.5). There was an excess of RH/non-RH pairs in the MC twins. Eight of 13 (62%) MC pairs and three of seven (43%) DC were RH/non-RH, respectively. Lateralization for language areas was quantified as the number of voxels in each hemisphere; the lateralization index was calculated as (number of active voxels of left hemisphere) minus (those of the right hemisphere)/ all active voxels. There were no dominant right hemispheres in the RH/RH twins, but two of the RH twins and three of the non-RH twins in the RH/non-RH pairs had dominant right hemispheres. Of these five pairs with one twin having a dominant right hemisphere, four were MC and one was of unknown chorionicity. Thus, 50% of the RH/non-RH pairs who were MC had dominant right hemispheres. No DC twins had dominant right hemispheres, and there were no pairs in which both twins had dominant right hemispheres. Because of the frequency of dominant right hemispheres in MC RH/non-RH pairs, the mean within-pair lateralization difference in MC RH/non-RH twins was greater than in any other group. There was also a marked male excess (62%) in the RH/non-RH twins compared with a 58% female preponderance in the RH/RH twins. Three of the five RH/non-RH twins with dominant right hemispheres were males. These results suggest that (later) MC twinning occurs at about the time when right/left orientation is being laid down, with a consequent excess of RH/non-RH twins in MC twins. The male excess in this group might be explained by the fact that X-inactivation is also occurring at this time, as well as by any difference in timing of expression of right/left asymmetry between developing male and female embryos in general. Future research might study the handedness of twin survivors of so-called 'vanished twin' pregnancies.

## 'Fine-tuning': detailed peripheral patterning

At one time, the field of dermatoglyphics had a place in the investigation of twin zygosity and *vice versa*. It has always been clear, however, that MZ twins are not concordant for dermatoglyphics, this being one of the oldest known means by which MZ twins are not

'identical'. Recent work[13] shows that the frequency and extent of discordance in dermatoglyphic patterns of MZ twins varies with chorionicity; MC twins show more within-pair variability than DC–MZ twins. There is also evidence of an effect from placental crowding: MZ twins with fused DC placentas show greater variability than those with separate placentas. This effect was also noted in like-sexed DZ twin pairs.

An association has also been described between asymmetric a–b ridge counts and discordant personalities[14]. Such twins may be poorly buffered for chance developmental events in the twinning process that discordantly affect many aspects of development.

## ALLOCATION OF FOUNDER CELLS TO MONOZYGOTIC TWINS

Discordant allocation of 'stem cells' during MZ twinning has been inferred from the sk/r case (discordant for Duchenne muscular dystrophy (DMD), Table 28.4)[15], (Figure 28.2) which was investigated for patch size of dystrophin-positive and -negative cells in muscle biopsies of both twins. The affected twin showed larger alternating patches of oppositely dystrophin-producing cells than the unaffected twin, indicating that the affected twin was derived from a smaller number of stem cells than the co-twin. These founder cells gave rise to larger territories (i.e. clones) of similarly X-inactivated cells than is the case in normal cell proliferation. The implication is that the twinning process involved unequal allocation of stem cells to the twins and that, as might be expected by chance, there was sk in the smaller twin. The larger cell mass giving rise to the co-twin was not affected by the loss of a few cells to the co-twin, and therefore showed r inactivation. Unequal founder cell allocation could, in turn, determine relative placental masses in DC–MZ twins and placental sharing of parenchyma in MC twins. At all events, the etiology of significant growth discordance in MZ twins is quite complex, and could result from unequal blastomere allocation and/or placental environmental issues. It may seem paradoxical that the more remote the MZ twinning event is from conception, the more functionally entwined are the fetal lives of those twins. An early twinning event produces a 'clean break'.

## DISCORDANT GENETIC AND EPIGENETIC PHENOMENA IN MONOZYGOTIC TWINS

X-chromosome inactivation has already been mentioned as being discordant in some female MZ twin pairs, with implications for timing and phenotype.

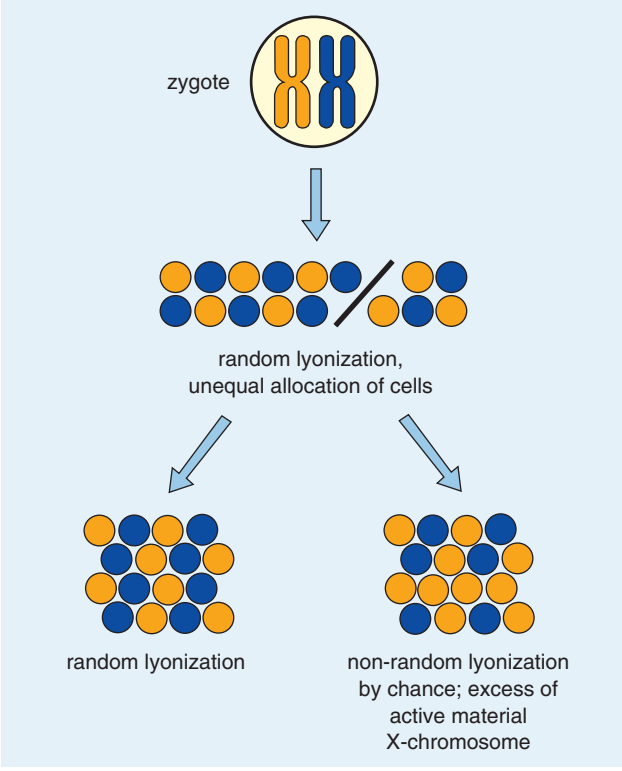


**Figure 28.2** Diagrammatic representation of unequal allocation of blastomeres after X-inactivation which might, by chance, lead to skewed X-inactivation in the smaller cell group, while the larger group remains substantially randomly inactivated. The smaller resulting twin would express an X-linked disease, maternally inherited, if the majority of inactivated X chromosomes were of paternal origin. Cells with inactivated paternal or maternal X chromosomes are shown in blue and yellow, respectively

Several other post-zygotic events also can cause discordant phenotype, including the following.

### Chromosomal mosaicism

The presence of two or more cell lines derived from the same zygote having different chromosomal constitutions (secondary to post-zygotic events) is well recognized in aneuploid singletons. Mosaicism can likewise occur in MZ twin pairs. Depending on the relative timing of the twinning and chromosomal events, the two or more cell lines may be distributed largely or exclusively in somatic (fixed) cells of one twin or the other. If the twins are MC, blood cells usually contain both cell lines because of prenatal transfusion of bone marrow-derived stem cells. Thus, blood cell chromosome results may not reflect discordance in fixed somatic cells of the twins, and the degree of mosaicism may vary between fixed cell populations, e.g. ectodermal cells and brain cells. For prenatal diagnosis, both amniotic cavities of MC–DA

twins should be sampled, whereas the amniotic cavity of MC–MA twins will presumably contain both cell lines. Chorionic villus sampling (CVS) is not recommended, even when samples are taken close to the cord insertions of each twin[16]. Fetal blood sample chromosomes likewise may not reflect mosaicism levels in fixed cells[17].

Mosaicism has been reported in MZ twins for all the common aneuploidies. Mosaicism for 45,X is of particular concern for three reasons:

(1) Whereas the original zygotic chromosome constitution could be 46,XX, with loss of an X chromosome, there could also be an original 46,XY zygote, followed by post-zygotic loss of the Y chromosome in one twin. A 45,X/46,XY conceptus can result in a 46,XY male and a mosaic 46,XY/45,X female. The 46,XY/45,X twin is likely to be reared as a female and, if the twins are MC (with fetal passage of testosterone via vascular anastomoses from the 46,XY co-twin), is at risk for fetal brain masculinization. At the same time, an apparently normal male co-twin may have a small representation of the 45,X cell line in some fixed cells. In many instances, parents may find it difficult to deal with gender issues in their unlike-sexed MZ twins.

(2) Confusion may arise if 45,X/46,XY MZ mosaic twins are diagnosed by ultrasound as being both MC and with unlike external genitalia. Rapid DNA-based zygosity testing from amniotic fluid samples may resolve the dilemma[18].

(3) Whether derived from a 46,XX or a 46,XY zygote, the MZ twin with a predominant or total 45,X constitution is likely to develop fetal jugulolymphatic obstruction sequence, endangering the life of the co-twin at about 20 weeks' gestation, when fetal hydrops usually sets in secondary to high-pressure lymphatic pleural effusions[19]. The question of selective termination may arise, and special considerations apply to MC twin pregnancies (see also Chapter 64).

### Imprinted genes

Discordance in MZ twin pairs is well recognized for diseases thought to result from abnormal imprinting of genes. Beckwith–Wiedemann syndrome (BWS) is caused by abnormal imprinting of one or more of a cluster of genes in the p15 region of chromosome 11. There is an excess of females among MZ twin pairs discordant for BWS. The gene cluster is coordinately regulated by expression of KCNQ10T1. Discordant BWS twins have defective imprinting of KCNQ10T1 in the affected twin, the normal twin showing normal imprinting[20]. It is not clear how the abnormal imprinting relates to the MZ twinning process, through unequal splitting, post-zygotic chromosomal rearrangements or abnormal imprinting at the crucial moment of twinning.

### Trinucleotide repeat sequences

Several progressive neurologic disorders are characterized by phenotypic expression only when a threshold of trinucleotide repeat number (TRN) is exceeded. Discordance has been found in some MZ twin pairs for TRN expansion in fragile X syndrome, even though peripheral blood lymphocytes were analyzed and the twins were known to be MC. A more severely affected twin had a complete mutation, whereas his less severely affected brother was 'mosaic' for premutation and full mutation[21]. This consideration could cause some difficulty when offering predictive testing for Huntington's disease to MZ twins[22].

### Phenotypic discordance with same genetic predisposition

Microdeletion of chromosome 22q11.2 produces a spectrum of disorders, including velocardiofacial syndrome and DiGeorge syndrome. MZ twins are usually discordant for the extent and severity of congenital heart disease when they have the 22q11.1 deletion. There may be a second epigenetic effect on the phenotype, but the reason for its discordant effect is unknown[23].

### Discordance for single gene mutation

It would be expected that MZ twins affected by an autosomal dominant disorder such as neurofibromatosis type I might show different somatic patterns of distribution of discrete lesions because of somatic mosaicism. However, MZ twins were recently described who are the first example in which the phenotypic discordance for a single gene disorder is caused by (post-zygotic) discordance for the causative point mutation[24].

### Discordance for major malformation

For major regional malformation (e.g. thyroid dysgenesis (see below), urinary tract malformation (see below), spina bifida, omphalocele, congenital heart disease, Figure 28.3), MZ twins are usually discordant. If this fact is not known, preparations may be made for selective termination of one twin on the assumption that the twin pair must be DZ and therefore DC. If in reality the twins are MZ and MC, death of the unaffected co-twin will ensue when intravascular agents are used. However, MZ twins tend to be concordant

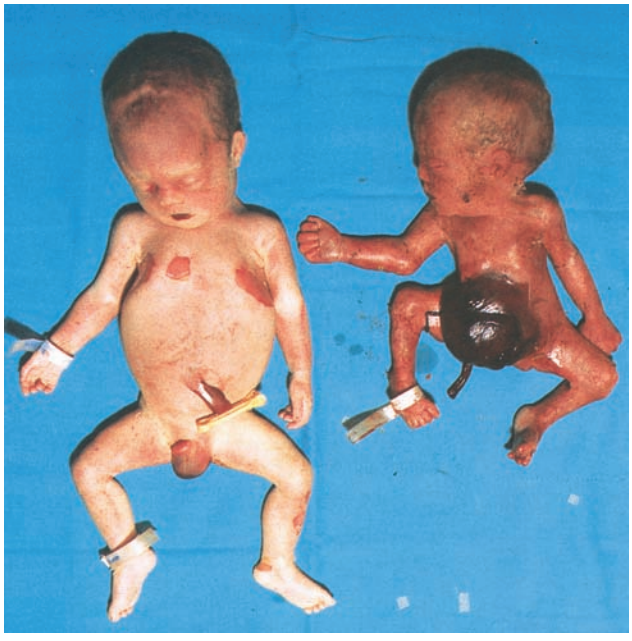

**Figure 28.3** When major malformations are present in monozygotic (MZ) twins, they are usually discordant. These MZ twins were discordant for cloacal dysgenesis

for major regional malformations such as cloacal dysgenesis and omphalocele-exstrophy-imperforate anus-spinal defects (OEIS) syndrome, and these anomalies are more common in MA than DA–MC twins. This suggests that these anomalies, involving structures close to the primitive node, occur towards the end of the window period for MZ twinning, close to the time when conjoining might soon result. Many cases of discordant congenital heart disease in MZ twins are of 'flow' type. These anomalies are thought to result from abnormal flow in the primitive heart chambers and great vessels during the actual time of cardiogenesis. The excess of 'flow' lesions in MC twins suggests that vascular imbalance can happen very early in gestation, and that these fluctuations are large but temporary. Genetic counseling for congenital heart disease in MC twins therefore must take into account factors that do not apply in singletons and DC twins.

For practical reasons, the issue raised by MZ twin discordance for malformation is whether there need to be different guidelines for attempted selective termination in MC twins compared with DC twins. There is a potential for injuring the intended survivor co-twin via vascular anastomoses. It could thus be suggested that selective termination is attempted only when the anomalous twin is deemed likely to die in the fetal period, thereby disturbing the dynamics of established interfetal vascular connections, and causing hypotensive brain damage to the survivor. In order to establish such guidelines, one would need to be know more about the fetal natural history of major malformations. For instance, it is known that jugular–lymphatic obstruction sequence is often lethal in the fetal period (at about 20 weeks) (for discussion, see above section on 'Chromosomal mosaicism'). However, malformations such as anencephaly may not necessarily have a benign fetal course. In a series of 11 MC twin pairs discordant for anencephaly[25], three pairs died in fetal life, presumably as the result of fetal death of the anencephalic fetus. There may have been exsanguination of the normal co-twin via fetal vascular connections.

### Pseudo-concordance caused by monochorionic vascular anastomoses: thyrois dysgenesis

About 85% of cases of congenital hypothyroidism are caused by thyroid dysgenesis, a sporadic disorder in which development and/or migration of the thyroid gland is abnormal. The remaining 15% of congenital hypothyroidism is caused by various autosomal recessive disorders of thyroid hormone biosynthesis. Both defects can be detected by newborn biochemical screening. However, MZ twins are frequently discordant for thyroid dysgenesis (seven of eight published pairs[26]). When such MZ pairs are MC, interfetal vascular connections may have two effects: first, the affected fetus may be protected from hypothyroidism by the transplacental transfusion of thyroxin from the thyroid of the unaffected co-twin; and, second, the affected twin may have a mildly abnormal newborn screening test for hypothyroidism, with risk of postnatal hypothyroidism through delayed diagnosis.

### Pseudo-concordance for phenotype in monoamniotic twins discordant for urinary tract malformation

Like all types of MZ twins, MC–MA twins may be discordant for major malformations. In singletons, MC–DA and DC twins, the presence of fetal anuria causes anhydramnios, together with typical 'Potter facies' and lethal pulmonary hypoplasia. However, the normal twin of an MA pair discordant for fetal anuria produces sufficient amniotic fluid to protect the anuric co-twin from the secondary, deforming effects of anhydramnios. Such twins do not die immediately from pulmonary hypoplasia and do not have the 'Potter facies' external phenotype[27]. Because of cord entwining, attempts at selective termination in discordant MA twins are ill-advised and fraught with difficulty[28].

## OBSTETRIC MANAGEMENT OF MONOZYGOTIC TWINS

In prenatal life, zygosity is not as important as chorionicity in determining outcomes. However, it is

**Table 28.6** Supposed genetic and environmental effects on concordance/discordance in monozygotic (MZ) and dizygotic (DZ) twins: the 'twin method'

| *Zygosity* | *Genetic influence* | *Environmental influence* |
|---|---|---|
| MZ | concordant | causes discordance |
| DZ | discordant | causes concordance |

not always recognized that chorionicity should be diagnosed with certainty in the first trimester, in order to allow for more frequent prenatal follow-up of MC pregnancies in the search for early signs of major complications. Furthermore, it is often assumed that MC twins, being MZ, are 'identical'. As mentioned above, however, MZ twins can be discordant for prenatally diagnosable major anomalies, and, when this is mistakenly thought to be incompatible with monozygosity, selective termination of pregnancy may be attempted using methods that cause death of both fetuses. Last, many health-care professionals fail to recall that about one-third of MZ twins are DC. Innumerable parents are confused when they are confidently told during the pregnancy or at the time of delivery that their like-sexed twins are 'fraternal' because they are dichorionic (i.e. have two placentas), only for those twins to be disarmingly similar at birth and throughout childhood. The most common reason for parental requests for zygosity testing is to dispel doubts about MZ status caused by inaccurate diagnosis of presumed dizygosity on the basis of DC placentation.

## ZYGOSITY AS THE BASIS FOR 'TWIN STUDIES'

At its most simplistic, the classic twin study model aims to distinguish 'environmental' from 'heritable' influences on development, behavior, growth and predisposition to disease, through analysis of degrees of concordance/discordance in MZ and DZ twin pairs (Table 28.6). Concordance for a given feature in MZ pairs with discordance in DZ pairs would be taken as evidence for genetic factors; the converse would apply to environmental influences. In most peoples' minds, MZ twins are 'identical' and DZ twins are 'fraternal', (even when the latter are female/female pairs). Nothing could be further from the truth, and the foundations of the classic twin studies are being threatened by the correction of some incorrect assumptions, many of which have been discussed in this chapter. Twin studies are jeopardized if they fail to take into account some developmental factors mentioned above, i.e. unequal allocation of founder cells to each twin (see Chapter 37), possible biological differences between DC and MC–MZ twins, adverse fetal events secondary to MC placentation (see Chapter 24) and several genetic/epigenetic post-zygotic mechanisms that cause subtle to marked phenotypic discordance (see above).

Equally misleading is the concept that MZ and DZ twins, regardless of chorionicity, share the same intrauterine environment. It is true that a given MZ or DZ twin pair inhabits an intrauterine environment that is equally affected by large-scale (macroenvironmental) factors such as maternal nutrition and cardiovascular and endocrine status. However, the intrauterine microenvironment may vary markedly between the twins. For example, the implantation of one placenta (or part of a MC placenta) over a fibroid will affect maternal perfusion. Further, placenta previa, velamentous cord insertion and vasa previa usually affect one twin only. In addition, birth order may affect fetal exposure to hypoxia and ascending infection. Finally, the particular vascular anatomy of each MC placenta may have large discordant effects on fetal nutrition and growth, as well as permitting the persistence of acardiac fetuses (see Chapter 94). Paradoxically, the genetic constitution of a twin may affect its own placental physiology, by causing the deposition of fibrinoid material that blocks maternal perfusion[29]. It is too simplistic to ascribe growth discordance in DZ twins to an *in utero* expression of their different genetically programmed growth potential, as it is equally likely that one twin is influencing its own microenvironment by affecting the function of its own placenta. In summary,

(1) There is no evidence that MZ and DZ twin pairs emerge into postnatal life unblemished by discordant intrauterine environmental effects, and with DZ twins showing at birth only those discordant effects of different genetic constitutions.

(2) Many (and perhaps all) MZ twins are already 'genetically non-identical' at birth to varying degrees.

(3) It is incorrect to assume that MZ twins experience postnatal events discordantly. There is evidence that MZ twins interact more closely than DZ twins and that this affects, for example, their longevity[30]. In view of these indisputable facts, it is absolutely necessary to reassess the validity of

'twin studies', unless they take into account the subtle range of variables in genetic/epigenetic events and prenatal/postnatal environmental experiences outlined above.

## THE IMPORTANCE OF ZYGOSITY AND OF CHORIONICITY IN THE POSTNATAL LIFE OF TWINS; THE LIMITS OF ZYGOSITY TESTING

Unfortunately, the majority of like-sexed twins do not know their zygosity. Three main reasons support this statement:

(1) There is a widespread assumption that MZ twins are absolutely 'identical'. Because small phenotypic differences (present in all MZ twins) are often sufficient to persuade parents that their twins are DZ, they are henceforth designated as such by this method and no other.

(2) Clinicians infrequently realize that MC placentation, diagnosed in the delivery room, is the most secure method to diagnose MZ twins, and parents are seldom informed that their MC twins are indeed MZ.

(3) Because many health-care professionals mistakenly think that all DC twins are DZ, they unhelpfully interpret the obstetric ultrasound diagnosis of DC twinning as tantamount to DZ twinning, misinforming the parents accordingly. As many health-care providers do not realize the implications of zygosity on the lives of twins, they downplay, discount and discourage its investigation as mere idle curiosity, and often on grounds of cost.

In the final analysis, zygosity is important because of the relatively high rates of concordance in MZ twins and discordance in DZ twins for a wide variety of traits and disorders that have genetic components in their causation. The rates of concordance for these traits in MZ twins vary considerably across a range of conditions that includes: psoriasis, major depression, schizophrenia, intelligence quotient (IQ), neurotic/extrovert personality, diabetes, asthma, cardiac disease, various cancers and multiple sclerosis[31]. Expectation of concordance (but not necessarily synchronous onset) for these disorders in MZ twins would allow early diagnosis and treatment. Within the cancers, there are some striking examples of high concordance against a background of low concordance. Childhood leukemia is a special case in point, because the molecular investigation of these cancers has frequently shown that the first oncogenic mutations are prenatal, and that the presence of interfetal vascular anastomoses in MC twins allows intertwin transfusion of mutated cells, which settle in both bone marrows. When one MC twin develops overt acute leukemia, the co-twin may be clinically unaffected, but the mutation may be present in circulating or bone marrow cells[32,33]. Furthermore, the mutation may be retrospectively detectable in mosaic form in newborn metabolic screening blood spots from both twins[34]. These events have also been tracked in MZ twins of a DZ triplet set, the DZ triplet being unaffected[35]. *In utero* metastatic spread has also been suggested as the origin for concordant but metachronous neuroblastoma in MZ twins[36].

Investigation of concordance for breast cancer in twins has produced conflicting results. However, some selected reports imply that there is increased concordance in MZ twin pairs. It is suggested that the predisposing genotype is complex, with components of hormone susceptibility and abnormal tumor suppression[37]. Furthermore, the *per annum* risk that a MZ co-twin will develop breast cancer is twice the risk that the index case will develop contralateral breast cancer[38]. Thus, there seems to be simple 'field effect', with each MZ twin having four breasts predisposed to disease. The same would presumably apply to other paired organs, including ovaries. The case for zygosity diagnosis in these cases is compelling. Against a background of a BRCA1 mutation, investigation of the combinations of successive oncogenic mutations in cancer tissues from a pair of MZ twins with concordant breast cancer showed high mutational similarity (82 of 97 markers tested)[39].

There is a mild genetic predisposition to testicular cancer, and Figure 28.4 shows how testicular cancer and precancerous lesions may co-exist in a MZ twin pair.

Zygosity is important when considering solid organ transplantation between twins. If one twin suffers end-organ failure through an environmental insult, (i.e. the organ failure is not caused by a known single gene disease), the co-twin is an ideal donor if the twins are MZ. Inter-MZ twin organ transplantation is documented with increasing frequency. DNA-based zygosity testing is essential. In one case, like-sexed twins assumed they were DZ, based on mild phenotypic dissimilarity; the recipient of a living renal transplant from his co-twin was treated with immunosuppression therapy for many years before the correct diagnosis of monozygosity was made[40] (Figure 28.5).

The nature and extent of genetic/epigenetic discordances in MZ twins indicate that there are no absolute criteria for the diagnosis of twin zygosity. In other words, there is no 'gold standard' for zygosity determination (see Chapter 94). The recent description of a pair of DZ (unlike-sexed) but MC twins (resulting from *in vitro* fertilization (IVF) and blastocyst transfer) implies that MC twins cannot

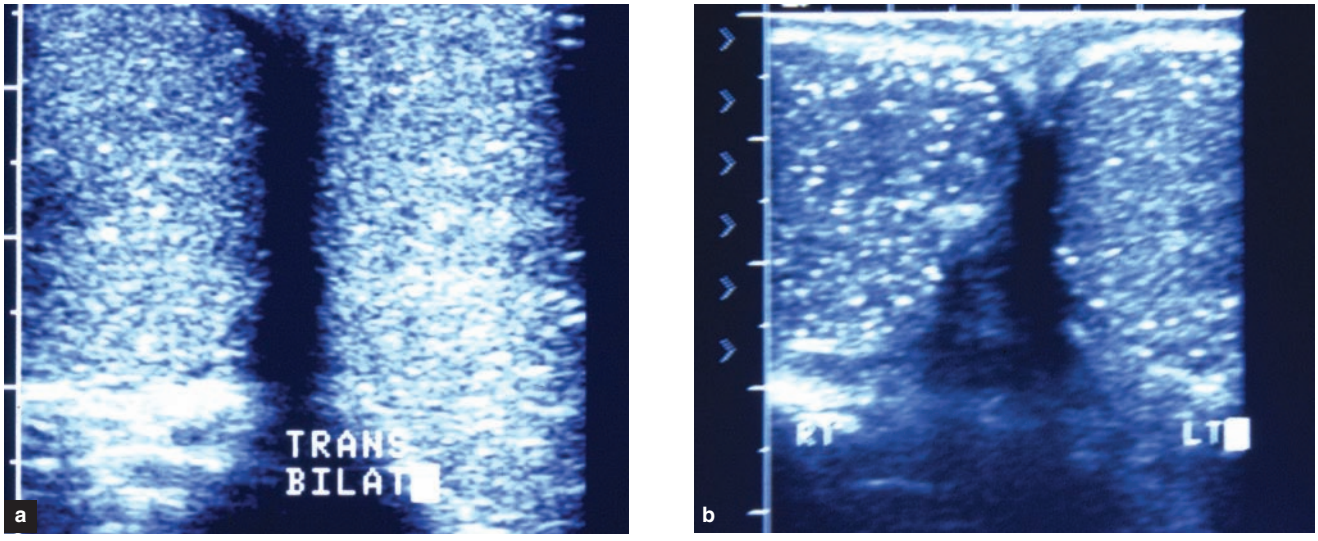


**Figure 28.4** (a) A monozygotic twin presented with a testicular mass, which proved to be an embryonal carcinoma with node metastases. Ultrasound examination showed testicular microlithiasis, which is a marker for predisposition to testicular germ cell tumors. (b) His co-twin also had microlithiasis, but testing for tumor markers was negative

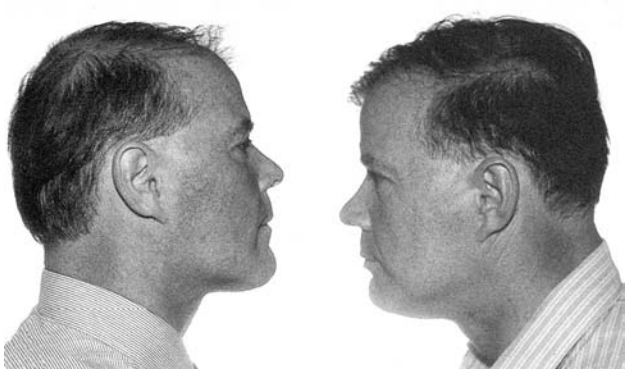

**Figure 28.5** These monozygotic twins thought they were dizygotic on the basis of minor phenotypic discordance, including opposite handedness. One twin was a living kidney transplant donor to his brother, who suffered environmentally induced renal failure. When monozygosity was proven many years later, the transplant recipient was uneventfully weaned from immunosuppression, which had been the cause of significant morbidity

always be accepted as MZ, although probably all naturally conceived MC twins are MZ[41]. Until recently, the basis for zygosity testing (whether at the level of DNA or proteins) rested on the finding of discordance such as to exclude MZ twinning. Discordance for genetic/epigenetic characteristics is now known to occur in most if not all MZ twin pairs, and these changes probably accumulate and accelerate with age and exposure to the environment. We do not know how many epigenetic 'errors' can creep into the genotypes of MZ twins before we must doubt their monozygosity[42]. There remains a clear need for zygosity diagnosis in early postnatal life. Commercially available testing is based on the mailing of buccal swabs. This is certainly preferable to blood sampling (especially because of the pitfalls in MC twins); provided that six to seven DNA sequences are analyzed, the method reaches statistical validity. But one is often pressed to determine the number of DNA sequences offered in a given test, and there has been no standardization or consensus.

## SUMMARY

The evidence presented above shows how complicated and subtle MZ twinning is. MZ twins are never 'identical'. The paradox is that they can be amazingly similar, resembling clones; yet they can also be startlingly unalike, as in twin reversed arterial perfusion. They are differentially affected by post-zygotic genetic, epigenetic and environmental factors which drive apart the phenotype and genotype within a given pair. It emerges that MZ twins are not genetically 'identical', as is widely supposed. Furthermore, their mutual experience of their postnatal environment minimizes discordance for acquired experiences that might cause phenotypic discordance. This model is the exact opposite of the classic one that has been used for many years in twin research. In effect, MZ twins are a 'wet laboratory' in which the extent of these influences can be recognized and quantified to a degree that is impossible in singletons or DZ twins.

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# The Phenomenon of Monozygosity in Iatrogenic Pregnancies

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29



## INTRODUCTION

Pregnancy success rates following assisted reproductive technologies (ART) increased dramatically during the past decade. However, the surge in successful outcomes has been associated with increased numbers of multiple pregnancies; indeed, approximately 33.4% of all pregnancies reported in the USA after ART are multiple[1]. These pregnancies inherently pose a higher risk to both mother and child compared with singleton pregnancies[2]. This phenomenon is described in detail in other chapters of this volume. Fortunately, however, the majority of these multiples are twins, and are associated with significantly lower overall risks than are higher-order multiple gestations.

Monozygotic (MZ) twinning represents a relatively rare form of multiple gestation. The incidence of spontaneous MZ twinning (i.e. twins which originate from a single embryo) in humans is relatively stable[3], and the medical risks associated with MZ twins are highly dependent upon whether the twins are contained within a single chorion or amnion – a phenomenon that is dictated by the timing of embryo splitting[3,4] (see Chapters 24 and 28). As expected, monochorionic and monoamniotic twins have a higher risk of exhibiting fetal abnormalities than diamniotic/dichorionic MZ twins. MZ twinning can be experimentally induced by tampering with the zona pellucida, either via chemical or mechanical methods[3]. Such observations preceded speculations that MZ twinning can be increased following ART[5].

## MONOZYGOTIC TWINNING IN ASSISTED REPRODUCTION

The association of MZ twinning following ART was first described in 1984[6]. Moreover, it was suggested that the incidence of monozygosity following *in vitro* fertilization (IVF) or IVF with intracytoplasmic sperm injection (ICSI) is increased as compared with spontaneous human pregnancies[7–10]. This phenomenon was initially thought to be due to zona pellucida manipulation which occurs with assisted hatching and/or ICSI.

More recently, however, with the increasing practice of blastocyst (day-5) transfer and the introduction of sequential media transfers, several clinics have reported increasing rates of MZ twins[11–15]. Paradoxically, blastocyst (day-5) transfer, a practice introduced to lower the number of embryos transferred and reduce the likelihood of higher-order multiple gestations, has possibly resulted in increased rates of MZ twinning. If the link between blastocyst transfer and MZ twinning is substantiated, patients must be carefully informed of this possible risk, and physicians should be aware of the clinical and scientific evidence underlying this phenomenon. As such, this chapter discusses the risks of MZ twinning in ART.

## MANIPULATION OF THE ZONA PELLUCIDA

It is currently thought that zona pellucida thickness is influenced by a woman's age and ovarian reserve, and correlates negatively with ART success[16].

Previously, artificially disrupting the zona pellucida was proposed as a method to increase implantation rates, particularly when the zona is judged as unfavorable[17]. A variety of techniques – both chemical and mechanical – were utilized for assisted hatching, including zona dissection, drilling and thinning. These methods were increasingly offered to older women and for women with diminished ovarian reserve, particularly when the zona pellucida appeared to be thick. It was postulated that the iatrogenically created zona pellucida gap might be responsible for pinching the hatching inner cell mass, thus resulting in embryo splitting. Animal studies supported this theory[18].

Several reports suggested that assisted hatching was associated with an increase in MZ twinning. In a large retrospective study, Hershlag and colleagues found that the performance of mechanical assisted hatching was associated with a statistically significant increase in MZ twinning (0/559 vs. 8/674; $p < 0.01$, nonhatching vs. hatching)[8]. The MZ twinning rate in this study was 1.2% per embryo transfer or 3.2% per clinical pregnancy. This was approximately eight times that found in spontaneous conceptions. A recent study by da Costa and colleagues[19] confirmed these findings, suggesting that hatching may be correlated with an increase in MZ twinning.

A large case–control study from the Centers for Disease Control and Prevention (CDC) found at least a two-fold increase in the risk of MZ twinning after performing assisted hatching in women undergoing IVF[20]. This association was not explained by the performance of ICSI, number of embryos transferred or infertility diagnosis. Unfortunately, because this study utilized the CDC–Society for Assisted Reproductive Technology (SART) 1996 National Database, it was limited by their methods of data collection and validation. Moreover, the data are insufficient to evaluate adequately the relationship of clinic-specific assisted hatching methods with MZ twinning, nor was the study able accurately to discriminate the prevalence of MZ twinning in each clinic.

In a large single-center study of over 4000 clinical pregnancies, Alikani and co-workers determined that assisted hatching, but not ICSI, was associated with a small risk of increased MZ twinning after ART[10]. The overall incidence of MZ twinning was 1.88% of all clinical pregnancies, representing a four-fold increase over that seen with spontaneous conceptions.

Not all studies concur with the findings cited above, however. In a large single-center report, we found that there was no increase in MZ twinning in the group of patients that underwent manipulation of the zona pellucida (ICSI or assisted hatching), compared with the group of patients whose embryos did not undergo zona manipulation prior to transfer[21].

In an evaluation of 731 pregnancies from an ART unit in Israel, no increase in MZ twinning was reported in patients undergoing assisted hatching[9]. These investigators found a low MZ twinning rate after performing assisted hatching (0.73%), which compared favorably to the group of patients undergoing conventional IVF without hatching (0.59%). Other studies also failed to report an increase in MZ twinning after assisted hatching[22,23].

Almost one-half of all IVF cycles utilize ICSI[1]. The injection of a single sperm into an oocyte results in a significantly smaller disruption of the zona pellucida than occurs with assisted hatching. Thus, most studies found no apparent association between an increase in MZ twinning and ICSI[7,9,20,21]. However, Tarlatzis and colleagues, in a small retrospective study, found an increase in MZ twinning after performing ICSI in patients undergoing a blastocyst transfer, as compared with patients undergoing blastocyst transfer following traditional insemination (0/76 vs. 6/102; $p = 0.033$)[14]. Limited by its small numbers and retrospective design, however, this study awaits further confirmation.

## BLASTOCYST EMBRYO TRANSFER

The first report of MZ twinning after blastocyst transfer without manipulation of the zona pellucida appeared in 1999[24]. Since then, additional reports have explored the potential link between MZ twinning and blastocyst transfer[7,12–15,19] (Figure 29.1).

Milki and co-workers found an almost three-fold increase in MZ twinning with blastocyst embryo transfer (11/197 vs. 7/357; 5.6% vs. 2%; $p < 0.05$)[7]. In this study, no association was found with assisted hatching or ICSI. Furthermore, over half of pregnancies associated with monozygosity were higher-order multiple gestations. In a multicenter report, Behr and associates found an almost 5% risk of MZ twinning after blastocyst embryo transfer[13].

An additional study by Sheiner and co-workers of almost 200 pregnancies, spanning a 2-year period, found a significant correlation between transfer of the embryo in the blastocyst stage and MZ twins[15]. These authors speculated that the delayed transfer in the blastocyst stage might further increase the incidence of damage to the zona pellucida, accounting for the increase in MZ twinning.

In a larger study, da Costa and co-workers found an over five-fold increase in the rate of MZ twins after blastocyst transfer as compared with a day-3 transfer[19]. The implantation rate was increased by 61% when utilizing blastocyst transfer (18.5% vs. 11.5%). However, these authors reported that almost

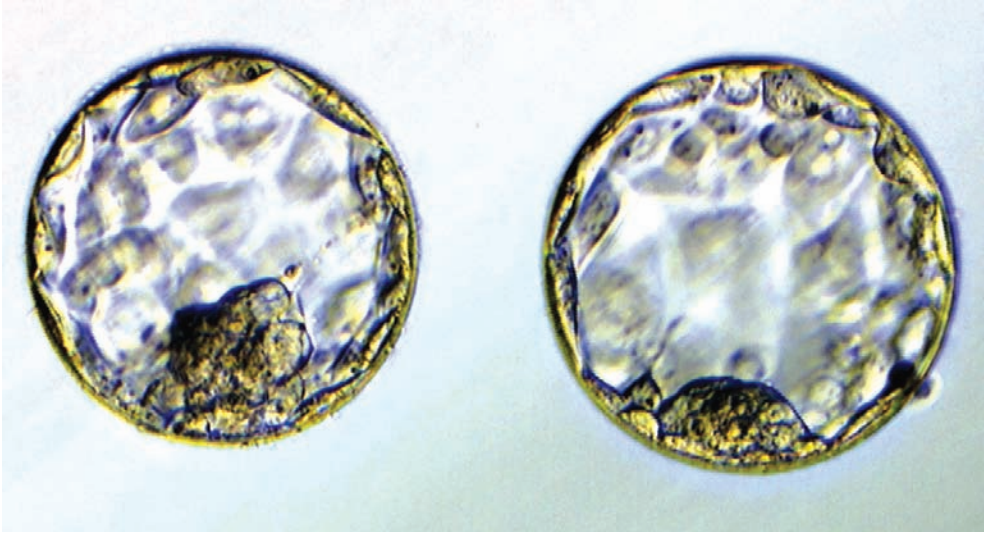

**Figure 29.1** Two blastocysts, approximately day-5 post-fertilization. The inner cell mass is seen as a condensed aggregate of blastomeres at the 6 o'clock position of each blastocyst

**Table 29.1** Monozygotic (MZ) twinning in *in vitro* fertilization: day-3 embryo transfer. Rates of twinning (%) are given in parentheses

| | *MZ twins* | *Non-MZ* | *p Value* |
|---|---|---|---|
| Age (years) | 33.7 (3.5) | 34.9 (4.8) | NS |
| Oocytes (*n*) | 7.8 (4.8) | 11.6 (5.2) | 0.01 |
| Embryos transferred (*n*) | 2.0 (0.7) | 3.5 (1.0) | <0.001 |
| Grade | 2.1 (0.70) | 1.8 (0.6) | 0.20 |

NS, not significant

4% of all blastocyst transfer pregnancies resulted in MZ twins (5/129). This was significantly greater than the less than 1% incidence found following day-3 embryo transfer (6/814). Unfortunately, all five MZ twins they reported suffered an adverse outcome.

Despite initial reports of increased implantation rates after blastocyst transfer, the findings of increased MZ twinning after prolonged culture have served to dampen the initial enthusiasm for performing blastocyst transfers. Further studies are needed both to confirm these observations and to delineate the possible cause for this phenomenon.

## FAMILIAL CLUSTERING

An interesting recent report speculated that MZ twinning after ART was increased in those patients with a familial history of multiple gestations[25]. Over 70% of all mothers with spontaneous MZ twins reported having twin relatives. This appears to be particularly so for ART mothers, as all 13 reported having twin relatives. The role of familial clustering in MZ twinning after ART warrants further evaluation.

## MONOZYGOTIC TWINNING: CORNELL EXPERIENCE

We recently evaluated 5614 consecutive IVF cycles performed at our center (from July 2000 to March 2003) to investigate the risks of MZ twinning after IVF following day-3 and day-5 (blastocyst) transfers, respectively. We also analyzed the risk of MZ twinning following frozen blastocyst transfer.

Overall, a clinical pregnancy rate of 44.3% (2302/5197) was noted for patients undergoing a day-3 embryo transfer. This was significantly lower than the clinical pregnancy rate of 66.2% for patients undergoing a blastocyst transfer (276/417; $p < 0.01$). MZ twinning occurred in less than 1% of all pregnancies (0.893%; 23/2578). MZ pregnancies

occurred significantly less often after day-3 embryo transfers as compared with day-5 embryo transfers (0.51% (12/2302) vs. 3.99 (11/276); $p < 0.001$).

When MZ twinning followed day-3 transfer, the cycle in question was associated with the recovery of fewer oocytes and fewer embryos available for transfer (see Table 29.1). Embryo morphology on day 3 was not associated with monozygosity. ICSI and assisted hatching were not associated with MZ twinning. We observed an eight-fold increased risk of MZ twinning in women undergoing blastocyst transfer as compared with women undergoing day-3 embryo transfer.

As blastocyst transfers become more common, so will cryopreserved blastocyst transfer. No report to date has established the risk of MZ twinning after cryopreserved blastocyst transfer. We therefore evaluated an additional 157 cryopreserved blastocyst transfers. Ninety-nine became pregnant (63.1%). Two of the pregnancies were MZ. This observation suggests that frozen–thawed blastocyst transfers may also be associated with an increased risk of MZ twinning.

## CONCLUSIONS

MZ twinning appears to be increased after ART. Pregnancy-associated maternal and fetal risks are increased with MZ twinning. There is controversy as to whether MZ twinning is associated with ICSI or assisted hatching. Newer data suggest that blastocyst transfer may increase the risk of MZ twinning by 3–5-fold. Further work is needed to clarify the underlying etiology for this phenomenon. It is, therefore, eminently important for all ART practitioners to inform and counsel their patients regarding these apparent risks.

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# Monozygosity Following Assisted Reproduction: Unanswered Questions

*I. Blickstein*

**30**



## INTRODUCTION

The common denominator of all assisted reproductive technologies (ART) is ovarian (hyper)stimulation, resulting in an excess of ripe ovarian follicles, and leading to multiple oocytes available for fertilization. Multiples conceived with ART are therefore likely to be polyzygotic. However, as early as the late 1980s, and almost simultaneously, two reports claimed the occurrence of monozygosity among ART twins[1,2]. Whereas the first was a hospital-based case series related to *in vitro* fertilization (IVF)[1], the other[2] was based on data from the East Flanders Prospective Twin Study (see Chapter 6). The latter dataset enabled Derom and colleagues[2] to deduce that monozygosity occurred significantly more frequently among pregnancies after artificial induction of ovulation (1.2%), compared with the expected frequency (0.45%) among spontaneous twins and triplets. These findings are of importance because no other biologic mechanism influencing the monozygotic (MZ) twinning rate has ever been identified (see Chapter 28).

In this volume, two separate discussions are devoted to the phenomenon of MZ division following ART (see Chapters 28 and 29). This chapter, however, highlights various unanswered questions related to this phenomenon.

## WHAT IS THE FREQUENCY OF ZYGOTIC SPLITTING FOLLOWING ASSISTED REPRODUCTION?

The true frequency of monozygosity after ART is not yet established. This limitation derives from the difficulty in establishing zygosity in large populations. Hence, proxy methods are frequently used for estimations. One of the most common estimations counts the number of monochorionic (MC) twins in the population of ART children, either by antenatal sonography or by postpartum placental examination. Although all MC twins are MZ, and all unlike-sex twins are DZ, zygosity is unknown by clinical means in all same-sex dichorionic (DC) twins. In spontaneous conceptions, where MZs account for roughly one-third of twins, and roughly one-third of the MZs have a DC placenta, the diagnosis of zygosity is unknown without genetic studies in four-ninths (~ 44%) of cases (Figure 30.1), and clinical estimates of MZs may miss as many as one-third of cases in spontaneous conceptions. Following the same line of argument, and given that the proportion of MZs in ART twins is different and that there might be more DC–MZs among these twins[1,3], the diagnosis of MZ twins may be missed (without genetic studies) in nearly 50% of cases. For example, using sonographic findings of MC placentation as the diagnosis of MZ twinning, a retrospective analysis of 731 pregnancies achieved after various ART found an incidence of 0.72% MZ twins after conventional IVF, and 0.72% and 0.86%, respectively, after IVF with either intracytoplasmic sperm injection (ICSI) or assisted hatching (AH), for an overall rate of 0.95%[4]. Although the rate of zygotic splitting following ART in this study was twice the spontaneous rate, the cited rate must be underestimated because the method of zygosity assessment did not count DC–MZ twins.

Another method to estimate zygotic splitting after ART is using Weinberg's rule. For instance, in a

| All spontaneous twins | | | | |
|---|---|---|---|---|
| Zygosity | DZ | | MZ (1/3) | |
| Chorion | DC | DC | DC | MC (2/3) |
| Gender | ULS | DC-LS | | LS |
| Diagnosis | Known | Unknown | | Known |
| % | 3/9 (33.3%) | 4/9 (44.4%) | | 2/9 (22.2%) |

**Figure 30.1** Zygosity determination by clinical means. DC, dichorionic; ULS, unlike-sexed; LS, like-sexed; MZ, monozygotic; MC, monochorionic

recent analysis of 23 321 ART pregnancies registered in Australia and New Zealand, there were 4343 (18.6%) twin pregnancies of at least 20 weeks' gestation and 559 (2.4%) triplet pregnancies[5]. Using Weinberg's rule, the author derived a MZ rate of 0.45%, similar to that in natural conceptions. However, it was never established that Weinberg's rule is applicable in iatrogenic conceptions. Given the differences in terms of proportions of zygosity and chorionicity, as well as the potential difference in the proportion of same-sex DZ twins (all determinants of Weinberg's rule), the results of studies based on Weinberg's rule should be interpreted with caution. Certainly, at the time that this methodology was formulated, it was not conceived that there might be changes in these proportions in ART pregnancies.

Splitting may also be inferred when the number of fetuses exceeds the number of embryos transferred, or in monoamniotic twins[6]. Although this methodology may be more accurate with single embryo transfer (SET, see below), it may underestimate the MZ frequency because of the inability to differentiate like-sex DC–DZ from DC–MZ twins on clinical grounds without DNA testing. Moreover, when two embryos are transferred, and one is lost whereas the other splits into DC–MZ twins, the number of fetuses does not exceed that of the transferred embryos. Nonetheless, data based on placental evaluation at delivery in cases when the number of embryos transferred was less than the number of fetal heartbeats, or when >1 fetal heartbeat per gestational sac was seen, found 1.2% MZ[6], almost a three-fold increase in frequency compared with spontaneous cases.

Another estimate of zygosity splitting assumes that if multiples occur following SET in an IVF procedure, they must be MZ (disregarding the potential but negligible contribution of superfecundation). In our first study of this possibility we used a clinic-based dataset of SETs in IVF without AH, from January 1994 to July 1998 at the Center for Reproductive Medicine, Dusseldorf, Germany. Six hundred and forty-five SETs resulted in 82 (12.7%) pregnancies, including four MZ twins (4.9%)[7]. This frequency among IVF conceptions was 12 times higher than that observed among spontaneous pregnancies. Because the results were derived from a rather small series, we further analyzed the 1991–98 population-based dataset provided by the UK Human Fertilisation and Embryology Authority, which include 15 644 cycles with SETs in 7832 IVF patients[8]. The multiple pregnancy rates after SET represent a 2.3% zygotic splitting rate among IVF conceptions, a figure six times higher than the rate after spontaneous pregnancies as quoted in the literature. It should be stressed that this method disregards cases of zygotic splitting occurring when more than one embryo is transferred.

Perhaps the most accurate data on the frequency of zygotic splitting after assisted reproduction comes from the East Flanders Prospective Twin Study (see Chapter 6), where all like-sexed DC twins undergo genetic zygosity assessment. Using data presented in that chapter, the overall frequency of MZ twinning following assisted reproduction – 4.5% – was ten times the spontaneous rate (0.45%). The frequency of MZ pregnancies following ovulation induction (6.38%) was 14-fold the spontaneous rate, and the frequency of MZ pregnancies following IVF procedures (2.6%) was six-fold the spontaneous rate (Table 30.1). The last is in full accord with our own estimates[8].

**Table 30.1** Zygotic splitting by method of conception, East Flanders Prospective Twin Study. Data refer to cases with known zygosity. Monozygotic (MZ) frequencies include MZ twins, MZ triplets and dizygotic (DZ) triplets. Adapted from Table 6.2 of this volume

| | *Ovulation induction* | *IVF procedures* | *Total* |
|---|---|---|---|
| Total (*n*) | 768 | 688 | 1456 |
| MZ (*n*) | 49 | 18 | 67 |
| Frequency (%) | 6.38 | 2.62 | 4.6 |

IVF, *in vitro* fertilization

## WHAT IS THE ETIOLOGY OF ZYGOTIC SPLITTING FOLLOWING ASSISTED REPRODUCTION?

As the mechanism of natural zygotic splitting is unknown[3], whatever speculation is put forward should not be in conflict with other opinions. The following is my own critical analysis of the available information.

### *In vivo* versus *in vitro*

All methods of assisted conception – with and without manipulation of the gametes or zygotes – were associated with zygotic splitting[3]. This may lead to the logical assumption that the common denominator resides *in vivo* rather than *in vitro*. This concept is supported by a recent investigation, in which the frequency of MZ twinning among IVF patients was not different between patients who did or did not undergo zona manipulation[6].

### Chance event

Although it is true that if more embryos are available for a given woman, there is a greater chance that one will undergo splitting[6], this explanation conflicts with the repeated observations of MZ twins occurring also more frequently after SET.

### Familial occurrence

Obviously, zygotic splitting is a post-fertilization event. Having said this, one cannot discard the possibility of existing intrinsic features, genetic or otherwise, which render a given oocyte more prove to splitting once it is fertilized. This theory may explain some familial clusters of MZs (see Chapter 28).

### Herniation versus repulsion of blastomeres

Currently, two theories are proposed to explain the occurrence of MZs. The first, and more extensively cited, describes the splitting as a hatching event, in terms of physical division of the early embryo, caused by a breach in the integrity of the zona pellucida, herniations of the blastomeres and splitting of the embryo. An alternative hypothesis, proposed by Hall in the mid-1990s, suggests that different cells of the early embryo might develop differently at the same time. The developmental discordance between adjacent cells might cause repulsion, i.e. splitting of the early embryo[3].

At first glance, it would appear that the abovementioned mechanisms of zygotic splitting cannot individually and simultaneously explain both spontaneous and iatrogenic MZs. It is possible that a third theory (Blickstein's) could combine both. In such a conjecture, one should assume that early embryonic cells that would eventually repulse to form MZ twins are encased within a zona pellucida, whose structure is programmed to facilitate splitting. It is also possible that these embryonic cells activate changes in the zona pellucida to enhance splitting. Stated differently, one may speculate that splitting-prone embryonic cells either are associated with an already existing splitting-enhancing zona or activate such splitting-enhancing changes. According to this conjecture, the zona pellucida not only prevents polyspermic fertilization, but also prevents zygotic splitting. Hence, tampering with the zona pellucida (as may be the case with ovulation induction and as is the case in many ART procedures) breaches this protective mechanism, and facilitates zygotic splitting.

## TIMING OF ZYGOTIC SPLITTING FOLLOWING ASSISTED REPRODUCTION: A DEVIATION FROM THE 'CLASSIC' MONOZYGOTIC PLACENTATION MODEL?

Classic teaching suggests existence of a clear time-sequence relationship between the splitting event and the type of MZ placenta (see Chapter 24). In this model, early zygotic division results in DC placentas, whereas later divisions (i.e. after day-3 post-fertilization) result in MC placentas. Moreover, zygotic splitting after 7 days is associated with MC–monoamniotic placentas. Very late divisions are associated with conjoined twinning. In IVF techniques, embryos are transferred at day 3 (the so-called cleavage stage) or later, at day 5 (the so-called blastocyst stage). According to this 'classic' model, if zygotic splitting occurs *in vitro*, day-3 embryos should transform to DC–MZ twins, whereas transfer of blastocysts would result in any type of MC twins. At present, there are no data to correlate the type of placenta with the stage of embryonic development at the day of transfer. For instance, it is known that monoamnionicity is almost the latest

possible splitting event[9]. On the other hand, the results reported by Slotnick and Ortega[10] suggest that monoamniotic multiple gestations may be increased in zona-manipulated cycles. These two observations[9,10] obviously conflict, because the data collected in the latter come from the era before blastocyst transfers were performed.

The only 'sure thing' is that late transfers (i.e. blastocysts) are associated with a significantly increased MZ twinning rate compared with day-3 transfers[11,12]. It is presently unclear whether the prolonged presences of the embryo in the culture medium or the culture conditions *per se* are responsible for this increased MZ twinning rate[13]. However, this 'sure thing' might also be questioned. If blastocyst transfers are indeed associated with increased splitting rates into MC twins, and if splitting rates are determined by counting the number of MC twins rather than counting the number of MZ twins, the comparison of blastocyst transfers with day-3 transfers would be erroneously skewed to show an increased frequency of zygotic splitting following blastocyst transfers.

All these considerations are based on the assumption that the 'classic' relationship between timing of splitting and type of placentation in spontaneous MZ twins is also present in iatrogenic pregnancies. In the absence of data required to establish when splitting occurs in ART pregnancies, timing of zygotic splitting in relation to placentation in ART gestations remains speculative.

## EPILOGUE

This chapter considers several speculations. However, speculations can easily exist when data are absent, and serve to refine the process of future data collection. Our present gap in understanding the phenomenon of early twinning may be bridged in the future by simple means such as correlating zygosity rather than chorionicity with different assisted reproduction procedures.

It is now clearer than ever before that zygotic splitting may be influenced by the type of ovarian stimulation protocol, the stage of embryo transfer, whether the transferred embryos are fresh or frozen–thawed, the type of zona manipulation technique, type of *in vitro* culture media and different patient characteristics (e.g. age). It is unrealistic to compare splitting rates in patients over 38 years who underwent blastocyst transfer following a prolonged stimulation protocol, ICSI and assisted hatching, with those in young patients who received cleavage-stage embryos without any zona manipulation following egg retrieval and embryo transfer in a natural cycle. This diversity suggests that a common denominator is required when data are analyzed. To date, no such common denominator exists.

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# The Phenomenon of Monozygosity: Monozygotic Twins in High-order Multiples

*G. A. Machin*

31



## INTRODUCTION

Monozygosity occurs in naturally conceived multiple pregnancies as well as those higher-order multiple pregnancies (HOMPs) conceived by assisted reproductive technologies (ART). (For zygosity in artificially conceived HOMPs, see Chapters 29 and 30.) Because many monozygotic (MZ) components of HOMPs are also monochorionic (MC), obstetric risks are very high, particularly in NC multifetal pregnancy. Whereas the frequency of MZ twinning in ART is surprisingly high, few NC triplets are trizygotic. No large body of information on the zygosity of NC quadruplets and quintuplets exists. This author has studied two sets of NC quadruplets. One set was MC, tetra-amniotic, and therefore MZ. The other consisted of a surviving pair who were MC diamniotic (DA) as well as an MC monoamniotic (MA) pair which had undergone multifetal reduction. At most, this quadruplet set was dizygotic (DZ), and they may all have been MZ. The Dionne quintuplets appear to have been MZ.

HOMPs offer the opportunity to study the differential effects of zygosity and chorionicity on fetal growth within the same uterus. Chorionicity is pivotal in the prenatal assessment and outcomes of HOMPs for two reasons: first, monochorionicity increases the risks of complications, and second, because of the potential need for multifetal reduction. Unless it is understood that HOMPs are likely to contain MZ twins which additionally may be MC and also discordant for major anomalies, poor outcomes may result, with loss of intended survivors. However, an MC twin pair is an option for reduction, because the most at-risk pair can be reduced by a single procedure[1].

## ZYGOSITY AND CHORIONICITY IN NATURALLY CONCEIVED TRIPLETS

Zygosity and chorionicity for 31 naturally conceived triplet sets in a population-based study are shown in Table 31.1 (C. Derom, personal communication). Nineteen per cent were completely MZ and only 26% were trizygotic (TZ). Furthermore, 16% were entirely MC and only 39% were trichorionic (TC). Stated another way, 61% of these sets were at risk for complications of monochorionicity. From a referral center, 15 triplet sets are analyzed in Table 31.2[2]. Forty per cent were entirely MZ and only 13% were TZ. Thirteen per cent were MC and only 40% were TC. Here again, 60% of these sets were at risk for MC complications, and, indeed, three sets of MZ triplets died of twin-to-twin transfusion syndrome.

There were no monoamniotic twins or triplets in either of the two series cited above. By combining the 12 MZ sets cited here, six twinning events occurred prior to blastocyst formation and 18 afterwards. In only one (TC) set did both splits occur before blastocyst formation, whereas there were seven MC sets, with 14 events occurring entirely after blastocyst formation.

Management of MC triplet pregnancy is complex, because all three fetal circulations are likely to be linked (Figure 31.1). Therefore, results of attempted laser coagulation for twin-to-twin transfusion (TTT) are unpredictable. In most cases of TTT in MC triplets, there is a single recipient, a 'principal' donor and an 'associate' donor linked to the principal donor by an artery-to-artery anastomosis.

**Table 31.1** Naturally conceived triplet zygosity and chorionicity, population-based (C. Derom, personal communication)

| | *TC* | *DC* | *MC* | *Total* |
|---|---|---|---|---|
| TZ | 8 | 0 | 0 | 8 |
| DZ | 4 | 13 | 0 | 17 |
| MZ | 0 | 1 | 5 | 6 |
| Total | 12 | 14 | 5 | 31 |

TZ, trizygotic; DZ, dizygotic; MZ, monozygotic; TC, trichorionic; DC, dichorionic; MC, monochorionic

**Table 31.2** Naturally conceived triplet zygosity and chorionicity, referral center[2]

| | *TC* | *DC* | *MC* | *Total* |
|---|---|---|---|---|
| TZ | 2 | 0 | 0 | 2 |
| DZ | 3 | 4 | 0 | 7 |
| MZ | 1 | 3 | 2 | 6 |
| Total | 6 | 7 | 2 | 15 |

TZ, trizygotic; DZ, dizygotic; MZ, monozygotic; TC, trichorionic; DC, dichorionic; MC, monochorionic

## GESTATIONAL AGE AT BIRTH IN TRIPLETS BY CHORIONICITY

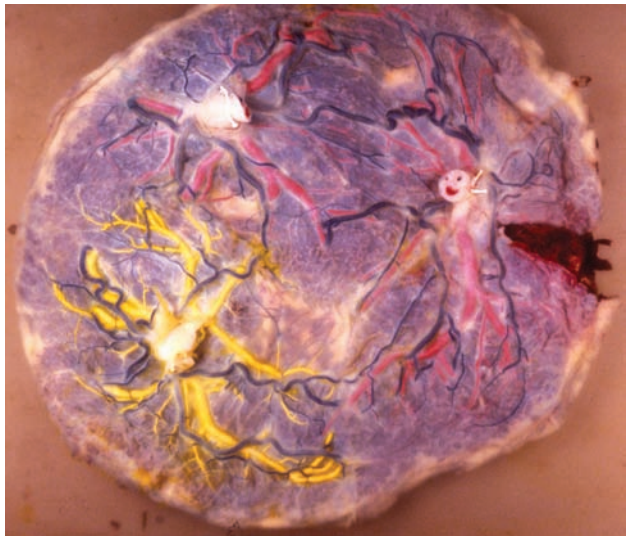
Figure 31.2 compares cumulative gestational age at delivery of TC and dichorionic (DC)/MC triplets and also of triplet gestations that underwent multifetal reduction from triplets to twins. Triplet sets containing MC twins (or those which were entirely MC) delivered about 1 week prior to TC triplets and 4 weeks earlier than twins originating as triplets and undergoing multifetal reduction.

## FETAL DEATH IN TRIPLETS

In one report[3], 30% of dichorionic triplets were complicated by twin transfusion or fetal demise (Table 31.3). In two other reports, rates of single, double and triple fetal demise were analyzed[4,5] (Table 31.4). These show a clear effect of monochorionicity in the increasing multiplicity of fetal demise in a given triplet gestation.

## FETAL GROWTH IN DICHORIONIC AND MONOCHORIONIC TRIPLET PREGNANCIES

DC triplet sets offer the opportunity to compare the growth of the 'singleton triplet' versus the MC twin pair, whereby the uterine 'macroenvironment' is in common, but the placental microenvironment may be different. (However, zygosity of the 'singleton' in relation to the MC twins may not be known.) The placental microenvironment connotes factors in cord and placental structure that are not secondary to the maternal-induced 'macroenvironment'. In particular, unequal parenchymal sharing of the MC placenta may significantly alter the fetal mass of the MC twins (see Chapter 27). In an analysis of 26 sets of DC triplets, the majority of DC triplets weighed more than the corresponding mean of the MC twins (Figure 31.3; Machin, unpublished data). The DC triplet weighed less than the mean MC twin weight in only two sets.



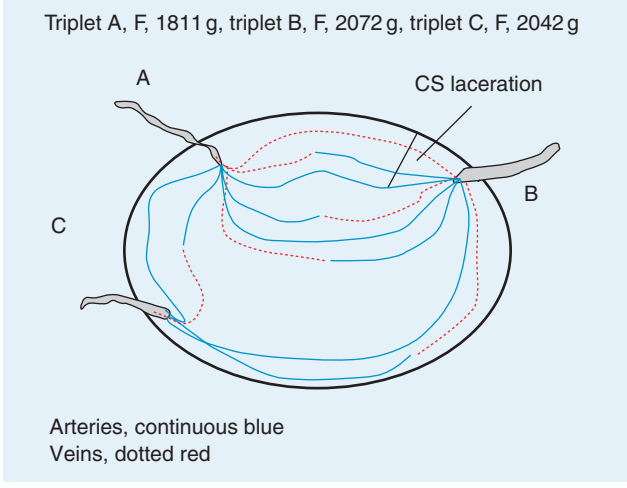



**Figure 31.1** Monochorionic (MC) triplets have ring-like arrangements of interfetal connecting vessels. This makes their behavior unpredictable and difficult to manage in the context of twin transfusion and fetal demise. CS, cesarean section

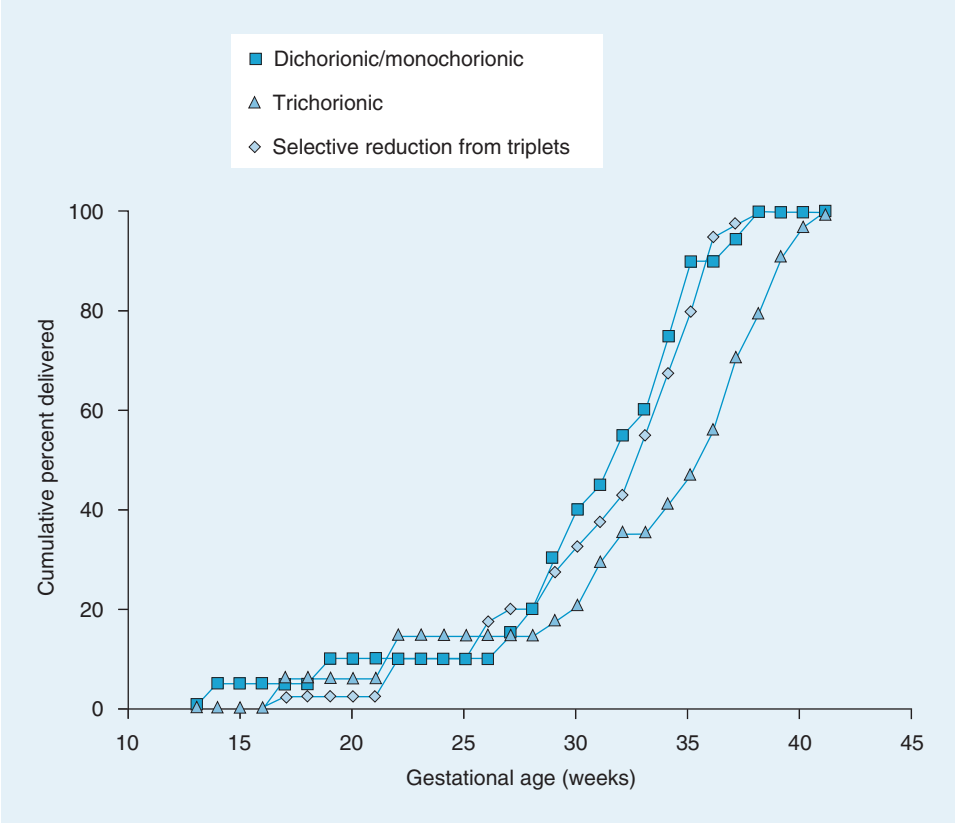



**Figure 31.2** Cumulative percentage born at each gestational week, comparing dichorionic (DC) triplets, monochorionic (MC) triplets and gestations with reduction from triplets to twins or singletons

**Table 31.3** Fetal survival rates in dichorionic (DC) triplet pregnancies[3]

| | *DC (n)* | *DC (%)* | *MC (n)* | *MC (%)* | *Total (n)* | *Total (%)* |
|---|---|---|---|---|---|---|
| Surviving fetuses | 13 | 76 | 23 | 68 | 36 | 71 |

MC, monochorionic

**Table 31.4** Fetal demise in triplet pregnancy[4,5]

| | *TC* | *DC* | *MC* |
|---|---|---|---|
| Sets/fetuses (*n*) | 6/18 | 6/18 | 8/24 |
| Survivors (*n* (%)) | 11 (61) | 9 (50) | 11 (46) |
| Single demise | 5 | 3 | 5 |
| Double demise | 1 | 3 | 1 |
| Triple demise | 0 | 0 | 2 |

TC, trichorionic; DC, dichorionic; MC, monochorionic

Discordance between DC triplet weight and mean MC twin weight in the remaining sets ranged from 4.8 to 34%. There was no definite trend by gestational age. Because growth discordance in MC twin pairs is usually caused by asymmetric cord insertions, it is

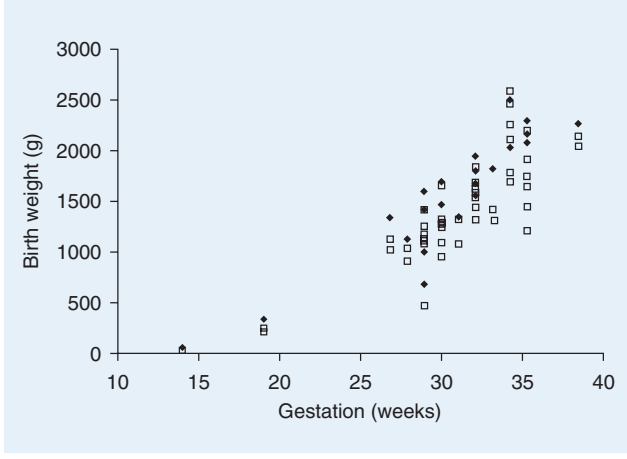



**Figure 31.3** Birth weights of dichorionic (DC) twins (solid diamonds) contrasted with those of monochorionic (MC) twins (open squares) in DC triplet pregnancies

**Table 31.5** Cord insertion type (%) in monochorionic (MC) twins, MC twins of dichorionic (DC) triplets and smaller MC twin in DC triplets

| *Author* | *Paracentral* | *Marginal* | *Velamentous* |
|---|---|---|---|
| Benirschke and Kaufmann, MC twins[6] | 57 | 30 | 13 |
| Machin, MC twins of DC triplets | 43 | 19 | 37 |
| Machin, smaller MC twin of DC triplets | 66 | 0 | 33 |

possible to assess the effect of the presence of the DC triplet on cord insertions of MC twins in triplet sets (Table 31.5).

## COMPLICATIONS OF MONOCHORIONICITY IN TRIPLET GESTATIONS

The prevalence of TTT and twin reversed arterial perfusion (TRAP) in triplet pregnancies is not known. Individual case reports indicate that management is necessarily complex. In the referral center report of 15 sets of NC triplets, three sets were affected by TTT[2]. Two TTT sets were DC and the other was MC. There were no survivors from the three sets, who were delivered at 19, 20 and 21 weeks of gestation[2].

There have been reports of six triplet sets with known outcome containing TRAP. In all cases, the DC triplet survived, but only two of six pump twins survived the perinatal period[7].

## MONOAMNIOTIC TWINS IN TRIPLETS

Only small numbers of DC–DA triplets are reported[7]. Cord entanglement was common, and the outcomes were worse than with MA twins.

## CHORIONICITY CONSIDERATIONS FOR MULTIFETAL REDUCTION IN TRIPLETS

A single procedure can be used to terminate both MC twins of a DC triplet pregnancy[1].

## SUMMARY

The presence of MC twins in a triplet pregnancy introduces factors other than preterm delivery. In general, the DC triplet may well survive despite physiologic disturbance between the MC twins. Antenatal diagnosis of chorionicity is essential in order to optimize outcomes.

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# Phenotypic and Genotypic Discordance in Monozygotic Twins

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## INTRODUCTION

Twins are classified into two major groups, dizygotic (DZ), which result from two different ova fertilized by two different sperm, and monozygotic (MZ), which derive from a single ovum fertilized by one sperm that divides to form two embryos[1]. The accepted origin of MZ twins from a single fertilized ovum implies that their genetic constitution should be identical. This fact underlies the lay terminology of 'identical twins'. On the other hand, DZ twins, originating from two independently fertilized ova, should be no more alike than any pair of siblings, and are characterized by the lay public as 'fraternal twins'[2]. As early as 1875, Galton postulated that any difference observed within an MZ pair should depend on environmental influences, whereas differences within a DZ pair should be attributable to both environmental as well as genetic factors[3]. This concept soon led to the widespread use of twins to compare the contribution of nature (heredity) versus nurture (environment) in the study of congenital anomalies, complex traits and diseases[4]. Indeed, this comparison has been useful in identifying the heritability of a specific characteristic. Although it is true that the vast majority of MZ twins are genotypically as well as phenotypically identical, several recent studies show that significant numbers of MZ pairs differ in their genotype as well as in their phenotype, or only in their phenotype (for more details see Hall[5,6]). This chapter focuses on the mechanisms causing genotypic and phenotypic discordance in monozygotic twin pairs.

## DIAGNOSIS OF ZYGOSITY

In the vast majority of instances, DZ twins have completely separate placentas and membranes (dichorionic–diamniotic placentation) (see Chapter 24). However, in some cases, the two placental disks show a variable degree of fusion, depending on the proximity of the implantation site. When this happens, vascular connections may be present. One of the positive effects of the recent epidemic of twins is the greater tendency to describe rare occurrences. Recently, DZ twins with monochorionic placentation have been reported as most likely arising from fusion of the chorions early in pregnancy or from trophoblastic fusion before implantation[7].

Placentation in MZ twins differs depending on the time when the twinning event occurred. When separation occurs early between day 0 and day 3, MZ twins have separate placentas and membranes. Separation taking place between day 4 and day 7, after the chorion has formed, results in MZ twins with monochorionic (MC) but diamniotic (DA) placentas. Twinning from day 7 to day 8–14, after the amnion has formed, results in a monochorionic–monoamniotic (MC–MA) placenta (see Chapter 24).

Conjoined twins most likely arise after day 14 when the primitive streak starts to delineate. As is discussed in several other chapters and later in this, MC placentas frequently have vascular connections which may lead to vascular imbalance (twin–twin transfusion syndrome) (see Chapter 33), disruptive congenital anomalies and microchimerism in DZ twins or mosaicisms in MZ twins.

Where necessary (in cases of same sex and two placentas), further determination of zygosity may be carried out by microsatellite and/or single nucleotide polymorphism (SNP) analysis on fibroblasts or buccal mucosal cells, to avoid errors from analysis of blood cells resulting from twinning chimerisms (see Chapter 94 on zygosity determination). However,

it must be recognized that no gold standard for zygosity determination by DNA exists.

## CAUSES OF MONOZYGOTIC TWINNING

The precise causes of monozygotic twinning are not yet known. However, a number of different mechanisms have been suggested (see Chapter 15 by Bomsal). Studies in animals indicate that delayed fertilization or implantation may lead to MZ twinning[5]. The increase of MZ twinning following the use of *in vitro* fertilization suggests that abnormalities or rupture of the zona pellucida may allow separation of the inner cell mass into two embryos. This mechanism could depend on the production of a direct lesion of the zona pellucida by intracytoplasmic sperm injection *per se*, or on some structural alteration such as hardening resulting from aging of the ova, or the effects of drugs or media in use in assisted reproductive technologies[8,9]. Apparently this effect occurs at a very early stage, as indicated by the high frequency of dichorionic–diamniotic (DC–DA) twins following this procedure[9].

Familial monozygotic twinning is a very rare event, and can be inherited from either the paternal or the maternal side of the family. In familial cases the defect may lie in the mutation of a gene encoding a protein responsible for zona pellucida integrity, the very same mechanism proposed for the increase in MZ twinning following assisted reproductive technologies[5,10]. Skewed X-inactivation, namely the occurrence of two different foci of inactivation, one expressing prevalently the maternal X and the other the paternal X, has been proposed as a mechanism for the production of the excess of females in MZ twinning[11,12]. The excess of females in MZ twins is higher in MC–MA and conjoined twins compared with DC–MC twins, indicating that this occurs mainly in late twinning events[13]. It has also been postulated that genetic (gene mutation, chromosome number) or epigenetic (imprinting) modifications arising in some cells of the blastocyst may lead the original cells to recognize differences which in turn result in separation of the original mass into two cell masses[5].

## CONGENITAL ANOMALIES

The large majority (approximately 70%) of MZ twins are concordant and healthy. However, congenital anomalies occur frequently (in about 10% of MZ twins) and may be concordant or discordant[5,14]. Several abnormalities, for instance acardiac and conjoined twins, are specific for MZ twins[15–17]. As far as fetus papyraceous (a twin having died and not being completely reabsorbed) is concerned, we do not yet know whether this abnormality occurs only in MZ twins.

MZ twin anomalies can be divided into three different groups on the basis of specific causal mechanisms: malformation, disruption and deformation[14,18,19]. Some malformations, such as conjoined and acardiac twins, as well as fetus papyraceous, are related in some way to the twinning process itself. On the other hand, congenital heart malformations may depend on placental vascular connections which can result in irregularity of blood flow in early cardiogenesis. Disruptions such as hemifacial microsomy, intestinal atresia, limb reduction defects, amyoplasia and aplasia cutis are most likely related to the shared placental circulation typical of MZ twins, which may result in secondary disruption or even to the intrauterine death of one twin. Deformations (clubfoot, craniosynostosis, hip dislocation) are most probably caused by intrauterine crowding.

## DISCORDANCE

In spite of their characterization as 'identical', MZ twins are quite often discordant in some phenotypic aspects. In approximately 10% of MZ twins, mirror-image features have been described (see Chapter 38). The most frequent are minor asymmetries of facial characteristics (ptosis, side of eruption of the first tooth, side of upsweep of the hair or eyebrow), handedness and side of wrinkles. These mirror-image features may be related to a disturbance of laterality (see Chapter 36 by Bocklage). Many mechanisms responsible for discordance in MZ twins have been described to date. The most commonly reported are mosaicism for chromosomal or single gene disorders, skewed X-inactivation, differences in genomic imprinting, uniparental disomy and asymmetric transmission of mitochondria. In addition to these genetic factors, differences in MZ twins have also been detected in neurologic and immunologic development, such as, for instance, discordance in brain surface anatomy[20] and in the immune response[21], in spite of the identical environment.

### Structural defects

MZ twins show an excess of structural defects as compared with DZ twins and singletons. Furthermore, a discordance in the occurrence or in the severity of the defect has been observed in a consistent proportion of MZ twins. Early-origin malformations such as cyclopia, holoprosencephaly, extrophy of cloaca and anencephaly are frequently discordant in MZ twins. These malformations are most likely the result of the same insult as causing the embryo duplication[18]. Discordance has also been reported for neural tube defects, tracheoesophageal fistula, vertebral anomalies, anal atresia, esophageal atresia with

**Table 32.1** Selected examples of discordant structural defects in monozygotic twins

| *Malformations* | *Disruptions* |
|---|---|
| Holoprosencephaly | amyoplasia |
| Anencephaly | hemifacial microsomia |
| Extrophy of the cloaca | bowel atresia |
| Anal atresia | aplasia cutis |
| Tracheoesophageal fistula | limb amputation |
| VATER association | microcephaly |
| | porencephalic cyst |
| | hydranencephaly |

VATER, vertebral defects, anal atresia, tracheoesophageal fistula, esophageal atresia, renal anomalies, ventricular septal defect and other cardiac anomalies

fistula, VATER association (a combination of the above plus renal anomalies), ventral body wall defects and cloacal dysgenesis (for review see Machin[22]) (Table 32.1). These discordances may result from unequal allocation of blastomeres at the time of separation, and/or differences in attachment to the placenta or type of chorion. Other discordances in MZ twins may arise from the existence of vascular anastomoses within the twin placenta determining differences in vascular blood flow, or from the presence of a dead twin with consequent transfusion of thromboplastic-rich blood into the living twin, leading in turn to vascular occlusion. The resulting vascular disruption may be the determinant of several discordant syndromes, i.e. hemifacial microsomia[23], amyoplasia[24], bowel atresia[25], hydranencephaly, porencephaly and multicystic encephalomalacia (for review see Phelan[16]).

Finally, it should be mentioned that approximately 10% of MZ twins show a marked discordance in birth weight[26] (see Chapters 24 and 35). Differences in vascular supply, placenta and chorionic characteristics, as well as the initial number of blastomeres allocated to each twin, may be responsible for these differences.

## Chromosomal mosaicism

Discordant phenotypes in MZ twins may result from chromosomal mosaicism. Two different mechanisms provide for a discrepant karyotype in MZ twins. One is related to a mitotic error arising before twinning, resulting in a mosaic showing a discrepant distribution of the two different cell lines between the two fetuses. Alternatively, the mitotic error may have occurred after the twinning process has taken place, resulting in a mosaic chromosomal aberration solely in one fetus. It is important to realize that the karyotype from lymphocyte culture could be misleading because of placental vascular anastomoses leading to blood chimerism. Therefore, karyotyping in MZ twins discordant for fetal abnormalities should be carried out in amniocytes and not in fetal blood cells. Further complexity may arise from the timing of the event leading to the mosaic and to the karyotype of the placenta, which could show confined placental mosaicism (for review see Machin[22]). Phenotypic discordance in MZ twins resulting from chromosomal mosaicism has been reported so far for trisomy 21 (one twin 46,XY, the other 47,XY+21; one twin 46,XY, the other 46,XY/47,XX+21)[27,28], trisomy 13[29] and other autosomal aberrations[30], as well as for X-chromosome aneuploidies (for review see Machin[22])[31,32] (Table 32.2). Some of the most common genotypes in discordant MZ twin pairs for X-chromosomal anomalies so far described are 47,XXY/45,X; 45,X/47,XXX; 45,X/46,XY; and 45,X/46,XX[33]. All these genotypes could arise from a single post-zygotic non-disjunctional event in a single 46,XY or 46,XX zygote.

**Table 32.2** Examples of monozygotic twins discordant for chromosomal aneuploidy

| | |
|---|---|
| 46,XY | 47,XY + 21 |
| 46,XY | 47,XY + 13 |
| 45,X | 47,XXY |
| 45,X | 47,XXX |
| 45,X | 46,XY |
| 45,X | 46,XX |

In addition to MZ twins discordant for a chromosomal aberration, MZ twins with concordant chromosomal aberration and discordant phenotypes have also been described[34–38]. Several hypotheses have been offered to explain these findings, including mosaicism with different proportions of abnormal cells, differences in blood flow, placental vascular anastomoses leading to twin–twin transfusion and thereby to blood chimerism, confined placental mosaicism, differences in epigenetic control (methylation), as recently postulated for MZ twins with chromosome 22q11 deletion, and discordant phenotype[39]. MZ twins discordant for X-chromosomal aneuploidy, such as those with 45,X/46,XY genotype, obviously also show sex discrepancy, one being female with the Turner phenotype and the other being a normal male. However, MZ twins concordant for the 46,XY karyotype and opposite sex have also been rarely reported. The postulated mechanisms for explaining this discordance are mutation and mosaicism in the sex-determining region Y (SRY) gene, mutation and mosaicism

**Table 32.3** Discordant phenotypes for an X-linked trait in monozygotic twins resulting from the effects of skewed X chromosome inactivation

| |
|---|
| X-linked muscular dystrophy |
| Color blindness |
| Hunter's disease |
| G6PD deficiency |
| Fragile X syndrome |
| Hemophilia B |

G6PD, glucose-6-phosphate dehydrogenase

involving downstream sex-determining loci, and cryptic 45,XO gonadal cell lines.

## Skewed X-chromosome inactivation

Non-random X-chromosome inactivation in a female heterozygous for an X-linked condition may allow clinical expression of the disorder. Skewed X-chromosome inactivation has also been suggested as a mechanism for discordant phenotype in female MZ twins, one of which is normal and the other manifesting clinically an X-linked disorder[1,12,40–46] (Table 32.3).

In support of the role of skewed X-inactivation in producing discordant phenotypes in MZ twins are the observations that female MZ twins heterozygous for an X-linked disorder have consistently shown a discordant phenotype. Genetic evidence is available indicating that the clinically affected twin has skewed X-chromosome inactivation involving predominantly the chromosome carrying the wild-type allele. In contrast, the normal twin shows predominant inactivation of the X chromosome carrying the affected gene or random X-inactivation. According to Machin[22], two distinct mechanisms may explain the phenomenon of non-random X-inactivation in MZ twins. According to the first and most accepted, two foci of opposite X-chromosome inactivation occur in the inner cell mass. Afterwards, the two clones with oppositely inactivated X-chromosomes display a repulsion phenomenon, thereby leading to the twinning event as well as to the discordant phenotype of the X-linked disorder. Alternatively, the X-chromosome inactivation in the inner cell mass is random, but the blastomeres are allocated unequally to the twins. Here the twin with a few progenitor blastomeres can have only non-random X-chromosome inactivation, thereby producing an embryo with either a predominantly inactivated X chromosome carrying the wild-type gene or a chromosome carrying the affected gene, which may lead to the production of a normal or an affected twin, respectively. In contrast, the twin receiving a larger number of blastomeres will most likely show a random or quasi-random X-inactivation. In the first mechanism, the X-inactivation would have occurred before the twinning event and could have had a role in separation of the inner cell mass. This is not the case with the second mechanism.

## Post-zygotic dominant gene mutation

Post-zygotic mutations leading to MZ discordance for autosomal or X-linked single gene-dominant disorders have been observed in spondylocostal dysostosis[47], Sotos syndrome[48], oral–facial–digital syndrome I (X-linked)[49], Rubinstein–Taybi syndrome[50], Cornelia de Lange syndrome, Aicardi syndrome[51] and Gerstmann–Strausler–Scheinker syndrome as well as tuberous sclerosis[52,53].

However, MZ twin discordance for the clinical severity of dominant disease seems to occur even more frequently, and has been observed for thanatophoric dysplasia[54–57] and especially for neurofibromatosis[58], and tuberous sclerosis[59,60].

## Post-zygotic recessive gene mutation

Post-zygotic recessive gene mutation leading to phenotypic discordance in MZ twins is certainly a rare occurrence. Walker[61] described cleft palate in one MZ twin and sporadic retinoblastoma in the co-twin.

## Disorders resulting from repeats expansion

Very few data on twins affected by repeats expansion disorders have been published to date. Kruyer and colleagues[46] described MZ twin brothers who differed in number of CGG repeats expansion in the fragile mental retardation 1 (FMR1) gene, indicating that the triplet expansion occurred post-zygotically. The same group also reported twin sisters with the same number of repeats in the FMR1 gene. In this instance one twin was affected and the other not. The discordance was related to preferential inactivation of the normal chromosome in the affected twin.

## Discordance in MZ twins resulting from epigenetic changes

A number of MZ twins discordant for the Wiedemann–Beckwith syndrome[62–69] have been reported, the large majority of whom are females (for review see Machin[22]). This phenotypic discordance has been attributed to differences in imprinting between the twins. Quite recently this hypothesis has been supported by the findings of discordant KCNQ10T1 (a gene located at 11p15.5 and possibly involved in the imprinting process) imprinting in a set of MZ twins discordant for this syndrome[70]. The excess of females among these twins discordant

for Wiedemann–Beckwith syndrome led to the proposal that the discordance observed was in some way related to the process of X-inactivation. Both MZ twinning and the process of X-inactivation occur at 8–10 days' gestation[71,72]. If the twin embryos have different patterns of X-inactivation, which is biochemically marked by methylation, chemical modification of histone tails and chromatin remodeling, it is possible that they may also have different propensities for autosomal inactivation[73].

The Silver–Russel syndrome is another syndrome that, in a consistent proportion of cases, may result from maternal uniparental disomy and therefore to lack of contribution of paternal genes located at 7p11.2-p13, which in the maternal genome are inactivated by an imprinting process. Recently a pair of MZ twins discordant for this syndrome have been described[71]. As is the case with the Wiedemann–Beckwith syndrome, discordance in the Silver–Russel syndrome is attributed to differences in the imprinting process between the co-twins.

### Complex disease

MZ twins have been reported discordant for multifactorial conditions such as idiopathic epilepsy (30%), type 1 diabetes (30–50%), multiple sclerosis (70%), rheumatoid arthritis (70%), schizophrenia (50%)[74] and bipolar disorders[75]. In the schizophrenic discordant twin pair, differences in the methylation status at some sites of the genome, which may have pathogenetic relevance (imprinted regions), were observed. Interestingly, a study by microarray analysis of two sets of MZ twins discordant for bipolar disorder led to the discovery of downregulated expression of a gene related to endoplasmic reticular stress response in both the affected twins[75].

## CONCLUSIONS

First, following the present discussion on discordance for genetic disorders in MZ twins, it seems reasonable to abandon the use of the expression 'identical twins' when indicating MZ twins. Second, we should remember that the finding of an early malformation complex in a singleton may be an indication that pregnancy started as a twin pregnancy and was followed by the death of a twin, which could have been the cause of the malformation complex in the co-twin. Third, MZ twinning may lead one to miss congenital hypothyroidism in one twin with thyroid dysgenesis because of the shared circulation with the euthyroid twin[76]. For the same reason, one may detect spurious high α-fetoprotein levels in the amniotic sac of a normal MC co-twin, the other showing high α-fetoprotein levels because he is affected by a neural tube defect. Because of the frequent observation of blood chimerism, karyotyping in MZ twins should be carried out on amniocytes and not blood cells. Finally, it should be pointed out that MZ twins remain an excellent resource for mapping monogenic as well as complex disorders. As far as monogenic disorders are concerned, Kondo and associates[77] quite recently took advantage of the analysis of a discordant twin pair for identifying the gene responsible for Van der Woude (cleft lip and palate with lip pits) and popliteal pterygium syndromes mapping at 1q32-q41. The authors have, indeed, compared the DNA sequence in the 350-kb critical region of the MZ twin pairs and found a single nucleotide difference between them, i.e. the presence of a nonsense mutation in exon 4 of the interferon regulatory factor 6 (IRF-6) gene in the affected twin, which has led to the identification of this gene as responsible for this disorder.

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# Conjoined Twins

*J. J. Oleszczuk and A. K. Oleszczuk*

**33**



## INTRODUCTION

Conjoined twins have always fascinated scientists, physicians and lay-people alike. Approximately 52 000 websites with the keywords 'conjoined twins' are found on Google.com, and over 1000 abstracts are listed in PubMed with these keywords. Despite the wide interest, the phenomenon of conjoined twinning remains an epidemiologic, embryologic and clinical mystery. This chapter aims at presenting the current knowledge on the history, epidemiology, embryology and clinical management of conjoined twins.

## HISTORY

The medical term 'conjoined twins', although originating in the 20th century, describes what arguably has been the best known anatomic malformation in human history – driven by its macroscopic and externally visible manifestation. The existence of cave drawings and carved and ceramic figurines of conjoined twins, as well as their occurrence in all kinds of animals, suggests that these malformations existed long before the human race finished descending from its ancestors.

The first depictions of conjoined twins appear in Egyptian tombs and on Roman coins. The phenomenon existed in ancient mythology with Janus, the two-faced Roman god of beginnings and endings, being the first 'famous' cephalopagus (Figure 33.1). One of the earliest documented cases of surviving conjoined twins was that of the Biddenden twins – Mary and Elizabeth Chulkhurst – born in England in AD 1100 and who, joined at the hips, lived to the age of 34 (Figure 33.2). Perhaps the most famous conjoined twins were Chang and Eng Bunker, born in Siam (now Thailand) in 1811 and joined by a small bridge of union at the umbilicus (omphalopagus).

**Figure 33.1** Roman coin showing the two-faced single-headed Roman god, Janus. The most appropriate medical term would be monocephalus diprosopus


**Figure 33.2** Mary and Eliza Chulkhurst were born joined at the hip (pygopagus), in 1100 in Biddenden, England. As well as them being pygopagii, all illustrations of these twins show joining at the level of the shoulder, a phenomenon that was not described in other conjoined twins

These twins gave rise to the popular term 'Siamese twins'. There were many better-documented cases of conjoined twins, a detailed account of which appears in reference 1.

## EPIDEMIOLOGY

The incidence of conjoined twinning is very difficult to estimate owing to several confounding factors. What can be ascertained is that the incidence of births with conjoined twinning is somewhere between 1 in 50 000 and 1 in 100 000 births (or 1 in 500–600 twin births) and that it varies among countries, most probably due to racial differences in overall twinning rates as well as ascertainment biases. It is likely, however, that the actual incidence of the phenomenon is greater, but because of spontaneous or induced abortions or births before 22 weeks' gestation (and the lack of reporting of these in national statistics), it is impossible to quantify the true extent of the embryologic phenomenon. What is also known is that the phenomenon is much more common in lower animals. The veterinary literature contains numerous reports of conjoined twinning among such diverse species as the hamster, guinea-pig, fish, goat, cow, mouse, chicken and buffalo.

## EMBRYOLOGY

Perhaps the most debated aspect of conjoined twinning is the embryologic origin of this phenomenon. Two contradicting theories exist – the fusion and the fission theories – and neither is likely to be definitively proved or disproved owing to the ethical limitations associated with human embryo research. The most comprehensive review of the controversies surrounding both theories is provided by Spencer in her recent book on conjoined twins[1]. The fission theory, which has been the generally accepted theory over the past 20 years, proposes that conjoined twins are a variation of monozygotic twins, but the division of the fertilized ovum is only partial. In other words, during the normal course of monozygotic twinning, an unknown stimulus causes the division to occur at around 13 days post-fertilization – a time at which the developing embryo is too large (or too old) to separate fully. Thus, the embryonic mass divides in its main bulk, but remains united at one pole or the other, or at a point between the two poles[2].

Proponents of the less accepted fusion theory argue, on the other hand, that the inner cell mass divides fully but the two monozygotic embryos stay close enough together to share either the amnion alone or both the amnion and the yolk sac. Then, as the embryos continue their rapid growth, they might come in contact with one another (always homologously) and become reunited ('fused') to result in either ventrally or dorsally conjoined twins. For a detailed, comprehensive (and quite complex) account of the fusion theory, a reading of Spencer's newest book is advised[1].

Reading the literature on both fission and fusion theories it becomes clear that consensus around this topic will not be achieved in the near future. It is equally important to note, however, that no matter which theory one accepts as true, both the clinical manifestations of conjoined twins and the overall management remain the same and are equally challenging.

## CLASSIFICATION

The many types of conjoined twins may be broadly classified as either equal or unequal. The equal forms (duplicatas completa) show equal or nearly equal duplication of structures. The unequal forms, belonging to the category duplicatas incompleta, include the parasitic variety in which there is unequal duplication of structures. In these cases, only part of the anatomic structure of the fetus is duplicated.

Classification of conjoined twins is typically based on the fused anatomic region followed by the

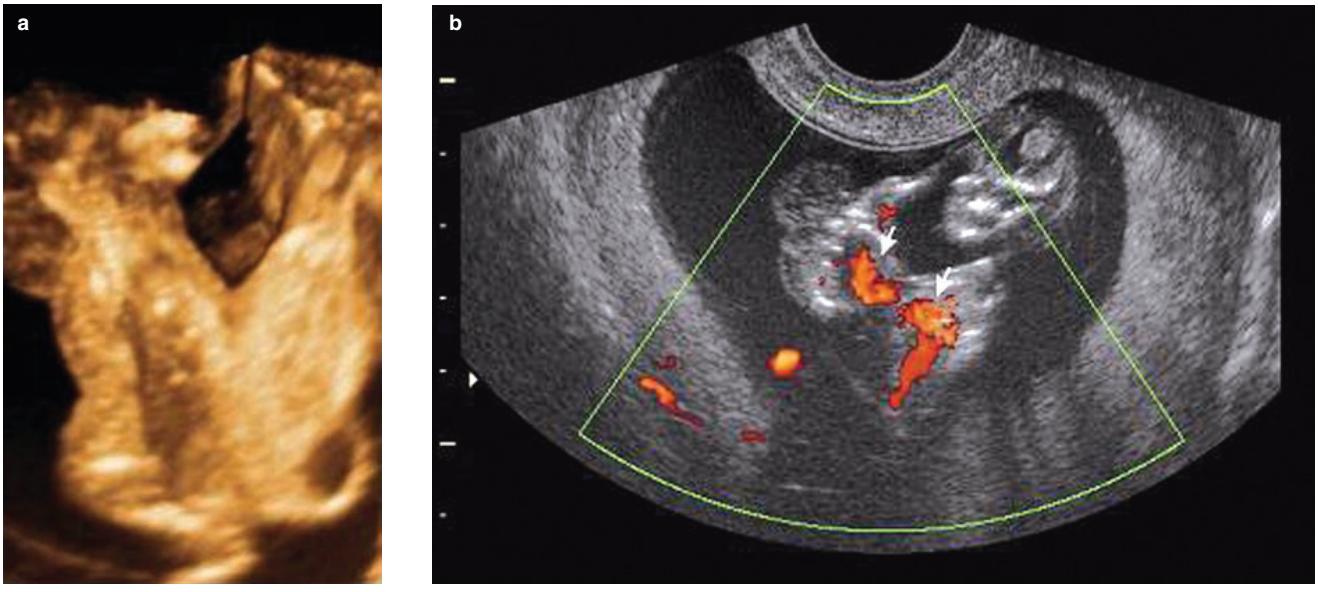


**Figure 33.3** (a) Three-dimensional ultrasound image showing thoracopagus twins. (b) Doppler ultrasound image showing thoracopagus twins. Two hearts are depicted by the Doppler scan (arrows). Images courtesy of Y. Hazan, Kaplan Medical Center, Israel

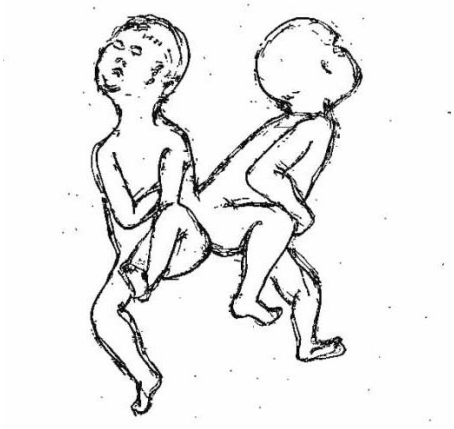

**Figure 33.4** Pygopagus twins. Illustration courtesy of Raya Gabay, RN, Kaplan Medical Center, Israel

Greek suffix, 'pagus', to indicate fastened. The following classification of equal and unequal types of conjoined twinning proposed by Potter and Craig[3] in their landmark book on fetal pathology.

## Diplopagus

These are conjoined twins in whom the components, or components' parts, are equal and symmetrical.

### *Each component is complete, or nearly so*

(1) Thoracopagus, sternopagus, xiphopagus and sternoxiphopagus: connection in or near the sternal region, usually median, and the components are face to face (Figure 33.3);

(2) Pygopagus: connection at the sacrum and the components are back to back (Figure 33.4);

(3) Craniopagus: connection by the heads, usually median (Figure 33.5);

(4) Ischiopagus: connection in the lower pelvic region with the axes of the bodies extending in a straight line in opposite directions (Figure 33.6).

### *The two components equal each other but each is less than an entire individual*

(1) Duplication beginning in the cranial region:

  (a) Monocephalus diprosopus (single head):

    (i) Partial duplication of frontal region and nose;

    (ii) Partial duplication of frontal region, nose and mouth;

    (iii) Duplication of the face either complete or with one eye of each face fused into a common median orbit (Figure 33.1);

  (b) Dicephalus (two heads, one body):

    (i) Dicephalus dipus dibrachius: two arms and legs with partial duplication of the spine and varying degrees of duplication of the median shoulder (Figure 33.7);

**Figure 33.5** Craniopagus twins. Illustration by Ambroise Paré, a famous 16th century surgeon

**Figure 33.6** Ischiopagus tripus (three legs). Plaster cast of twins born in Warren county, Ohio, October 12, 1870. See Appendix for description of the case. Image and text © 2004 Mütter Museum of the College of Physicians of Philadelphia

(ii) Dicephalus dipus tribrachius: similar to dibrachius but with a median third arm or arm rudiment;

(iii) Dicephalus dipus tetrabrachius: components united at the pelvis with varying degrees of fusion of the upper parts of the trunk but each component having a head and a pair of arms. The pelvis is partially duplicated but only two legs are present;

**Figure 33.7** Full-term dicephalic twins, delivered in 1929. One head (left) shows also a cleft lip and palate. © 2004 Mütter Museum of the College of Physicians of Philadelphia

(2) Duplication originating in the caudal region (dipygus):

(a) Monocephalus tripus dibrachius: partial duplication of the pelvis with a third median leg that may be rudimentary or complete;

(b) Monocephalus tetrapus dibrachius: partial or complete duplication of the pelvis with four legs, the pair belonging to one member often being fused in a sirenomelic limb;

(c) Cephalothoracopagus: two nearly complete components joined front to front over more or less the trunk region, but with a single neck and with heads more or less completely fused into a single compound mass (Figure 33.8):

(i) Deradelphus: one face with two ears and a single normally formed cerebrum;

(ii) Syncephalus: one face with four ears, two on the back of the head. The cerebrum is single or partially duplicated (Figure 33.9);

(iii) Janiceps: two faces on opposite sides of the head with half of each belonging to each component (Figures 33.10 and 33.11);

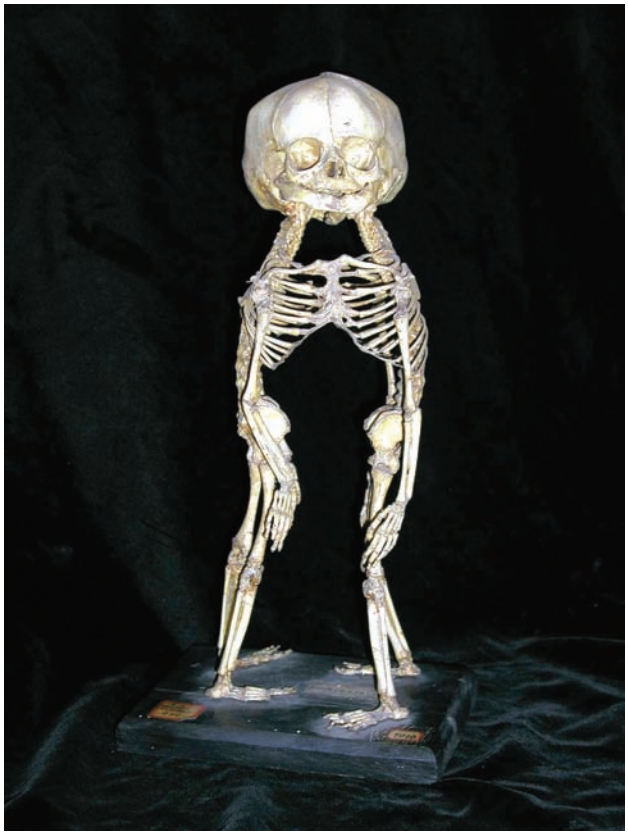

**Figure 33.8** Skeleton of cephalothoracopagus twins. See Appendix for description of the case. © 2004 Image and text Mütter Museum of the College of Physicians of Philadelphia

**Figure 33.9** Cephalothoracopagus, syncephalus type. After a 1547 etching by an anonymous artist. These are the famous conjoined twins of Lowen[4] of interest, both male and female genitalia are depicted by the artist

(3) Duplication of both cranial and caudal regions (dicephalus dipygus):

   (a) Dicephalus tripus tribrachius: two members with a common trunk but two heads, two or three arms and three legs (Figure 33.12);

   (b) Similar to tripus tribrachius but with either upper or lower extremities or both completely duplicated;

   (c) Complete duplication of head, arms and legs with anterior or lateral fusion of the trunk area.

### Heteropagus

These are unequal and symmetrical conjoined twins in which one component is smaller and dependent on the other. The two members have very unequal degrees of development, one (autosite) being normal or nearly so, and the other (parasite) being incomplete and attached to the first as a dependent growth, usually attached at some point on the ventral surface.

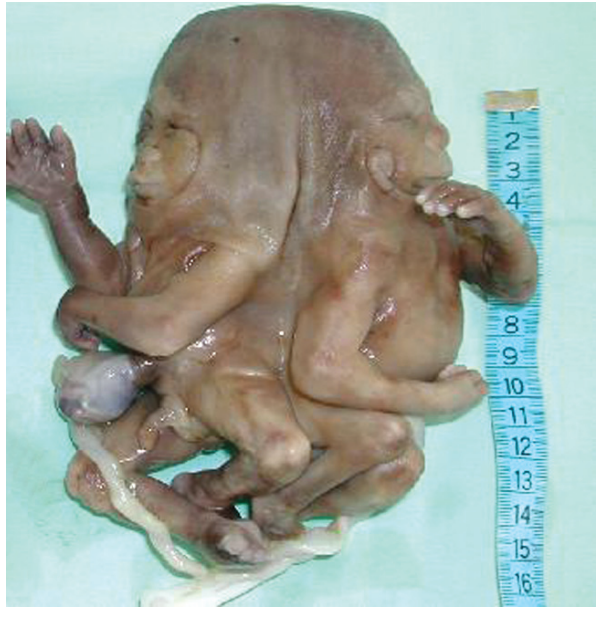

**Figure 33.10** Cephalothoracopagus janiceps. Conjoined twins with two faces on opposite sides of the head. Figure courtesy of Dr Ido Solt, Rambam Medical Center, Haifa, Israel

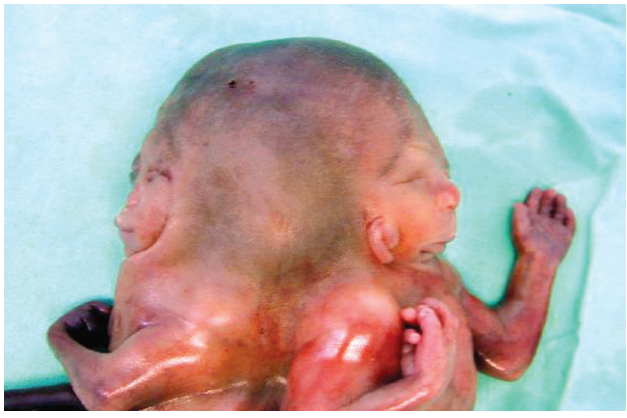

**Figure 33.11** Close-up of cephalothoracopagus janiceps. Conjoined twins with two faces on opposite sides of the head. Figure courtesy of Dr Ido Solt, Rambam Medical Center, Haifa, Israel

*Parasite attached to the visible surface of the autosite*

(1) Parasite having arms, or a head and arms, usually attached to the autosite at or near the epigastrium;

(2) Parasite having legs and varying portions of abdomen usually attached at or near the epigastrium;

(3) Parasite having arms and legs with or without a head with attachment at or near the epigastrium;

(4) Parasite attached to the head of the autosite;

(5) Parasite attached to the palate of the autosite;

(6) Parasite attached to the back, sacrum or pelvis of the autosite.

*Parasite developed in the autosite, usually in the thoracic or abdominal cavity, but occasionally in other regions (usually classified as tumors)*

(1) Fetus-*in-fetu*: well-differentiated parasitic growth showing some degree of internal symmetry and cranial caudal differentiation (see Chapter 43);

(2) Teratoma: amorphous growth derived from the germ layers and lacking differentiation.

Additional attempts have been made to standardize the terminology of conjoined twins. Cuq and Woronoff[5] proposed a classification that divides the types of conjoined twinning into orders, suborders, tribes, families, genera and varieties. The more simplified classification proposed by Guttmacher and Nichols (Table 33.1)[6] is also used by some authors.

The most common type of conjoined twinning, constituting approximately 59% of all cases, involves conjunction in the mid-body (thoracophagus, xiphopagus, omphalopagus or some combination thereof). In contrast, unequal conjoined twins are rare, accounting for less than 10% of cases[7,8].

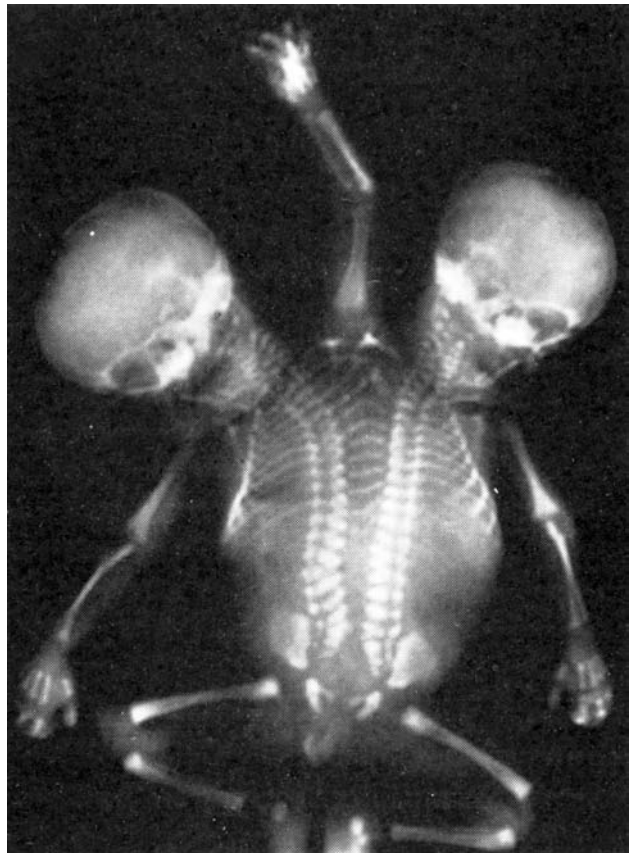

**Figure 33.12** Dicephalus dipus tribrachius. X-ray of skeleton showing common arm with fused humerus and three bones in the forearm. Reproduced with permission from reference 3

**Table 33.1** Types of conjoined twins (modified from reference 6)

| |
|---|
| *Inferior conjunction* |
| Diprosopus: 2 faces, 1 head, 1 body |
| Dicephalus: 2 heads, 1 body |
| Ischiopagus: inferior sacrococcygeal fusion |
| Pygopagus: posterolateral sacrococcygeal fusion |
| *Superior conjunction* |
| Dipygus: 2 pelves, and 4 legs |
| Syncephalus: facial + thoracic fusion |
| Craniopagus: cranial fusion |
| *Middle conjunction* |
| Thoracopagus: thoracic fusion |
| Omphalopagus: fusion from the umbilicus to the xyphoid cartilage |
| Rachipagus: vertebral fusion above the sacrum |

## ANATOMY

Many reports describe the gross anatomy of conjoined twins, although most of these data are based on postmortem findings. The internal anatomy of conjoined twins generally depends on the site and extent of the union. In some, organs may be shared or just connected. In others, the union may be only a thin bridge of skin and muscle with no shared or connected organs. Conjoined twinning is additionally associated with a high incidence of congenital anomalies; frequently, these anomalies are not associated with the site of conjoining.

### Craniopagus

Craniopagus twins may be united in the vertex, occiput or parietal areas, and in varying degrees of facial orientation and rotation. Asymmetry may occur to the extent that the vertex of one twin may be joined to the parietal region of the other.

The classification of craniopagi, as proposed by Winston[9], is divided into four types according to the deepest shared structure:

(1) Type A: scalp is shared but each brain has its own dura mater;

(2) Type B: dura is shared but an intact plane of dura separates the brains;

(3) Type C: pia or arachnoid is shared but the brains are still discrete;

(4) Type D: brains are contiguous.

This classification relates to the chance for survival after separation: A = 75%, B = 50%, and C and D = 30%[10]. When a Type D junction is present, the cerebral hemispheres are always involved.

### Thoracopagus, sternopagus, xiphopagus

Organs are usually dissymmetric with the extent of sharing dependent on the degree of fusion. The condition of the heart(s) is crucial for the determination of survival and the feasibility of separation, especially in thoracopagus twins[11]. The pericardium is shared in 90% of cases and, in 75%, the hearts are so extensively joined that surgical separation is precluded[13]. Possible abnormalities are known to include atrial fusion with or without an atrial septal defect (ASD), ventricular fusion with or without a ventricular septal defect (VSD), atrial and ventricular fusion, a single atrioventricular valve, truncus arteriosus and many others[12].

The pleural, pericardial and peritoneal cavities can be in open communication. Generally, the liver is shared to some degree, and a common gastrointestinal tract is found in 50% of cases[13].

**Table 33.2** The Seo classification of conjoined hearts and their surgical separability[14]

| *Type* | *Degree of fusion* | *Separability* |
|---|---|---|
| I | no significant fusion | easy |
| II | fusion of the great vessels | easy |
| III | atrial fusion | possible |
| IIIa | mirror-image right atrial fusion | possible |
| IIIb | other type of atrial fusion | possible |
| IV | atrioventricular fusion | not possible |
| V | single heart in one of the twins | not possible |

Seo and colleagues introduced a new classification of the cardiovascular system in conjoined twins (Table 33.2)[14]. The classification has five types and is based on the degree of fusion and the symmetry of the hearts and great vessels. Types I and II are easily separable. Separation of hearts with interatrial fusion (type IIIa and IIIb) may be possible, and analysis of the conduction system is important. The heart with atrioventricular fusion (type IV) and single hearts (type V) are inoperable[14].

### Omphalopagus

The area of fusion involves the abdomen between the xiphoid process and the umbilicus. Approximately 40–50% of omphalopagus twins do not have concomitant thoracic fusion[15]. Conjoined structures can include any portion of the gastrointestinal tract, liver or biliary system and bladder. Omphaloceles occur in one-third of omphalopagus twins but are infrequent (< 10%) when the fusion involves the xiphoid process. Gastroschisis is generally not found in omphalopagus or xiphopagus twins, but does occur with thoracopagus. A recent report, however, detailed a case of omphalopagus twins joined by gastroschisis[15].

### Pygopagus

In cases of pygopagus twinning, the areas of fusion may occur anywhere along the dorsal surface of the body but generally are limited to the pelvic region. Internal anatomy is variable, the sacrum and coccyx are usually shared, whereas the free portions of vertebral columns are generally complete[3]. The digestive tracts of the twins usually unite to form a single rectum and anus. There is commonly a single bladder and urethra, although there may be two, three or four kidneys. Considerable variation exists in the genital structures; both one and two vaginas and uteri have been reported.

### Ischiopagus

The bodies of ischiopagus twins are fused in the region of the pelvis as far as the level of the common umbilicus; above this, each infant is normally developed[3,13]. The sacrum and pelvis are often combined, with associated abnormalities of the lower spines. The extremities are subsequently displaced laterally. Vaginal, urethral and anal orifices may open between each pair of legs, or, if a tripus (fused leg) is present, only one genital opening will be present. There may be associated aortic fusion, common systemic circulation or shared gastrointestinal systems. The intestinal tract is usually joined at the terminal ileum which then empties into a single colon. Four kidneys and two bladders are usually present; one ureter from each twin may be found to empty into the other's bladder. Regardless of the degree of fusion of the genital systems, four gonads are usually present.

### Associated anomalies

Congenital malformations usually occur in almost all sets of conjoined twins. These malformations most likely result from the factors associated with the etiology of conjoining as well as crowding *in utero*. Although the majority of these malformations are associated with the site(s) of fusion, 60–70% of reported cases also have anomalies not associated with the area of fusion. Most commonly these include neural tube defects and orofacial clefts[16]. Overall, the most common malformations involve the cardiovascular system.

Discordance of the malformation is common when it involves the site of joining. However, true primary discordance, where the malformations are discordant in non-joined organs, are rare. This type of discordance most likely occurs because one twin has a greater liability to dysmorphogenetic events[17].

## OTHER CONJOINED TWIN FORMS

### Conjoined twins complicating triplet pregnancies

Sepulveda and colleagues[18] reported two cases of conjoined twins complicating a triplet pregnancy diagnosed by two-dimensional ultrasound in the first trimester and evaluated further by three-dimensional ultrasound. A review of the literature over the past 30 years revealed 11 other cases diagnosed prenatally by ultrasound. Overall, three (23%) of these 13 pregnancies were achieved by assisted reproductive technologies and ten (77%) were diagnosed before 18 weeks. Four women opted for termination of the entire pregnancy and three were managed expectantly, with two delivering before 32 weeks. Two monochorionic pregnancies underwent selective feticide, with intrauterine demise of the non-conjoined fetus in both cases. All four dichorionic pregnancies undergoing selective termination or spontaneous embryo reduction to a singleton in the first trimester resulted in term delivery of the non-conjoined fetus. The rare condition of conjoined twins in a triplet pregnancy poses a significant obstetric challenge from both diagnostic and management points of view. Accurate determination of chorionicity in these cases plays a critical role in determining management and outcome.

### Conjoined triplets

No discussion of conjoined twins would be complete without some reference to conjoined triplets and quadruplets, of which there are very few properly documented cases (not including the multiple intracranial fetal inclusions and the fetuses-*in-fetu*). Geoffroy Saint-Hilaire (cited in reference 10) postulated two possible ways in which three fetuses could be joined: one common site of union for all three, or two sites, with one triplet united on each side of an intermediate fetus. A variation of the latter, however, is a parasite attached to one of equal conjoined twins[10].

The best-known human tricephalus was born in Italy in 1831 and reported by Reina and Galvani in 1834. This was a male with three heads on two necks on one trunk, very carefully and thoroughly dissected and reported. There were three arms; a double upper thorax and two vertebral columns; a single umbilicus and imperforate anus but normal male genitalia; three larynges but two tracheas and four lungs; and three esophagi with a single stomach, duodenum and pancreas. Reina was criticized for having amputated the first two heads as they presented, one after the other, but he was unable to complete the delivery until there was only one head left; he defended himself by noting that there was no precedent for him to follow[13].

If the 'fusion theory' of the embryology of conjoined twins is correct, it should be possible to extend it to explain conjoined triplets. Therefore, it must be proposed here that Reina's three-headed infant was a tricephalus parapagus resulting from the (ventral) laterocaudal union of the cloacal membranes of three embryonic disks very close together on one yolk sac, with the same (but double) aplasia of contiguous anlagen that affects parapagus twins – Saint-Hilaire's theory of 'one common site of union for all three'[13].

The case of Martin de Pedro (1879) apparently consisted of female twins normal above the umbilicus but with six lower limbs; the two pairs on each side of the midline were well formed, while two incomplete limbs on the back had only four 'fingers' each. These ischiopagus twins shared one pelvic ring with two sacrums and two symphyses pubis. The orientation of the two ani, two sets of external genitalia and duplicate lower genitourinary tracts was 'anterior'

and 'posterior', typical of classic ischiopagus; in addition, however, there were two limbs attached dorsally, in the location usually occupied by a pygopagus parasite[13].

## MANAGEMENT

### Prenatal diagnosis

Conjoined twins can be diagnosed during a routine antenatal check-up with the help of ultrasonography. In the absence of clear-cut signs of fusion, additional sonographic findings summarized by Koontz and colleagues include[19]:

(1) The lack of a separating membrane;

(2) Inability to separate the fetal bodies;

(3) Detection of other anomalies in a twin gestation;

(4) More than three vessels present in the umbilical cord;

(5) Both fetal heads persistently at the same level;

(6) Backward flexion of the cervical and upper thoracic spine;

(7) No change in the relative positions of the fetuses despite attempts at manual manipulation of the twins.

Serial examinations are indicated to monitor fetal growth, the nature of the fusion and the development of hydrops, and to detect fetal demise. Doppler umbilical arterial velocity waveform analysis can reveal a characteristic 'double layer' spectral velocity waveform from the umbilical arteries. This is the result of signals originating from two separate arterial supplies adjacent to each other in a single umbilical cord. Such a characteristic feature provides an additional sonographic sign in the diagnosis of conjoined twins[20].

Magnetic resonance imaging can also be used prenatally to determine more precisely the extent of fusion and to begin planning for immediate postnatal management (i.e. survivability within a few hours after delivery). No prenatal imaging technique will be sufficiently precise to aid the surgeon in determining the approach to surgical separation and probability of success. Such decisions and conclusions can only be taken after careful postnatal considerations as described below.

### Labor and delivery

The lack of empirical evidence in terms of planning labor and delivery suggests that common sense must dictate the preferred timing and mode of delivery. It is unquestionable that scheduled delivery in a tertiary- or even quaternary-care center is ideal so that procedures required to evaluate the twins can be carried out shortly after birth. The method of delivery depends upon the prenatal assessment of the likelihood of survival. Despite anecdotal evidence of successful vaginal deliveries[21], cesarean section remains the method of choice in third-trimester deliveries. Vaginal delivery could be considered for stillbirths and for forms of conjoined twins that are incompatible with life, but the individual risk to the mother should be carefully evaluated before making the final decision.

### Postnatal imaging

Conjoined twins present a unique challenge to pediatric surgeons and radiologists. Planning of surgical separation is aided by accurate preoperative imaging. The area of fusion largely determines the imaging modalities used. Thoracic conjunction is most common and requires cardiac assessment, preferably by echocardiography, but contrast studies can enhance the finer details[18,22]. Magnetic resonance imaging and computed tomography provide excellent anatomic and bone detail, demonstrating organ position, shared viscera and limited vascular anatomy. Contrast-material radiography allows evaluation of the gastrointestinal and urogenital tracts. A shared liver requires assessment of anatomy, vascularization and biliary drainage. Angiography helps to define specific vascular supply, which is useful in determining the distribution of shared structures between the twins at surgery.

Each set of conjoined twins is unique. An imaging strategy to define accurately anatomic fusion, vascular anomalies and other associated abnormalities is important for surgical planning and prognostic information[22]. A very useful diagnostic 'cheatsheet' has been provided by Sepulveda and colleagues[18], which clearly shows the preferred imaging modalities used in different types of conjoined twinning (Table 33.3).

## CONCLUSIONS AND RECOMMENDATIONS

Conjoined twins are rare, and most obstetricians will not be personally exposed to such cases during their professional lifetimes. Although embryologic origins of conjoined twinning are still a matter of controversy, it is clear that for the practicing clinician the important question to consider is, 'Are the twins separable?', with a subset of questions related to the ethics of separation.

The key 'macro' recommendation coming from our own experience and from other cases in the literature is the pressing need to create (or designate) 'level-5' centers – international referral centers – to deal with conjoined twinning. Such centers should

**Table 33.3** Imaging modalities used in diagnosing the anatomy of conjoined twins[18]

| | | System evaluated* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| *Twin type* | *Overview* | *Cardiovascular* | *Hepatobiliary* | *Pulmonary* | *Upper GI* | *Lower GI* | *Urologic* | *Genital* | *Neurologic* | *Vascular* |
| Thoracopagus | plain radiography, MR imaging | echocardiography, cardiac catheterization | yes | yes | yes | no | no | no | no | yes |
| Omphalopagus | plain radiography, MR imaging | echocardiography | yes | yes | yes | maybe | no | no | no | yes |
| Pygopagus | plain radiography, MR imaging, CT of spine | echocardiography | no | no | no | yes | yes | yes | maybe | maybe |
| Ischiopagus | plain radiography, MR imaging, CT of pelvis | echocardiography, cardiac catheterization | maybe | maybe | maybe | yes | yes | yes | no | yes |
| Craniopagus | plain radiography, MR imaging, CT of skull | echocardiography | no | no | no | no | no | no | yes | maybe |
| Parapagus | plain radiography, MR imaging, CT of pelvis | echocardiography, cardiac catheterization | maybe | maybe | yes | yes | yes | yes | no | yes |
| Cephalopagus§ | plain radiography, MR imaging, CT of skull | echocardiography, cardiac catheterization | maybe | maybe | no | no | no | no | yes | yes |
| Rachipagus | plain radiography, MR imaging, CT of spine | echocardiography | no | no | no | no | no | no | maybe | no |

MR, magnetic resonance; CT, computed tomography; GI, gastrointestinal

**Table 33.4** Management tips

*Tip 1*
Work under the presumption that conjoined twins are separable and think ahead to postnatal period, constantly asking the question: 'How should best possible postnatal management be provided?'

*Tip 2*
Use available literature to create a 'long list' of potential level-4 facilities across the world using existing experience and success as key criterion for evaluation
Do NOT limit your search to your own country
Create 'shortlist' by limiting your picks to 1–2 countries with highest feasibility
Use local medical societies to confirm your shortlist

*Tip 3*
Get the surgical team involved as early as possible – possibly still during the prenatal period – to leverage that experience in guiding your prenatal and postnatal management and planning imaging tests

be appropriately funded by various governmental and non-governmental organizations to insure financially feasible referral practices (Table 33.4).

## APPENDIX

### Ischiopagus tripus (Figure 33.6)

The following description was written by Dr Ralph M. Townsend in *Photographic Review* 1870–71;1:58. 

'These twins were born in Warren county, Ohio, October 12, 1870. The delivery being natural and easy, and accomplished in half an hour before the arrival of the attending physician. By reference to the plaster cast it will be seen that these babes have a common trunk, terminating at either extremity in a well-shaped neck and head. Each end of the trunk is formed of a perfect thorax with its contained viscera, then comes the swell of the belly, and the children insensibly grade into one another. As they lie extended upon their backs they look as if two children had been cut transversely across at their umbilici, and then accurately welded together.

Exactly in the center of their common abdomen is a scar, marking the attachment of the umbilical cord, of which there was but one, along with one placenta, and these of unusual size.

Springing at right angles from the right side of the abdomen is a well-formed pelvis supporting a perfect pair of legs and feet, with the exception that one of the latter is in a condition of equino-varus. To these extremities are attached the genital apparatus and anus of an ordinary female child. Upon the opposite side of the abdomen there appears to be a rudimentary pelvis in the shape of an ilium, feeling under the skin something like a scapula. Branching from this also at right angles to the body, is a compound rudimentary leg, its anterior aspect looking backwards, terminating in a foot containing two ossa calces and eight toes, the great toes being outermost, and the lesser ones side by side.

When the child lies upon its belly, with its arms folded into the side and its legs extended, it is cross-like in shape, one arm of the cross being represented by the rudimentary leg.

The spines, on first inspection, seem to be continuous, but closer examination shows that they come together like two Js with their crooks laid end to end, the crooks turning towards the right and being attached to the complete pelvis.

One of these children is ruddy, muscular and full of vigorous vitality; but the other is thin, its chest is deficient in development, and its face looks prematurely old. The mother first nursed them both, but now gives all her milk to the smaller one, feeding the larger child from the bottle.

The father of these children is a tall, gaunt Pennsylvanian, 43 years of age, a farmer; the mother is Ohioan, 33 years of age, of massive frame and heavy face. She has had three other children, all healthy, the eldest being 13 years of age. She knows of no cause to which to ascribe the production of such strange progeny.

The pulse of these children is not uniform, beating at one examination six times faster to the minute in the arm of one child than in the arm of its companion. The sensation is also different. One does not feel when the other is pinched: one feeds while the other sleeps; and their separate attentions are simultaneously attracted by different objects. It is the opinion of their physician, Dr H. Besse, of Ohio, that they have separate bladders, owing to one bearing down and making water and a few minutes after the other, with like exerting, repeating the operation. The history of these cases, however, is that they have but one bladder and one rectum.

These children were placed at the disposal of Dr S. W. Gross, to whose courtesy I am indebted for

the opportunity of making this report. They were also the subjects of a clinical lecture at the Jefferson Medical College, by Dr H. F. Getchell, who ranked them in the order Catadiyma, genus Ischiopagus, and species Ischiopagus Tripus. To show how typical this child is to its class, the lecturer exhibited cuts of three similar cases, one born in Oxford, England, in 1552, one in Ceylon, many years after, and one in Cadiz, Spain, in 1818. The former two died at birth, the latter survived five days. This then is a much greater curiosity as a representative of a recognized class, all recorded cases of which have died at or soon after birth, than if it were a mere chance formation.

The history of all conjoined twins is that the death of one is immediately followed by the death of the other, and the present case seems to afford no chance for deviating from this rule. At present their digestion and assimilation are good. They are visited daily by hundreds of people, and maintain rare infantile good humor in spite of the somewhat awkward handling and examining they are ofttimes subjected to.'

The twins lived over 13 months; the emaciated one died first and a few moments later the other followed. No autopsy was allowed.

### Skeleton of cephalothoracopagus twins (Figure 33.8)

From *Transactions of the College of Physicians of Philadelphia*, Vol. 1. © 2004 Mütter Museum of the College of Physicians of Philadelphia.

The skeleton measures 33 cm in length. The head has an occipito-mental diameter of 10 cm and a biparietal diameter of 8.8 cm. The anterior and superior surface of the head is single; the duplication commences at the base of the cranium. The bones of the face are those of a single head with the exception of an effort at processes of the superior maxillary. The frontal and parietal bones are those of a single head; there are two occipital bones. To the condyloid processes of each are articulated the atlas of each vertebral column. There are two temporal, and two imperfect sphenoid bones.

Below the head the skeleton is completely double. The thorax was a single cavity, having two sterna to which the ribs and clavicles are articulated in a very peculiar manner. The right ribs and clavicle of the right skeleton and the left ribs and clavicle of the left skeleton articulate with the posterior sternum. The left ribs and clavicle of the right skeleton and the right ribs and clavicle of the left skeleton articulate with the anterior sternum. The other bones of each skeleton were developed and articulated as usual.

This conjoined twin was delivered in 1851 by Dr Warrington of Philadelphia, Pennsylvania, this being the third pregnancy of a woman 28 years old. The four feet presented first; the head was born last and the whole labor was unattended by any disaster to the mother. Their appearance at birth was that of two children having a thorax in common but with a single head. There was a fissure of the lower lip of the face in the median line. On the back of the head there was a symmetrical double ear, the meatus of which was imperforate. The four upper and the four lower extremities were perfect, equally developed and natural in their positions.

The umbilical cord was very thick and consisted of two umbilical veins and four umbilical arteries, one of which was very large, and the other very small; each part entering its own placenta.

The mouth was a single cavity, containing two tongues separated posteriorly by an irregular mass covered with skin, which was probably a rudimentary cheek or lip. The fauces and upper part of each pharynx were distinct; each contained two tonsils.

The pharynges communicated and, from the funnel-shaped cavity formed by their junction, there proceeded a single esophagus terminated in a stomach containing a single cavity though its shape was such as to give the idea that two stomachs had been fused by their lesser curvatures.

From the pylorus, there extended a single intestinal canal, which, at a distance of two feet from the stomach divided into two distinct tubes, each about 40 cm in length. These had the characters of the small intestine and terminated regularly in the ileo-colic valve. The large intestine was completely double, there being one for each child, each was perfect from the cecum to the anus, not excepting the appendix vermiformis and contained the usual amount of meconium.

The liver was single, large and symmetrical; it contained two lobes about the same size and a single gall-bladder. A spleen and two well-formed kidneys were found in each trunk. The genitals, which were female, were perfectly developed, both externally and internally in each pelvis. Organs of respiration normal for each child, except that at the apices of the lungs of the right child a large vessel entered.

There were two hearts; one was rudimentary and situated between the lungs of the left child; it was conical in its shape; consisted of but one single cavity and from its base there proceeded a single vessel. The other was developed irregularly; it was situated under the sternum to which are articulated the left ribs of the left child. From the base of this heart there arose an aorta for each child which occupied its usual position on the vertebral column.

The larger arterial branches were regularly given off, with the exception of the umbilical arteries of the right child, one of which was very large and appeared to be the continuation of the primitive iliac; the other was exceedingly small.

The ascending vena cava of the left child did not pass through the liver, but, after being joined by the descending vena cava, the common trunk thus formed passed behind the heart emptying into the right auricle. The ascending vena cava of the right child did not seem to exist below the liver, but the blood vessels from the lower extremities opened into the portal vein which was large proportionally. The pulmonary artery communicated with each aorta.

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# Trends in Congenital Malformations, Chromosomal Anomalies and Infant Mortality among Twin Births

*C. V. Ananth and J. C. Smulian*

34

INCIDENCE OF CONGENITAL MALFORMATIONS

US TWIN BIRTH COHORT

CONGENITAL MALFORMATIONS/ CHROMOSOMAL ABNORMALITIES

TRENDS IN CONGENITAL MALFORMATIONS

TRENDS IN INFANT MORTALITY

> '*… Birth defect surveillance has become a very important public health tool for tracking rates and trends in the prevalence of these abnormalities and is useful in establishing risk factors and potential etiologies.*'
>
> John Smulian, 2002

## INTRODUCTION

The dramatic increases in twin births in recent years in the United States and other countries, have been accompanied by dramatic reductions in twin neonatal and infant mortality over the past two decades[1–3]. For example, the number of twin births in the United States increased by 52% between 1980 ($n$ = 68 339) and 1997 ($n$ = 104 137), whereas the corresponding rate of twinning increased by 42% from 18.9 to 26.8 per 1000 births in the same period[1]. At the same time, the rate of infant mortality among twins in the United States declined by 42% between 1980 and 1997 from 50.0 per 1000 twin live births in 1983–84 to 29.2 per 1000 twin live births in 1995–96[4]. In spite of the impressive declines in twin infant mortality rates, most reductions in infant deaths are attributed to declining rates of death from birth asphyxia, neonatal sepsis and respiratory distress syndrome[5,6]. Surprisingly, infant mortality rates from congenital anomalies have increased, and consequently, congenital anomalies have emerged as the leading cause of infant deaths[7–9].

The evidence that congenital malformations are more common in twin than in singleton gestations is strong[10–15]. The overall frequency of malformations is two-fold higher in Blacks than in Whites and higher among males than among females[10,14]. Among twins, rates of minor and major malformations are generally higher in monozygotic than among dizygotic twins[10]. However, at least one population-based study in the United States showed no difference in the rate of malformations in twins based on placental zygosity[16].

In this chapter, we discuss the international incidence of congenital malformations and chromosomal anomalies in twin births, based on data gathered from several birth defects monitoring programs. We also present recent data on trends in congenital malformations and/or chromosomal anomalies in twin live births in the United States between 1989–91 and 1998–2000. Finally, we discuss the impact of these malformations and anomalies on infant mortality in United States twin live births between 1989–91 and 1998–2000.

## INCIDENCE OF CONGENITAL MALFORMATIONS

The reported incidence of congenital malformations from different countries among twins is given in Table 34.1[10,13]. These data were accrued from nine registries using specific protocols. Four registries – England and Wales, Finland, France (Paris) and Hungary – were population-based, whereas those from Israel (Tel-Aviv), Italy (IMER and IPIMC), Mexico (RYVEMCE) and South America (ECLAMC) were hospital-based.

The incidence of malformations in twins varies by placental chorionicity. For instance, data from the British Columbia Health Surveillance Registry (up to 1975) indicate that whereas the overall rate of

**Table 34.1** Worldwide incidence of congenital anomalies/malformations in twin births. Table entries, with the exception of those pertaining to the United States, were adapted from references 15, 10 and 13, with permission

| | | | Congenital malformations | |
|---|---|---|---|---|
| *Country/study* | *Year(s)* | *Total twin births* | *n* | *Rate* (per 10 000) |
| England and Wales | 1986–94 | 140 694 | 1951 | 13.9 |
| Finland | 1992 | 1712 | 64 | 37.4 |
| France (Paris) | 1987–92 | 8004 | 309 | 38.6 |
| Hungary | 1982–91 | 27 454 | 716 | 26.1 |
| Israel | 1988–92 | 690 | 47 | 68.1 |
| Italy – IMER | 1988–92 | 2236 | 93 | 41.6 |
| Italy – IPIMC | 1983–94 | 27 462 | 720 | 26.2 |
| Mexico – RYVEMCE | 1978–95 | 10 954 | 442 | 40.3 |
| South America – ECLAMC | 1982–92 | 41 650 | 1230 | 29.5 |
| United States (CPP)[10] | 1959–66 | 1195 | 219 | 1833.0 |
| Japan[13] | 1979–90 | 1936 | 42 | 216.9 |
| United States (present study) | 1989–91 | 240 349 | 2664 | 11.1 |
| United States (present study) | 1998–2000 | 336 258 | 2971 | 8.8 |

CPP, Collaborative Perinatal Project

congenital malformations in twins was 600 per 10 000 twin births, the rate was about 2.5-fold higher in monochorionic than in dichorionic twins[17]. Among 1195 twins from the Collaborative Perinatal Project (CPP) conducted in 12 hospital-based centers in the United States, 219 (1833 per 10 000 total twin births) displayed malformations[10]. Compared with singletons in the CPP study, congenital malformations were higher in twins, although the increased risk in twins was almost entirely restricted to monozygotic twins, and the rate of malformations in dizygotic twins was similar to that of singleton births. Of note, the very high rate of malformations in the CPP study may be attributable, at least in part, to the study design whereby infants underwent an examination for dysmorphology shortly after birth, a process which undoubtedly increases the rate for detection of subtle malformations.

A study from metropolitan hospitals in Tokyo, Japan showed that among 1936 twins, 217 per 10 000 twin births had a malformation, compared with 147 per 10 000 singleton births[13]. Anomalies of the cardiovascular system (72 per 10 000 twin births) and those of the musculoskeletal system (72 per 10 000 twin births) contributed most to the overall rates. However, a study from Spain[18] found no difference in the rate of overall congenital defects in twins compared with singletons (237 versus 221 per 10 000 twin and singleton births, respectively).

## THE UNITED STATES TWIN BIRTH COHORT

The United States linked natality and infant mortality data files for the years 1989 through 1991 and 1998 through 2000 were utilized to examine changes in the rates of reported malformations, as well as trends in infant mortality in twin live-borns with a congenital malformation and/or chromosomal anomaly. These data were assembled by the National Center for Health Statistics of the United States Centers for Disease Control and Prevention and correspond to data abstracted from live birth and infant death certificates (NCHS)[19]. Gestational age was estimated from an algorithm used by the National Center for Health Statistics based primarily on the last menstrual period (LMP). If the last menstrual period was missing or the birth weight was incompatible with the menstrual estimate of gestational age, a clinical estimate of gestational age, also contained on the birth and infant death data files, was used by the National Center for Health Statistics instead[20]. In a small fraction of births, when the date or month of the last menstrual period was missing but not the year, gestational age was imputed[21].

## CONGENITAL MALFORMATIONS/ CHROMOSOMAL ANOMALIES

We examined the reported incidence of the following congenital malformations identified at birth: neural tube defects including spina bifida and anencephaly; nervous system anomaly; hydrocephaly and microcephaly; circulatory anomalies, including those related to the heart; renal agenesis; omphalocele or gastroschisis; and musculoskeletal anomalies. Chromosomal anomalies, including Down's syndrome, were also evaluated. All rates are expressed per 10 000 twin live births.

**Table 34.2** Changes in the distribution of congenital malformations/chromosomal anomalies identified at birth between 1989–91 and 1998–2000: United States twin live births

| | *Malformations/anomalies identified at birth* | | | | |
|---|---|---|---|---|---|
| | *1989–91 (n = 240 349)* | | *1998–2000 (n = 336 258)* | | |
| *Congenital malformations and/or chromosomal anomalies* | *n* | *Risk (per 1000)* | *n* | *Risk (per 1000)* | *Adjusted relative risk* (95% confidence interval)* |
| No malformation/chromosomal anomaly | 237 273 | — | 332 881 | — | — |
| Any malformation/chromosomal anomaly | 3076 | 128.0 | 3377 | 100.4 | 0.78 (0.74–0.82) |
| 1 malformation/anomaly | 2664 | 111.4 | 2971 | 88.2 | 0.79 (0.75–0.83) |
| 2 malformations/anomaly | 347 | 14.2 | 366 | 11.5 | 0.74 (0.64–0.86) |
| 3 malformations/anomaly | 53 | 2.1 | 35 | 1.2 | 0.46 (0.30–0.72) |
| ≥ 4 malformations/anomaly | 12 | 0.5 | 5 | 0.1 | 0.32 (0.11–0.92) |

*Relative risks were adjusted for maternal age, gravidity, maternal education, marital status and maternal race/ethnicity

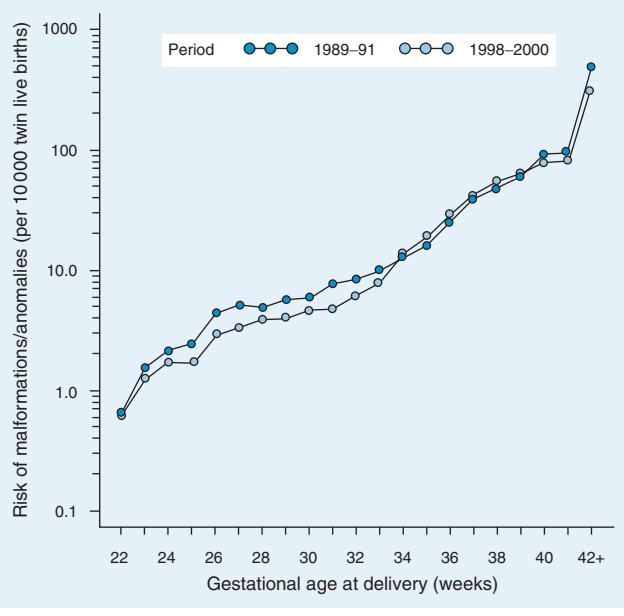


**Figure 34.1** Trends in gestational age-specific risk of congenital malformations/chromosomal anomalies among twin live births in the United States, 1989–91 and 1998–2000

We derived trends in gestational age-specific congenital malformations and chromosomal anomalies, as well as that of infant mortality using the fetuses-at-risk approach[22,23]. Changes in infant mortality (defined as deaths to live-born twins within the first year) were estimated between the two periods 1989–91 and 1998–2000 before and after sequentially adjusting for the presence of a particular malformation, as well as for potential confounders. These confounders included maternal age (six categories: 15–19 through ≥ 40 years), maternal education (< 12 and ≥ 12 completed years of school), maternal race/ethnicity (Whites, Blacks and other race/ethnicity) and marital status (single or married). Changes in neonatal mortality were expressed as relative risks (with 95% confidence intervals), and were derived from logistic regression models.

## TRENDS IN CONGENITAL MALFORMATIONS

In the United States, the overall rate of congenital malformations/chromosomal anomalies among twins declined from 12.8 per 100 000 twin live births in 1989–91 to 10.0 per 100 000 twin live births in 1998–2000 – a relative decline of 22% (Table 34.2). Interestingly, the rates declined the most among twins identified with ≥ 3 and ≥ 4 malformations.

Gestational age-specific risk of congenital malformations/chromosomal anomalies (per 10 000 twin live births) in twins increased with advancing gestational age during the 1989–91 and 1998–2000 periods in the United States (Figure 34.1). Interestingly, the risk was higher up to 33 weeks in the 1989–91 compared with the 1998–2000 cohort, whereas risks were similar at later gestational ages.

The overall risk of any congenital malformation/chromosomal anomaly declined by 22% between 1989–91 and 1998–2000 among twin live births in the United States (Table 34.3). However, most of the decline was restricted to twin live births that occurred at < 33 weeks. The decline was steeper among chromosomal anomalies (relative risk 0.54, 95% confidence interval 0.46–0.64) than among those that were non-chromosomal. Renal agenesis actually showed a non-significant trend of increasing

**Table 34.3** Changes in congenital malformations/chromosomal anomalies identified at birth between 1989–91 and 1998–2000: United States twin live births

| | *Malformations/anomalies identified at birth in twin live-borns* | | | | |
|---|---|---|---|---|---|
| | *1989–91 (n = 240 349)* | | *1998–2000 (n = 336 258)* | | |
| *Congenital malformations and/or chromosomal anomalies* | *n* | *Risk (per 10 000)* | *n* | *Risk (per 10 000)* | *Relative risk* (95% confidence interval)* |
| Any malformation/chromosomal anomaly | 3076 | 128.0 | 3377 | 100.4 | 0.78 (0.74–0.82) |
| Any chromosomal anomaly | 311 | 12.9 | 271 | 8.1 | 0.54 (0.46–0.64) |
| Down's syndrome | 145 | 6.0 | 118 | 3.5 | 0.48 (0.38–0.62) |
| Neural tube defect | 273 | 11.4 | 268 | 8.0 | 0.73 (0.61–0.86) |
| spina bifida | 108 | 4.5 | 95 | 2.8 | 0.65 (0.50–0.86) |
| anencephaly | 172 | 7.2 | 177 | 5.3 | 0.76 (0.61–0.94) |
| Hydrocephaly | 162 | 6.7 | 167 | 5.0 | 0.77 (0.62–0.96) |
| Nervous system anomaly | 149 | 6.2 | 120 | 3.6 | 0.56 (0.44–0.71) |
| microcephaly† | 217 | 9.0 | 201 | 5.9 | 0.68 (0.56–0.83) |
| Circulatory anomaly | 1719 | 71.5 | 1903 | 56.6 | 0.79 (0.74–0.84) |
| heart anomaly | 721 | 30.0 | 817 | 24.3 | 0.80 (0.72–0.89) |
| Renal agenesis | 64 | 2.7 | 104 | 3.1 | 1.25 (0.91–1.71) |
| Omphalocele/gastroschisis | 119 | 5.0 | 131 | 3.9 | 0.78 (0.61–1.00) |
| Musculo-system anomaly | 545 | 22.7 | 659 | 19.6 | 0.85 (0.77–0.96) |

*Relative risks were adjusted for maternal age, gravidity, maternal education, marital status and maternal race/ethnicity;
†microcephaly excludes infants diagnosed with anencephaly

incidence (2.7–3.1 per 10 000 twin live births) between 1989–91 and 1998–2000.

Several factors may be responsible for the trends in malformations among live-born twins noted here. Foremost among them is that, with the more widespread use of assisted reproductive methods including ovarian stimulation and *in vitro* fertilization than formerly, more and more twin gestations are conceived as dichorionic rather than monochorionic. This circumstance decreases the proportion of twins that are monochorionic. Even if assisted reproductive methods are associated with a very small increase in malformations, this effect would be significantly diluted by the net overall effect of much larger numbers of dichorionic twins with lower malformation rates than those of monochorionic twins. Second, the declining rates of malformations, especially lethal forms such as spina bifida among United States live-born twins, as a result of increased prenatal diagnosis and surveillance, may have led to a greater frequency of interventions such as pregnancy terminations and/or selective fetal reductions[7,24]. This may be particularly true for twin fetuses with severe anomalies that are likely to be terminated early in pregnancy[9], thereby resulting in a reduction of congenital malformations and/or chromosomal anomalies over time.

Indeed, methods of prenatal diagnosis have improved markedly during the recent decade with the general availability of ultrasound, biochemical screening techniques including maternal serum α-fetoprotein and multiple marker tests, amniocentesis or chorionic villus sampling and, more recently, first-trimester fetal nuchal translucency examination. These techniques, accompanied by better and improved prenatal care (including recommendations for use of folic acid), may have, to a large extent, accounted for the declining rates in congenital malformations and chromosomal anomalies noted here.

## TRENDS IN INFANT MORTALITY IN THE PRESENCE OF CONGENITAL MALFORMATIONS

Gestational age-specific trends in the risk of infant death (per 10 000 live births) in twin gestations in the United States in 1989–91 and 1998–2000 among infants with congenital malformation/chromosomal anomaly are shown in Figure 34.2. The risk of infant death was higher at every gestational age in the 1989–91 compared with the 1998–2000 cohort. Furthermore, the disparity in the risk of infant death was not only wider between the 1989–91 and 1998–2000 periods, but the disparity disappeared when pregnancies ended at ≥ 34 weeks.

The adjusted risk of infant mortality fell by 28% between 1989–91 (346.1 per 10 000 twin live births)

and 1998–2000 (192.4 per 10 000 twin live births) in the United States (Table 34.4). Over the same period, infant deaths with any malformation and/or chromosomal anomaly also declined by 34% (adjusted relative risk 0.66, 95% confidence interval 0.58–0.75). The decline in infant mortality was greater for infants with identified chromosomal anomalies (50% decline) than for those with malformations that were not chromosomal in nature. The risk of infant mortality among twins with nervous system, circulatory, omphalocele/gastroschisis or musculo-system anomalies also declined significantly across the two periods. Although there was a trend toward declining risk of infant deaths in twins with a neural tube defect or renal agenesis between 1989–91 and 1998–2000, this comparison did not reach statistical significance.

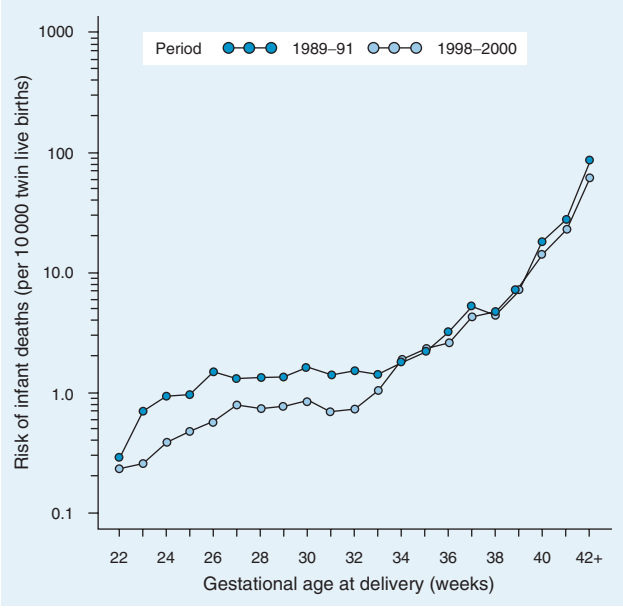


**Figure 34.2** Trends in gestational age-specific risk of infant death among infants with reported congenital malformations/chromosomal anomalies among twin live births in the United States, 1989–91 and 1998–2000

## SOME CAVEATS

Several limitations of the data presented here require some discussion. First, the overall rate of malformations in multiple births may be affected by selection bias to some extent. Physicians caring for women carrying multiple fetuses may be more likely to look for malformations than someone caring for a singleton pregnancy. This issue is even more pronounced in light of the adverse outcomes associated with multiple births that were conceived through assisted reproductive methods compared with natural conceptions. Second, the discordance in birth weight between the two fetuses in a twin pregnancy is associated with increased risk of malformation

**Table 34.4** Trends in infant mortality rates between 1989–91 and 1998–2000: United States twin live births

| | *Infant mortality in twin live-borns* | | | | |
|---|---|---|---|---|---|
| | *1989–91 (n = 240 349)* | | *1998–2000 (n = 336 258)* | | |
| *Congenital malformations and/or chromosomal anomalies* | *n* | *Risk (per 10 000)* | *n* | *Risk (per 10 000)* | *Relative risk* (95% confidence interval)* |
| Overall | 8318 | 346.1 | 6547 | 192.4 | 0.72 (0.70–0.75) |
| Any malformation/chromosomal anomaly | 538 | 22.4 | 472 | 14.0 | 0.66 (0.58–0.75) |
| Any chromosomal anomaly | 47 | 2.0 | 37 | 1.1 | 0.50 (0.33–0.78) |
| Down's syndrome | 14 | 0.6 | 8 | 0.2 | 0.35 (0.14–0.84) |
| Neural tube defect | 87 | 3.6 | 90 | 2.7 | 0.81 (0.60–1.09) |
| spina bifida | 18 | 0.8 | 15 | 0.5 | 0.69 (0.34–1.37) |
| anencephaly | 72 | 3.0 | 77 | 2.3 | 0.83 (0.60–1.15) |
| Hydrocephaly | 33 | 1.4 | 35 | 1.0 | 0.85 (0.53–1.38) |
| Nervous system anomaly | 29 | 1.2 | 21 | 0.6 | 0.51 (0.29–0.90) |
| microcephaly† | 82 | 3.4 | 80 | 2.4 | 0.76 (0.55–1.04) |
| Circulatory anomaly | 303 | 12.6 | 255 | 7.6 | 0.63 (0.53–0.75) |
| heart anomaly | 158 | 6.6 | 154 | 4.6 | 0.73 (0.58–0.91) |
| Renal agenesis | 24 | 1.0 | 28 | 0.8 | 0.93 (0.54–1.62) |
| Omphalocele/gastroschisis | 32 | 1.3 | 25 | 0.7 | 0.56 (0.33–0.95) |
| Musculo-system anomaly | 66 | 2.8 | 52 | 1.6 | 0.62 (0.43–0.90) |

*Relative risks were adjusted for maternal age, gravidity, maternal education, marital status and maternal race/ethnicity;
†microcephaly excludes infants diagnosed with anencephaly

in the smaller twin. Third, anomalies tend to cluster within a twin sibship (i.e. both twin fetuses with the same anomaly), thereby leading to higher frequencies of concordant malformations. Finally, the role of a biologic clustering phenomenon of malformations will likely require sophisticated statistical approaches for describing the rate of specific malformations in twin pregnancies. While all these limitations will probably affect some of the data presented in this chapter, the extent to which these factors may be responsible for the patterns noted here remains unknown.

## SUMMARY

Whereas the rate of twinning has increased, the rate of twin births with malformations (selected for study) has decreased overall, as has the risk for mortality among those with malformations. Investigation of the factors contributing to these trends will require the development of population-based data sets that track detailed information on twin conceptions, pregnancies and births in the context of malformations.

## ACKNOWLEDGMENTS

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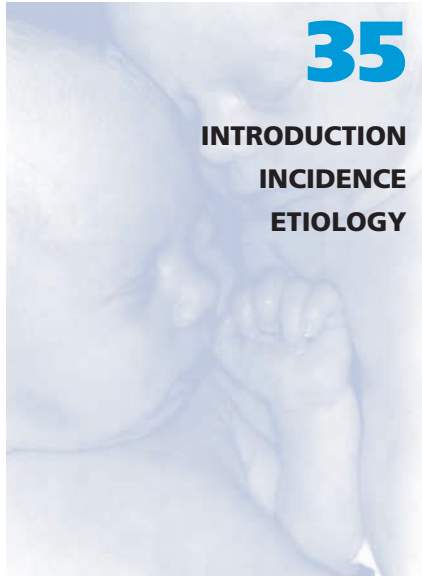
# Pregnancy Loss: Multiple Pregnancy versus Multiple Birth

*M. S. Verp*




## INTRODUCTION

It is now accepted that the risk of loss of one or more embryos/fetuses in a multiple gestation is higher than the risk of loss of a singleton pregnancy. Most losses occur very early in gestation, and are only detected because an initial ultrasound examination shows one or more gestational sacs that subsequently 'vanish'. The subject of the vanishing fetus is addressed in detail in Chapter 17 of this book. In a similar fashion, fetuses in multiple gestations have a higher likelihood of perinatal loss, also addressed elsewhere in this volume (see Chapter 1). This chapter reviews the literature on the partial or complete loss of multiple pregnancies between the embryonic period and the time of fetal viability. Both the incidence and the potential etiologies of such losses are discussed.

## INCIDENCE

A number of studies, published before the advent of routine early ultrasound examination, examined material from unselected spontaneous abortions, comparing the prevalence of twins in spontaneous abortion populations with the prevalence of twin deliveries amongst all pregnancies ending in live birth. For example, Creasy and colleagues[1] studied 1803 spontaneously aborted pregnancies with an identifiable fetus or gestational sac. Twins were identified in 36 instances, for an estimated prevalence of 2.0%. The prevalence of twin births in a similar population was 1.0%. A similar study by Livingston and Poland[2] identified 1939 spontaneously aborted pregnancies with a fetus or embryo; 53 or 1/35 of these were found to have twins, for a prevalence of 2.8%. Live births of twins were only 0.9%, or one-third as common in their population. Kajii and colleagues[3], Uchida and associates[4] and Tanimura and Tanaka[5] have reported very similar findings in populations from Canada, Switzerland and Japan, respectively. Data from all authors indicate that twin gestations resulting in spontaneous abortion are two- to three-fold as common as those ending in the live birth of twins. Moreover, because of the difficulties of recognizing and collecting both specimens in a twin gestation, twin gestations may be underestimated when examining spontaneous abortion material.

More recently, several authors have calculated the natural loss rate of multiple gestations, following first-trimester ultrasound diagnosis. In the recent study of Dickey and colleagues[6], for example, following identification of a multiple gestation before 12 weeks, 36% of twins, 53% of triplets, 65% of quadruplets and 19% of singletons suffered loss of one or more embryos/fetuses. Data from this publication and others are shown in Tables 35.1 and 35.2. However, as noted by Ross and Khorram[14], the rate of survival to term per gestational sac was equal in twins and singletons. Earlier gestational age at detection is associated with a higher loss rate, as would be expected (Tables 35.1 and 35.2). Increasing maternal age was positively associated with spontaneous loss when two gestational sacs were seen prior to the 7th gestational week (33% reduction in patients < 30 years old, 37% between ages 30 and 39 and 61% in those 40 or older)[6]. Loss was less common among ovulation-induced multiples (33%) than among those conceived following spontaneous ovulation (62%). Dickey and co-workers suggest an explanation, i.e. that gestational sac size is more equal in the former group because of ovulation from equal-sized follicles[6].

Other authors have also noted a higher loss rate among triplets than for singletons (Table 35.2). Here

**Table 35.1** Spontaneous abortion of twin gestations

| Author(s) | Twin pregnancies detected with known outcome (*n*) | Gestational age at detection (weeks) | With complete abortion (*n* (%)) | Resulting in singleton (*n* (%)) | Resulting in twins (*n* (%)) |
|---|---|---|---|---|---|
| Levi[7] | 101 | < 10 to > 15 | NA | 16 (15.8) | 85 (84.2) |
| Levi and Reimers[8]* | 111 | ≥ 10–14 | NA | 8 (7.2) | 103 (92.8) |
| Seoud *et al.*[9] | 151 | 6–7 | 17 (11.3) | 31 (20.5) | 103 (68.2) |
| Dickey *et al.*[6] | 526 | 6 | 64 (12.2) | 140 (26.6) | 323 (61.4) |

*Data as reported in reference 10; NA, not applicable

**Table 35.2** Spontaneous abortion of triplet and quadruplet gestations (to 24 weeks)

| Author(s) | Multiple pregnancies (*n*) | Gestational age at diagnosis (weeks) | With complete abortion (*n* (%)) | Resulting in singleton (*n* (%)) | Resulting in twins (*n* (%)) | Resulting in triplets (*n* (%)) | Resulting in quads (*n* (%)) |
|---|---|---|---|---|---|---|---|
| Lipitz *et al.*[11]* | 106 | < 9 | 22 (20.8) | NA | 2 (1.9) | 82 (77.4) | NA |
| Smith-Levitin *et al.*[12]* | 66 | NA | NA | NA | 12 (18.2) | 54 (81.8) | NA |
| Leondires *et al.*[13]* | 81 | 9 | 8 (9.9) | 3 (3.7) | 8 (9.9) | 62 (76.5) | NA |
| Dickey *et al.*[6]* | 127 | 5.5–6.5 | 10 (7.9) | 14 (11.0) | 48 (37.8) | 55 (43.3) | NA |
| Dickey *et al.*[6†] | 19 | 5.5–6.5 | 3 (15.8) | 0 | 7 (36.8) | 6 (31.6) | 3 (15.8) |

*Triplets; †quadruplets; NA, not applicable

again, Dickey and colleagues[6] noted a maternal age effect in spontaneous abortion of triplets. Spontaneous abortion of all gestational sacs prior to 12 weeks' gestation occurred in 6.1% of the total group, and one or more sacs were lost in 47% of women aged < 30 years, 51% with maternal age 30–34 years and 65% of patients 35 and older.

Information about higher-order multiples is less abundant. Seoud and associates[9] found a loss rate of 20% for one or more fetuses in a small series of five quadruplet pregnancies. Dickey and colleagues[6] noted spontaneous reduction of one or more gestational sacs in 65% of quadruplet pregnancies diagnosed before 12 weeks' gestation (Table 35.2).

## ETIOLOGY

Just as is the case with singletons, multiple etiologies are likely for pregnancy loss in multiple gestations. Some causes for pregnancy loss, however, may be specific to multiple gestations. In 1980, Livingston and Poland examined 53 pairs of twins (52 embryos, 54 fetuses) in a series of 1939 spontaneously aborted embryos and fetuses[2]. Eighty-eight per cent of the embryos were morphologically abnormal, as were 21% of the fetuses, which was similar to the rate in singletons (84% of embryos and 26% of fetuses). Noted abnormalities included growth disorganization and cardiac defects. Most of the twin fetal specimens were discordant for abnormality. The authors' impression was that the monozygotic : dizygotic ratio was 17.5 : 1, compared with a 0.8 : 1 ratio in live-borns, the implication being that the excess loss of twins may be primarily in monozygotic twins, perhaps due to abnormal vascular connections. Others, however, have found a monozygotic : dizygotic ratio closer to that found in live-borns, although still elevated[2,15].

Uchida and associates[4] studied 15 twin pairs in a series of 661 spontaneous abortions. Five of the twin abortuses were trisomic (two in a single pregnancy) for a chromosomal abnormality rate of 17% (5/29), which is lower than the singleton rate in this series (47%). Examples of discordant twin karyotypes were one set with 46,XX and 47,XX, +22, and another set with 46,XX and 47,XY, +16. Two of the twin sets were conjoined, a condition almost always associated with normal chromosomes. In a similar study, Kajii and associates[3] examined 11 twin pairs in 639 spontaneously aborted specimens. Of 15 karyotyped twins, five (33%) were abnormal, compared with 54% of the successfully karyotyped singletons. Creasy and

colleagues[1] also noted a lower rate of chromosomal abnormalities in karyotyped twin abortuses (0/42 versus 287/941 of singletons).

Specific visible malformations were identified in 7.3% of twins versus 3.9% in the singleton abortuses in the report by Creasy and colleagues[1]. It is axiomatic, however, that if a pregnancy continues following the death of a single embryo/fetus in a multiple gestation, that embryo/fetus will have a pathologic or chromosomal examination in only the most exceptional circumstances. In contrast, an abnormal singleton embryo/fetus with demise and expulsion has a much greater chance that a chromosomal or structural evaluation will be performed and the abnormality detected. As a result of this fundamental difference in access to pathologic examination, the rates cited above for chromosomal or structural abnormalities in multiple gestations may be artifactually low when considering the loss of only one embryo/fetus of a multiple gestation.

As suggested from the above commentary and further explored by Boklage[16,17], the causes of early pregnancy loss are numerous and, for the most part, not unique to multiple gestations. However, in addition to the risks incurred by singletons, twins have an excess of certain specific defects including those involving midline fusion or embryonic symmetry determination (see Chapters 28 and 36). Asymmetry of the process of monozygotic twinning may result in unequal division of primordial embryonic or trophoblastic cells. Disparate-sized placentas are not unusual at birth in monozygotic twins, suggesting that major disparities in placental size could be responsible for early pregnancy failure of one or more fetuses of a monozygotic gestation.

Based on his studies, Boklage[16,17] believes that same-sex dizygotic twins are at greater risk of anomalies and of early fetal mortality than are opposite-sex twins. The mechanism responsible for such an increase in risk, however, remains elusive. Boklage also found an excess of males amongst abortuses in multiple gestations[16,17], whereas Baldwin[15], and Livingston and Poland[2], both found an excess of females.

Other hypothesized causes of early loss of multiple gestations are first-trimester 'crowding' of the developing gestation and lack of adequate sites for placental implantation[6,18]. Random initial implantation may determine the ability of the placenta to grow with gestation, and ultimately affect fetal growth as well.

Similar to singleton losses, losses of late first-trimester/early second-trimester fetuses in multiple gestations tend to be a mixture of those with fetal malformation/fetal death and, particularly amongst those aborted somewhat later, obstetric complications such as ascending infection, and cord/placental abnormalities (see other chapters in this volume).

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# The Biology of Human Twinning: a Needed Change of Perspective

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## THE FOUNDATIONS

Certainty and science by definition are never the same thing. The orthodox version of the biology of human twinning is founded on pillars of 'common knowledge', falsely and passively simplified by neglect of attention and curiosity. That foundation serves as the basis from which neophytes and veterans alike begin and continue investigations with the best of scientific intentions. Most of the fundamentals of the common knowledge of human twin biology are supported only by repetition, rather than the repeatable-or-refutable observations essential to scientific credibility. These unquestioned answers, taken on faith to bridge the void of ignorance, are not the stuff of science. They may appear serviceably plausible *ad hoc*, but are worse than useless because they disguise unanswered questions with the false certainty of unquestioned answers. Whereas most other chapters in this volume offer coherent packages of what their authors have come to believe they know, this one is about the difference between not knowing and not being able to learn because things we think we know already prevent further learning.

## THE WEINBERG PILLAR

Many of the fundamental elements of the orthodox biology of human twinning as held in common knowledge have no basis beyond conclusions drawn from the use of the Weinberg tautology. Generally called the 'Weinberg difference method', or the 'Weinberg rule', this pillar of orthodoxy arose in good faith over a century ago as a means of estimating zygosity fractions in samples of twin pairs, in the absence at that time of any practical way to sort twin pairs by zygosity accurately. Flaws in the logical structure of Weinberg's idea as applied to these purposes are widely reported[1–8]. The most fundamental is the tautology itself: what some consider to be answers to questions at issue in applications of the Weinberg procedure are among the initial assumptions necessary for any of its uses.

Wilhelm Weinberg died in 1937. It no longer matters whether or how he questioned the assumptions required for the use of his zygosity fraction estimation method[9,10]. The problem lies in every continuing use of the Weinberg approach, or of any conclusion dependent upon it, without proper attention to its assumptions. When any exercise in logic reaches conclusions that repeat its own premises, those conclusions are logically false, regardless of any bits of truth which happen to fall among them. If no other validation is available, if the circular logic of Weinberg estimation is the only source of understanding, then there is no valid understanding.

The mathematical basis for the Weinberg estimation of zygosity fractions is the binomial distribution, the simplicity and straightforwardness of which is as misleading as it is comforting. Even this easy path has rules upon which its appropriate use depends absolutely. Statistical independence – meaning that no one of a set of events under consideration has any influence on another one of those events – is fundamental to the structure and uses of the binomial distribution. Because the events in question are functions of living organisms, this logic requires absolutely that same independence in the things that cells must do to generate those events.

Consider what it means when we assume the binomial independence of sexes of dizygotic (DZ) co-twins. Given that (= 'If and only if …') DZ co-twins arise independently by the independent fertilization of independently ovulated oocytes, then they may be expected to be independent in sex, just like any pair of individuals derived from independent fertilization of independent oocytes. 'Independence' appears six times in that sentence; importantly, simultaneity is not there. Independence is the point, and simultaneity, if it matters at all, is a problem. The simultaneity of DZ co-twin individual fertilizations is necessarily a departure from independence (in time), and a likely source and correlate of other departures, given the crucial importance of the timing of fertilization relative to the progress of oocyte maturation[11–16]. The oocyte is the largest and most complex of all human cells. The preparation for its many and complex functions comprises the most fundamental and comprehensive system of processes in all of the business of becoming human.

If half of all individual members of DZ pairs are male and half female, and if the events in question satisfy all of those necessary assumptions of independence, then and only then, DZ twin pairs, at fertilization, may be expected to assort binomially as one-quarter each two males and two females, and one-half boy–girl pairs: if $m = 0.5$ and $f = 0.5$ and $(m + f) = 1$, then $(m + f)^2 = 1 = mm(1/4) + mf(1/2) + ff(1/4)$. Plotting the expected fraction of boy–girl pairs ($2mf$) versus the fraction male ($m$), or fraction female ($f = 1 - m$), from zero to one, easily makes it clear that the fraction of boy–girl pairs among DZs has very little sensitivity to deviations in sex ratio within a range likely to be observed. Correction for departures from $m = f = 0.5$ observed at birth is negligible in effect and off the point. Even a 60 : 40 or 40 : 60 sex ratio, however imposed, predicts 48% boy–girl pairs, a difference from 50% that could not reach acceptable (2SD) statistical significance in any sample smaller than 2500 pairing events. Much more critical is the question of independence, whether each sperm is drawn from a 50X : 50Y pool randomly and independently with respect to any variable which might affect viability or development. If the paired events are not fully independent, this nice mathematical exercise is totally and irremediably inappropriate. James, for example, has given us good reasons to doubt that the sexes of DZ co-twins are independent[2,3,6].

Weinberg zygosity fraction estimation is applied to numbers of same-sex and boy–girl pairs observed at birth, based on assumptions about what is presumed to have happened at fertilization. Those observations at birth, and any interpretation to be made of them, are necessarily presumed to extrapolate seamlessly from the circumstances of fertilization, through all of the intervening events and processes of embryogenesis and fetal development. Given further that (again, = 'If and only if …') all events and processes of embryogenesis and fetal development affect all members of boy–girl and same-sex DZ (SS-DZ) twin pairs identically, so that the (assumed) binomially independent sex-pairing distribution at fertilization might be maintained through embryogenesis and gestation to live birth, then the number of SS-DZs at birth should equal the number of boy–girl pairs.

If, and only if, ovulation and fertilization and embryogenesis and all of fetal development were totally independent and equal between males and females, and perfectly equivalent between boy–girl pairs and SS-DZ pairs, then, and only then, applying the 'Weinberg rule' by subtracting the number of live-born boy–girl pairs (assumed to equal the number of SS-DZ pairs) from the total number of live-born SS pairs, the 'Weinberg difference' between the total number of SS pairs and the number of boy–girl pairs should estimate the number of monozygotic (MZ) pairs among the SS pairs in the sample.

The mass of unquestioned answers represented by these fundamental assumptions, and the consequent intellectual inertia, overmatch by far any value in estimating the zygosity fractions of any group of twins. Even if we could consider and test the assumptions behind these calculations and emerge believing their results, the zygosity fraction numbers thus derived tell us nothing true or useful about any individual or twin pair or developmental event, regardless of whether the process comes out well or anomalously. In spite of this, over a century ago, this idea of Weinberg's seemed as agreeably straightforward as scriptural revelation. Moreover, it has served for generations as the apparently logical foundation for the pillars of orthodox twin biology, its assumptions having been carried along with little concern. Generations of researchers have published conclusions and speculations depending absolutely on these beliefs, continuing long after it became clear, for example, that boys, and members of same-sex pairs, suffer greater frequencies of failure at every observable stage throughout gestation. These simple facts from repeated observation clearly make those necessary assumptions untenable, but generations of researchers have behaved as if they had no way to know this and no reason to question the very foundations upon which they continued to frame and build their experiments and papers.

Simply stated, 'givens' are essential to all uses of the Weinberg zygosity estimating protocol. They are 'if and only if' conditions. The MZ = SS – OS Weinberg-rule zygosity fraction estimates cannot be believed if all these things are not true at the same time:

normal, independent ovulation;
normal, independent fertilization;
normal, independent embryogenesis;
normal, independent fetal development;
complete genetic *and epigenetic* independence for all DZ co-twins;
and (only by virtue of all of the above)
complete developmental equivalence for SS and boy–girl DZ pairs and singletons, yielding no change of sex fractions or sex-pairing fractions throughout gestation.

By these rules, all developmental anomalies occurring among twins in excess of normal background population frequencies are forever and absolutely reserved for MZ twins only.

These premises are assumed, whether or not stated, throughout the scope of twin biology orthodoxy, as if they were known, proven facts supported by repeated scientific observations. They are nothing of the kind. Double ovulation is a hypothesis. This is not a matter of opinion – it is a matter of definition. Unsupported repetition can elevate hypothesis to myth, but not to theory, let alone to enshrinement as common knowledge as if fact. Only by making predictions that are borne out by critical testing can any hypothesis, no matter how popular, earn elevation to theory. Being the simplest of alternatives, if alternatives are appropriately considered, often enhances the credibility of an idea. This idea has implications and makes predictions which are not really all that simple, many of which have never been tested and several of which fail when tested.

For example: 616 twin pairs were collected among more than 53 000 births followed from the first prenatal visit to 1 year after birth in the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) Collaborative Perinatal Project[17]. About 80% of those pairs were blood-typed for zygosity diagnosis. The original investigators were stymied by the minority of pairs who could not be diagnosed for zygosity because at least one member (was dead and therefore) could not be blood-typed. They set aside the chorionicity and blood-typing data, and retreated to Weinberg estimates, which ground out the expected result attributing the excess fetal and neonatal mortality among twins to the MZs[17].

We found it reasonable to compare the Weinberg estimated sorting of MZs and DZs, alive and dead, with the corresponding results from numbers identified by chorionicity and blood-typing. The Weinberg estimates predicted more MZs than were identified by blood-typing, but not because more MZs were dead and unavailable for blood-typing, as Weinberg results would suggest. Most of the Weinberg estimated MZs could be identified by genotyping and/or chorionicity data, and most of them were alive (as they had to be for blood-typing, if they were dichorionic). The result: estimated-but-unidentified MZs (the difference between the Weinberg estimated number of MZs and the number identified by blood-typing or chorionicity) had to account for three deaths each to satisfy the Weinberg estimate of the zygosity distribution of mortality.

This bizarre distortion is too much to ask of sampling error, unless a very large fraction of blood-type MZs were actually DZs. That prospect is unlikely unless heterozygosity is much reduced among families who have had twins. That would be a dramatic surprise if it should ever be documented, with troublesome implications for a great many studies using twins to estimate heritabilities. Such a departure from the assumptions underlying those methods should have been noticed, but the genotypes of parents are rarely collected or included in such studies.

Three alternative means of estimating the zygosity fractions, without using the Weinberg approach and without requiring anything logically or biologically impossible, gave mutually consistent results showing that SS-DZs suffered mortality much greater than that among boy–girl pairs, and at least as great as the mortality among the MZs[5,18]. Here the logic of the Weinberg process is most obviously and perniciously circular, because of its worst necessary assumption. Application of the Weinberg tautology to sort developmental anomalies (up to and including fetal and infant death) by zygosity requires the assumption that boy–girl twins are exactly developmentally representative of all DZs, so that differences in anomaly frequencies between SS and OS twins must be due to the MZs among the SS pairs. Only if the anomaly in question is exactly equally likely and exactly developmentally equivalent in boy–girl pairs and in SS-DZs can Weinberg estimates be imagined to yield valid zygosity fractions for twins with anomalies of development. Nevertheless, the expectation that MZs provide the lion's share of all anomalies, and that DZs are simultaneous but otherwise developmentally normal singleton womb-mates, has become so firmly entrenched in 'common knowledge' that sound data indicating the contrary are routinely ignored. The Weinberg way of thinking is clearly false with respect to fetal and neonatal deaths of twins. Both members of boy–girl pairs are in much less danger of fetal or neonatal death than the members of SS pairs of either sex, of either zygosity[5,18]. It is simply not true that boy–girl twins are developmentally representative of all DZ twins, that all of development occurs for boy–girl twins in the same ways as for SS-DZ twins, that the embryogenesis and fetal development of DZ twins is identical to the development of singletons or

that MZ twins are responsible for the great majority of the anomalies that are excessive in frequency among twins.

The 616 twin pairs in the Collaborative Perinatal Project sample are too small a number to extend this investigation with statistical confidence to all of the developmental anomalies that occur with excessive frequency among twins. Frequencies of specific individual malformations are small enough that most of them do not appear in this sample. It is, however, common and biologically reasonable to consider all developmental anomalies up to and including infant death to be part of a continuum. It seems unlikely that a proper analysis with a sample of sufficient size should yield a different answer for non-lethal anomalies from that for early deaths.

## ORTHODOXY, HERESY, FAITH AND DOUBT

Many readers might be eager by now to take heated issue with my assertion above that the double ovulation origin of DZ twins is an unsupported assumption. For generations, students and practitioners have found no cause to consider alternatives. With few exceptions, the entire literature of twins and twinning reads as if anyone with sense enough to find his supper dish must know that the double ovulation origin of DZ twins and the corollaries dependent upon that assumption are facts beyond dispute. I doubt, however, that anyone can find where, when, by whom, how the double ovulation origin of any pair of naturally conceived human DZ twins has been observed or documented in any way that it might be considered a scientific fact. The certain knowledge of abiding faith is by definition different from any product of science. I have read the literature related to twins and twinning for over 35 years, and believed what I was told for about the first 10 or 15 of those years. Every source I have seen either directly states the double ovulation assumption as a given or includes a reference to provide authority for a statement of double ovulation as a given. The included reference may include an earlier reference, which may include another and so on, but, regardless of the chain's length, the other end of the chain of references is always a statement, without physical evidence, of the false but simple common knowledge that DZ twins arise from multiple ovulation.

Some of those chains of references conclude with a reference to one or another of Aristotle's pronouncements on the subject of twins. The esoteric erudition implied by citing Aristotle dims dramatically upon reading what he actually had to say, in context. You might pick your way through the old Greek, translate it or read one or more of the translations previously done by others[19]. Aristotle lived, worked and died over 2000 years before the invention of microscopy cleared a path for cell theory, and yet another few centuries before we gained any understanding of gametes, fertilization or developmental biology. We now know, and Aristotle, although considered by many the premier biologist of his day, did not know, that no biological event can be considered explained without an explanation of what cells, via molecules, must do to cause and complete that event. It is not merely a matter of language. Aristotle pronounced, without doubt and without physical evidence, that the vital force arising from the interaction of seminal and menstrual fluids could vary according to the temperatures and pressures of those fluids and yield different products at birth. His arguments from first principles may suffice as a basis for common knowledge, but not for anything approximating science.

Nearly everyone has been so comfortable with the notion that DZ twins just arise from ordinary, independent double ovulation that no one ever bothered to collect any evidence or pay attention to evidence that came unbidden. It has been a matter of faith. Relinquish that comfort. There is no sound reason to believe it, there are numerous observations offering good reason to consider it false, and the difference matters – very much.

## VARIATION IN FREQUENCY OF TWINNING

The frequency of twin births varies over human racial groups. Twins are significantly more frequent in sub-Saharan African populations and significantly less frequent in populations of the Far East than among Europeans, where Weinberg was born and trained and among whose descendants most of the work discussed here has been carried out. This variation in the frequency of twinning is a repeated observation. The facts have a structure that is rather less simple than this sounds, and the meaning assigned to it by the traditions of orthodox twin biology does not merit its long standing as a pillar of the orthodoxy.

By way of Weinberg estimates of zygosity fractions from large public-record samples of twin births in various racial subpopulations, it long ago became common knowledge that the frequency of MZ twinning at birth is approximately constant over human racial subpopulations, and that racial variation in twinning frequency must therefore be due entirely to a variation in the frequency of DZ twinning events. Dependent upon the assumptions that DZ twins arise from independent double ovulation and that all of development proceeds in the same ways for boy–girl pairs as for SS-DZ pairs, this particular conclusion from Weinberg estimates is the basis for the general understanding that there is a racially variable (and

therefore inherited) tendency to double ovulation and thus DZ twinning, whereas MZ twinning belongs to an entirely unrelated causal system, an accidental developmental anomaly because it happens at approximately constant frequency in all human subpopulations. These are fundamental tenets of the orthodox biology of human twinning.

Very few population samples of statistically useful size and structure have had zygosity fractions estimated by any analysis more careful than Weinberg estimation. The largest such sample is the Belgian twins of the East Flanders Prospective Twin Study, where twinning frequency approximates that of the rest of Europe[20]. In that sample, the Weinberg estimate yields a zygosity fraction approximation that is not statistically significantly different from the results of genotyping. This is the largest sample ever more or less fully genotyped, and still much too small for statistically valid consideration of all the anomalies more frequent in twins. The Weinberg approach yields a statistically acceptable approximation of zygosity fractions for normal twins of European ancestry.

Among twins in Nigeria, where live-born twinning frequencies include the highest of any presumably random populations ever measured, genotyping results and Weinberg estimates disagree in several ways[21,22]. The total frequency of twins per live birth, and the boy–girl fraction among live-born twin pairs, are greater in Nigeria than among Europeans, but those measures vary considerably among Nigerian ethnic subgroups. There is no evidence within Nigeria of the correlation between total and boy–girl twinning frequencies that is the basis of that pillar.

Because some 20% of Nigerian boy–girl pairs shared all the genetic markers used for genotyping, just like the MZs, Nylander estimated that a similar fraction of SS-DZs must have been misdiagnosed as MZs and used Weinberg expectations to correct the genotyping results. The logic of that adjustment is fully compatible with the philosophy of the Weinberg tautology. The adjusted answer is no more plausible, no more scientific, no more justified by findings of fact than if the genotyping had never been done. That statistical manipulation does make some sense, and it makes a substantive difference in the result. It was not used with the Belgian sample[20–23]. One must wonder at the inefficiency of the chosen set of markers for the Nigerian samples, or the reduced allelic diversity of those Nigerian populations.

Because the Belgian and Nigerian versions of the 'same' answer were arrived at so differently, they cannot be simultaneously correct. The conclusion that the frequency of MZs per live birth is constant worldwide while that of DZs accounts for all interpopulational differences is unfounded, and untenable as a basis for any scientific consideration. Although the Nigerian genotyping results can be 'adjusted' to an approximation of Weinberg results that makes it credible to the motivated believer, the conclusion that DZ twinning frequency differs greatly between European and African births, but MZ twinning frequency does not, is falsely made, however deeply cemented into the pillars of the orthodoxy.

The observed and recorded differences among populations in chorionicity fractions among the MZs[20–22] urge the consideration that there is more to the biology of twinning than its frequency. The fraction of monochorionic among Nigerian MZ twins is different from that of twins of European ancestry. According to our best understanding of the embryogenic implications of chorionicity[24], African MZ twinning must happen earlier in embryogenesis than the European variety. The biology of MZ twinning is not the same in Europe and Africa, even if we cling without evidence to the belief that its frequency is the same. Interestingly, several other reproductive events and processes happen earlier for mothers of African ancestry in the USA: earlier menarche, earlier first pregnancy, earlier delivery (shorter gestation) in her average pregnancy (mean, median and mode – not a skew towards prematurity as defined in terms of a white majority) and earlier last pregnancy.

The declaration of racial variation of (only) DZ twinning frequency generally includes the observations that Japanese mothers have the lowest observed frequency of twin births, a low fraction of boy–girl pairs and roughly the same Weinberg MZ frequency as European and African samples. It would be of great interest to make the same genotyping and placentation comparisons in a sample of Asian twins of statistically useful size. The common knowledge assertion that Asian twins include the smallest fraction of DZ twins is supported only by Weinberg estimates. I have found no published indication that any representative sample of Asian twins of statistically useful size has been collected with chorionicity and genotype information appropriate to testing Weinberg estimates critically against zygosity genotyping[25].

There is no evidence that the frequency and biology of MZ twinning is constant over human subpopulations; there is no reason to believe that DZ twinning is responsible for all variation in twinning frequency; there is no reason to imagine that the binomial distribution of sex-pairing assumed to occur at conception should be or could be maintained through embryogenesis and gestation all the way to live birth; and the orthodox folk science of human twin biology is, at best, not founded in observations subject to repetition or refutation. The

difference matters a great deal to the potential that twinning may have to add to our understanding of human developmental genetics in general.

## TWINNING AND (OTHER?) MALFORMATIONS

The frequency of malformations and other developmental anomalies is elevated among twin births. This is another repeated observation[26–33]. Again, the orthodox interpretation leaves the facts well behind. Because of results from Weinberg estimates among samples of affected twin pairs, the orthodoxy holds that the excesses of these anomalies among twins belong overwhelmingly, if not perhaps entirely, to the MZs. This belief is so firmly a part of the orthodox twin biology credo that we have seen monozygosity assumed without question for any SS twin pair of which either member has one or more of the malformations known to be more common in twins. Twice I have stood and denounced that assumption being made on the podium in international meetings. At least twice in papers sent to me for review, I have managed to keep instances of that presumption out of print. In each of those manuscripts, observed differences in genotype were mentioned and dismissed as errors not worthy of retesting because they disagreed with the orthodox presumption and must therefore be certainly wrong. At the unwelcome cost of giving it another undeserved citation, the article of Schinzel and colleagues[34] seems to be the most common reference used in papers where justification for that leap is offered. Not one of the conclusions in that article is supported by genotyping.

In spite of high multifactorial heritability values from singleton pairs-of-relatives estimates, and in spite of the prevailing assumption that they concentrate overwhelmingly in MZ pairs, the malformations in question are not often concordant in the affected twin pairs. Discordancy in presumed* MZ twin pairs in spite of high heritabilities computed from singleton pairs-of-relatives analyses is often cited as evidence for 'environmental' contributions to the causes of the anomaly in question, the environmental contributions remaining without statistically significant identification after generations of effort.

Although the orthodoxy holds that MZ twinning is itself an accidental developmental anomaly that occurs at a constant frequency over all the world's populations, and the malformations associated with twinning are – according to Weinberg-shaped traditions – overwhelmingly due to the MZs, nevertheless those malformations associated with twinning are not themselves constant over subpopulations. Neural tube defects (NTDs), for example, vary substantially in frequency, and are highly correlated with total twinning frequency (variation in which is attributed by the orthodoxy to variation in DZ twinning frequency only), but they are not significantly correlated with the Weinberg estimated MZ[35].

Another repeated observation is that: the frequency of non-righthandedness (NRH) is significantly elevated among twins[36–41]. According to the first century of the twinning literature, this minority version of brain function asymmetry development also belongs overwhelmingly to the MZs – another common knowledge attribution not supported by sound evidence. This element of the orthodoxy is not directly derived via the Weinberg tautology, but from a corollary arising from those same underlying assumptions about differences in the embryonic origins of MZ and DZ twins. Assuming that DZ twins arise from independent double ovulation, it is correspondingly assumed they have undergone normal, independent embryogenesis with only the same list and frequencies of anomalies as found in singletons. MZs, on the other hand, are anomalous by definition, because they must somehow 'split' a single embryo into two shares, and that 'splitting' must be expected to have effects on the subsequent development of the two 'partial' embryos that must now rearrange their development to become two whole people instead of just one. If we believe that, we probably should suppose that such rearrangements would have long-term effects.

What has passed for an answer to this question, beginning in the 1920s and still holding some currency, came from experiments with embryonic newts by Austrian embryologist Hans Spemann[42]. Spemann's career yielded the concept of embryonic induction (for which he won the 1935 Nobel prize in Medicine) – that a given embryonic cell type may specifically differentiate to perform functions which induce specific paths of differentiation in other, recipient cell(-type)s. One step on Spemann's path to that insight still ripples across the common-knowledge layers of human twinning biology. Sometimes, a newt embryo that he had tied almost 'in half' with a hair rearranged itself to form (by definition, MZ) twin embryos. One feature of those outcomes holds a special place in twinning lore to this day. Often, one of these mechanically generated MZ newt twins had situs inversus, with the normal asymmetries of its unpaired viscera reversed, heart and stomach right of midline instead of left, liver more left than right and so on.

This observation not only was taken as a compelling visualization of what must be the origin of MZ twins, but also was believed to explain the excess of NRH in twins. Spemann's results were interpreted to indicate that every pair of human twins whose members

* They must be MZ because they are SS and there is a malformation, and everybody knows that malformations in twins are peculiar to MZs.

differed in handedness simply must be MZ twins and – even more specifically – 'late-splitting' MZ twins, for whom the 'late split' had disturbed developmental a/symmetry relationships that had already been established in the embryo prior to the MZ twinning event by which it began to become two.

Since Spemann's work predated the establishment of blood-typing as our first credibly objective means of genotyping, a generation of twins were diagnosed MZ *by and because of* 'mirror-image' handedness, in spite of other failures of the expected similarity: red hair and blond, blue eyes and brown, according to some accounts even boy and girl … no matter. Their 'late splits' and embryonic 'mirror-imaging' sufficed to explain away all of their differences in other features as consequences of the developmental disturbances caused by their 'late' MZ 'splitting' and manifested by their 'mirror-image' handedness. Every paper that attributed the excess NRH among twins to MZs included data collected under such expectations in the 1920s and 1930s. The newly collected data in each of those same papers showed no significant zygosity difference (for review see reference 36).

For a more careful consideration of this question, with the help of member clubs of the National Organization of Mothers of Twins Clubs, we collected data from over 800 three-generation twin families, 773 of which included usable handedness information from over 10 000 people. Compared with general population samples under the same criteria, and with their own second-degree relatives, non-righthandedness is in fact more frequent in twins and their first-degree relatives. There is no zygosity difference in the frequency of NRH among twins or their relatives, and no significant difference between twins and their singleton siblings. The anomaly of brain function asymmetry development which begins in embryogenesis and appears after birth as NRH occurs in DZ twins and their close relatives at least as often as in MZs and their relatives, and has nothing to do with anything peculiar to gestation or birth as twins[36].

Parents of twins are almost twice as often non-righthanded as their same-sex siblings (the maternal aunts and paternal uncles of twins who were not themselves parents of twins). Twins of both zygosities equally, and equally with their single-born siblings, inherit their NRH from their parents. Each NRH parent (mother or father equally) increases the probability of NRH in each child by a factor of about 1.5. DZ co-twins differ in handedness ('mirror-image'!) rather more often than MZs; classic 'twin-study' heritability comes out at about 0.7[36]. Others have since confirmed the absence of a relationship of non-righthandedness with zygosity or chorionicity[37,38], our best estimator of the timing of MZ twinning events[24]. The 'lateness' of the MZ twinning event also has nothing to do with it.

With no need for, and no value in, imagining any mechanical analogy with Spemann's newts, MZ twinning remains necessarily the establishment of two body symmetries, with back–belly, head–tail and left–right polarities, from a group of cells which could be expected to form a single body if only everything about it were like almost all other embryos. The MZ twinning event is not a 'splitting'. Eventually two embryos must become separated in order to become two people, but that is a consequence of the twinning process, not a cause. The MZ twinning event originates within the embryo and has nothing to do with any mechanical force applied externally such as Spemann's ligation. About a third of white European MZ twins, and half of African MZs, are dichorionic – they represent a cellular commitment to twinning that had to occur before the differentiation of the chorion and therefore still inside the same single zona pellucida, within which confinement there is no space to accomplish a physical separation.

MZ twinning *is* a symmetry anomaly: two three-dimensional body symmetries unfold from a group of cells that should normally build only one. Non-righthandedness is a departure from the normal asymmetry of brain function development beginning in embryogenesis. According to the observed distributions of brain function asymmetry, DZ twinning *is* – equally with MZ twinning – a symmetry anomaly, and one which travels with equal ease through either parent. This is difficult to reconcile with the assumption that DZ twins arise universally from independent double ovulations and independent embryogenesis just like that of singletons, except for simultaneity.

The embryogenesis of DZ twins is at least as different from that of singletons as is that of MZs. DZs do not, in general, arise from perfectly ordinary embryos of which there just happen to be two at a time. The fact that mothers and fathers share quite equally the relationship with anomalies of asymmetry development in their twins of both zygosities is difficult to reconcile with the double ovulation hypothesis, given that only mothers ovulate. Carmelli and her collaborators, in a sample of some 400 Mormon families with repeated OS-DZ twinning in their genealogies, found that almost exactly half of those twin pairs were related only through males[43]. Golubovsky and St Clair have reported further evidence of paternal transmission of DZ twinning tendency[44–46]. The answer to the question of how the father can 'cause' DZ twinning will not be simple[46], and we may be certain that it will not be readily believed when we find it, but there is no room left for believing that DZ twinning can come only from the mother, as the double ovulation story would have it.

The malformations which are excessively frequent in twins are the same ones most common in all live births: the midline, or fusion, malformations, including particularly the NTDs, cleft lip with or without cleft palate (CL/P) and congenital heart defects (CHDs). These are disorders of embryogenic a/symmetries of development, anomalies of structures built from embryonic left and right halves which must meet in the embryonic midline, fuse and remodel to form the final structures. In NTDs, the edges of the neural plate do not properly close the neural tube; the brain or spinal cord is left open and malformed. In orofacial clefts, parts of the face that should meet in or near the midline and fuse do not complete the process. Most CHDs are failures of fusion and remodelling of the cardiac tubes.

These malformations share associations that could guide compelling contributions to understanding normal human developmental biology through an understanding of the departures from those paths that are excessively frequent in twinning. These a/symmetry malformations are excessive not only in twins (where their traditional attribution primarily to MZs has arisen entirely from repetition of conclusions from Weinberg estimates), but also among the sibs and offspring of twins. Among the sibs and offspring, in general there are no significant differences in these associations as a function of twin zygosity, but the excess of twins among the parents of children with NTDs is significantly concentrated in DZs.

Just as with twinning itself, these malformations are associated with excesses of NRH among people with these anomalies and their first-degree relatives. Children born with CL/P, and their parents, are non-righthanded more often than the general population, and unilateral CL/P far more commonly affects the left side. Right unilateral CL/P is equivalent to bilateral CL/P in increased genetic risk to siblings or offspring[39–41].

Genetic and developmental relationships between minority brain function asymmetry and fusion malformations, between minority brain function asymmetry and twinning and between twinning and fusion malformations are not distinguishable by zygosity. All assertions to the contrary are without sound supporting evidence, arising entirely from Weinberg assumptions. Anomalies of embryogenic a/symmetry development are not at all peculiar to MZ twinning processes[39–41]. The only hope of getting it altogether right is to genotype every pair of twins born from now on, giving priority if necessary to those in which either member is born with any anomaly.

## CRANIOFACIAL DEVELOPMENT IN TWINS

A set of teeth is a highly coherent subsystem of the craniofacial structure. The distribution of left–right asymmetries in that structure differs between twins and singletons. Multivariate statistical analyses identify with great accuracy whether a given individual set of dental diameter measurements came from a singleton or a twin. DZ twins are at least as different from singletons in the rules and outcomes of their craniofacial development as are the MZs, and in primarily the same ways. Much of the difference has to do with a/symmetries. DZ and MZ twins differ equally from singletons in the normal asymmetries of craniofacial structure as represented by the dental subsystem. Contrary to the common knowledge that abnormal embryogenesis in (only) MZ twinning may generate developmental stresses that increase the random ('fluctuating') component of developmental asymmetry, MZ and DZ twins alike show significant reductions from the normal asymmetries observed in singletons. They are less asymmetrical than 'normal' in this craniofacial subsystem of the head, just as their excess non-righthandedness is a reduction from 'normal' asymmetries in brain function development in general-population singletons[47,48]. The embryogenesis of craniofacial asymmetries in DZ twins is at least as different from 'ordinary' singleton embryogenesis as is that of MZs.

There are clear sex differences in craniofacial development among singletons and twins in same-sex pairs. By notable contrast, both male and female members of OS-DZs are statistically so exactly intermediate between normal gender-specific structures that they cannot be distinguished by measurements which separate sexes in singletons or SS twins almost perfectly[4,47–50].

In summary: the developmental histories of DZ co-twins are not independent; OS-DZs are not developmentally representative of all DZs; and DZs are not the developmental equivalent of singletons. The twin–singleton differences observed in these studies have more to do with asymmetries established in embryogenesis than with anything else – exactly the focus of the problems long supposed to be characteristic more or less exclusively of MZs.

## CLOSING POINTS

A great deal of work remains to be done on questions of how development elaborates from a single cell to the full multidimensional adult human with its many cells, cell types and cell networks and their corresponding variety of functions that must reliably operate at the right times and in the right places to allow survival and reproduction. Given that the functions at issue include all of human mentation and behavior, I submit that there is no more compelling or more complex question among all of science's efforts to address the meanings of being human or the business of becoming human. Twins of

both zygosities, equally, differ from singletons in their paths through embryogenesis and the establishment and elaboration of those parts of development that depend upon the asymmetric behaviors of cells. We cannot at present specify how twins come to do those things differently. When we can learn what events and mechanisms are the subjects, objects and operators of these differences, we will certainly improve our understanding about how the usual versions of the normal processes work. Studies of twins and twinning from this emergently different perspective, which has almost nothing to do with Galtonian considerations for estimating heritabilities, await in great variety and offer careful thinkers prospects of great adventure. The orthodoxy that has been elaborated primarily in support of those Galtonian endeavors is wrong even for those considerations, its pillars hollow and weak but large enough, when we stand too close, to block our view in the direction of deeper meanings. There is work to be done on a world of unanswered questions hidden behind those unquestioned answers.

## ACKNOWLEDGMENTS

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# Twins in Genetic Research

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37



## INTRODUCTION

This chapter introduces the field of genetic research, in which twin studies are a powerful approach to exploring the genetic basis of complex traits. Twin studies take advantage of the existence of mono- and dizygotic (MZ and DZ) twins and use the comparison of resemblances of MZ and DZ twins as the basis for analysis of variations in human traits and diseases. We describe the basic methodology for twin studies, including recent extensions exploiting advances in molecular genetics. We illustrate the value of twin studies by giving a few selected examples from various fields of medicine and psychology, and provide an overview of twin registries which collect data on twins and their relatives worldwide. These registries have been established to obtain an insight into the genetic epidemiology of complex traits and diseases, to study the interaction of genetic factors with sex, age and lifestyle factors and to study the causes of comorbidity between different traits and diseases. Obesity, diabetes, hypertension and psychiatric disorders are examples of common diseases that are a result of various genetic susceptibility factors interacting with environmental risks. Twin registries have been instrumental in establishing the genetic component in susceptibility to these conditions. So far, however, it has been difficult to identify the responsible genes. Because of the design and the often (very) large sample sizes of twin registers, they offer unique opportunities for selected sampling for gene hunting, employing both linkage and association studies.

Genetic epidemiology aims to disentangle and quantify the contributions of genes, shared environment, individual-specific environment and their interactions to variations in human traits. Research questions address the etiology of individual differences (what statisticians call variation) in health and disease, or in continuously varying traits such as height, weight or blood pressure. Variation for a trait in a particular population may be caused by genetic differences between individuals and/or by differences in their environment. The effects of genes and environment may be additive, or they may interact with each other. To explore the etiology of individual differences, or the etiology of clustering of these differences within individuals, it is necessary to collect data from non-random samples. The study sample can include relatives who are genetically related but who grew up in unrelated environments (the so-called adoption design), or relatives who grew up in similar environments but who are of different genetic relatedness (for example the twin design). If the exposure to environmental risk factors can be assessed, these designs also allow the quantification of gene–environment interaction in shaping a particular trait.

Recent advances in statistical modeling allow the simultaneous analysis of many variables in genetic studies. Such advances make new types of analyses possible, such as the multivariate analysis of causes of comorbidity between disorders; analysis of the development of psychopathology over time; the inclusion of covariates in linkage analyses; and the estimation of heritability and linkage conditional to exposure to environmental risk factors. These improvements in

**Figure 37.1** Augustine of Hippo

data analysis have in turn led to the establishment of large registries of twins that no longer focus on the assessment of a single phenotype, but collect a wide range of traits and environmental risk factors in twins, as well as in their family members.

## HISTORY OF TWIN RESEARCH

Twins have captured the curiosity of researchers for centuries, and proposals to use them as a natural experiment in empirical studies stem from as early as 415 by Augustine of Hippo[1] (Figure 37.1). Galton's classic article on twins[2], published in the 19th century, is often cited as the first iteration of the classical twin method, although it is uncertain whether Galton knew of the distinction between MZ and DZ twins. The systematic analysis of similarity of MZ and DZ twins was introduced by Hermann Werner Siemens, a dermatologist, who formulated the twin rule of pathology: any heritable disease will be more concordant in identical twins than in non-identical twins, and concordance will be even lower in non-siblings[3]. When studying moles, Siemens came up with the clever idea of combining correlation analysis and twin data. He correlated mole counts in one twin with mole counts in the co-twin and contrasted this correlation between MZ and DZ twin pairs. The correlation for mole count in MZ twins, who share all, or nearly all, of their genetic material was 0.4. In DZ twins, who are genetically 50% identical on average, the correlation was only 0.2. The results indicated the importance of genetic factors to the variation in mole count. The larger genetic resemblance in MZ twins is associated with their larger resemblance for the phenotype under study.

## TYPES OF TWIN STUDY DESIGNS

### Classical twin studies

The classical twin study compares phenotypic resemblances of MZ and DZ twins. MZ twins derive from a single fertilized egg and therefore inherit identical genetic material. DZ twins are genetically as similar as other siblings and share, on average, 50% of their segregating genes. Comparing the resemblance of MZ twins for a trait or disease with resemblance of DZ twins therefore offers an initial estimate of the extent to which genetic variation determines phenotypic variation of that trait. If MZ twins resemble each other more than DZ twins, then the heritability ($h^2$) of the phenotype can be estimated from twice the difference between MZ and DZ correlations. For example, typical MZ and DZ correlations for depression are around 0.4 and 0.2[4], and therefore heritability is estimated at ~40%. A different pattern of correlations is usually observed for lifestyle factors, indicating the importance of the shared family environment. For smoking initiation during adolescence, typical MZ and DZ correlations are 0.9 and 0.7, leading to a heritability estimate of 40%, but also pointing out the importance of shared environment[5]. The proportion of the variance that is due to shared environment is the difference between the total twin correlation and the part that is explained by heritability (i.e. $r_{MZ} - h^2$ in MZ or $r_{DZ} - h^2/2$ in DZ twins). For smoking initiation, this estimate is around 50% (0.9 – 0.4 based on MZ data or 0.7 – 0.2 based on DZ twin data).

The application of this type of analysis led to substantial changes in the way we think about the determinants of health and disease and the causes of individual differences in normal and abnormal behavior. During the past decade, a shift has taken place from strict environmental explanations to a more balanced view that recognizes the importance of genes, for example in autism and in attention deficit hyperactivity disorder in children, or in the development of dependence on nicotine, alcohol and other drugs in adults.

## Improvements in analysis

Quantitative traits assessed in MZ and DZ twins are traditionally analyzed using analysis of variance (ANOVA) and intraclass correlations to summarize twin resemblance. In large samples the intraclass correlation equals the better known Pearson correlation coefficient. Resemblance between twins for qualitative traits, such as the presence or absence of disease, can be summarized with concordance rates or with tetrachoric correlations. Tetrachoric correlations give the resemblance between relatives for the underlying disease liability and may be used to obtain the heritability of disease liability by doubling the difference between MZ and DZ correlations.

Although heritabilities based on (differences between) correlations can give a good first approximation of heritability, they are of limited use when analyzing and comparing data from different groups, or from longitudinal designs. Multigroup analyses can involve comparison of the genetic architecture of traits in males and females, in groups with different exposures to environmental risk factors or in different cohorts. Structural equation modeling (SEM), or covariance structure modeling, is a more general approach to the analysis of familial resemblances. In SEM, genotypic and environmental effects are modeled as the contributions of unmeasured (latent) variables to the possibly multivariate phenotypic differences between individuals[6]. The latent factors represent the effects of many unidentified influences. For a genetic factor, these effects are due to a possibly large but unknown number of polygenes. The contributions of the latent variables are estimated as regression coefficients in the linear regression of the observed variables on the latent variables. A number of widely available software programs, such as LISREL or Mx, allow estimation of parameters by means of normal theory maximum likelihood (ML) and weighted least squares (WLS). A useful estimator in the Mx program is the raw data likelihood estimator, which handles data from selected samples and from studies in which part of the sample might have missing data. This last situation commonly arises in longitudinal studies.

SEM can accommodate the analysis of sex differences in heritability estimates through the simultaneous analysis of data from male and female twins. It is also possible to test whether the same genes are expressed in males and females by including DZ twins of opposite sex. If the resemblance between twins of the opposite sex is less than would be expected on the basis of the heritability in males and females, this suggests that different genes influence the same trait in the two sexes. Similarly, heritability that is conditional on environmental exposure can indicate the presence of genotype × environment (G × E) interaction[7]. G × E interaction can be detected by including environmental measurements on the basis of which the twin sample can be stratified. For example, the heritability for depression in married women is lower than in unmarried women. Evidence for the effect of G × E interaction on personality comes from a study in Dutch adolescent twins. A religious upbringing greatly reduces the influence of genetic factors on disinhibition, a trait that closely resembles novelty seeking and that is associated with substance use and abuse[8].

## Beyond the classical designs

Extending the MZ–DZ design to include parents, siblings, spouses and offspring of MZ and DZ twins offers the possibility to assess the presence of cultural transmission, G × E covariance, non-random mating and social interactions within and between generations[9]. A simple version of the extended twin design, i.e. a study of young-adult twins, their middle-aged parents and a second group of middle-aged twins (of the same age as the parents of the first group of twin pairs) makes it possible to assess the effect of age differences on heritability and on differential gene expression as a function of age. Using this design as a short-cut for a true longitudinal study, Snieder and colleagues obtained evidence that partially different genes influence lipid levels in plasma at different ages[10]. This may be important information for gene-finding studies, as there might only be a limited time period during which genes, which vary over the course of an individual's life, can be detected. Other extended twin studies look at the offspring of MZ twins who are genetically half-sibs but socially cousins. The MZ-offspring design also allows for testing of maternal effects and imprinting by comparing the offspring of male and female MZ pairs.

## The analysis of comorbidity

The causes of association and comorbidity between traits can be investigated by generalizing the univariate twin study to multivariate designs, in which more than one phenotype per person is analyzed. Multivariate twin studies ask questions such as: 'does variation in exercise behavior cause variation in depression, or do the traits cluster because they are influenced by a common set of genes?' Or to give another example: 'do low birth weight and hypertension cluster because one disorder increases risk for the other, or is there a common genetic vulnerability?' The answers to such questions lie in the cross-twin cross-trait correlations in MZ versus DZ twin pairs, i.e. the correlation of birth weight in one twin with blood pressure in the other twin. If these

cross-correlations are higher for MZ than for DZ twins, this suggests that the association between traits is genetically mediated.

Twin registries can be extremely helpful to geneticists by coming up with good phenotypes for molecular genetic studies. In such studies, comorbidity, that is, the co-occurrence of two or more disorders, is often seen as a problem: does one exclude patients with comorbid disorders, or can they be included in the study? A solution to this problem may lie in analysis of the causes of comorbidity. A multivariate twin design can establish the extent to which the comorbid phenotypes share a common genetic basis. The full multivariate analysis of such phenotypes should offer more power to detect genes through genome-wide linkage analysis. Marlow and colleagues conducted multivariate genome-wide analyses of quantitative-trait loci that influence reading- and language-related traits, and found that the results of these analyses were substantially clearer than those of previous univariate analyses[11].

Multivariate analyses are also needed for simultaneous modeling of phenotypes (such as depression) and endophenotypes or intermediate phenotypes (such as neuroticism or cortisol levels) to determine their common genetic etiology. The power to detect linkage will only be increased through the use of endophenotypes if their association is due to pleiotropic genetic effects[12].

### Case–control studies

Twins are particularly useful in case–control studies, and MZ twins form the ideal case–control study, as they are perfectly matched for genotype and family background. Martin and co-workers studied vitamin C administration in one twin and a placebo in the co-twin. Contrary to popular belief, vitamin C had no effect on the common cold[13]. As alluded to above, studies of the effects of fetal and infant growth on later health (the so-called Barker hypothesis[14]) in twins investigated the etiology of the association between fetal growth and later disease. In the case–control design, this translates into testing whether, within pairs, the twin with the lowest birth weight has the highest risk of developing the disease. An alternative approach looks at differences in birth weight in MZ and DZ twin pairs and at their association with differences in cardiovascular and metabolic parameters. If these associations are due to shared genetic factors, difference scores are uncorrelated in MZ, but not in DZ twins. For blood pressure, the association between low birth weight and high blood pressure in later life seems to be mediated by common genes[15].

In a more general version of the case–control design, MZ discordant twins, only one of whom has a disease, are used to investigate which non-shared environmental influences are related to the disorder[16]. Such discordant MZ pairs might also form the perfect case–control design for gene-expression studies to distinguish between genes that are related to the causes of disease and genes that are expressed as a consequence of disease. Alternatively, such differential expression, congruent with disease discordance, might indicate causal genes that are differentially activated by epigenetic factors[17]. Conversely, detection of somatic mutations of the same gene in the tumors from MZ twins, both of whom have the tumor, might be a powerful way to detect predisposition genes[18].

## DECIPHERING THE HUMAN GENOME

Recent advances in genetics, such as completion of the human genome sequence, increased understanding of DNA sequence variants, the availability of low-cost genome-wide tools to monitor them and the development of powerful statistical tools, have all opened new avenues of investigation in human genetics. There is a danger, however, that the usefulness of these tools is limited when applied to human complex traits. Ascertainment bias, problems with phenotypic assessment, lack of follow-up of the phenotypes over time and environmental noise that can arise, for example, from variation during development might all contribute to the fact that the genes that underlie complex traits and diseases in humans have been difficult to identify. During the past decade considerable effort has been devoted to whole genome screens so that quantitative trait loci (QTLs) for complex traits and diseases can be detected. For complex human traits, there is an increasing recognition of the need to understand their population genetics and biometric properties so that phenotypes can be defined in a manner that maximizes the chances of successful gene mapping. In the following section we discuss how twin studies can be of help in this endeavor.

## THE USE OF TWINS IN MOLECULAR GENETIC STUDIES

### Basic principles

The concordance between MZ twins sets the upper limit on predictions of individual risk that can be made on the basis of the human genome sequence. Discordant MZ schizophrenic twins, for example, illustrate that disease outcome can be very different for two individuals with identical genetic make-up. The MZ twin concordance thus provides important information regarding disease penetrance. If MZ

twins are genotyped at candidate loci, they provide information about locus-specific penetrances.

Twins also offer specific advantages in genome-wide genotyping, such as linkage or association studies, to map QTLs. DZ twins are siblings of the same age. For traits that change with age, the fact that DZ twins are of the same age decreases within-pair variance and therefore increases power for linkage studies. Twins are also matched for a broad range of pre- and postnatal factors, and are more likely than other siblings to have the same father. The value of combining linkage analyses for Mendelian traits in large pedigrees with twin-based QTL linkage was demonstrated in mapping a cholesterol-lowering gene termed CLG[19]. Its mapping to chromosome 13 was initially based on a single Arab pedigree. The subsequent linkage study in German DZ twins not only confirmed the locus, but also added information on the relevance of the as yet unknown gene by showing its influence on lipid levels in the general population.

Risch and Zhang proposed that stringent selection of extreme discordant and concordant (EDAC) pairs might be the only reliable strategy for QTL mapping in humans[20]. Large registries of twins (see below) contain phenotypes of thousands, sometimes tens of thousands, of twins and their family members, and are a suitable source of informative families for linkage studies. Several such QTL mapping projects are currently under way. For example, genes that influence neuroticism and depression are sought in selected samples of twins and their siblings[21]. To ensure that extremely discordant pairs are not selected because of age differences between them, DZ twins of the same age are used. For ordinary sibs, age differences might create large phenotypic differences between them.

Once a trait has been shown to have a significant heritability, the quest for involved genes and their variants is the next logical step. This includes two distinct approaches, linkage analysis (the relation between a chromosomal segment, termed 'locus', and traits) as well as association analysis (the relation between variants of a gene, termed alleles, and a trait). We briefly explain these two approaches as well as some underlying principles of molecular genetics in the following.

## Genotyping

DNA as the substrate for molecular genetics is usually extracted from leukocytes. A vial of 10 ml blood is sufficient for most studies. Buccal cells are additional potential sources of DNA, especially in infants. Some researchers prefer DNA from buccal cells over DNA from blood samples for zygosity typing[22]. The technology for genotyping is now a field of its own, with ever-increasing cycles of innovation. One important distinction that is useful to understand better the principles of molecular genetics is the difference between tests for the length of a DNA fragment (e.g. a 'microsatellite' marker) and tests for mutations or polymorphisms (e.g. single nucleotide polymorphisms or SNPs).

Markers for linkage analysis are highly polymorphic fragments of the DNA of known location in the genome. Microsatellite markers are DNA fragments with a number of repetitions of short sequences (CGAT***CACA…CACA***GTGTT). Most of these markers have repetitions of two base pairs and are termed variable number tandem repeats (VNTR). Markers with three or more repetitive bases allow better discrimination between variants. The genotyping starts with an amplification of the locus harboring the marker by polymerase chain reaction (PCR), a stepwise process that doubles selected parts of the chromosome over and over again. The movement of the fragments in a medium such as a gel or a capillary is dependent on its length. The copied fragments are labeled by specific dyes that can be made visible in a DNA sequencer, leading to the band pattern that almost became a trade-mark of genetics. Specific computer programs transform these patterns into numbers that serve as house numbers and can be traced within families.

SNPs form a very common type of sequence variation. A sequence variation of just a single nucleotide (e.g. CG***A***GAC and CG***T***GAC) may have functional relevance if it changes the resulting protein structure or the regulation of the gene. Even without such consequences, SNPs may be informative when in close proximity to yet undiscovered gene variants. The co-appearance of genetic variants is termed linkage disequilibrium.

## Linkage analysis with quantitative traits

Researchers use linkage analysis to try to 'link' DNA markers, whose precise location on one of the 23 pairs of chromosomes is known, to a disease locus or a locus which influences a complex trait. Linkage analysis requires a family-based approach, in which the transmission of genetic markers between generations is tested in relation to the transmission of traits/phenotypes. If a particular DNA marker variant segregates in a pedigree with a disease, then one can assume that the marker locus is close to the disease locus. In linkage analysis of complex traits and continuously distributed phenotypes, the basic concept is identity by descent (IBD). For a marker at a given locus, a child randomly inherits one of the two maternal variants and one of the two paternal alleles. Offspring from the same parents can thus inherit 0, 1 or 2 of the same marker alleles. If similarity for the phenotype corresponds with similarity in marker

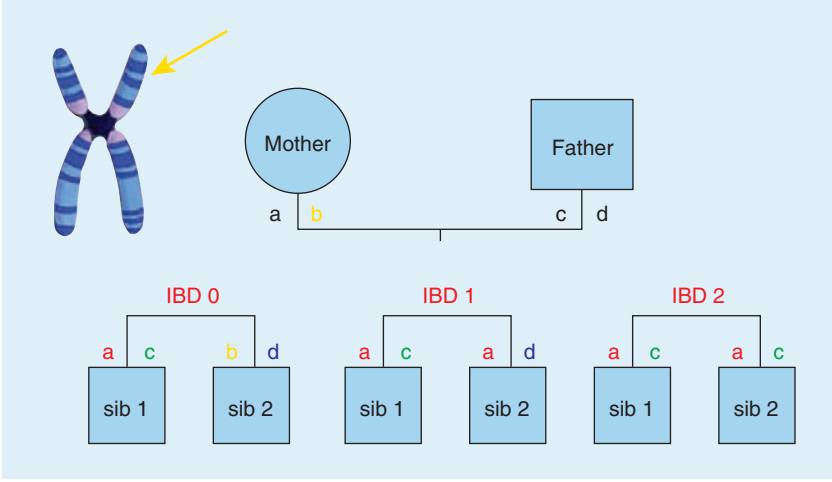


**Figure 37.2** Example of a mating between two parents who are both heterozygous for a particular DNA marker. Mother carries alleles 'a' and 'b' and father 'c' and 'd'. Examples of the identity by descent (IBD) status for sibling pairs in the offspring generation are given below the parental generation. In a non-selected population the expectation for the proportion of sibling pairs sharing 0, 1 or 2 alleles IBD is 25%, 50% and 25%, respectively. If the marker is close to a disease locus, the patients will more often be IBD1 or 2

alleles, then again the marker locus is close to the trait locus. When the trait locus influences a quantitative phenotype, it is often referred to as a quantitative trait locus (QTL). The term QTL is also used for complex traits, which have an underlying continuous, genetic liability. In the case of siblings and DZ pairs, three distinct groups can be distinguished. If both sibs inherited the same parental alleles (IBD2), they are identical for alleles at that locus. In contrast, sibs who inherited different parental variants (IBD0) are as different as unrelated subjects for the marker and for genes in that chromosomal area. The remaining group of siblings who share just one of the parental alleles, but not the other allele (IBD1), are as similar for the marker locus as sibs for the total genome (recall that siblings and DZ twins share on average 50% of all segregating genes) (Figure 37.2).

For genetically influenced traits, MZ twins are more alike than DZ twins, and unrelated subjects show the lowest degree of similarity. Likewise, sib pairs who are IBD2 have higher correlations for a particular trait than those who are IBD1 and IBD0, if the marker locus is close to a relevant gene locus. To test the significance of that relation, both regression analysis and variance component analysis methods are widely used and are available in software packages such as Merlin, SOLAR or Genehunter.

MZ twin data do not contribute towards detecting linkage, as MZ twins share all their genetic material identical by descent. However, analyzing MZ phenotypic data simultaneously with linkage data in DZ twins and sibling pairs makes it possible to distinguish between the effects of background genes and shared family environment on the amount of familial variance not accounted for by the QTL.

## Association analysis

In association analysis, the interest is usually to look at the influence of allelic variants of a known gene on a particular trait. Linkage analysis compares familial resemblance as a function of IBD status, while association analysis compares the mean levels of the trait (or the absence/presence of disease) in carriers of particular alleles. Linkage thus analyzes variances and covariances, and association compares mean values between groups. This implies that the statistical power in association studies is usually larger than in linkage analysis. Association analysis does not require family structures. In its simplest form, it amounts to counting the numbers of a given allele in patients and healthy controls. Mean differences for a measured quantitative trait can be tested between groups defined by genotype for continuous traits, rather than by comparing genotypes between groups defined by affection status. For a locus with two alleles, A1 and A2, trait levels are compared in subjects with homozygote A1A1, heterozygote A1A2 and homozygote A2A2 genotypes (Figure 37.3).

Even in the absence of functional relevance of a polymorphism, significant differences between genotype groups can and do arise. These can reflect linkage disequilibrium (LD), meaning that the polymorphism is close to a causal variant. Significant results can also be created by population stratification, a term that refers to the fact that between different groups within a population (e.g. groups with a

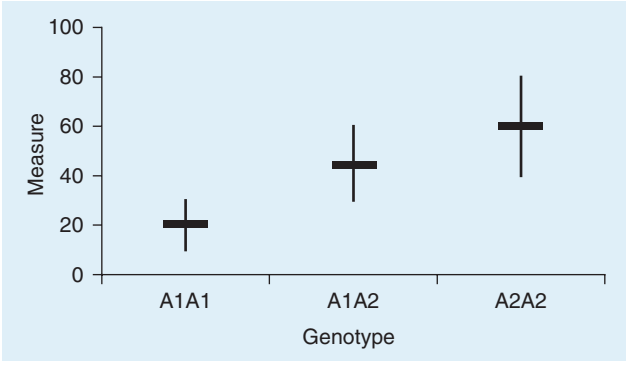


**Figure 37.3** Example of association of a quantitative trait ('measure'). Allele A2 has an additive increasing effect as can be seen from comparing subjects without that variant (A1A1) with heterozygous and homozygous carriers of A2

different ethnic background) disease frequencies as well as allele frequencies may vary. The twin design can control for such effects by comparing phenotypes within DZ pairs, taking advantage of the fact that the two twins always belong to the same stratum within the population. If genotypic differences within pairs predict trait differences, this presents strong evidence that the candidate gene is the causal gene (or that it is very close to the causal gene). MZ twins can be used for a special kind of association test. If the differences in trait values within MZ pairs are related to their genotype, this fact constitutes evidence for interaction between genotype and environment, i.e. the genotypes differ in their sensitivity to the environment[23].

## TWIN REGISTRIES WORLDWIDE

The twin registers of the world hold an enormous potential for research on the genetics of complex traits. The best of these have existed for decades, and have carefully collected longitudinal data on very large samples of twins and their families. These data include a wide range of important biobehavioral traits and diseases as well as environmental risk factors. Many registries also have large collections of DNA from thousands of subjects. Some registers are population based and, as twins occur pretty much at random in the population, represent some of the best resources for evaluating: first, the importance of genetic variation in liability to disease, through the comparison of similarity in monozygotic and dizygotic twins; second, the significance of genotype by environment (e.g. lifestyle) interaction; and third, the contribution of polymorphisms, in particular typed genes, to the total genetic variance and, by implication, the amount of genetic variance yet to be accounted for. These facts, and the existence of these resources, might not yet be well appreciated in the wider community of genetic and clinical researchers interested in multiple births.

### Getting off the ground

Many of the current twin registries are spin-offs from specific research projects, usually in the field of psychology or medicine. The East Flanders Prospective Twin Study, one of the most comprehensive collections of perinatal twin data, was started after the observation of lower degrees of intrauterine hypoxia in second-born twins. The Berlin Twin Register began as a study of the genetics of blood pressure regulation associated with mental stress. Once scientists gain experience with twin research and the databases that support it, they realize the potential of such studies beyond the original question, as well as the necessity to 'nurse' this resource. Resources permitting, a twin collection develops into a register. To define a register, of either twins or patients with a given disease or any other distinguishing characteristic, issues such as sample size and range and sophistication of the data need to be taken into account. For epidemiologic research, existing or emerging population-based registers, including those in Northern Europe, Italy, Korea or Sri Lanka, are of extreme value because of their lack of ascertainment bias. In some countries, sampling of twin pairs is based on computerized population registers, either using direct information on multiple births or applying complex filters that include sharing of date of birth, family name at birth or place of birth or partly sharing identification numbers. Many researchers now realize the value of large data collections for molecular genetic studies and have begun to include siblings, parents and offspring of twins in their research projects.

### Data collection

Administrators of most registries maintain contact with the twins and their family members through websites, by sending out newsletters and through mailed surveys. Even DNA samples from buccal swabs have been collected by post[24]. Data collection by mailed questionnaires often results in large data sets such as that from over 45 000 twins and their relatives on neuroticism, a strong risk factor for the development of depression. This effort concluded that familial resemblance for this trait has a simple genetic basis, and rejected alternative models for familial resemblance, such as cultural transmission[25].

Although sample size is clearly important in genetic epidemiology, together with the amount of data that can be collected through questionnaires and large-scale survey studies, benefits also derive from the scope or depth of phenotypes that need to be collected in laboratory settings. To study genetic basis of disease, intermediate phenotypes often must

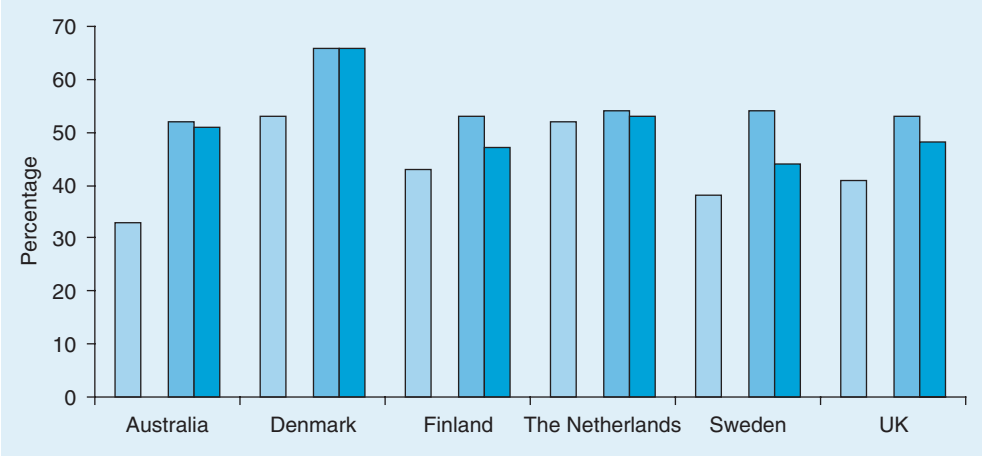


**Figure 37.4** Heritability for migraine (light blue), systolic (medium blue) and diastolic (dark blue) blood pressure from six twin registries participating in GenomEUtwin[26]. Articles at: www.ists.qimr.edu.au/journal. html

be determined in more extensive and costly studies. The selection of subsamples can either be random or selective on prior phenotyping from the larger registers (as for example in the Australian or Scandinavian registers) or smaller twin cohorts collected for specific studies. The register of Italian twin athletes and the study of growth before birth and later adult health are good examples of successful in-depth studies on a small scale.

Centralized health databases also greatly facilitate efficient data collection. For example, Finland and other Scandinavian countries have centralized registers for hospital discharge data and for fully reimbursable medications. This information is accessible with a unique personal identifier that is given to each individual at birth and allows record linking for all twins without any self-selection as potential bias. Personal identifiers of twins are used as a query filter for the health databases, and matching records can then be transferred into the twin database.

## CONCLUSION AND PROSPECTS

Twin studies have demonstrated a significant genetic contribution to population variation for multifactorial traits such as body height and weight, neuroticism or blood lipid levels and complex diseases such as obesity, depression or cardiovascular disease. Many of these traits and diseases are currently on the increase worldwide, and are influenced by risk factors that include diet, smoking and lack of exercise. Although such 'lifestyle' risk factors that are important for the development of complex diseases are often considered 'environmental', they might themselves be influenced by genes. Twin studies have been useful in assessing the extent to which variation in lifestyle and healthy behavior might be heritable. In fact, recent twin studies have provided considerable evidence that 'lifestyle' risk factors aggregate in families owing to shared genes, in addition to the shared environment. For example, twin studies suggest that differences in eating patterns, smoking initiation and persistence, sports participation and even religious beliefs are all influenced by genetic variation. Heritability for a particular disease thus may reflect the direct influence of disease genes, the influence of genes responsible for variation in lifestyle factors, or the influence of genes which modify the influence of lifestyle on disease risk.

The value of large, unbiased study samples needed to verify the role of genetic variation that underlies common traits is well recognized. We have now moved to an era in which genotyping is relatively cheap and rapid, and the major cost of a study of a complex trait involves family collection and trait phenotyping. This view is reflected by a recent decision by the European Community to fund a large integrated project called GenomEUtwin. The participating twin cohorts, from Scandinavia, The Netherlands, the UK, Italy and Australia, form a collection of more than 0.6 million pairs of twins. Over 30 000 DNA samples, accompanied by informed consent for genetic studies of common diseases, have been collected from these population-based twin cohorts. Combining the data from the major twin registries of Europe will integrate the efforts of the leading genetic and epidemiologic researchers in the field of twin research. In this project, epidemiologic and phenotypic data collection will be integrated. Initial 'proof of principle' genome-wide genotyping efforts will be targeted to 10 000 twins for stature, body mass index (BMI), blood pressure and migraine. These traits all show significant heritability

(Figure 37.4) which, surprisingly, differs very little across countries.

Twins and their family members are often enthusiastic participants in research studies. The increase in the twinning rate in The Netherlands and other countries ensures viability of the application of the classical twin design in genetic epidemiology, in medical, behavioral and psychiatric genetics. Only the close collaboration of geneticists, gynecologists and researchers can ensure optimal use of the twin design.

## ACKNOWLEDGMENT

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## APPENDIX

| *Twin studies* | *Number of pairs* | *Primary interest* | *Origin of twins* |
|---|---|---|---|
| Australian Twin ADHD Project (ATAP) http://psych.curtin.edu.au/people/hayd.htm | 1959 | attention deficit hyperactivity disorder and childhood behavioral disorders | Australia |
| Australian Twin Registry[1] www.twins.org.au | 27 582 | general resource for medical and scientific research | Australia |
| Western Australian Twin Register www.ichr.uwa.edu.au | 4729 | asthma and allergy, attention deficit hyperactivity disorder, early speech and behavior | Australia |
| East Flanders Prospective Twin Survey (EFPTS)[2] c.derom@pi.de | 6050 | epidemiology, placentation (chorion type), congenital anomalies, perinatal factors, Barker hypothesis | Belgium |
| University of British Columbia Twin Project[3] http://www.psychiatry.ubc.ca/ | 816 | personality and the personality disorder | Canada |
| Chinese National Twin Program (CNTP) cchp@public3.bta.net.cn | 4576 | establish a population-based national twin registry and study etiologies of common diseases and health-related behavior | China |
| The Danish Twin Registry[4] askytthe@health.sdu.dk | 65 000 | aging and age-related health, metabolic and cardiovascular disease, specific diseases | Denmark |
| The Finnish twin Cohort[5] jaakko.kaprio@helsinki.fi | 15 000 | health, personality, substance abuse | Finland |
| Berlin Twin Register[6] (HealthTwiSt) www.healthtwist.de | >900 | complex diseases, health-related quantitative traits, pharmacogenetics | Germany |
| German Observational Study of Adult Twins (GOSAT) and the Bielefeld Longitudinal Study of Adult Twins (BiLSAT)[7] angleitner@uni-bielefeld.de | 2509 | longitudinal assessment of temperament and personality; generalizability of behavioral genetic findings across methods of personality assessment | Germany |
| Italian Twin Registry www.gemelli.iss.it | 120 000 | aging, dementia, cardiovascular diseases, multiple sclerosis, celiac disease, diabetes, asthma, allergies, thyroid diseases, behavioral disorders | Italy |
| Register of Italian Twin Athletes (RITA) casini@iusm.it | 4719 | human biology and development, sport and high-level performance | Italy |
| Twin Register of Rome (TERRY) casini@iusm.it | 13 228 | lifestyle, development, aging | Italy |
| Osaka University Aged Twin Registry hayakawa@sahs.med.osaka-u.ac.jp | 12 000 | aging, dementia, physical diseases, lipids, cognition, lifestyle, life satisfaction, quality of life | Japan |
| Korean Twin Registry sungjohn@kangwon.ac.kr | 154 783 | complex human diseases and traits | Korea (South) |
| Seoul Twin Family Study www.ktrc.org | >4615 | cognitive abilities | Korea (South) |
| Norway Twin Registries[8] mina.bergem@psykiatri.uio.no | >40 000 | mental health, obesity, asthma, allergies, health behaviors and perceptions, perinatal influences on health outcomes | Norway |

(*Continued*)

Continued

| *Twin studies* | *Number of pairs* | *Primary interest* | *Origin of twins* |
|---|---|---|---|
| The NIPH Twin Panel[9] jennifer.harris@folkehelsa.no | 7668 | physical health, mental health, asthma, allergies, obesity, health-related behaviors | Norway |
| National Twin Registry of Sri Lanka www.infolanka.com/org/twin-registry/ | 20 294 | establish nationwide population-based twin register for multidisciplinary research and international collaborations | Sri Lanka |
| The Swedish Twin Registry[10] www.mep.ki.se | 57 405 | cancer, cardiovascular diseases, dementia, depression, substance use/abuse, cognition, personality, aging, (common complex diseases) | Sweden |
| The Swedish Young Male Twins Study Finn.rasmussen@imm.ki.se | 1783 | risk factors for metabolic syndrome and cardiovascular diseases; overweight and behavioral risk factors | Sweden |
| Netherlands Twin Register (NTR)[11] www.psy.vu.nl/ntr | 30 335 | development behavior and emotional problems. Cognition, depression, addiction and cardiovascular risk factors | The Netherlands |
| St Thomas' UK Adult Twin Registry[12] www.twin-research.ac.uk | 10 000 | cardiovascular, metabolic, musculoskeletal, dermatological and ophthalmological diseases | UK |
| Study of growth before birth and adult health g.mcneill@abdn.ac.uk | 123 | risk factors for coronary heart disease | UK |
| Twins' Early Development Study (TEDS) a.trouton@iop.kcl.ac.uk | 16 810 | longitudinal assessment of verbal and non-verbal cognitive development and delay, language development and delay, childhood behavior problems | UK |
| Northern Region Multiple Pregnancy Register Christopher.Wright@ncl.ac.uk | 1216 | multiple pregnancy, obstetric and pediatric management and outcomes of pregnancy | UK (North East) |
| Mid-Atlantic Twin Registry www.matr.vcu.edu | 23 000 | behavioral and psychiatric | USA |
| National Academy of Sciences–National Research Council (NAS–NRC) Twin Registry www.iom.edu/twins | 15 924 | somatic and psychiatric disease, aging, social, psychological and demographic variables | USA |
| Southern Illinois Twins www.siumed.edu/playlab | 126 | peer interaction behaviors, preschool cognitive development | USA |
| Vietnam Era Twin (VET) Registry Birute.Curran@med.va.gov | 7500 | veterans health, effects of combat, psychiatric disorders, substance abuse | USA |
| International Twin Study tmack@usc.edu | 17 229 | etiology of disease, genetic markers | USA and Canada |
| California Twin Program http://twins.usc.edu/ | 13 096 | etiology of disease, genetic markers | USA (California) |

Continued

| *Twin studies* | *Number of pairs* | *Primary interest* | *Origin of twins* |
|---|---|---|---|
| San Diego twin blood pressure study at UCSD http://elcapitan.ucsd.edu/hyper | 200 | blood pressure, autonomic 'intermediate phenotypes' for high blood pressure | USA (California) |
| Southern California Twin Register www-rcf.usc.edu/~lbaker | 2600 | social and moral development, childhood behavior problems, cognitive abilities | USA (California) |
| Georgia Cardiovascular Twin Study www.mcg.edu/institutes/gpi | 534 | longitudinal development of bio-behavioral antecedents of cardiovascular disease in youth | USA (Georgia) |
| Minnesota Twin Family Study (MTFS)[13] www.tc.umn.edu/~mctfr | 4723 | substance use, related child and adult disorders | USA (Minnesota) |
| Minnesota Twin Registry www.psych.umn.edu/psylabs/mtfs/ | 5599 | individual differences | USA (Minnesota) |
| NY Obesity Research Center Child Twin Registry (Project "Grow-2-Gether") http://cpmcnet.columbia.edu/dept/obesectr/NYORC/twins.html | 50 | food intake, body composition | USA (New York) |
| Wisconsin Twin Panel www.waisman.wisc.edu/mrddrc | recruitment began with 1989 births | childhood behavioral disorders | USA (Wisconsin) |

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# The Mirror Phenomenon in Monozygotic Twins

*D. Teplica and K. Peekna*

**38**



## BACKGROUND

For years it was commonly believed that approximately 25% of monozygotic (MZ) twins exhibited what was loosely referred to as the 'mirror phenomenon'. In this situation, what was seen anatomically on the left side of the body in one twin was seen on the right side of the other twin. Mirror-image features in twins commonly include moles, birthmarks, tooth eruption patterns and hair whorls. According to some authors, the mirror phenomenon is also a partial explanation for why more than a third of MZ twins are left-handed, double the rate in the general population. In contrast, only rarely are the internal organs reversed in one of the twins (situs inversus)[1].

The current explanation for this phenomenon relates to zygotic splitting at a relatively advanced stage, usually at day 7 or beyond[1,2]. In earlier zygotic splitting, twins are formed by the separation of the zygote into two cells or two small clusters of cells that are derived from one fertilized egg. To the best of our knowledge, there is no three-dimensional orientation to these cells or tiny cell clusters. In later splits, however, it is considered logical that the developing cell mass has already attained some degree of polarity, that is, a right and a left side. In this construct, following division of the cell mass, both sides are like the mirror reflection of each other, rather than an exact duplicate[1]. This construct may be flawed, however, as it presumes that the split always favors laterality rather than a transverse or arbitrary separation. Because no three-dimensional observation of the splitting process has been made *in vivo*, and because polarity is not visible to the observer in *in vitro* culture preparations, the details of this process remain speculative.

Although numerous studies have been published regarding concordance of anatomic features in MZ pairs, to our knowledge none has adequately controlled for the mirror phenomenon. In addition, no specific diagnostic test to establish the presence of mirroring has been previously published. Therefore, the frequency of mirroring has not been established for MZ twins. To address this practical deficit, this chapter describes the basic tools and a methodology to establish definitively the presence or absence of the mirror phenomenon.

## STANDARDIZED PHOTOGRAPHY OF THE FACE

In the past, the presence of the mirror phenomenon rested upon casual inspection of the face or examination of snapshots. Neither method is accurate or scientifically valid. Casual inspection provides no data trail for interobserver validation, whereas snapshots are invariably produced rapidly with no attention to anatomic registration of head position. As such, they provide flawed anatomic information for judgment.

The biomedical-imaging community has established the need for standard protocols to obtain anatomically accurate photographs of the whole body or its parts[3–5]. The production of standardized facial images for scientific analysis must adhere to criteria that eliminate environmental and technique-based variance that could bias analysis. As an example, something as simple as capturing images in a pair of MZ twins from slightly different distances would completely preclude accurate comparison of anatomic size from the resultant photographs.

**Table 38.1** Image production guidelines

***Photographic environment***

Place a black backdrop at least 4 ft behind the subject
Minimize ambient light
Use a rotating stool to facilitate subject positioning
Mark the floor and walls with directional lines at 45° increments using low-tack tape
Place points of focus onto the walls for the subjects to orient their gaze

***Equipment***

Use a professional-quality traditional or digital 35-mm camera with manual override capabilities
A 105-mm focal length lens (or similar) will minimize distortion of facial anatomy
Use ring flash or a similar system to minimize harsh shadows created by unidirectional lighting
A sturdy tripod must be locked in position
Two studio strobes at 45° angles from the midline enhance depth rendition
A simple light meter minimizes the chance of exposure errors

***Subject preparation/positioning***

Remove all make-up and jewelry if possible
Hair should be fastened back so that facial anatomy is not obscured
Position the subject's bony anatomy so that the Frankfort horizontal plane is parallel with the floor
Ask the subject to relax the face and make no expressions
Photograph twin 'A' first each time to eliminate confusion later

***Camera distance and settings***

Set the focus of the lens at a 1 : 10 reproduction ratio (so that anatomy at the focal distance is exactly one-tenth life-size on the film) and tape the lens so it cannot move
For a 105-mm lens, this means that the focal center of the lens will be almost exactly 44 in from the subject when the anatomy is in focus. 'Pull focusing' should be used – the taped lens is moved toward and away from the subject until the infraorbital rim is in focus
For digital cameras, the head size must be standardized to include all head and neck anatomy, and should be cropped in a standardized way in the viewfinder to include black space around the perimeter of the patient's anatomy. This should be done in manual mode with all subjects captured from one distance at one focal length
Capture images at 45° rotational increments (right lateral, right oblique, frontal, left oblique and left lateral)
The 'worm's eye view' can be added if anatomy of the nose is to be evaluated (45° from below the horizontal plane)
If there are interesting features that deserve special additional views, it is helpful to have a second camera available with close-up settings preset, so that standardization does not have to be disrupted. Unusual nevi, anomalies, dynamic findings (dimples, wrinkle patterns, tooth patterns seen during smiling, etc.) can all be imaged in this way

***Film and processing***

Professional-grade transparency film or fine-resolution digital capture should be used
Standardized film processing must be done by a quality-controlled laboratory using a batch technique (to avoid variations in color due to chemical inconsistencies)
Careful labeling and registration of all rolls is done in known sequence to avoid confusing the twins within a pair

***Digital image processing and analysis***

Digital images are uploaded directly. Traditional film can be scanned using a slide or film scanner
Image overlapping, rotation, translation and subtraction must be handled at full resolution
Label digital files carefully to avoid confusion of the twins. Placement of an 'R' in text format on the image above the *subject's right-hand* side (the upper left-hand corner of the image) will prevent inadvertent storage of flipped data

Similarly, different lenses can distort perception of reality, and the use of two different film stocks can completely change the color of skin structures.

To avoid errors in documentation and analysis, variables during the image-capture phase of data collection must be controlled. Table 38.1 presents a list of criteria for standardization. Standardization requires a studio setting, whether one is working in the field, or in a controlled laboratory setting indoors. Figures 38.1 and 38.2 show the respective studio

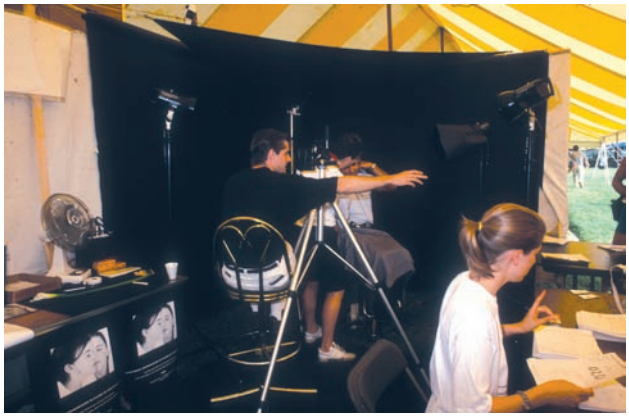


**Figure 38.1** Photographic studio constructed in circus tent, Twinsburg, OH, August 1989

**Figure 38.2** Photographic studio constructed in a laboratory in the University Hospital, Katholieke Universiteit, Leuven, Belgium, May 2004

setups used in Twinsburg, Ohio (Figure 38.1), and in Ghent, Belgium (Figure 38.2) to obtain the images shown in this chapter. The Twinsburg archive was established in 1989 in collaboration with the Center for Study of Multiple Birth in Chicago, and the Belgian Archive was created in 2004 in collaboration with the East Flanders Prospective Twin Survey. In each case, the studios conformed to the requirements outlined in Table 38.1. Moreover, they facilitated capture of a full series of facial images at 45° increments, rather than just the frontal view required for simple analysis of the mirror phenomenon. This allowed for cross-checking of surface skin features from more than one angle, in order to increase diagnostic accuracy. Figure 38.3 shows an entire representative sequence.

## CRITERIA FOR SKIN EXAMINATION

The body surface is unique for several reasons. First, the skin is the largest organ system. Second, it is the only system where anatomy is directly visible. Third,

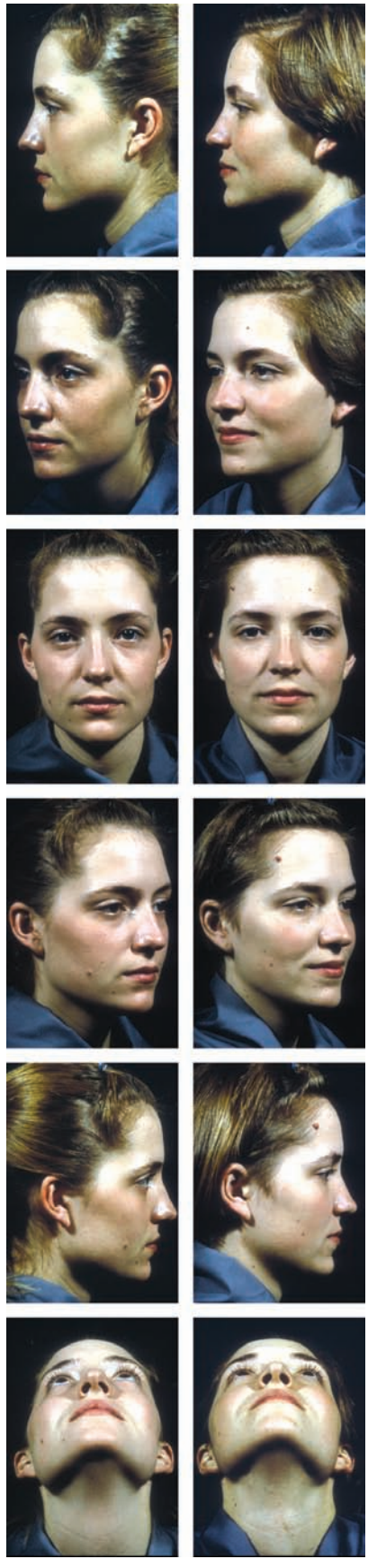


**Figure 38.3** Representative sequence of twin A and twin B as described in Table 38.1

**Table 38.2** Skin analysis

| |
|---|
| *Aging patterns* |
| Gravitational sag |
| Wrinkles |
| Gray hairs |
| *Physiologic responses* |
| Oil production |
| Sweat production |
| Freckle formation |
| Vasodilatation |
| *Inflammatory conditions* |
| Acne |
| Rosacea |
| Psoriasis |
| Cystic processes |
| *Neoplasms* |
| Keratoses |
| Benign nevi |
| Skin tags |
| Malignant skin tumors |
| *Hair findings* |
| Presence or absence of hair in any region |
| Balding patterns |
| Vectors of growth |
| Whorls |
| Texture |
| Color |

and most important, systemic functions including aging, physiological responses and inflammatory processes can easily be seen with the naked eye.

Skin examination is best performed by a health professional with a basic understanding of normal and abnormal features of each of the categories outlined in Table 38.2. It is recommended that all criteria be evaluated in each twin pair. When evaluating aging characteristics, the observer should look for concordance or discordance of gravitational sag, skin wrinkling patterns, and the location and pattern of graying of individual hairs or clusters. Figure 38.4 shows typical concordant aging phenomena. Figure 38.5 shows the striking similarity in two elderly women who have but one downwardly curving gray hair in each of their right eyebrows.

Physiologic responses to the environment can also be directly observed on the surface of the skin. This fact intensifies the requirement for studio control and examination of the twins at the same time. Oil production, sweating patterns, freckling and surface vasodilatation, among other features, are all readily apparent. As shown in Figure 38.6, both sweat production on the left temple and oil production on the alar rim of the nose are identical.

It is commonly held that the environment inspires inflammatory processes in unique ways in separate individuals. This is clearly not the case in some sets of MZ twins, as seen in the acne eruption pattern on the tips of the noses in the adolescent pair shown in Figure 38.7. We are unaware of any genetic explanation that could account for the simultaneous occurrence of any inflammatory process in exactly the same three-dimensional location and at exactly the same point in time. However, the senior author (D.T.) has observed numerous instances in both the Twinsburg archive of facial anatomic images and in the Belgian photographic archive of concordant acne flaring, cyst eruption, psoriasis outbreaks and rosacea patterns.

Both benign and malignant neoplasms are easily visible. The benign neoplasms commonly seen on the face include seborrheic keratoses, intradermal nevi and skin tags. Although no dialog is present in the literature discussing differential migratory patterns of ectoderm and mesoderm leading to slight differences in the location of skin lesions within MZ pairs, it is clear that this must be considered when evaluating twins for concordance of skin structures[3,4]. The same may be said regarding the size of the lesion, which may vary significantly from one twin to the other.

As seen in Figure 38.8, on first glance there is only a suggestion of concordance of skin neoplasms on the right-hand side of the faces of the MZ pair, Louis and Donald Keith. On closer analysis (Figure 38.9), however, a seborrheic keratosis is present on the right cheek of Louis (left image), located 4.5 cm in front of the tragus of the right ear. On the lateral view of Donald, the slightly smaller growth is located only 2.0 cm in front of the same ear. A single lentigo is present on the right lateral neck of Louis located directly beneath the lobule of the ear. In contrast, this lesion is located 2 cm behind the lobular attachment in Donald. A single vertical crease is present on both earlobes in the same location. Most striking is a triad of intradermal nevi that are present on the right side of the face in both twins. In Louis, it is clear that this triangularly arranged cluster of benign neoplasms migrated closer to the midline during embryologic development. Finally, and unrelated to issues of neoplasia, it is interesting to note that both have five transverse forehead creases, three upwardly oriented 'crow's feet' wrinkles projecting from the lateral canthus of the right eye (one of which splits into a 'Y' shape in each) and two downwardly angled wrinkle lines extending over the right zygoma. It is hard to imagine how the development of such similar structures might occur in separate individuals 55 years after zygotic division, unless it were genetically predetermined.

It is even more challenging to explain that the three-dimensional predisposition to neoplastic transformation and subsequent appearance of basal cell epithelioma can occur in a concordant manner eight decades after birth. Figure 38.10 illustrates this

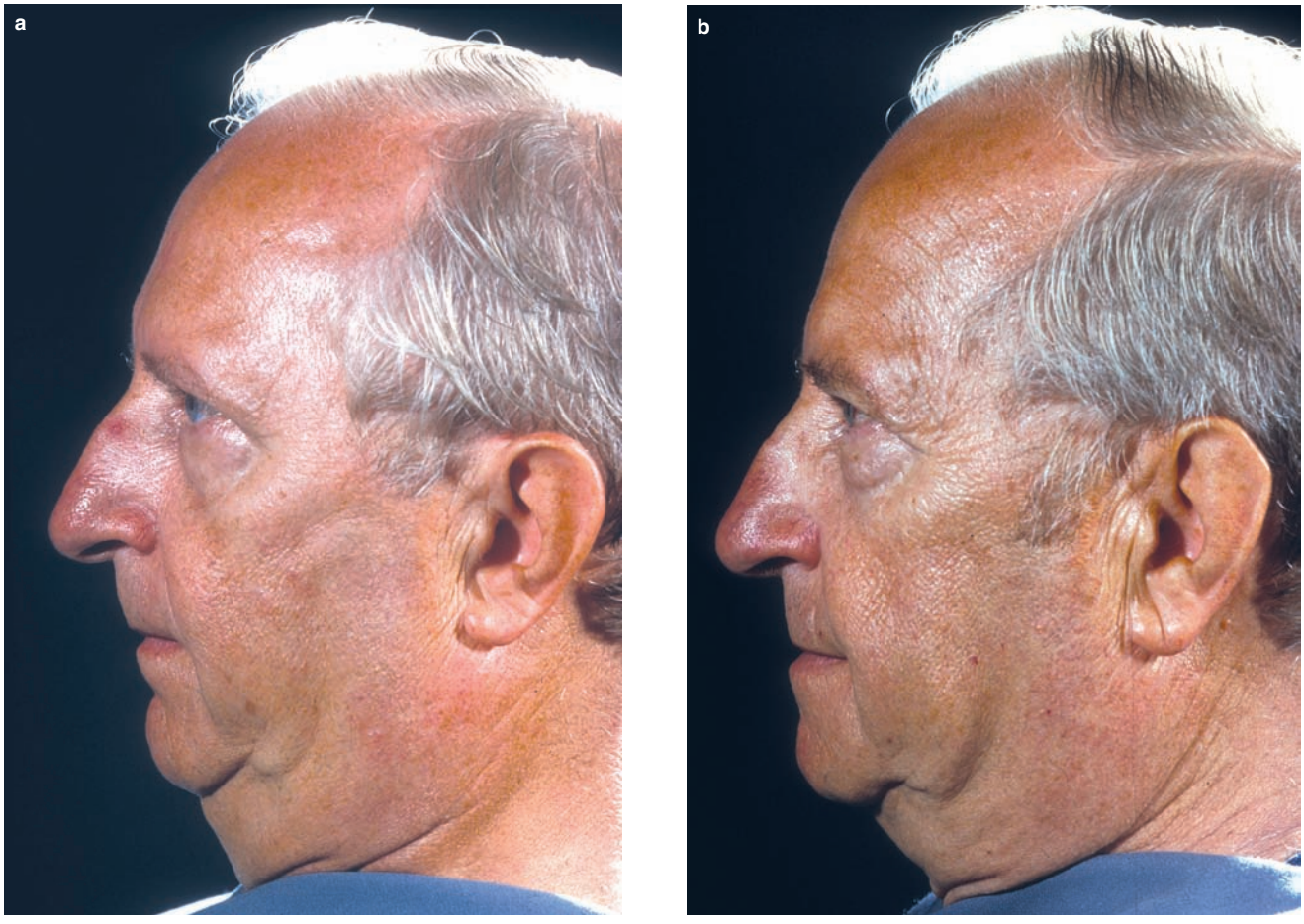



**Figure 38.4** Concordant aging phenomena, including nearly identical nasolabial folds, jowl formation, submental fat pad enlargement, chin ptosis, rosacea of the nose, pre-auricular skin creases, brow ptosis, graying patterns and balding patterns

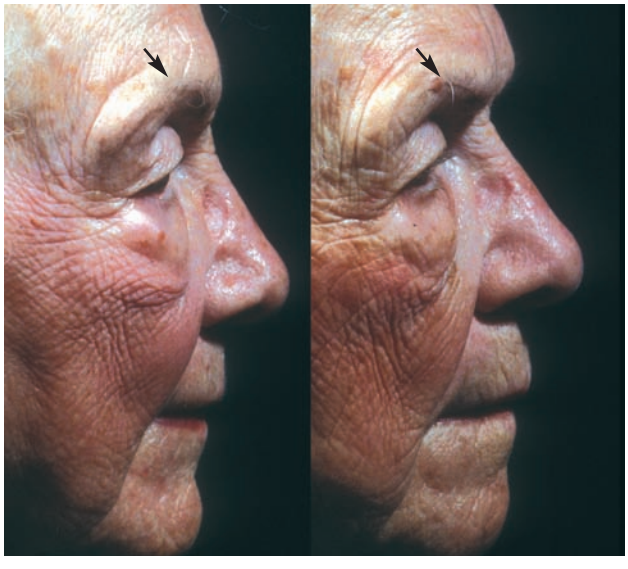


**Figure 38.5** Arrows point to single downwardly curving gray hairs in identical positions on the right eyebrow

finding with a pair of MZ twins, each of whom developed basal cell tumors of the helical rim of the left ear. Twin A on the left bears a linear scar where a dermatologist excised the lesion 1 year prior to the development of a similar lesion at the exact same site on the helix of twin B on the right. As was the case with the Keith twins, other striking similarities exist in the skin examination, including skin wrinkling patterns, and sweat production, as well as the similar development of lentigos and actinic keratoses in response to sun damage.

## MIRROR ANATOMY

Once standardized images have been produced as outlined above, and the skin examination has been completed and recorded for future reference, analysis can begin. It is important to remember that although concordance is often striking, it may not always occur on the same side of the face or body. Figure 38.11 shows two birthmarks of slightly different size and shape located 8 cm distal to the antecubital crease on the medial surface of contralateral forearms in an MZ pair of adolescent girls. In a pair of adult MZ males, identical skin tags can be seen on opposite sides of the lateral neck bases (Figure 38.12).

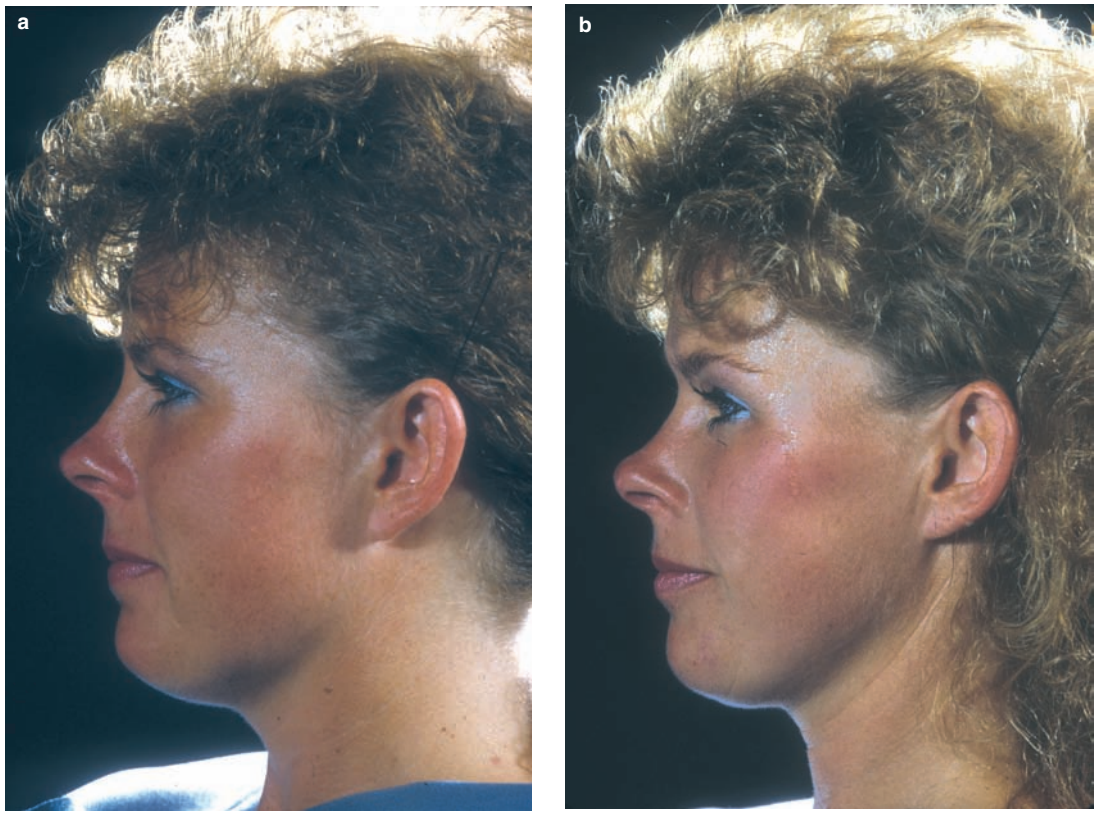



**Figure 38.6** Identical patterns of sweat formation on the left temple of each twin along with similarities in oil production on the alar rims of the noses

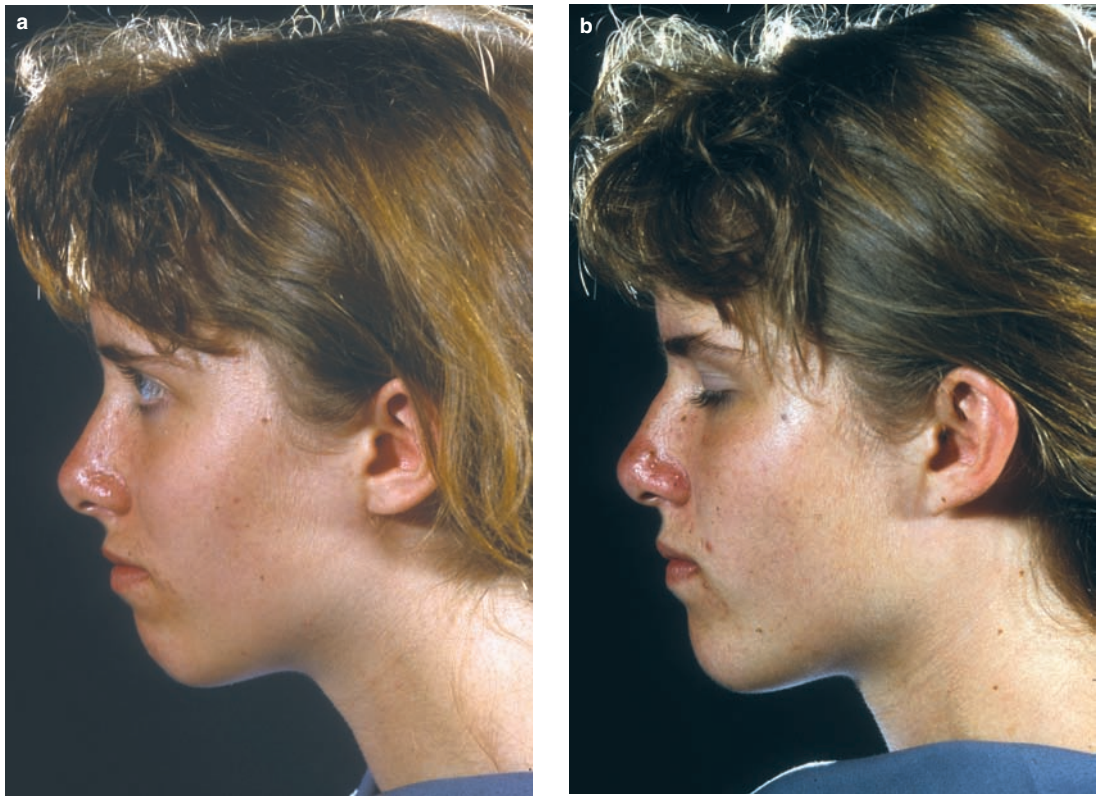



**Figure 38.7** Concordance in eruption of acne on the tips of the noses of both twins at exactly the same time

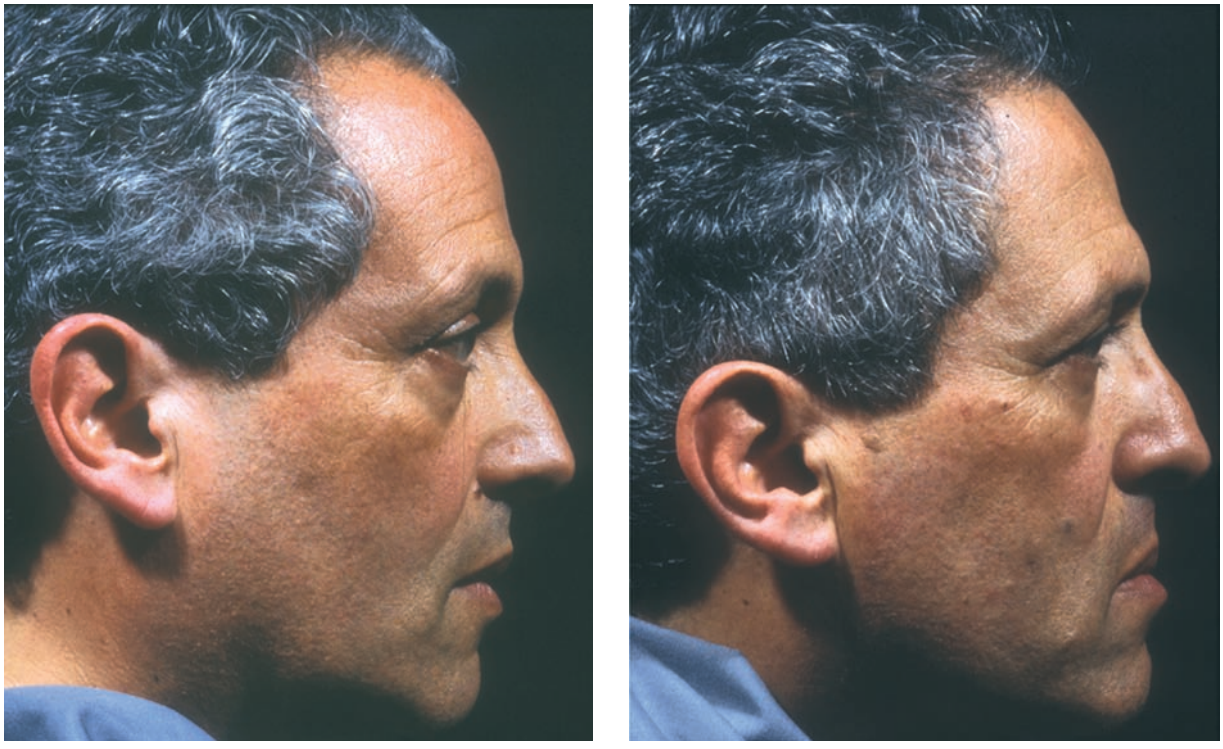


**Figure 38.8** At first glance, concordance of skin structures on the faces of monozygotic pair Louis and Donald Keith is not immediately apparent

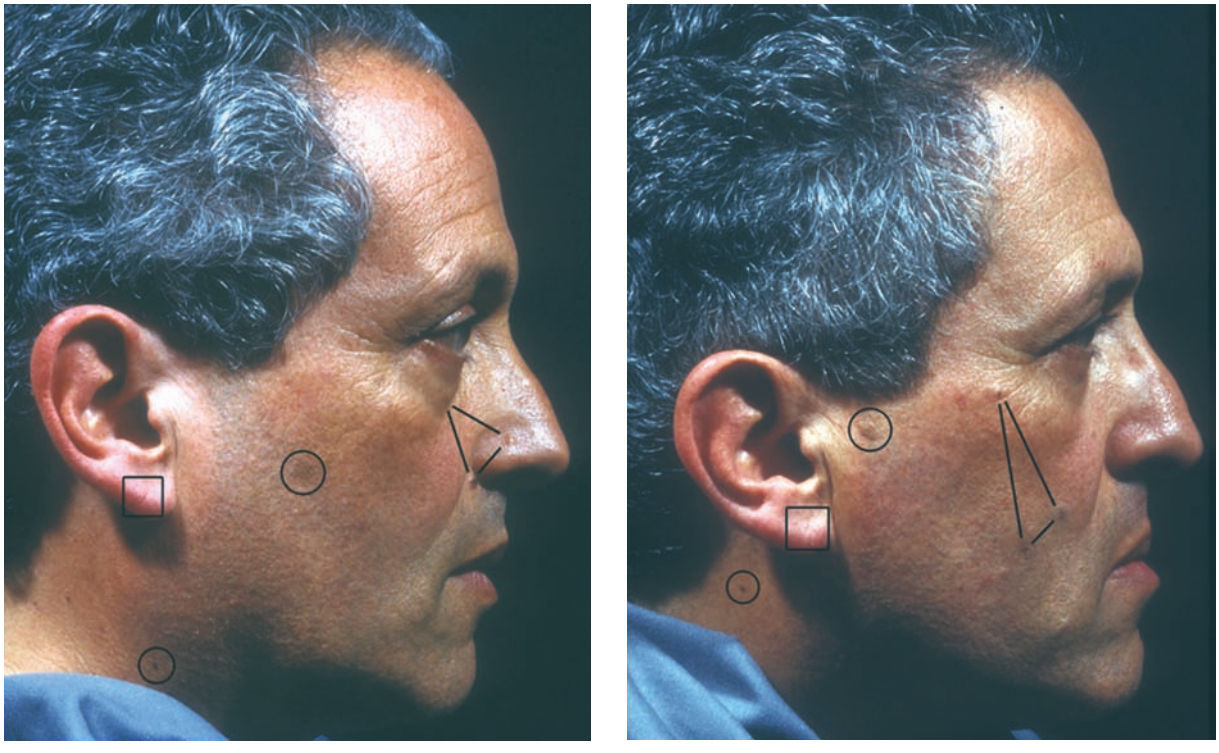


**Figure 38.9** Careful analysis reveals striking similarities, including the same vertical creases in the earlobes, five transverse forehead creases, three upwardly oriented crow's feet projecting from the lateral canthus, and two downwardly angled wrinkle lines extending over the right zygoma. Additionally, if one considers the variable migratory rates of embryologic tissues as they proceed toward anterior fusion, one can understand that specific skin lesions ultimately occur in slightly different locations along the lines of embryologic transit. Seen here are a similar configuration in a triad of nevi, a single seborrheic keratosis on each right cheek, and a benign lentigo on each neck

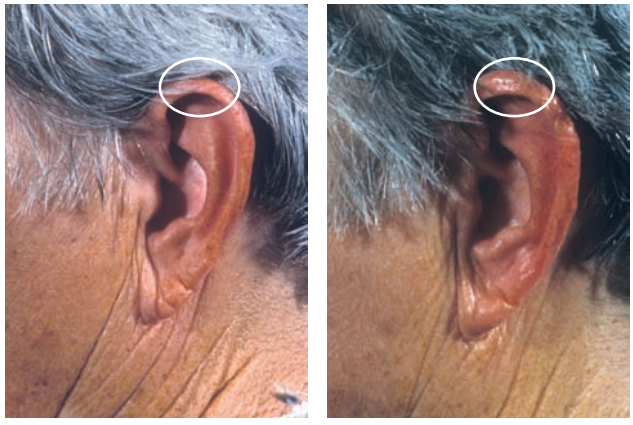


**Figure 38.10** Concordance of location of basal cell epitheliomas on the left helical rim of two monozygotic twins. Twin A on the left bears a linear scar following excision 1 year prior to the discovery of the tumor in exactly the same spot on twin B when the pair presented for study in Twinsburg, OH in 1989

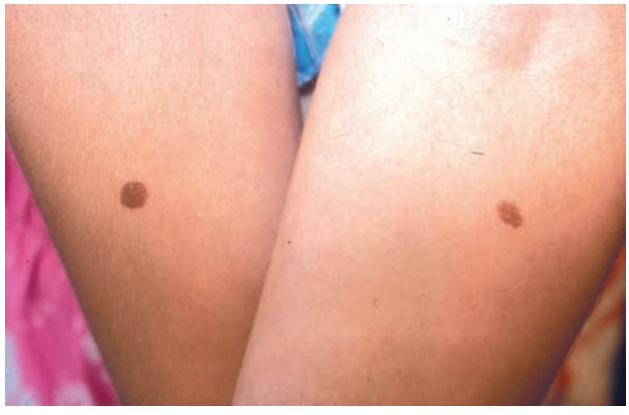
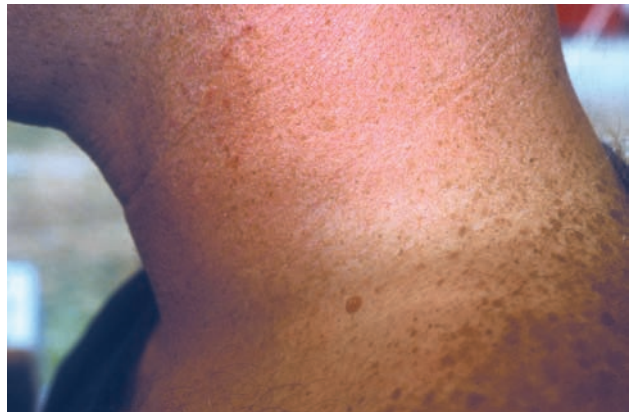


**Figure 38.11** Concordant junctional nevi on contralateral forearms in an adolescent female monozygotic pair

A further consideration relates to the age of the twin pairs being studied. It is important that the pairs have experienced pubertal changes, because facial growth and full expression of features is needed. Many young children do not exhibit enough variance of anatomy or skin findings to support this type of examination.

The diagnosis of the mirror phenomenon is facilitated by the use of standardized photographic images of the faces coupled with detailed skin examinations. If physical examination of the face is used alone, then one must have significant training in the analysis of skin structures. Moreover, it requires the continued presence of the twin pair during the analysis phase. In contrast, if standardized photographic images are also created, the findings of the skin examinations can be substantiated and cross-checked by different observers. Also, additional analyses can be performed at a later date, when the twins are no longer present.



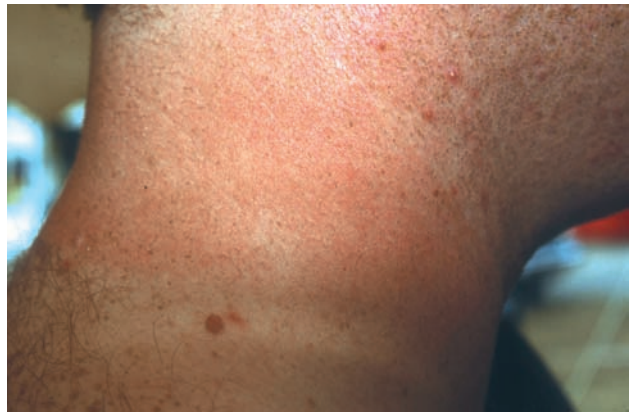


**Figure 38.12** Concordant skin tags on the lateral line of the base of the neck on contralateral sides of a monozygotic pair of young adult males

## PHOTOGRAPHIC ANALYSIS WITH DIGITAL OVERLAY

Even in the age of sophisticated digital imaging, Kodachrome® film remains the gold standard for image density. In other words, there are more bits of information recorded within the structure of Kodachrome than one can currently achieve in a digital photograph, although this statement may require modification by the time this volume goes to press. Having said this, recent developments in digital photographic capture and manipulation allow for more rapid and reproducible analysis of anatomic similarity and variance. This fact essentially mandates that images be analyzed digitally, regardless of how they are obtained.

Using Adobe Photoshop®, a method of image processing has been devised to allow for anatomic comparison and diagnosis of the mirror phenomenon. If images are obtained with traditional film techniques (preferably Kodachrome), they must first be scanned with a high-resolution scanner into Photoshop or a similar image processing platform.

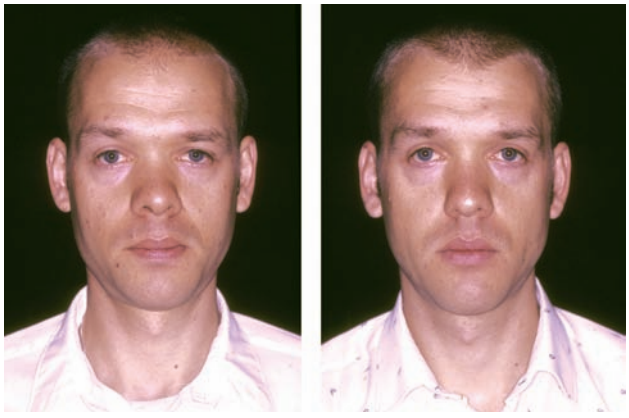


**Figure 38.13** Representative standardized pair of anterior views of twin A (left) and twin B (right)

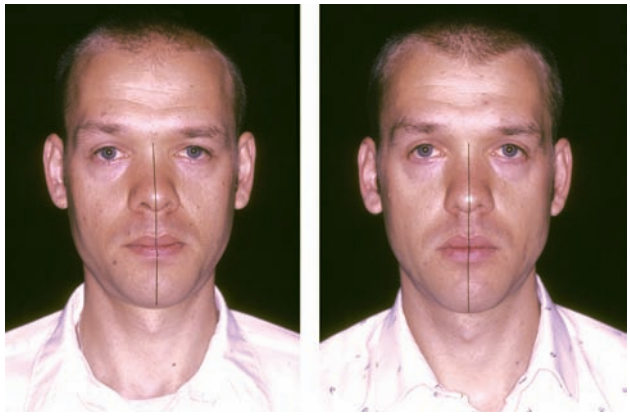


**Figure 38.14** Midline established using anatomic landmarks

Photographic data obtained by digital technique can be processed directly.

The first step as shown in Figure 38.13 is to create pairings of standardized images of the faces of MZ twins A and B. Next, one can establish the anatomic midline of each face (Figure 38.14). Visible points on the midline are connected to form a line that can be drawn as an overlay on top of each facial image. The midpoint of the radix (attachment of the nose to the forehead) is connected by a line to the midpoint of the place where the collumella of the undersurface of the nose joins the philtrum of the upper lip. This line continues to the midpoint of the white roll of the upper lip, down to the inferior border of the lower lip and through the midline of the mentum (chin) to its lower border.

The interpupillary distance must then be standardized by enlarging or reducing one of the two facial images, so that the specular highlights (reflections of the flash unit in the pupil of each eye) can be overlapped. Figure 38.15 is an example of an overlap of the images of twins A and B with interpupillary distances standardized and specular highlights exactly aligned. In this figure, note that the midlines are not yet aligned. Using software image rotation technique, the midlines can now be superimposed, with the realization that the pupils will shift out of register. This is expected because bony orbital symmetry is not known to exist in any individual. In other words, the eyes are not perfectly aligned when the midline is vertical.

Next, the two images can be digitally 'subtracted' from each other using the 'difference' manipulation technique available in Photoshop and other software systems. This maneuver yields an image with a visible 'ghost' of white around the perimeter of the image and alongside major facial structures which represents the variance between the two images (Figure 38.16). This seems to occur because in the vast majority of cases the variation in anatomy between corresponding sides of the faces in two twins (L and L) is less than the variation between the two sides (L and R) on the face of one twin alone.

## OBSERVATIONS

When an MZ twin pair exhibit the mirror phenomenon with regard to skin examination, almost 100% of the time the difference in overlap images exhibits a symmetrical 'ghost' (Figures 38.17 and 38.18). By contrast, if a monozygotic pair is nonmirror in anatomy, the overlap difference shows asymmetric 'ghosting' (Figures 38.15 and 38.16). The use of a flipped image of either twin A or twin B will invariably yield the opposite result (Figure 38.19).

An initial study was performed using 15 pairs of female and 12 pairs of male twins whose monozygotic status was established by blood-work and placental examination at birth by Drs Robert and Catherine Derom and colleagues[6]. Using both skin examination and photographic overlap analysis, we found that the mirror phenomenon was present in 44% of the 27 pairs using skin examination alone and in 48% by photographic overlap analysis alone. When results from both techniques were considered, 52% of the pairs exhibited the phenomenon.

## SUMMARY

Past studies of concordance in anatomic structures have failed to take into account the mirror phenomenon. Indeed, no diagnostic tool was available to establish its presence or its frequency. Recent advances in photographic standardization and manipulation have opened new avenues for investigation of anatomic laterality. When combined with detailed skin examination, the senior author's photographic overlapping technique can reproducibly establish the diagnosis of the mirror phenomenon.

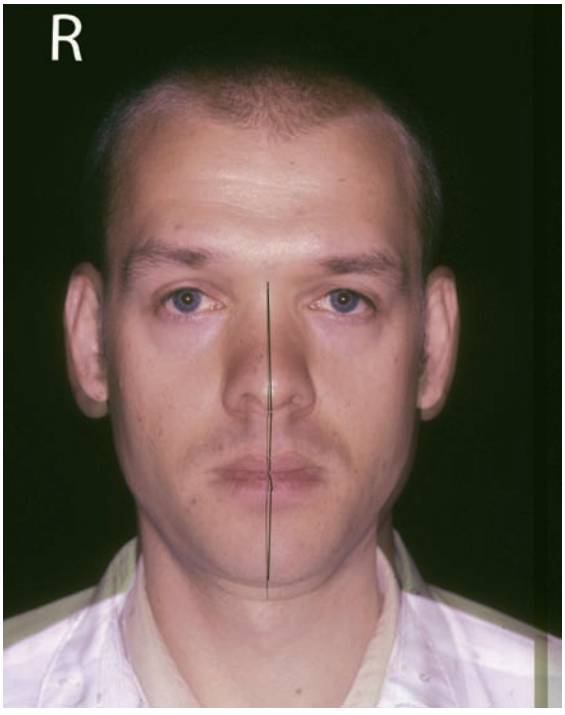



**Figure 38.15** Example of overlap of twins A and B with standardized interpupillary distances and specular highlights (reflective spots of light in each pupil) exactly aligned

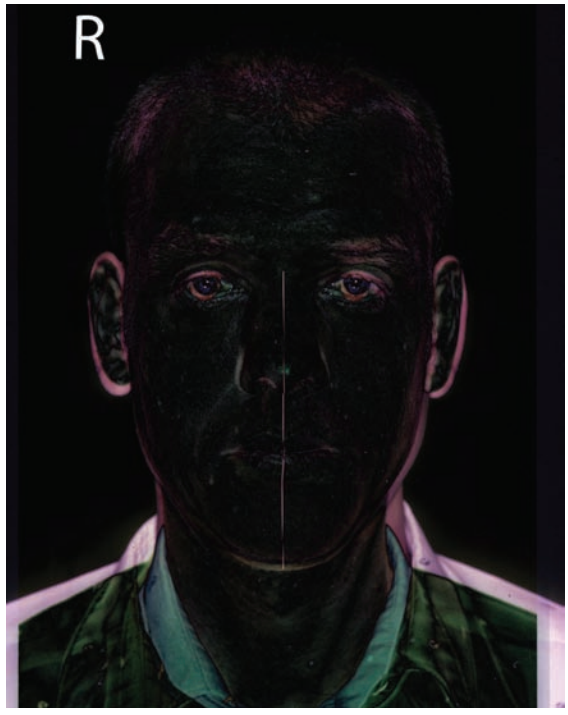



**Figure 38.16** Digital difference between overlapped images of twin A and twin B, showing variance which is seen as 'ghosting'. In this case the light colored 'ghost' is asymmetrical when the right side is compared to the left. Of note, skin exam in this pair shows features on the same side in both individuals

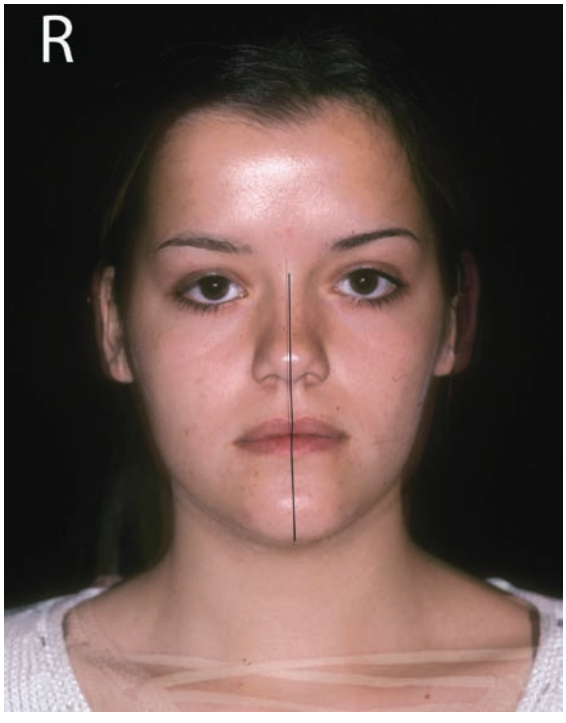



**Figure 38.17** Example of overlap of twins A and B in a representative female pair with mirror opposite features

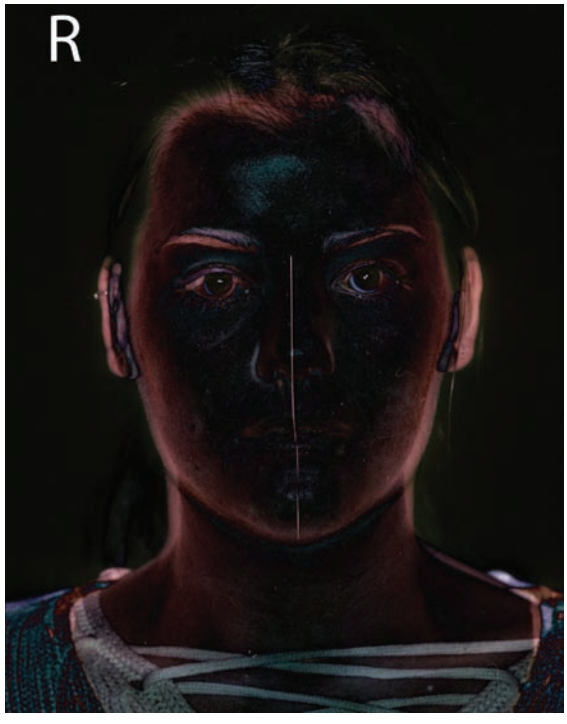



**Figure 38.18** The mirror phenomenon in this pair is indicated by the presence of symmetrical 'ghosting', the opposite of what occurred in the non-mirrored pair shown in Figure 38.16

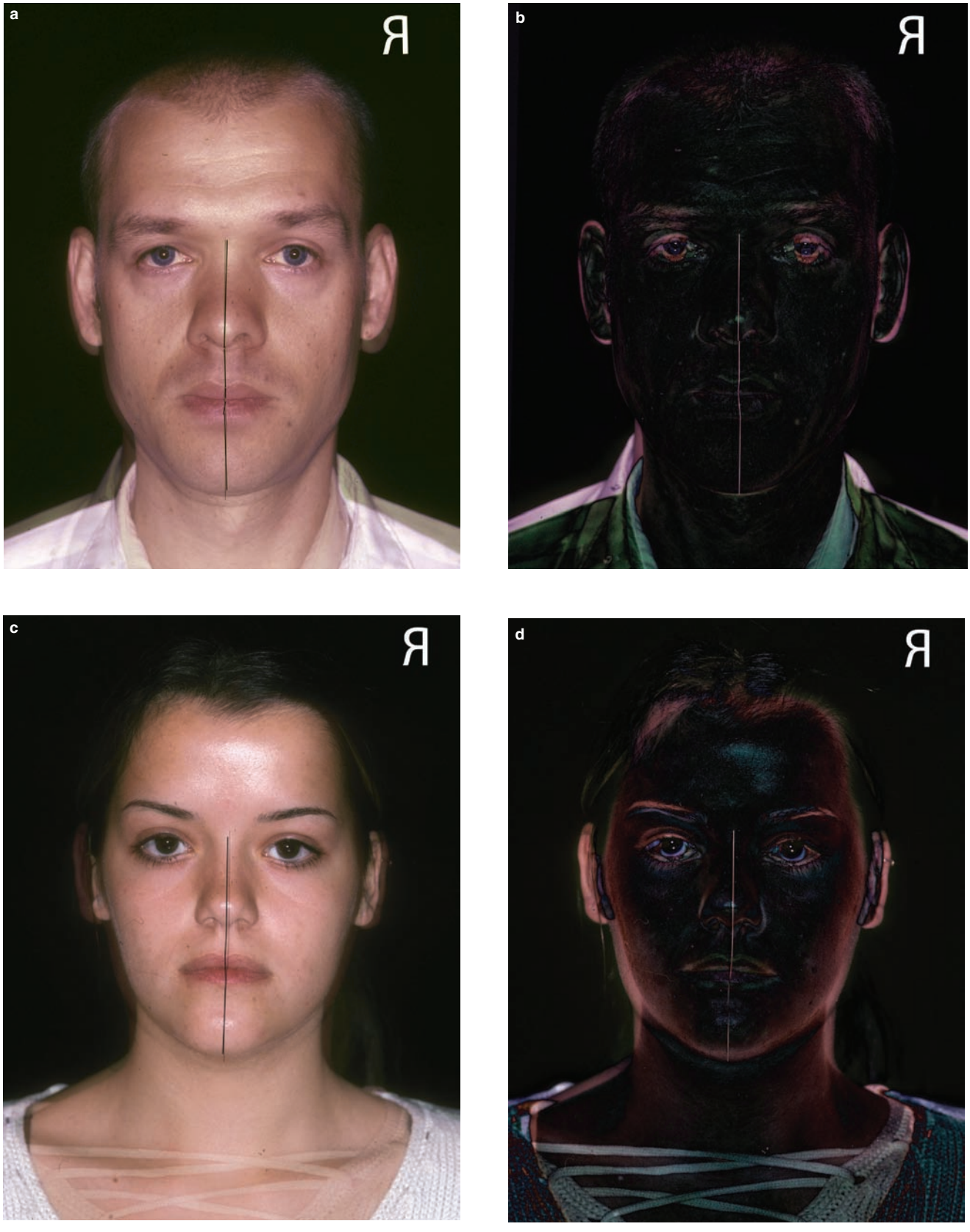



**Figure 38.19** When one of the two images within the overlap is digitally flipped, the pattern of ghosting (symmetrical or asymmetrical) reverses. Thus, the asymmetrical ghost seen in Figure 38.16 becomes more symmetrical in 38.19b above. Likewise, the symmetrical ghosting seen in Figure 38.18 becomes more asymmetrical in 38.19d above

Although it was previously thought that approximately 25% of monozygotic pairs exhibited mirroring, our detailed analysis shows that approximately 50% have opposing anatomic laterality when studied by either detailed skin surface analysis, by photographic overlap technique or by a combination of the two.

It also appears as though the concordance of secondary skin structures is extremely high if one controls for the mirror phenomenon and understands that there can be variation in the rates of embryologic tissue migration prior to fusion of the anterior midline. One must also realize that the degree of expression of any finding may vary. Studies of anatomic concordance of surface features should be relaunched with these factors in mind.

## ACKNOWLEDGMENTS

Production of the Twinsburg Archive was made possible by generous grants from Eastman Kodak Company and the Surgical Scientist Training Program of the National Institutes of Health. Creation of the visual database would not have occurred without the foresight, guidance and encouragement of Dr Thomas J. Krizek and the Section of Plastic and Reconstructive Surgery at the University of Chicago Hospitals. Project support for all phases of the study was received from Donald and Louis Keith and the Center for Study of Multiple Birth. The production of the Belgian Archive was accomplished with the remarkable generosity and insight of Dr Catherine Derom and Dr Robert Derom of the Center for Human Genetics, Katholieke Universiteit, Leuven, Belgium. We must also note invaluable assistance received from Ingegorg Berckmoes, Melissa Bourgeois, Ronell Brown, Scott Brill, Dan Canaday, Emily Carlson, Joe Ciarrocchi, Lut De Zeure, Joel and Steven Dworkin, Chris Fagan, Dr Larry Gottlieb, Shirley Luna, Michael Peres, Mary and Joseph Teplica and Rama Vaitla.

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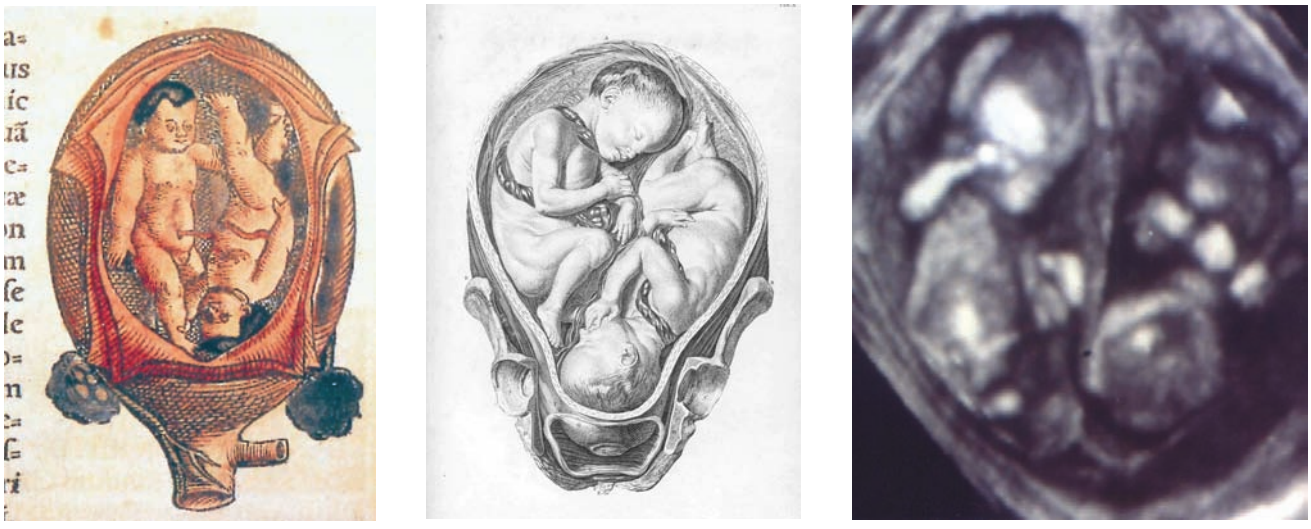
# SECTION III
# PRENATAL DIAGNOSIS

**39-year-old male monozygotic, monochorionic, mirror twins, Belgium, 2004.**

Participants since birth in the East Flanders Prospective Twin Study. Twin A left, Twin B right.

As recently as 25 years ago, the presence of a large-for-gestational-age uterus often led to use of X-rays to differentiate between twins and a large infant. Equally often, the diagnosis of a multiple gestation was made intrapartum, after the delivery of the first twin. Older texts emphasizing the better outcomes of twins diagnosed antepartum and the inevitably less advantageous outcome of the second twin, were pleased if the prenatal diagnosis of twins was made at all. With modern imaging, however, the required threshold for diagnostic accuracy has been much raised. Currently, the diagnosis of multiples is considered insufficient, and clinicians wish to know the chorionicity of a given pregnancy, to exclude structural anomalies, and to use ultrasound-guided diagnostic procedures to establish the continuing well-being of the twins.



*Advances in imaging.* Left, medieval illustration: no details on placenta(s) and membranes are shown. Middle, William Smellie's *A sett of anatomical tables, with explanations, and an abridgment, of the practice of midwifery* (1754): a double-layer intertwin membrane is depicted. Right, ultrasound image, 2003: fetal anatomy is visualized. Image courtesy of A. Kurjak

It goes without saying that not all modalities for prenatal diagnosis are available worldwide, nor is the necessary expertise for this purpose. Nonetheless, this section discusses the use of as complete a compendium as possible of these innovative techniques in the prenatal diagnosis of multiple pregnancies.

*I.B. and L.G.K.*

# Contents of Section III

# Diagnosis of Chorionicity and Amnionicity

*I. E. Timor-Tritsch and A. Monteagudo*

**39**



## INTRODUCTION

The early diagnosis of chorionicity and amnionicity in multiple pregnancy forms the basis of the modern perinatal approach. Without knowing these basic parameters, it is virtually impossible to manage multifetal pregnancy adequately. At the outset it must be emphasized that the determination of chorionicity and amnionicity, as well as dating the gestation, are not only most accurate but also easiest to perform in the first trimester. An additional advantage of scanning the pregnancy at these early stages is that, owing to a generous amount of amniotic fluid, numerous anomalies, such as those of the body contours, brain, limbs, etc., visible at this stage of the pregnancy can be detected. Likewise, natural spontaneous reductions, which occur commonly in multifetal gestations, can easily be documented. Of equal importance, early diagnosis of multifetal pregnancies allows the perinatologist or the obstetrician to counsel the patient properly for fetal as well as maternal risks. Routine sonography during the first trimester of singleton pregnancies, once a matter of great debate, is slowly becoming recognized worldwide as being of great importance. In multifetal pregnancies, on the other hand, an early approach to sonographic evaluation is absolutely essential. A short 2–3-min ultrasound examination performed by an individual with experience, and using a modern machine, during the first trimester can reliably assess chorionicity and amnionicity. In stark contrast, the same task performed during or beyond the second trimester may be an extremely labor-intensive and tedious process, at the end of which even experienced sonologists and sonographers will frequently be wrong in correctly assigning chorionicity and amnionicity.

In order to understand fully the implications of this chapter, the reader is advised to be familiar with the notion of placentation and zygosity, which are more than adequately described in other chapters of this book (see Chapters 24 and 25).

Our focus is on the role of ultrasound in the two major periods of pregnancy during which it is applied in clinical practice: the first 14–16 weeks of pregnancy, and after the 16th week of gestation.

## DETERMINING CHORIONICITY AND AMNIONICITY IN THE FIRST TRIMESTER

In spite of the fact that transabdominal sonography (TAS) has been and continues to be an important aspect of obstetric sonography, the real value of ultrasound is provided by transvaginal sonography (TVS). TVS is superior in providing information at early gestational ages when TAS generates an image with lower resolution, which diagnostically is less explanatory than the comparable image provided by the vaginal ultrasound probe. This statement is based not only on our clinical experience but also on some early studies, which used technology that now must be considered outdated[1–4]. For example, Kurtz and colleagues[4] evaluated 9–12-week twin gestations and used the following ultrasound criteria: number of placental sites, membrane thickness and the 'lambda sign'. Of the 166 cases, only 105 provided enough information to ensure correct evaluation using the transabdominal probe. Ninety-two per cent were correctly diagnosed by detecting a thick membrane. Placental site alone yielded a correct diagnosis in only 26% of cases, and by using the lambda sign only 7% were correctly diagnosed. Finally, a thin membrane was only 88%

effective in diagnosing monochorionic (MC) twins. In their conclusion, the authors cogently suggested that TVS should be used to assess better the status of the membranes and placental sites, rather than TAS.

It is important to state that the detection of certain qualities of the intertwin membranes such as their thickness, origin and definitely their number is highly dependent upon the resolution of the machine and the transducer used. Top-of-the-line equipment, with transducer frequencies of 5–8 MHz, should be able to provide excellent resolution. Some less expensive machines with high-frequency probes should be able to provide at least a diagnostic-quality image of the membrane take-off and its thickness.

First-trimester multifetal pregnancy can best be evaluated as a function of its gestational age. Assessments should be based upon counting the chorionic sacs, counting the embryos or fetuses and the number of beating hearts, and finally assessing the nature of the amniotic and chorionic sacs.

## Determination of chorionicity

The chorionic sacs are implanted and detectable by sonography on one side of the central cavity line (created by the arising endometrial linings of the anterior and the posterior wall) within the appropriately thick decidua. The sacs appear as round sonolucent structures which are flanked by a bright echogenic ring representing the chorion (Figure 39.1). Their sizes range between 2 and 5 mm in diameter, and they can be detected as early as 4–5 postmenstrual weeks, depending upon the resolution of the transvaginal probe[5–8]. By simply counting the number of chorionic sacs, one can determine whether the pregnancy is dichorionic (DC; Figure 39.1a), trichorionic (Figure 39.1b) or multichorionic. Therefore, it is possible to determine precisely the chorionicity of a multifetal pregnancy by the fifth postmenstrual week. In spite of our experience of a reliable count of the sacs, Doubilet and Benson[9] reported that TVS undercounted multiple gestations at the gestational age of 5–6 postmenstrual weeks. It appears that the scans were (at least partly) performed by TAS, which accounts for these results.

As far as the terminology of the 'sac' is concerned, 'chorionic sac' is the correct term based upon nomenclature commonly used in embryology texts. On the other hand, 'gestational sac' is a term used in ultrasound, and it does not correctly indicate the histologic nature of the 'sac'.

## Determination of the number of embryos

At around 5 weeks or shortly thereafter, using TVS (definitely by the sixth well-dated postmenstrual week), chorionic sacs are sufficiently large that within them the yolk sacs and embryos can be imaged. However, to use the number of chorionic sacs and the number of yolk sacs alone to determine the number of embryos can be misleading. Therefore, it is wise to wait until the embryonic heartbeats are visible. This generally occurs at or shortly after six postmenstrual weeks. At this age, the yolk sacs are located in the extraembryonic space and the fetal pole becomes evident very close by (almost attached) (Figure 39.2). Whereas the embryonic heart begins to beat on day 21 after conception, this does not become sonographically evident until the end of the fifth or the early sixth postmenstrual week (35–42 postmenstrual days). Initially the frequency of the heartbeats is about 80–90/min. As the pregnancy

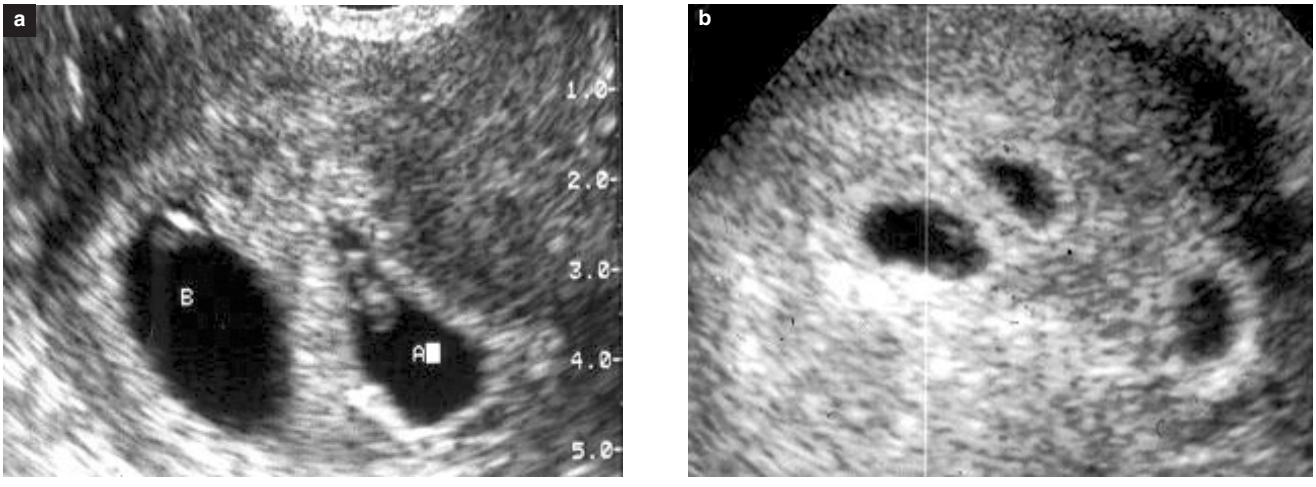



**Figure 39.1** Determination of the number of chorionic sacs. (a) At 5 postmenstrual weeks the number of chorions in this twin pregnancy is clear. Note the hyperechoic chorionic rings. (b) The same can be said about this trichorionic triplet pregnancy at the same age

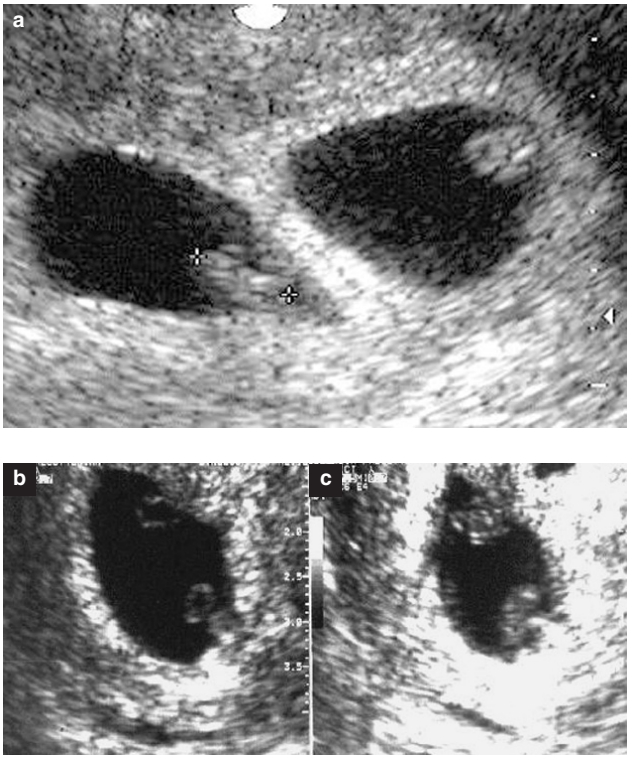



**Figure 39.2** Determining the number of fetuses in a multifetal pregnancy. (a) Two embryos and two heartbeats are seen at 6 postmenstrual weeks and 2 days. (b) Two yolk sacs are seen within one chorionic sac. (c) In the same pregnancy two embryos are seen. Note that the amnions are not yet seen, as at this time they are snugly surrounding the embryos

progresses, around the ninth postmenstrual week, the heart rate reaches around 150–160 beats/min.

In the final analysis, determining the number of embryos present in a multifetal pregnancy should rely on detection of the number of beating hearts. Since the final determination must wait until at least the sixth postmenstrual week, this time frame becomes ideal for correctly judging the number of embryos in a particular pregnancy. One should always be aware that natural cessation of embryonic heartbeats can occur, and this probability should be taken into consideration when the follow-up scan is scheduled at around week 8–9 to determine amnionicity. The issue of the vanishing twin (or triplet, etc.) is not discussed in this chapter (see Chapter 17).

As in our observations, Bromley and Benacerraf[10] used the number of yolk sacs as a criterion to determine amnionicity in early first-trimester MC twins. Twenty MC–diamniotic (DA) pregnancies and two MC–monoamniotic (MA) pregnancies were reviewed at ages less than 8 weeks' gestation. Two yolk sacs were identified in all but one case. Therefore, these authors concluded that sonographic identification of the number of yolk sacs in MC twins enables the diagnosis of DA twins early in the first trimester. Similar observations have been published by others[11]. We believe that with use of a high-frequency transvaginal probe, the number of embryos and yolk sacs can reliably be detected earlier, at 6–7 weeks' gestation.

### Determination of amnionicity

At around 6.5–7 postmenstrual weeks the amnion starts to distance itself from the surrounding embryo, and this process can be visualized. This is probably the first time, using a high-resolution vaginal probe, that the tiny amniotic cavity and amniotic membrane can be imaged sonographically. However, only at around 7 or 7.5 weeks can this process be reliably detected with most transvaginal probes (Figure 39.3a). To determine reliably the number of amnions in a MC pregnancy, in which two embryos are seen within the chorionic sac, it is wise to wait until at least the eighth postmenstrual week (Figure 39.3b). By this time the amnion and amniotic cavity have become totally detached from the embryonic body and are sonographically visible. The yolk sacs are seen in the extraembryonic space, which becomes progressively restricted, 'pushing' the yolk sac towards the chorion. This process is the result of the increasing amount of amniotic fluid[5–7]. Three-dimensional ultrasound is an additional and useful tool to assign amnionicity correctly in a multifetal pregnancy at such early ages (Figure 39.3c). An early scan also correctly assigns the amnionicity in the case of a MC–MA gestation (Figure 39.3d).

## THE MEMBRANES AS MARKERS OF CHORIONICITY AND AMNIONICITY

Chorionicity can be quickly determined up to about nine postmenstrual weeks, just by looking at the ultrasound image of a multifetal pregnancy. Beyond this gestational age, however, a closer look at the image is required, and, in some situations, it is necessary to search for indirect clues of chorionicity. Of these clues, the first two are well known and clearly described in the literature.

First, in a *DC–DA* twin pregnancy one can see a single fetus in each sac. The adjacent chorions create an easily recognized wedge-shaped structure that has been referred to in the literature for more than 20 years variably as the 'delta sign', 'lambda sign' or 'twin peak sign'[12,13]. Regardless of the number of chorions in a given multifetal pregnancy, this wedge-shaped 'twin peak sign' will always be seen between two adjacent chorionic sacs if examination is not delayed into the second trimester or beyond. In the

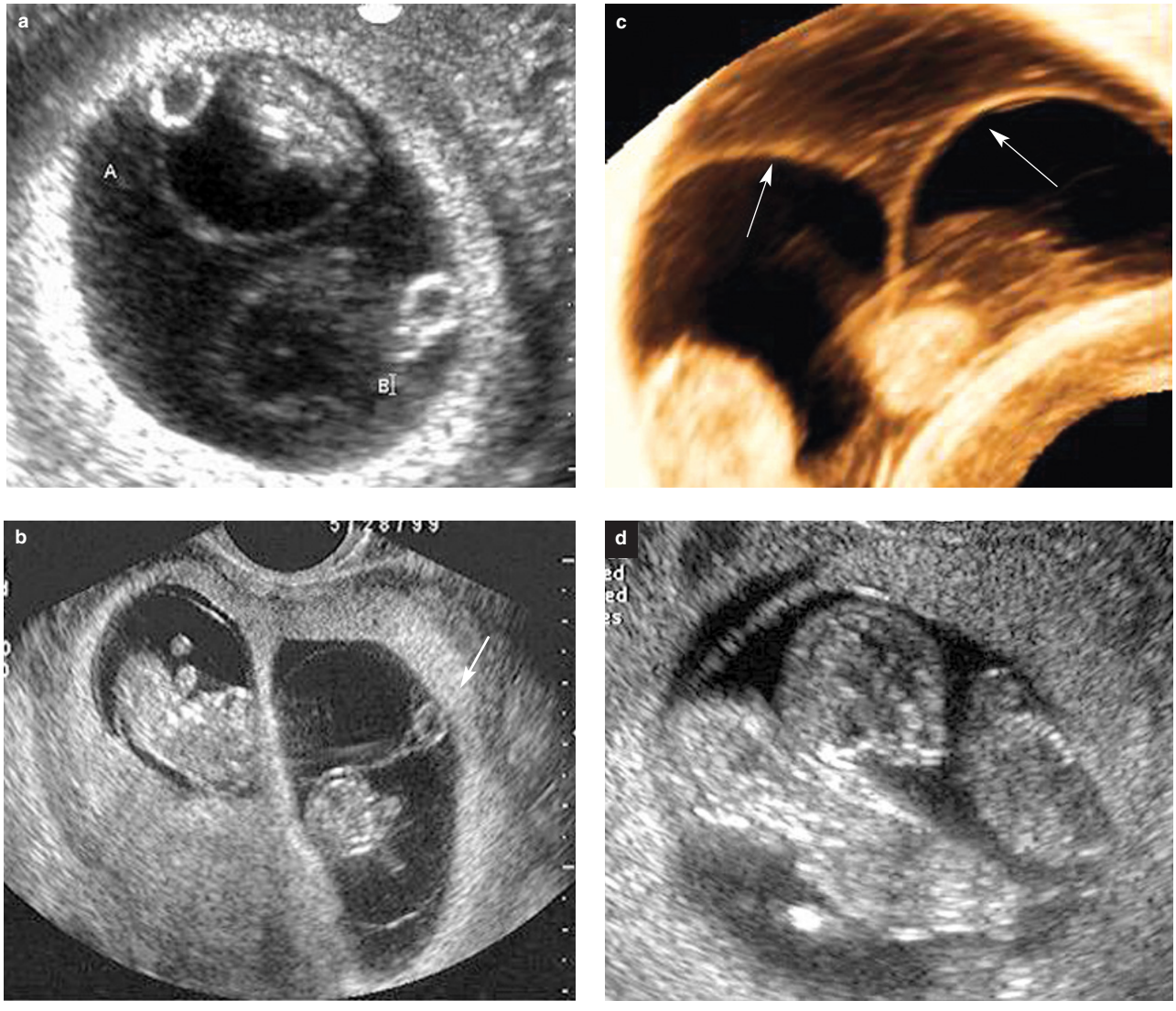



**Figure 39.3** Determining the amnionicity. (a) At 7–7.5 postmenstrual weeks the amnions distance themselves from the embryonic body in this monochorionic–diamniotic twin gestation. The arrows point to the two distinctly seen amnions. (b) Shortly after the eighth postmenstrual week the amnions 'move' towards the shared chorion, 'pushing' the yolk sac/s (arrow) aside within the progressively narrowing extraembryonic celom. (c) Three-dimensional rendering of the amniotic membranes (arrows) in a monochorionic–diamniotic twin gestation. In this case, due to the early pregnancy (9 postmenstrual weeks), the membrane did not yet assume the typical T-shaped 'take-off'. (d) In the case of a monochorionic–monoamniotic gestation, at 9 postmenstrual weeks no membrane can be seen between the fetuses

case of a DC twin pregnancy, two such wedge-shaped structures are seen (Figure 39.3b). However, in the case of a pregnancy with more than two chorionic sacs, one should be able to count more wedge-shaped structures than chorionic sacs (Figure 39.4a–c). Accordingly, the number of 'twin peak signs' is no indication of how many chorionic sacs exist within a given pregnancy.

The situation is entirely different for the *MC–DA* twin pregnancy. In these instances, the two adjacent amniotic sacs obliterate the extraembryonic space so that the amnions touch each other and form a relatively thin intertwin membrane. The junction of the two sacs with respect to the uterine wall at an approximately 90° angle creates a typical T-shaped junction or T-shaped 'take-off' (see 'The interfetal membranes', below). Figure 39.5 shows an unusual MC–triamniotic gestation.

Last, we mention the rare occurrence of *MC–MA* multifetal pregnancies. If the separation of a zygote occurs on day 8–10 after its fertilization, MC–MA twins result. Such pregnancies present substantial medical problems.

Fortunately, determination that a twin pregnancy is indeed MA is relatively easy, even in the very early stages of gestation. At eight postmenstrual weeks it is clear that no amniotic membranes are present between the embryos and only one yolk sac

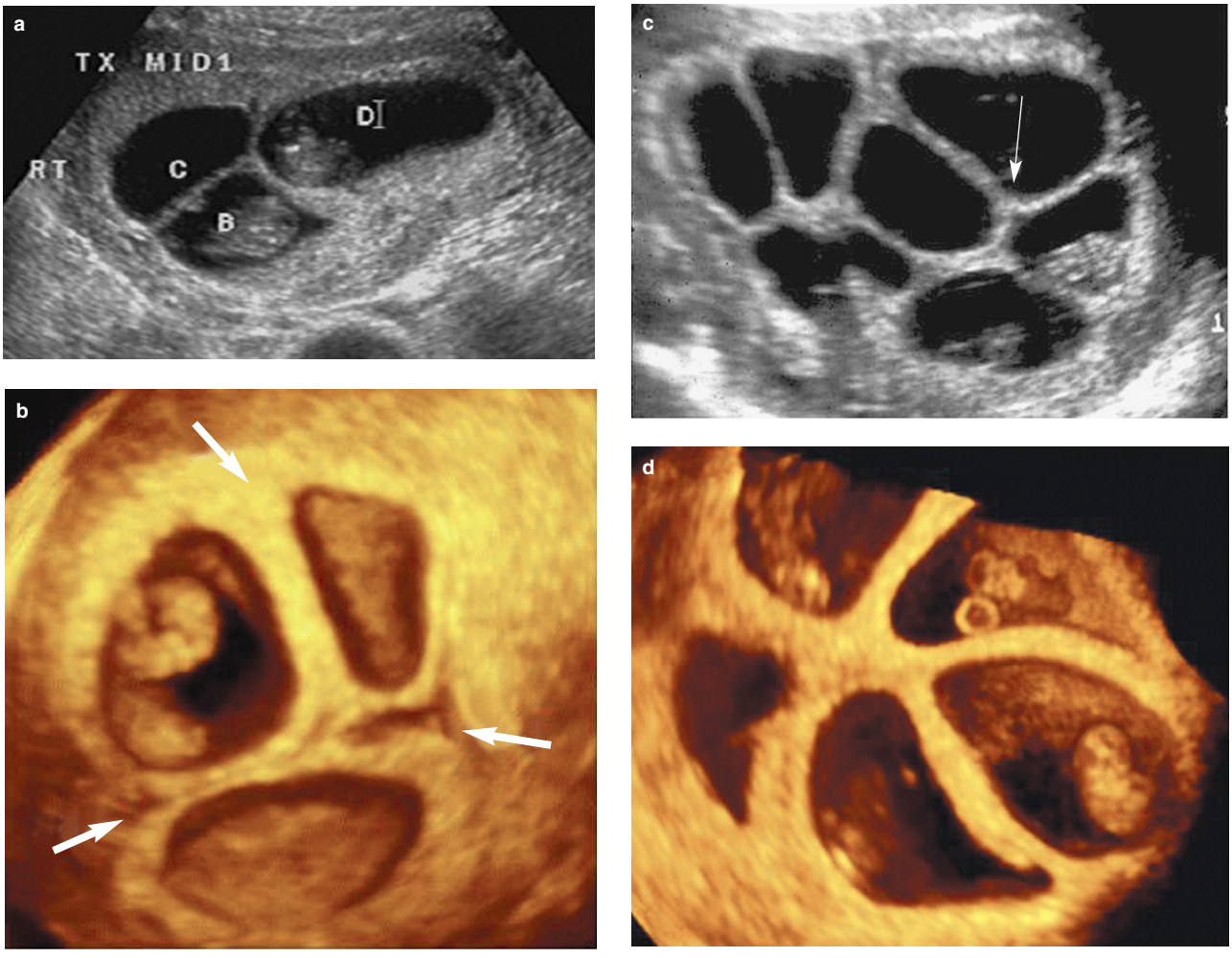



**Figure 39.4** Determining chorionicity. (a) A trichorionic gestation at 8 postmenstrual weeks. Note the 'Y' sign at the meeting point of the three chorionic sacs (long arrow) and the delta ('twin peak') signs (short arrows) between two adjacent chorionic sacs. (b) A three-dimensional ultrasound rendering of an 8.5-week trichorionic–triamniotic triplet pregnancy. The arrows point to the triangular 'delta' or 'twin peak' signs. In one of the sacs the amnion is visible (small arrow). (c) This is a multichorionic and multiamniotic multifetal pregnancy. Each of the 12 live fetuses had its own chorion, amnion and tiny placenta. On the plane of this image, however, only eight could be included. The arrow points to one of the many 'Y' shared junctions created by three adjacent chorions. (d) A three-dimensional rendering of a quintuplet pregnancy with five chorions and five amnions (7 postmenstrual weeks)

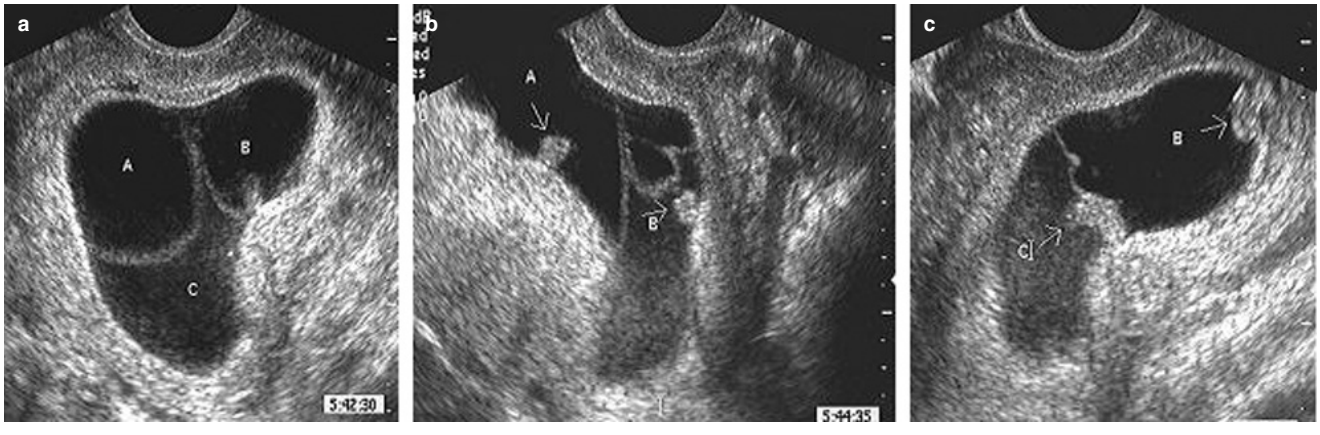



**Figure 39.5** Unusual monochorionic–triamniotic gestation with three dead embryos. (a) The three amniotic sacs. (b) Embryos A and B. (c) Embryos C and B

is visualized (Figure 39.6a). Later, at or shortly after nine postmenstrual weeks, this diagnosis is even easier to establish, although it is important to rule out the possibility of conjoined twins. When two embryos or fetuses assume a parallel, head-by-head position (Figure 39.6b), one must determine whether they move away from each other and/or slide alongside each other. Such changes in position relative to each other ensures that indeed they are not conjoined.

From the very outset, it is of paramount importance to look for cord entanglement between the fetuses in a MA situation, as this phenomenon has been visualized as early as 12 weeks. Moreover, cord entanglement may lead to the demise of one or both members of the pregnancy. To detect cord entanglement so early in pregnancy, one has to place the sample-volume feature of the color Doppler mode on the presumed bunch of cords seen between the two fetuses and try to detect consistently different pulse rates belonging to the two fetuses[14] (Figure 39.6c).

At times, a special and very rare form of a MC pair of embryos/fetuses is seen in a rather bizarre circumstance: that is, together with one additional fetus in a DC–DA triplet pregnancy (Figure 39.6d). Sometimes the MC pair may have concordant anomalies[15] or even be conjoined (Figure 39.6e and f).

Our own work using a high-frequency transvaginal probe in the early and simple assessment of chorionicity and amnionicity in the first 14 weeks of multifetal pregnancy was reported in the early 1990s[8]. We included 212 pregnancies in which we detected 64 sets of twins, 87 triplets, 41 quadruplets, 18 quintuplets, one set of sextuplets and one of septuplets. Nine of the twin pregnancies were MC, two of the triplet sets were DC–triamniotic and four of the quadruplets were trichorionic–quadramniotic. In all 15 'MC' pregnancies, the number of yolk sacs matched the number of fetuses. No MC–MA pregnancies were encountered in this study. Pathology was available for 43 of the 54 patients delivered at our institution. In all cases, TVS correctly predicted the pathologic chorionic and amniotic findings. Our conclusion was that in the first and early second trimester, TVS allows for quick and accurate determination of the chorionicity and amnionicity. Of equal importance, the time required to assess the pregnancy in trained hands was usually within 1–2 min[6].

At about the same time, Bromley and Benacerraf[10] identified 22 MC twins which had been scanned between 6 and 9.5 weeks of gestation. Their results showed that in the 20 MC–DA pairs, ultrasound performed before 8 weeks identified the yolk sacs in all cases, whereas the amniotic sac was not detected in any. In all but one case of MC–DA pregnancy, two yolk sacs were identified at 6 weeks. At 8 weeks, in only half of the MC–DA twin pregnancies was the amniotic membrane identified. In the two MC–MA twin sets, the single yolk sac and amniotic cavity were seen at 9 weeks. These authors concluded that the number of yolk sacs imaged correlated with the number of amnions, and that the number of yolk sacs could be identified at least 2 weeks before the number of amnions. These observations corroborate the findings in singleton pregnancies described by other authors[11].

In another study, Copperman and colleagues[16] attempted to determine whether chorionicity could be accurately predicted using first-trimester TVS. Forty-seven twins conceived by *in vitro* fertilization and embryo transfer were studied by TVS at 41 days after embryo transfer. Sonographic findings were compared with placental pathology. Forty-four DC–DA and three MC–DA twins diagnosed by sonography were confirmed. The authors concluded that their 100% accuracy was because the scans were performed at an early gestational age by TVS. This last study clearly reinforces our opinions that an early, first-trimester scan is essential and accurate, in addition to being a quick method of reliably accessing chorionicity and amnionicity in multifetal pregnancies. [Editors' Comment: Moreover, it supports the contention of many practitioners worldwide that all patients who present for prenatal care should be offered ultrasound early in pregnancy.]

In summary, when scanning a twin pregnancy in the first trimester:

(1) Chorionicity can be assessed by the fifth postmenstrual week;

(2) A number of embryos can be ascertained by the sixth postmenstrual week at the onset of cardiac activity;

(3) Amnionicity can be reliably assessed by the eighth postmenstrual week. If each chorionic sac contains a single yolk sac and one embryo with cardiac activity then the amnionicity equals the chorionicity (DC–DA, trichorionic–triamniotic, etc.). If a chorionic sac contains two yolk sacs and two embryos with cardiac activity, then either the number of amnions may be greater than the number of chorions (MC–DA), or the number of amnions and chorions may be equal (MC–MA). In this latter case, one must wait until at least the eighth postmenstrual week when the amnions are clearly visible. If a chorionic sac contains one yolk sac and two fetuses with cardiac activity, then the amnionicity and chorionicity are equal (MC–MA).

Table 39.1 can be used to assess the appearance of amniotic structures in twin pregnancies. This table

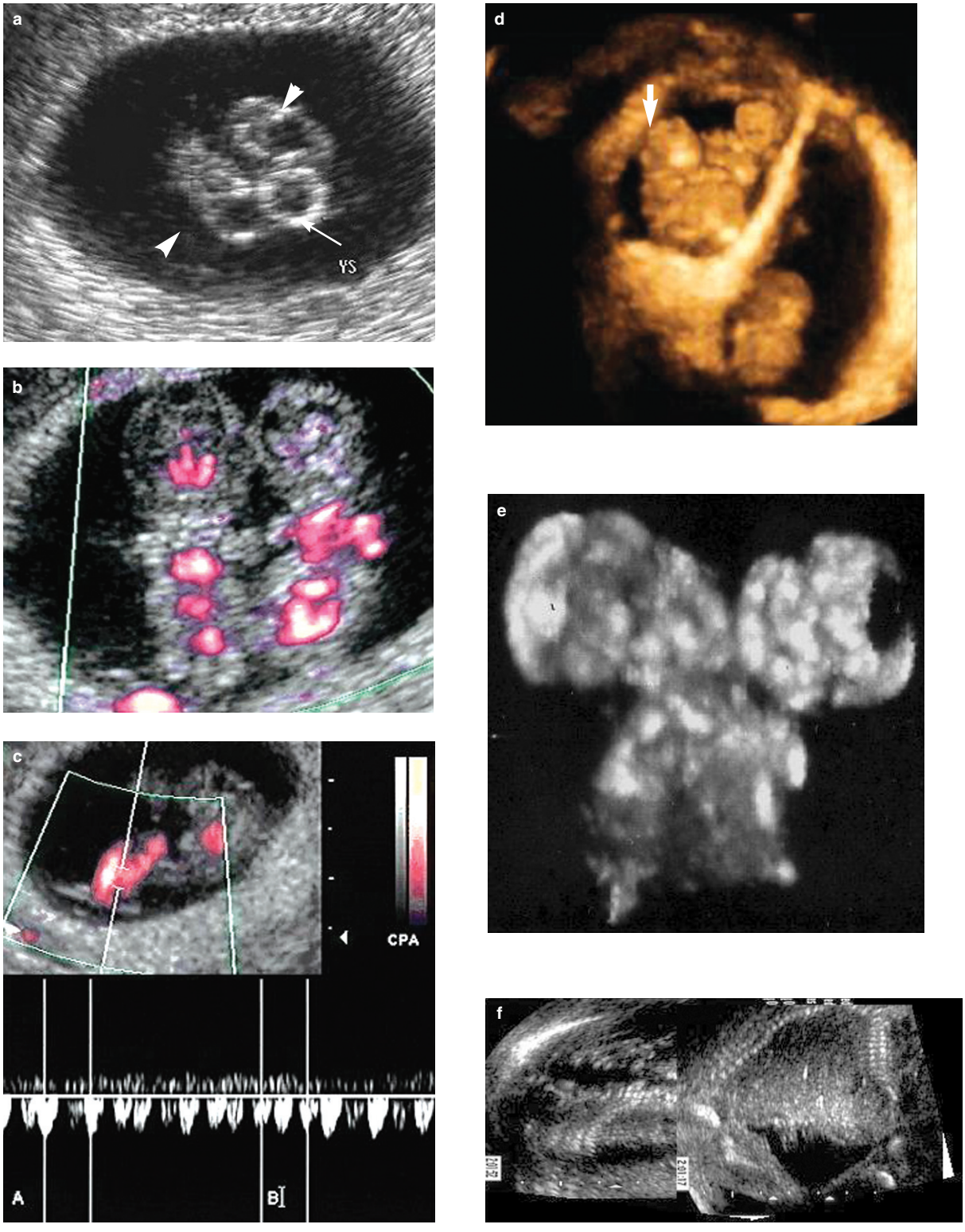



**Figure 39.6** Monoamniotic pregnancies. (a) At 8 postmenstrual weeks the rhombencephalon (arrowheads) of the embryos is imaged together with the single yolk sac (YS, arrow). (b) At 9 postmenstrual weeks the fetuses are seen side by side. No membrane is seen between them and they were observed moving away from each other, ruling out conjoined organs. (c) The cords in these monoamniotic twins were consistently seen entangled. The sample-volume 'window' was placed on this area of cord between the fetuses. Different heart rates were elicited, proving the entangled nature of the cords. (d) Three-dimensional rendering of a dichorionic–diamniotic triplet pregnancy with a monochorionic twin pair (arrow). (e) Conjoined twins. Three-dimensional rendering of an omphalopagus pair at 18 postmenstrual weeks. (f) Conjoined twins. Cephalothoraco-omphalopagus

**Table 39.1** Sequential, gestational age-dependent sonographic appearance of embryonic structures in twin pregnancies. From reference 17

| *Timing of transvaginal scan* (weeks) | *Number of gestational sacs* | *Number of yolk sacs* | *Number of fetuses* | *Number of amniotic sacs* | *Chorionicity and amnionicity* |
|---|---|---|---|---|---|
| 4–5 | two | | | | dichorionic |
| | one | | | | monochorionic |
| 5–6 | two | two | | | dichorionic |
| | one | two/one* | | | monochorionic |
| 6–7 | two | two | two | | dichorionic |
| | one | two/one* | two/one† | | monochorionic |
| 7–8 | two | two | two | two | dichorionic–diamniotic |
| | one | two/one* | two | two | monochorionic–dichorionic |
| | one | two/one* | two/one† | one | monochorionic–monoamniotic |

*A single, double or partially divided yolk sac may be seen; †conjoined twins may be seen at this time

can also be applied to multiples of higher orders, replacing the pertinent variables with the numbers of chorionic sacs, yolk sacs, fetuses and amniotic sacs seen.

### Multifetal pregnancies of higher order

The higher is the number of chorions and embryos/fetuses present in a multifetal pregnancy, the harder it is sonographically to assess their number and chorionicity as well as their amnionicity. Patience, time and experience are required to evaluate the above, even at early gestational ages.

It is axiomatic that a large number of combinations of chorionicity and amnionicity occur in multifetal pregnancies of higher order. The importance of this fact lies not only in the appropriate clinical management of these pregnancies presenting exceptionally high risk to mothers as well as their fetuses, but also in considering the possibility of multifetal pregnancy reduction. Although multifetal pregnancy reduction is discussed elsewhere in this book (see Chapters 63 and 64), it is important to point out that the approach to multifetal pregnancy reduction is based largely upon a very early scan, preferably between weeks 9 and 13, in order to determine the correct management plan.

Furthermore, regardless of the approach used to consider or discard the notion of multifetal pregnancy reduction, an additional aspect has also to be taken into account. This is the issue of prenatal genetic diagnosis in cases of multifetal pregnancy or those of higher order. In these cases, correct determination of chorionicity as well as amnionicity is crucial to avoid significant errors in management (see Chapters 45 and 48).

## THE SECOND AND THIRD TRIMESTERS

Unfortunately, the importance of ultrasound in managing twins is not appreciated by all practitioners in obstetrics and gynecology. Not all are aware that the most important and consequential ultrasound examination of multifetal pregnancy takes place before the end of the first trimester. We have stressed, and continue to stress, that adequate first-trimester evaluation of a multifetal pregnancy makes the subsequent second- and third-trimester ultrasound examinations much more meaningful, as well as simpler and shorter, frequently illustrating this point with the following example. A quadruplet pregnancy was scanned by us at 17 postmenstrual weeks. After quite prolonged scanning using transabdominal and transvaginal ultrasound, the four fetuses were determined to be in the same chorion but within separate amnions. This particular scan required 90 min. Only at the end of a 90-min examination could we conclude appropriately that this was a MC–quadramniotic quadruplet pregnancy. If, on the other hand, we had scanned this patient earlier, between 9 and 12 postmenstrual weeks, not more than 5–10 min would have been required[18].

Assessing amnionicity and chorionicity during the second and third trimesters may present serious challenges, even to the most expert practitioners of ultrasonography. The three basic determinants of chorionicity and amnionicity in the second and third trimesters are fetal gender, placental location and interfetal membranes.

### Determination of fetal gender

Most early studies of sonographic sex determination (sometimes called fetal 'sexing') used transabdominal

**Table 39.2** Accuracy of ultrasound for gender determination (sexing). From reference 17

| Reference | Scanning route | n | Gestational age (weeks) | Success rate (%) | | | Error (%) |
|---|---|---|---|---|---|---|---|
| | | | | Males | Combined | Females | |
| Stocker and Evens (1977)[19] | TAS | 366 singletons; 352 twins | > 30 | 99.5 | — | 91.5 | 4.4 |
| Shalev *et al*. (1981)[20] | TAS | 12 pairs | 20–40 | 100 | 98.6 | 97 | 1.4 |
| | | | 20–40 | 100 | 100 | 100 | 0 |
| de Crespigny and Robinson (1981)[21] | TAS | 137 | 24 | NA | 66 | NA | 2 |
| Weldner (1981)[22] | TAS | 101 | 32 | 75 | — | 73 | 3 |
| Lavery *et al*. (1983)[23] | TAS | 545 | 15–24 | — | 36 | — | 0 |
| | | | 25–40 | — | 50 | — | 0 |
| Bronshtein *et al*. (1990)[25] | TVS | 171* | 13–14 | 91.7 | 76 | 93.3 | NA |
| | | 235** | 13–14 | — | 80 | — | NA |
| | | 139* | 15–16 | — | 88 | — | NA |
| | | 546** | 15–16 | 99.7 | 96.7 | 100 | NA |
| Scardo *et al*. (1996)[24] | TAS | twins, 50 pairs | > 28 | — | 94 | — | 0 |

*First 2 years of experience; **second 2 years of experience; TAS, transabdominal sonography; TVS, transvaginal sonography; NA, not available

ultrasound. Table 39.2 is a summary of some, but clearly not all, of the existing articles on ultrasonographic fetal sex determination. Most articles report using TAS to determine fetal sex between 10 weeks and term[19–24]. With the introduction of TVS, and after understanding that early determination of chorionicity and amnionicity is best accomplished in the first trimester, emphasis was placed on using TVS for sex determination[8,25]. This latter approach relies on high-resolution, high-frequency probes; however, owing to their relatively shallow depth of penetration, they are difficult to use after 16–17 weeks, even though the fetus can sometimes conveniently move into the desired position. If, on the other hand, the fetus is in a breech presentation, transvaginal ultrasound can be used even later in pregnancy. The overall accuracy of sexing in various published articles is around 90% in males and about 97–98% in females. It is important to mention that, in a multifetal pregnancy of higher order, visualizing the external genitalia in all fetuses presents a much greater degree of difficulty.

Twins which have different genders are always DZ and, hence, always DC. If, however, in a set of twins the fetal sex is correctly determined by ultrasound in the second and third trimesters and these are found to be discordant, the pregnancy has to be considered DC (Figure 39.7a).

In the second and third trimesters, the best imaging planes for the external genitalia are the following: a median section showing the scrotum and the phallus pointing cephalad (Figure 39.7b) and on the axial plane, parallel to and below the flexed thighs (Figure 39.7c) and, for the female fetus: coronal planes through the labia (Figure 39.7d), on a median section through the downward pointing clitoris (Figure 39.7e). Lately, three-dimensional rendering of the genitalia has become available. If the technical parameters permit, clear pictures of the male and female genitalia are possible in the second and third trimesters (Figure 39.7f and g). As noted previously, most articles dealing with sex determination were written after examining singletons. In determining fetal sex in multifetal pregnancies, we hope that the results of these articles are successfully duplicated in twins, triplets, quadruplets, etc.

More accurate determinations of fetal gender began with the introduction of TVS. Two articles mentioned the accuracy of sex determination of twin pregnancies. One is relatively old and used TAS[20]; in spite of this, the authors correctly determined the gender in all 24 fetuses of 12 twin pregnancies. The other is more recent[24]. In this case, 100 twins at a gestational age of almost 30 weeks were examined to determine chorionicity, amnionicity and zygosity based upon sonographic variables. Fetal sex was determined for both twins in 94% of the fetuses. All fetal genders were correctly assessed. These authors confirmed that, in multifetal pregnancies, it becomes increasingly difficult to determine fetal sex with

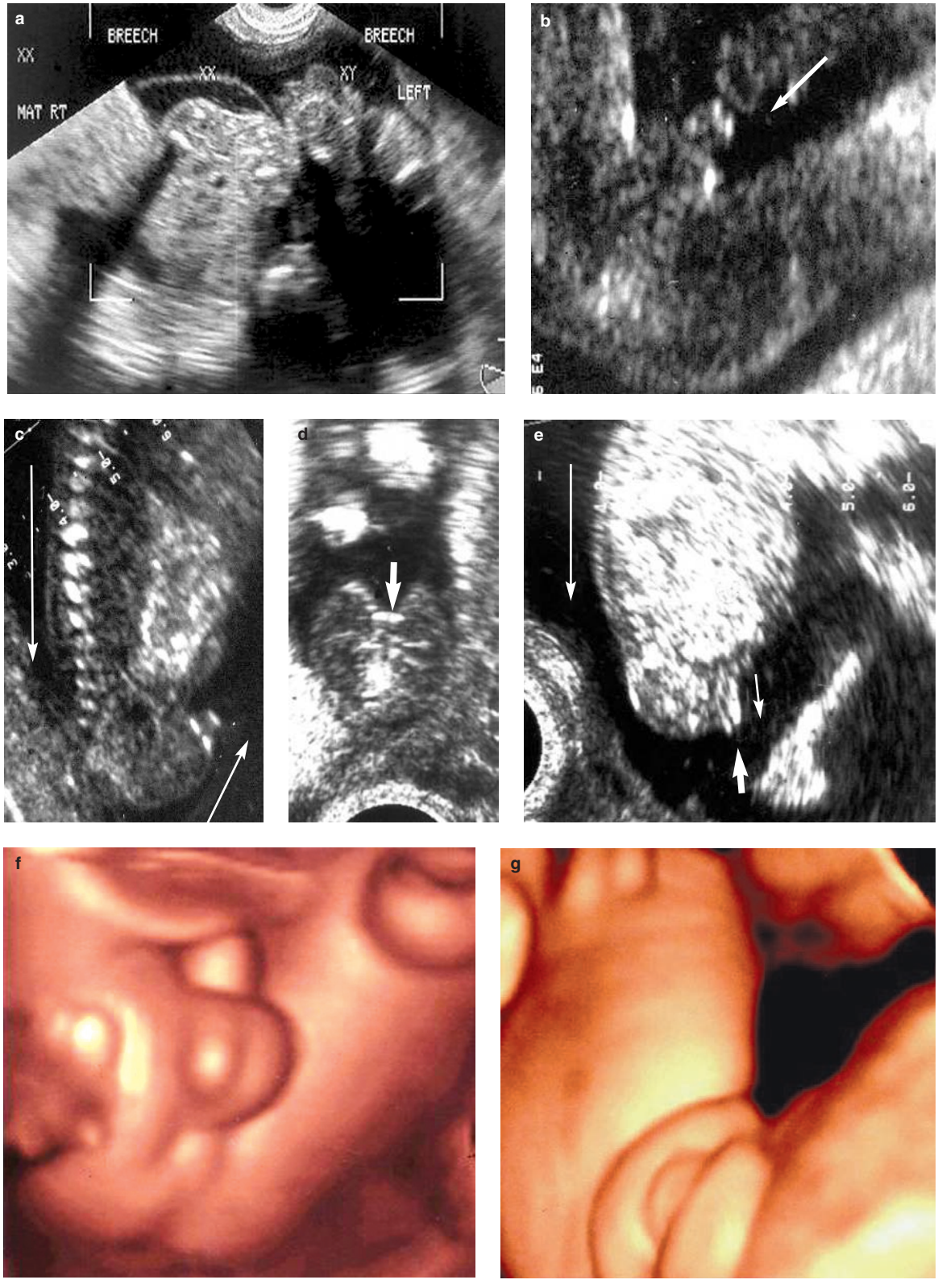



**Figure 39.7** Evaluation of fetal gender. (a) Both fetuses are in breech presentation. The transvaginal scan revealed a female (XX) and a male (XY) fetus. A thick intertwin membrane is also seen. This is therefore a dichorionic–diamniotic twin pregnancy (reproduced with permission from reference 26). (b) At 16 postmenstrual weeks the male genitalia are clearly seen (arrow). (c) The phallus points cranially (upward arrow) in the opposite direction from that of the feet (downward arrow). (d) At the same age, the female genitalia are shown (arrow). (e) The clitoris points caudally (downward arrow) in the same direction as the feet (downward long arrow). (f) Three-dimensional ultrasound at times is able to show clearly the male genitalia. (g) Three-dimensional ultrasound image of the female genitalia

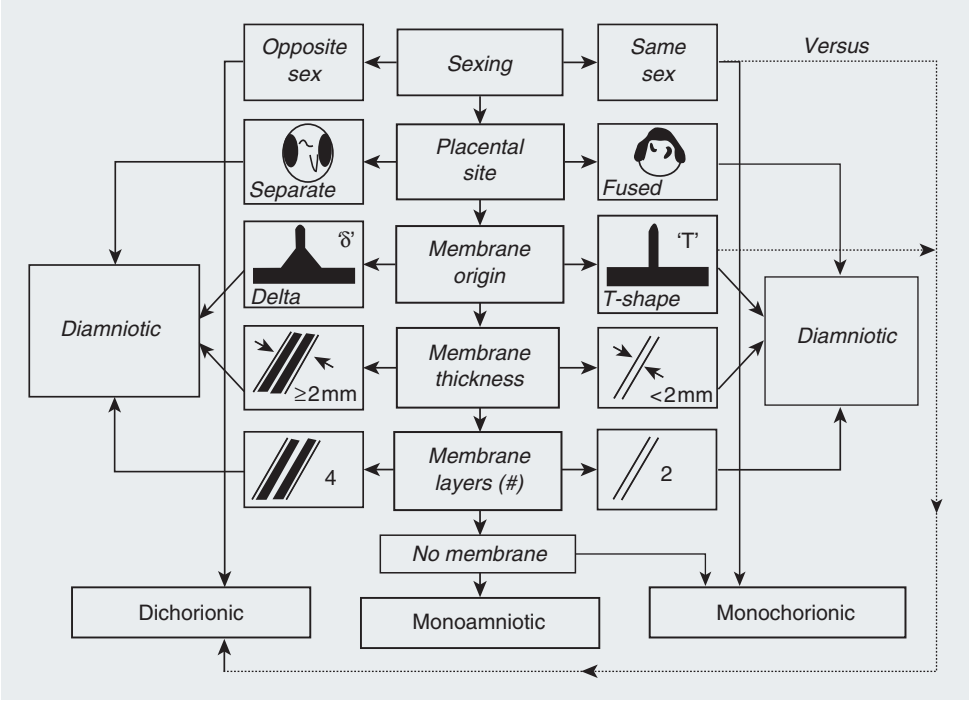



**Figure 39.8** Several sonographic markers are available for assessment of chorionicity and amnionicity in the second and third trimesters. This algorithm can be used to make such an assessment

increasing gestational age. Additional articles[26,27] claim that chorionicity can be correctly assessed based on fetal sex in about 35% of cases discordant for sex. In an article by Scardo and co-workers[24] it is clear that in 100 twin pregnancies the correct sex was determined sonographically in 94% of cases at a gestational age of close to 29 weeks. These authors also report the observation that if the genitalia were seen, fetal sex was never incorrectly assigned. In this study, the finding of opposite sex in predicting dichorionicity had a sensitivity of 51.3% with a specificity of 100% and a positive predictive value of 100%. The negative predictive value, however, was only 39.3%. The same sex as a predictor of monochorionicity carried a sensitivity of 100% and a positive predictive value of 39.3%; however, the negative predictive value was 100%.

In 2000 we developed a simple algorithm to determine chorionicity and amnionicity in second- and third-trimester ultrasound[26]. We used the following parameters to construct the algorithm: sexing of the fetuses, placental location, membrane thickness and the number of layers in the membranes. Obviously, if male and female fetuses are seen in a twin pregnancy this must be DC–DA. However, like-sex twins are present in approximately 50% of DC–DA pregnancies. When like-sex twins are seen, the placenta or placentas must be evaluated in order to make the diagnosis of chorionicity (Figure 39.8).

## Placental location

Assessing and determining the site as well as the number of placentas in a multifetal pregnancy is clearly indicative of chorionicity and amnionicity, but does not yield an overly high sensitivity in the detection of dichorionicity or high specificity in determining monochorionicity. Simply stated, it is very difficult to distinguish a single from a fused placenta in twins (Figure 39.9a and b). This is true for all ages of the multifetal pregnancy. However, if the two placentas in the case of twins are detected on opposite sides of the uterine wall, and the placental cord insertions can be followed to those placentas which are situated at diagonally opposing uterine locations, this supports the diagnosis of two separate placentas, and hence dichorionicity (Figure 39.10a and b). This circumstance occurs in about one-third of twin gestations. Mahoney and colleagues[28] found a sensitivity of 32% when assessing two placental sites, and their predictive value was 100%. In spite of this, when only one placenta was detected the accuracy of prediction for MC pregnancy was only 49%. Scardo and co-workers[24] studied the sonographic determination of one placenta to predict monochorionicity. Sensitivity was 95.8%, specificity 57.9%, positive predictive value 51.8% and negative predictive value 97.7%. If the authors had not mistakenly labeled one DC placenta by ultrasound, which was their only false detection in

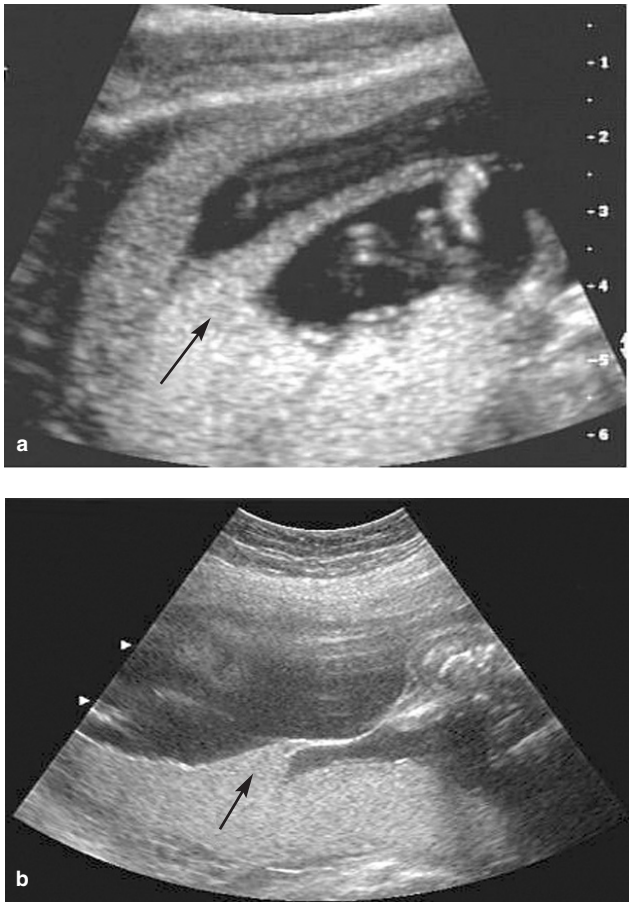



**Figure 39.9** The 'lambda' ('delta', 'twin peak') sign in first-trimester dichorionic or multichorionic pregnancies. (a) The 'take-off' of the membrane (arrow) in the early first trimester is obvious. (b) The triangular 'take-off' of the intertwin membrane in the late first trimester (arrow)

an extremely obese patient, their negative predictive value would have been 100%[24].

A very effective way to determine placental location is to follow and trace the cord insertion[29,30]. This was done successfully in singleton pregnancies using color Doppler ultrasound by Pretorious and colleagues[30]. In twins the same method was used by Westover and associates[29] in 80 cases. These latter authors evaluated pregnancies at less than 24 weeks, 24–30 weeks and more than 30 weeks. Their successful visualization of both cords before 24 weeks was 100%, between 24 and 30 weeks six of eight cords were detected and after 30 weeks only two of nine cords were successfully imaged. However, the correct prediction of insertion type, if the insertion was indeed seen, was 100% before 24 weeks, 11 of 13 (85%) between 24 and 30 weeks and 90% past 30 weeks.

Our ability to detect two placental cord insertions in twin pregnancies dropped significantly as the gestational age advanced (personal observation). If the cord insertions were seen sonographically, we also demonstrated a high predictive value for insertion type, regardless of gestational age.

## The interfetal membranes

The presence of an interfetal or intertwin membrane needs to be determined, because the presence or absence of this structure can change the clinical management of a twin pregnancy. If no intertwin membrane is seen, a MC–MA twin pregnancy must be suspected. Classically, this type of twinning is associated with high perinatal mortality for both

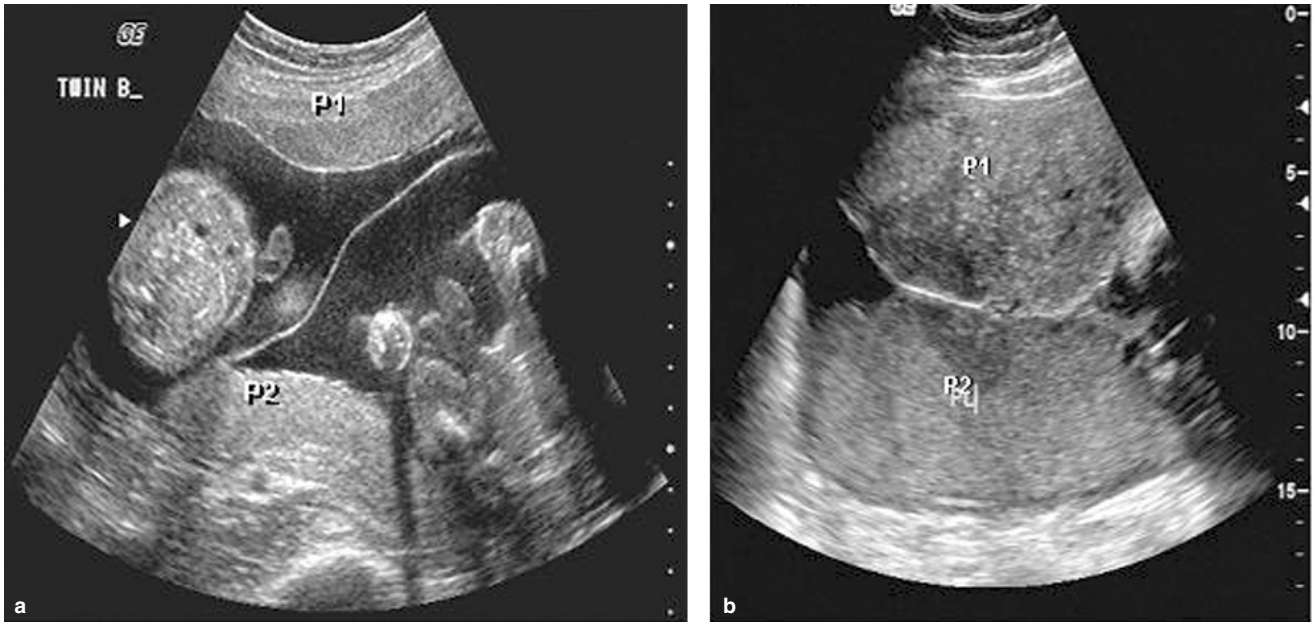



**Figure 39.10** Detection of the placental sites. (a and b) The two placentas (P1 and P2) are on opposite sides of the uterus. These are clearly dichorionic twin gestations

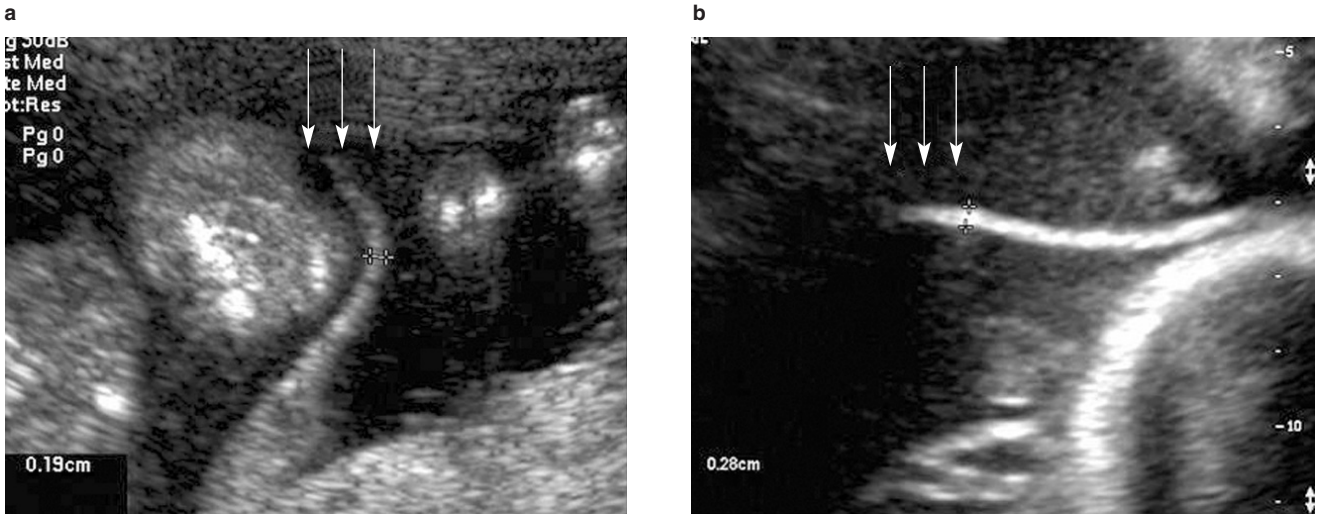



**Figure 39.11** Technical aspects of intertwin membrane assessment. (a) If the membranes are parallel with the direction of the sound waves, measurement of the thickness yields a false value. The membrane measures 1.9 mm. (b) For better imaging of membrane thickness as well as detecting the layers, the membranes should be positioned at a 90° angle to the incandescent sound waves (arrows). The actual membrane thickness is 2.8 mm

twins. However, improved outcomes are seen with close antenatal monitoring. Tessen and Zlatnik[31] reported an overall survival rate for MC–MA twins of 70% and a survival rate for both twins of 65%. Other, similar reports also concur.

If two separate placental sites are identified, as described above, it is less important to scrutinize the membranes further. However, in cases in which a single placental site is identified, the following method can aid in classifying the pregnancy as DC or MC. Three important clues help to assess chorionicity and amnionicity:

(1) The origin of the membrane;

(2) The thickness of the intertwin membrane;

(3) The number of layers present in the intertwin membrane.

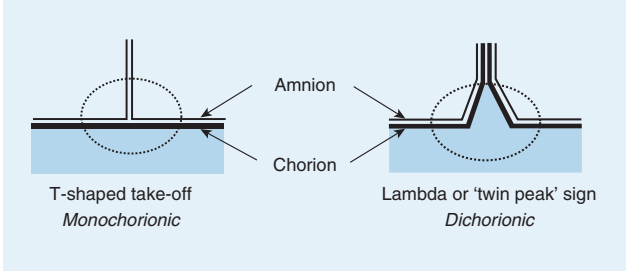



**Figure 39.12** This line drawing depicts two kinds of intertwin membrane origins or 'take-offs'. At the left a T-shaped take-off represents a monochorionic placenta with two emerging amnions. There is only one chorion. On the right a dichorionic, fused placenta with wedge-shaped 'take-off' is seen creating the 'lambda' ('delta', 'twin peak') sign. The circles highlight the important feature of the two kinds of membrane origin

### *Identifying the origin of the membrane*

Determining membrane thickness and counting the layers of the interfetal membrane with sonography is dependent upon ultrasound frequency, orientation of the membrane to the ultrasound transducer and experience of the sonographer or sonologist. The higher is the frequency of the ultrasound probe, the better is the resolution of the image. Having said this, penetration of the sound waves is limited, and, therefore, in very advanced gestations a lower-frequency transducer may have to be used, potentially jeopardizing the actual imaging of these layers.

Membrane orientation in relation to the transducer probe is a key factor in trying to image the layers of the interfetal membranes (Figure 39.11). The membrane to be studied needs to be oriented at a right angle to the direction of the incoming sound waves to take advantage of the axial resolution of the machine, which is always superior to the lateral resolution of ultrasound equipment. A membrane placed parallel with the incoming sound waves will be poorly seen, and will appear thinner than it actually is owing to the less sharp lateral resolution of the equipment.

When two DC placentas are fused, the area of fusion of the placentas creates a wedge- shaped structure (Figure 39.12, right) variously termed the 'lambda' (when imaged in the first trimester) 'delta'

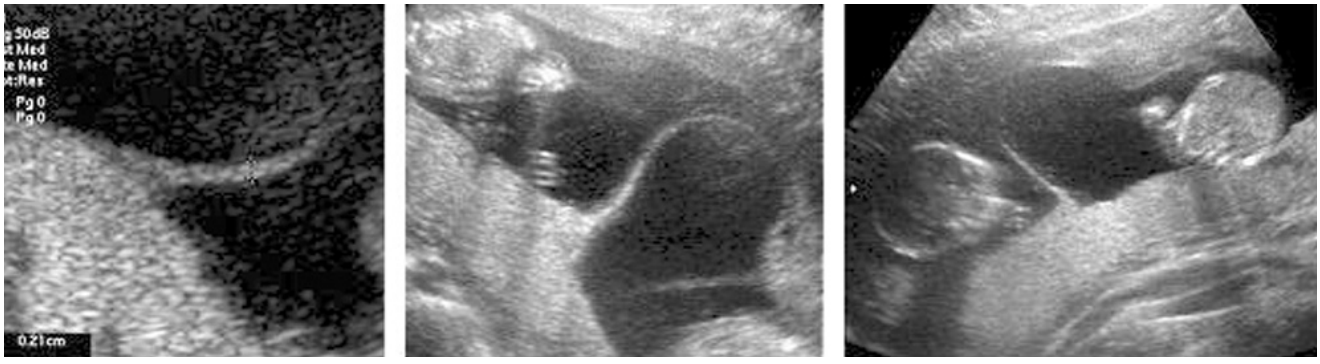


**Figure 39.13** The 'lambda' ('delta', 'twin peak') sign in the second and third trimesters. The three images represent slight variations of the membrane 'take-off' in dichorionic gestations

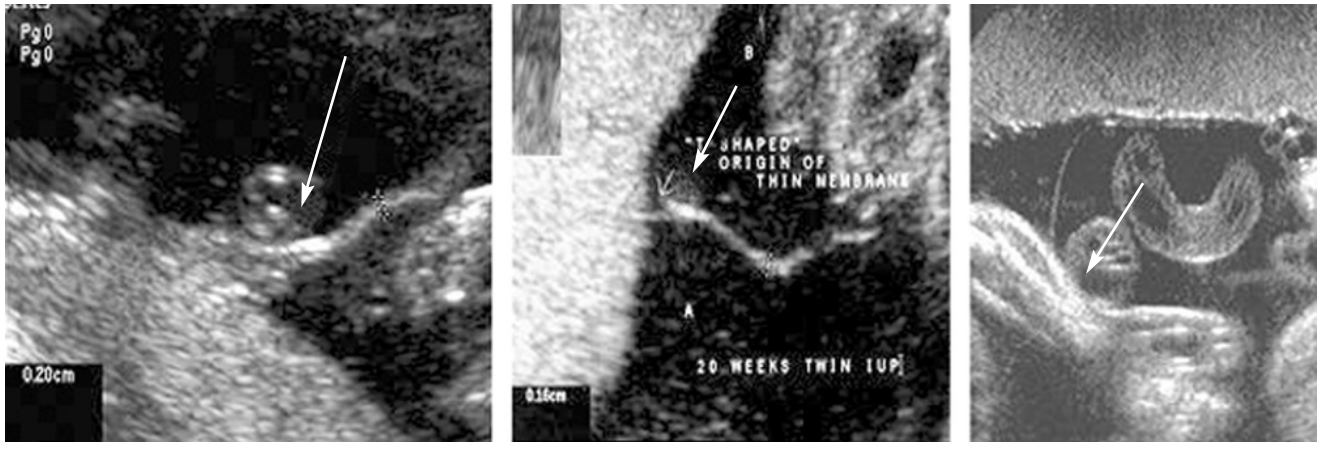



**Figure 39.14** The T-shaped 'talk-off' of intertwin membranes in monochorionic pregnancies (arrows) is easily detected in the first and second trimesters

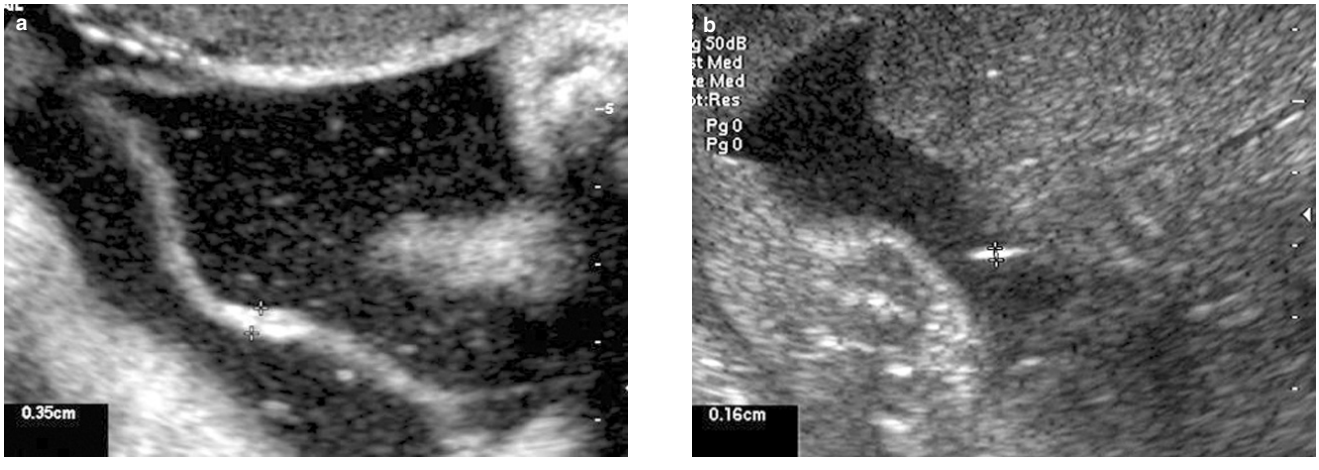



**Figure 39.15** Assessing membrane thickness. (a) The correct position (at right angles to the sound waves) of the intertwin membrane in this dichorionic gestation measures 3.5 mm. (b) The intertwin membrane is thin (1.6 mm) in this monochorionic–diamniotic twin pregnancy

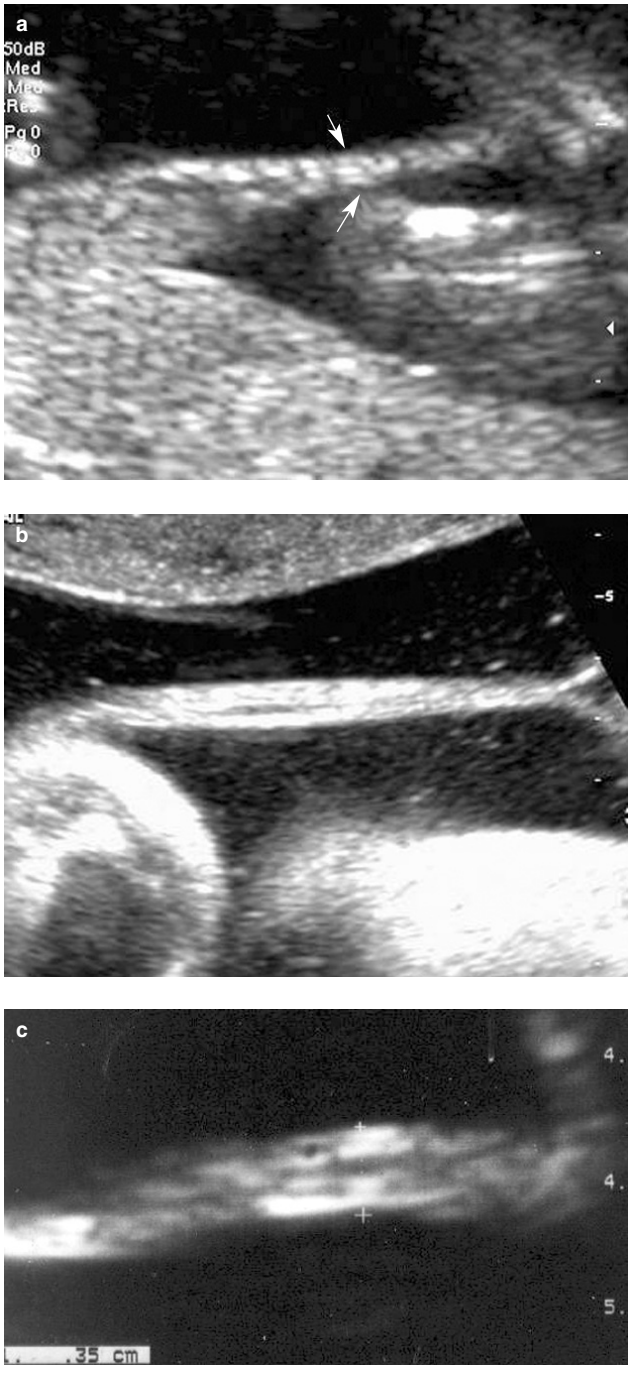



**Figure 39.16** Assessing the layers in the membranes of dichorionic–diamniotic gestations. (a) In an early pregnancy the wedge-shaped 'take-off' and more than two membrane layers are seen. (b and c) Correctly positioned membranes examined with high-resolution transducers show clearly that there are four layers

or 'twin peak'[4,12,13]. When seen, both the lambda and the twin peak signs are reliable markers of di- or multichorionicity (Figure 39.13). Using the 'lambda sign', Bessis and Papiernik[12] were able to predict correctly 20 of 24 DC pregnancies. Kurtz and colleagues[4] found the 'lambda sign' to be present in only six of 85 DC–DA twin pregnancies. Finberg[13] made a similar observation and referred to this structure as the 'twin peak sign'. Using this sign, he was able to predict multichorionicity in 15 twin and five triplet pregnancies scanned between 14 and 35 weeks' gestation. Finberg concluded that the presence of the 'lambda' or 'twin peak sign' is a reliable indicator that the pregnancy is DC, but their absence does not rule out the presence of dichorionicity[13].

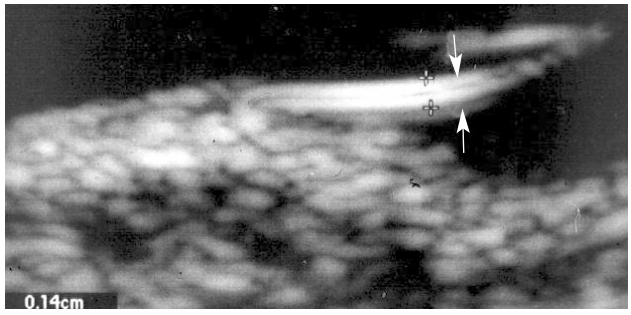



**Figure 39.17** Assessing the layers in the membrane of a monochorionic–diamniotic gestation. Two layers are seen. Their combined thickness is 1.4 mm

In the MC–DA twin pregnancy, the amniotic sacs grow within the single chorionic sac as pregnancy progresses, and subsequently the extraembryonic space is obliterated. The amniotic sacs continue to grow until they come together forming a relatively thin intertwin membrane. The relationship of these two sacs to the uterine wall is at a 90° angle, similar to the letter 'T'. This 'T-shaped' take-off of the membrane (Figure 39.12, left) is a reliable sign of monochorionicity (Figure 39.14).

### *Determining membrane thickness*

In dizygotic twins, the opposing membranes are always thick because each membrane is composed of four layers. These thick membranes are formed by each twin's chorion in addition to its amnion. Thick membranes measuring 2 mm or more (Figure 39.15a) have a predictive value between 89 and 95% for dichorionicity[2,32]. On the other hand, a thin membrane measuring less than 2 mm (Figure 39.15b) may have a predictive value of up to 82% for monochorionicity[31]. In addition, this thin membrane may be difficult to measure, and may be described as 'hairlike' or 'too thin to measure'[1,2,16].

Most authors agree that the assessment of membrane thickness is easiest in the first trimester, as progressive thinning of the membranes occurs as pregnancy progresses. Increasing fetal size, crowding and decreasing amount of amniotic fluid are variables that make ultrasound difficult to use in

assessing the membrane thickness, as well as counting membrane layers more difficult with advancing gestational age.

### *Counting the layers of the intertwin membrane*

The membranes of a DC–DA placenta, when seen through a microscope, have four layers (from one surface to the other: amnion–chorion–chorion–amnion), and those of an MC–DA placenta have two layers (amnion–amnion). The four layers of a DC–DA intertwin membrane (Figure 39.16) and the two layers of an MC–DA intertwin membrane (Figure 39.17) can be visualized by sonography, using a high-frequency transducer and obtaining a right-angled orientation of the probe in relation to the interfetal membrane (see above). The interfetal membranes of a DC–DA twin pregnancy appear relatively thick. When such a thick membrane is identified, a DC pregnancy can be diagnosed in 89–90% of cases[1,2,24]. In contrast, if the membrane has a thin 'hairlike' appearance, it is more likely that only two opposing amnions are present. This circumstance is a reasonably good marker of monochorionicity[32]. It is important to note that sometimes the interfetal membranes of an MC–DA twin pregnancy can appear relatively thick. Therefore, to confirm the initial impression, interfetal membranes should be further scrutinized by 'zooming in' in an attempt to count the layers.

## SUMMARY

With the increasing frequency and success rates of ovulation induction and assisted reproductive technologies, multifetal pregnancies have become a common occurrence. Early diagnosis and determination of chorion and amnion type plays an important role when multifetal pregnancy reduction or when antenatal testing (chorionic villus sampling or amniocentesis) is contemplated. A scan during the first or early second trimester can provide accurate diagnosis of the twin gestation, i.e. identification of the number of gestational sacs, chorionicity and amnionicity. Early diagnosis additionally allows closer monitoring and more precise counseling regarding the course and eventual outcome of the pregnancy. If monochorionic twinning is diagnosed, the patient can be counseled regarding the potential perinatal complications that may be encountered during the course of pregnancy.

To reiterate, first-trimester scanning allows counting of the number of chorionic sacs, starting at 5 weeks' gestation. However, the final number of embryos can be determined only beyond six menstrual weeks with the appearance of cardiac activity. If only one live fetus is found in each chorionic sac, the number of amniotic and chorionic sacs will be equal. By 9–10 weeks, the amniotic sacs of an MC–DA twin pair will have become contiguous and create a thin intertwin membrane separating the DA twins. In an MA twin pair, a single amnion will surround both fetuses. By using TVS, accurate visual determination of the chorionic and amniotic type can be made, ideally between 9 and 10 weeks. Without doubt, the earlier is the sonographic determination of chorionicity and amnionicity, the better are the chances of a good management plan for the multifetal gestation.

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**ADDITIONAL COMMENT**

# Determining zygosity in early pregnancy by ultrasound

*S. Tong*

Currently, ultrasound can determine monochorionicity with near 100% certainty, but can predict zygosity in only 55–65% of twin pregnancies by correlating chorion type with the sex of twins[1] (see Chapter 39). This is because same-sexed dichorionic twin gestations can be either monozygotic (MZ) or dizygotic (DZ).

A novel method has recently been proposed to determine zygosity in almost all cases of spontaneous twinning. The method makes note of the number of corpora lutea (CLs)[2], the ovarian structure which reflects ovulation. In the presence of a dichorionic (DC) twin pregnancy, the identification of one CL (Figure 1) would suggest that twins are MZ, whereas two CLs (Figure 2) would imply DZ twins. If need be, this construct could be further correlated with chorionicity where, by example, two CLs (presumed DZ) and monochorionicity (MC, certain MZ twins) would suggest that the predicted zygosity is incorrect.

In a small series of 33 twin gestations, it was shown that chorionicity was compatible with zygosity in all cases by using this method[2]. Further use of this methodology clearly requires verification with a prospective study comparing ultrasound prediction of zygosity with DNA fingerprinting of twins after delivery. In addition, the gestations in which this technique can be used also requires further evaluation. Whereas ultrasound is able accurately

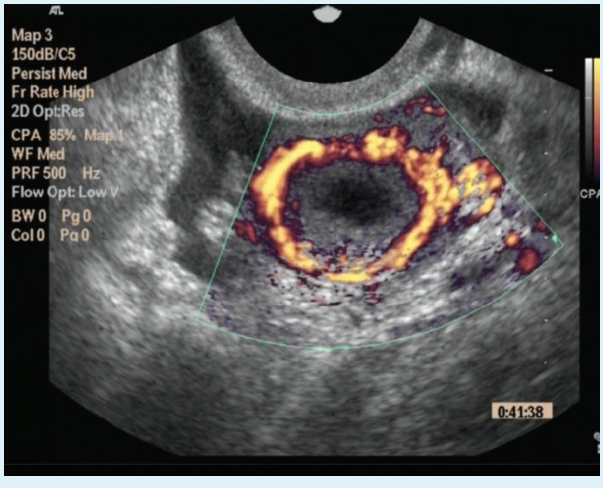


**Figure 1** Doppler image of ovary with a single corpus luteum. Image courtesy of Simon Meagher, Monash Ultrasound for Women, Melbourne, Victoria, Australia

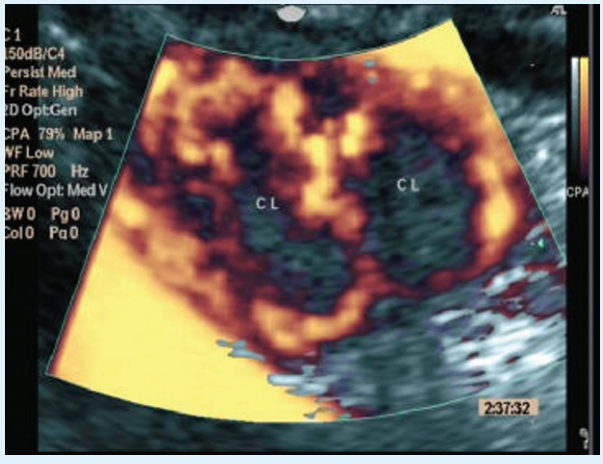


**Figure 2** Doppler image of ovary with two corpora lutea (CL). Image courtesy of Simon Meagher, Monash Ultrasound for Women, Melbourne, Victoria, Australia

to identify the CL in 95–98% of cases between 5 (+0 days) and 8 (+6 days) weeks of gestation[3,4], it is unknown whether this structure can be reliably characterized at later gestations. Also, it will not be useful in twins conceived using *in vitro* fertilization, since the number of CLs will not correlate with the zygosity of the twins.

The potential application of this method is zygosity determination without the need of costly postpartum tests. With increasing evidence suggesting that future twin studies should take placentation[5] into account as well as zygosity, this method may also be a useful research tool, assigning both chorionicity and zygosity at the same time.

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# Three-Dimensional Sonography

*A. Kurjak and N. Veček*

**40**



## INTRODUCTION

Three- and four-dimensional (3D and 4D) sonographic imaging is based on computer data processing of classic two-dimensional (2D) images. Numerous improvements in data processing capacity in the past two decades now enable the rapid synthesis of multiple adjacent sections and extraction of important data. The resultant images provided by this technology are so highly processed that a single 3D image, either surface-rendered or transparent, is as informative as several planar images obtained from different sections. Furthermore, multiplanar imaging overcomes previous limitations of unobtainable sections due to unfavorable fetal position. In other words, no fetal position makes it impossible to obtain a desired section. At present, the only limiting factor in modern sonography for visualization of a desired structure is the amount of adjacent amniotic fluid.

In the past few years, 3D sonographic visualization has progressed from a static to a near-real-time imaging modality. Acceleration in scanning and rendering capabilities of the last generation of 3D machines has provided 3D imaging in almost real-time. This latter imaging technique is now characterized as four-dimensional sonography (4D US). If one performs 4D US, obtaining the 3D image reconstruction is less time-consuming.

Despite great progress in imaging of 3D and 4D US, 2D sonography remains the primary modality in most areas of medical practice for diagnosing and evaluating multiple pregnancy. However, some limitations of 2D US can be overcome by the use of 3D and 4D US and additional information can sometimes be obtained.

This chapter systematically presents the advantages of 3D and 4D sonography in multiple pregnancy.

**Table 40.1** Advantages of multiplanar imaging in management of multiple pregnancy

| |
|---|
| *First trimester* |
| Elimination of undercounting phenomenon |
| Improved prediction of spontaneous abortion |
| Improved prenatal classification of uterine anomaly |
| *Second trimester* |
| Improved diagnosis of vanishing twin phenomenon |
| Early detection of fetal anomalies |
| Improved evaluation of fetal malformation |
| Improved determination of placentation |

## THREE-DIMENSIONAL MULTIPLANAR IMAGING

The major advantage of 3D US is the ideal visualization of a desired structure regardless of its anatomic limitations. This advantage can be used when the finding of 2D sonography is incomplete, in terms of either the number and quality of gestational sacs in the first trimester or fetal anatomy or placentation in the second trimester, due to poor or inconvenient anatomic relations (Table 40.1).

Pregnancy number before the 6th week is determined by counting the number of gestational sacs (Figure 40.1). However, if the initial scan is prior to 6 weeks, the examiner must be aware of what has been characterized as the late-appearing twin phenomenon – or 'undercounting'. The late appearance of twins is recognized on the basis of a discrepancy between two sonograms in which comparison of an initial sonogram, usually obtained at 5.0–5.9 weeks,

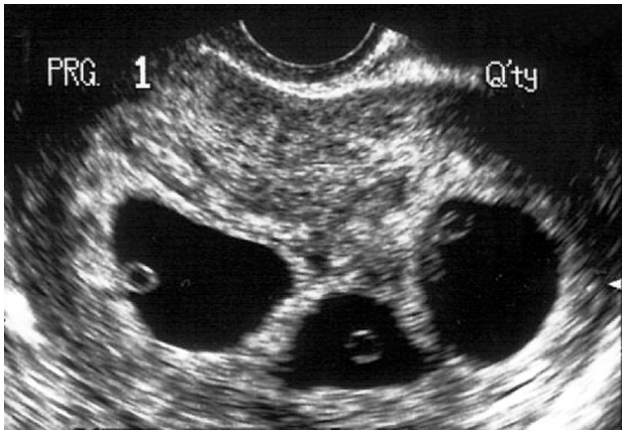


**Figure 40.1** Transvaginal ultrasound scan of triplets at 6 weeks of gestation. There is a high probability for triplets as each gestational sac contains a single yolk sac. However, quadruplets cannot be excluded from this static sonogram

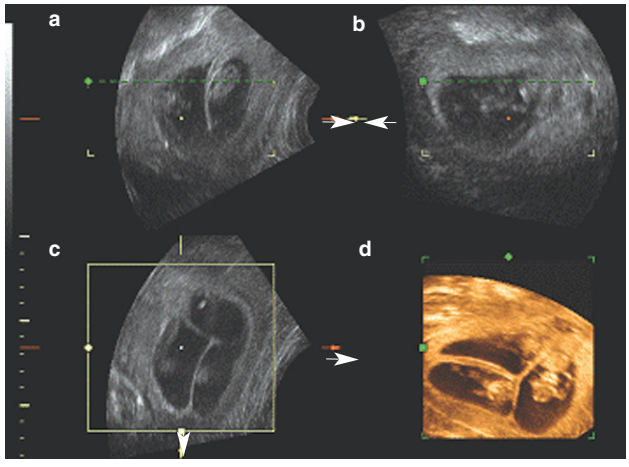


**Figure 40.2** 3D multiplanar view in determination of accurate number of gestational sacs. Transvaginal multiplanar view of a triplet pregnancy at 12 weeks. This example illustrates the possible pitfall regarding undercounting of gestational sacs. The advantages of the coronal section are presented (c). In the transverse section, only two gestational sacs are present (a), whereas on sagittal section (b) only a single gestational sac is seen. On the coronal section, three gestational sacs with the Y-sign are seen (c). The most informative mode of 3D sonography is its surface-rendering mode (d). Using this mode, in addition to the correct number of embryos, the separation phenomenon can be seen which was unobtainable with conventional sonography. Using conventional 2D sonography, sagittal (a) and transverse sections (b) of the uterus are seen. The first two images (a and b) represent the limits of 2D in which a twin pregnancy is diagnosed. However, on the third, coronal plane section (c) three gestational sacs are clearly seen. The diagnosis of triplets was finally confirmed by 3D reconstruction (d)

and a subsequent sonogram obtained at 6 or more weeks demonstrates more embryos or fetuses than the previously counted gestational sacs.

Three-dimensional volume acquisition provides the possibility of simultaneous depiction of three orthogonal planes of examination. Moreover, it is possible to perform systematic examinations of acquired volumes with three different directions of scanning. For example, use of the frontal (coronal) plane enables examination of the uterine cavity in sections which are unobtainable with conventional 2D sonography (Figure 40.2). Further, 3D sonography enables appropriate counting of gestational sacs without the risk of undercounting, even in the hands of less experienced ultrasonographers. Therefore, interobserver variability in detecting the number of gestational sacs is significantly lower. Even quadruplets and quintuplets are recognizable without great difficulty (Figure 40.3). This advantage strongly suggests that 3D US should become the new standard in the early management of high-order multiple pregnancies. Before the introduction of 3D ultrasound, 11% of dichorionic twins were initially undercounted as singletons, and 16% of higher-order multiple gestations were also undercounted in one study[1].

The quality of the gestational sac is an important parameter for the management of multiple gestations. Quality parameters include:

(1) Gestational sac diameter;

(2) Ratio of mean sac diameter to crown–rump length;

(3) Presence or absence of an embryo within the gestational sac.

First-trimester spontaneous abortion might be predicted from alterations in gestational sac size. For this purpose, nomograms relating the ratio of mean sac diameter to crown–rump length (S/CR) to gestational age (last menstrual period (LMP)) were constructed[2]. Using this method, a sensitivity of 78.3%, a specificity of 97.8% and a false-positive rate of 2.2% can be achieved. Under such circumstances, the S/CR measurement in early pregnancy is a simple and reliable method of predicting first-trimester abortion. The embryo is recognizable sonographically at 7 weeks of gestation (Figure 40.4). Therefore, reliable confirmation of the presence or absence of an embryo(s) within each gestational sac should then be performed. An empty gestational sac in a high-order pregnancy should be recognized as the 'vanishing twin' phenomenon (Figure 40.5) (see Chapter 17). The viability of each embryo can be

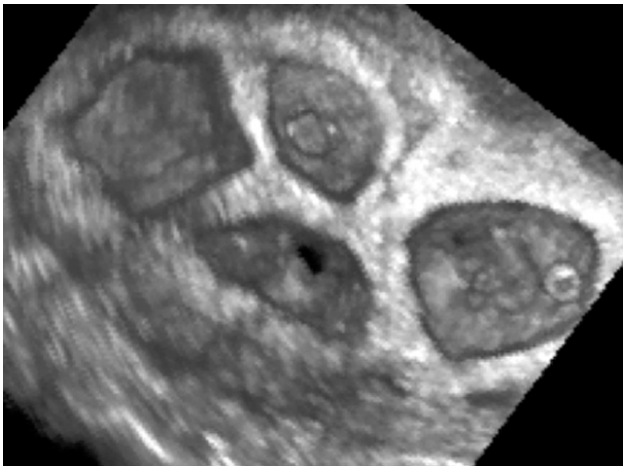

**Figure 40.3** 3D diagnosis of an accurate number of gestational sacs. In contrast to 2D manual slicing, an analysis of 3D volugrams with 3D surface-rendering mode reveals the accurate number of this quadruplet gestation

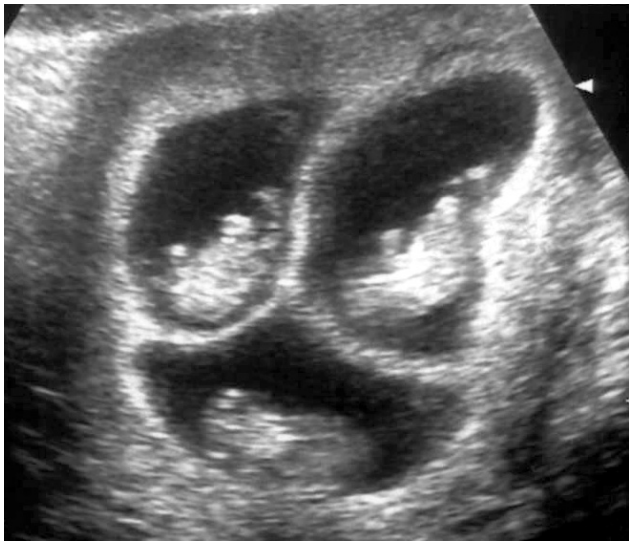

**Figure 40.4** Transvaginal ultrasound of triplets at 8 weeks' gestation: three embryos in three gestational sacs (trichorionic–triamniotic triplets)

confirmed using color Doppler imaging of embryonic circulation (Figure 40.6) (see Chapter 41).

A recent meta-analysis showed that more than 50% of pregnancies with three or more gestational sacs undergo spontaneous reduction before 12 weeks[3]. The surviving fetus(es) weigh less and are born earlier than unreduced pregnancies with the same initial number of fetuses. Whenever spontaneous reduction is suspected in high-order multiple pregnancy based on the results of conventional sonographic examinations, the additional use of the surface-rendering mode is recommended. If one uses

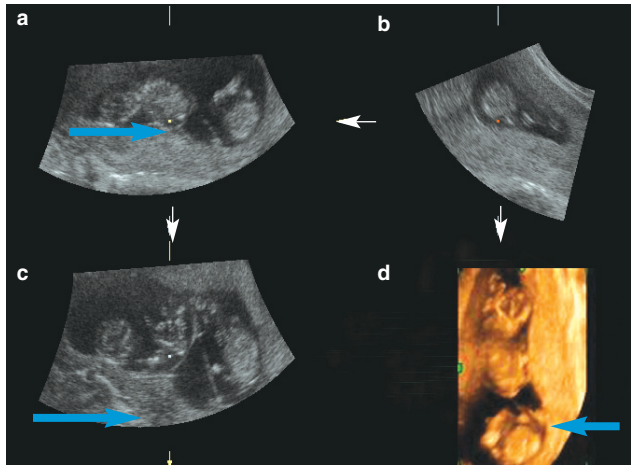


**Figure 40.5** Transvaginal multiplanar view of missed triplet pregnancy at 12 weeks' gestation. The superiority of the surface-rendering mode (d) over the multiplanar view is presented. In the transverse section, two fetuses within their gestational sacs are present, whereas the third gestational sac has a triangular shape and seems empty (a). On sagittal section only a single fetus within a gestational sac (b) is seen. On the coronal section, three gestational sacs with the Y-sign are seen (c). According to images in the transverse and coronal sections there is suspicion for a missed triplet. The surface-rendering mode confirmed definitively that the gestational sac was empty with the diagnosis of missed triplet (d)

the surface-rendering mode, distinguishing between spontaneous reduction and normal pregnancy in a high-order pregnancy is easily accomplished (Figure 40.5).

In 1988, the American Fertility Society (AFS), now known as the American Society for Reproductive Medicine (ASRM), formalized the system currently in use for the classification of uterine anomalies. In this system, Müllerian anomalies are divided into seven groups[4]. Classification of uterine malformations is important because successful pregnancy outcome of twin gestations was considered possible in the following groups: II (unicornuate uterus), III (didelphic uterus) and IV (bicornuate uterus)[5–7]. By way of reference, successful twin pregnancy required that each fetus occupy a separate horn of the didelphic uterus[5]. Despite this general proposition, Vecek and colleagues recently reported successful twin pregnancy with both fetuses occupying the same uterine horn[8].

Before the introduction of 3D sonography for the accurate classification of uterine malformations, direct examination of the uterine fundus was required, by way of laparotomy, laparoscopy or hysterosalpingography. Stated another way, accurate

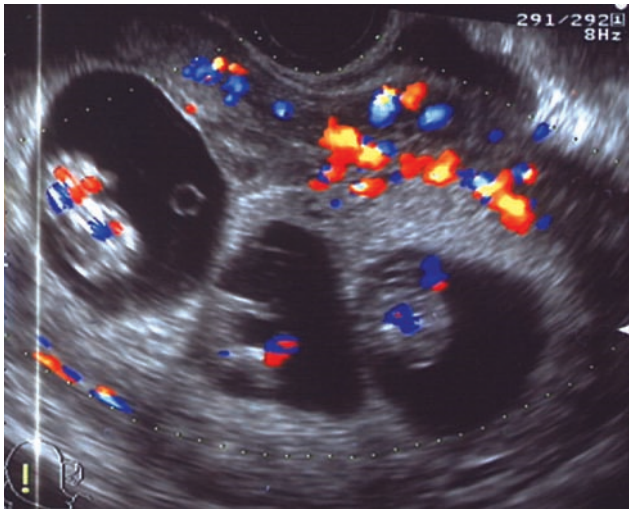


**Figure 40.6** Diagnosis of the viability of each triplet: color Doppler reveals three viable embryos

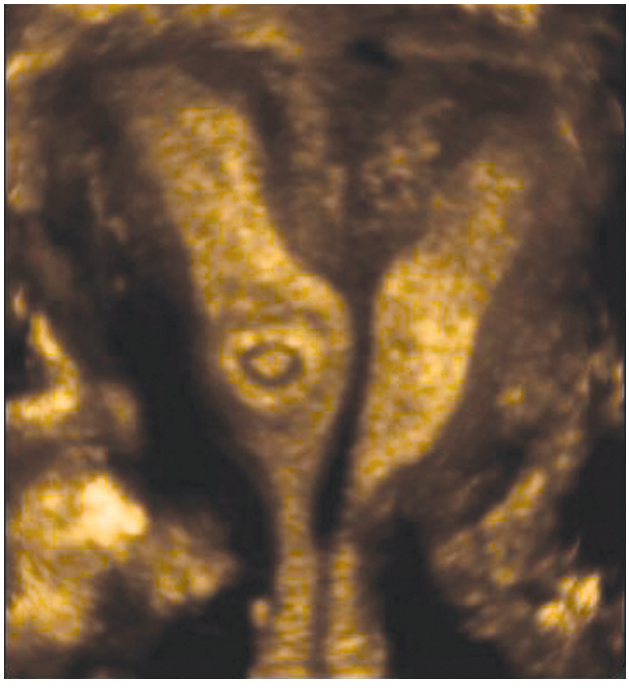

**Figure 40.7** A singleton pregnancy in a didelphic uterus. Three-dimensional sonographic examination of a malformed uterus provides the sonographer with an accurate classification of the uterine anomaly and pregnancy number. For this purpose a coronal section is important because it provides visualization of the fundal region and length of the septum

prenatal classification was unachievable without invasive procedures. If, on the other hand, one performs 3D sonography, on a multiplanar view analyzing the coronal section, pregnancy number and type of malformation can be concomitantly seen. Since the coronal section is unobtainable by transvaginal 2D sonography, whenever multiple pregnancy is recognized in a malformed uterus an additional 3D examination is recommended. A singleton pregnancy in a didelphic uterus is presented in Figure 40.7.

**Table 40.2** Malformations in multiple pregnancy

| |
|---|
| *Unique to twinning* |
| Twin-to-twin transfusion syndrome |
| Conjoined twins |
| Twin reversed arterial perfusion (acardia) |
| Fetus-*in-fetu* |
| *Not unique to twinning* |
| Neural tube defects |
| Hydrocephalus |
| Congenital heart disease |
| Esophageal atresia |
| Anorectal atresias |
| Intersex |
| Genitourinary anomalies |

In a singleton pregnancy, the empiric risk for major fetal malformations is approximately 3%. In trichorionic triplets, the empiric risk for major fetal malformations within each fetus is independent of the others, so the probability of having at least one malformed fetus is approximately 9%[9] (see Chapter 34). According to data from the Eurofetus Study, the sensitivity of routine 2D sonography for detecting a malformation is 61.4%[10], and the sensitivity is lower in a multiple pregnancy as a consequence of overcrowding. Because 3D ultrasound offers an ideal visualization rate of the desired structure, achieved by manipulation within the volugram data, it is reasonable to expect that the use of this technology will increase the sensitivity of detection of malformations in multifetal pregnancies. Furthermore, 3D sonography improves the diagnostic capability by offering more information in evaluating fetal malformations, particularly in terms of malformations of the cranium, face, spine and extremities and body surface[11].

## MALFORMATIONS IN MULTIFETAL PREGNANCIES

A wide variety of malformations may be present in a multifetal pregnancy (see Chapter 43). According to one classification, 'malformations unique for twins' is the term applied to malformations that occur exclusively in multiple pregnancies, whereas 'malformations not unique for twins' is the term applied to malformations that also occur in singletons but are more common in twins (Table 40.2). Knowledge of sonoembryology enables the diagnosis of fetal

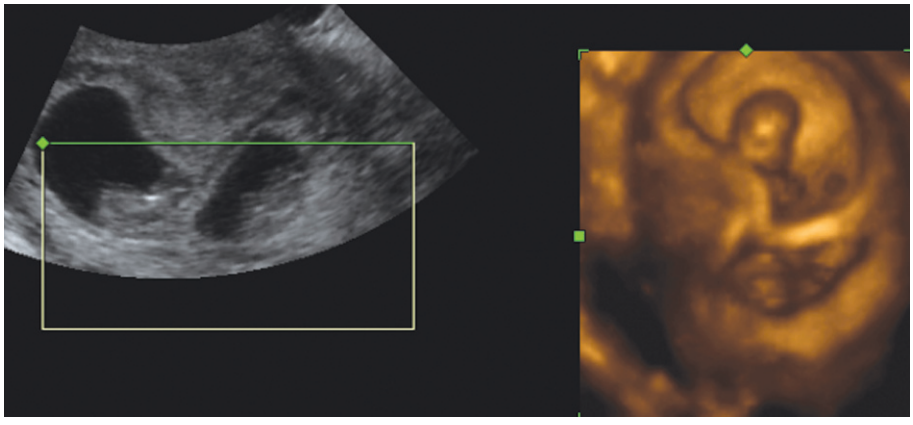

**Figure 40.8** Comparison between 2D and 3D sonoembryology. Both modalities provide the examiner with essential information concerning the management of twin pregnancy including number of fetuses and chorionic status. The spatial visualization in early pregnancy improves visualization of both fetuses and their gestational sacs. The relationship between the size of the fetus and gestational sacs can also be assessed

malformations in the first trimester. 3D sonography is useful to visualize embryos and young fetuses and to recognize their surface morphology[12] (Figure 40.8).

3D sonography is useful for confirmation of conjoined twins and fetus-*in-fetu*. Maggio and colleagues reported in 1985 the first-trimester ultrasonic diagnosis of conjoined twins[13]. Since then, several groups have proposed diagnostic criteria[14–16]. Despite great progress concerning early (first trimester) diagnosis, delineating the organ(s) shared by the twins cannot be accomplished before the second trimester. Moreover, the examiner must be aware that the diagnostic criteria proposed by Maggio and colleagues are sometimes problematic, because two cases of false-positive diagnosis of conjoined twins have been reported[17,18]. Unfortunately, 2D transvaginal sonography limits the number of examination planes to the sagittal and the transverse. Because the uterus can be examined only in these two planes, it is possible that the examiner would fail to visualize the coronal section. Stated another way, conjoined twins can be overlooked. This problem can be solved using both modalities of 3D sonography: the multiplanar along with the surface-rendering view. Using multiplanar imaging, the visualization rate of coronal sections through the fetus is 100%, owing to the unlimited number of sections which can be generated by data manipulation. Maymon and colleagues reported that in a case of conjoined twins at 10 weeks of pregnancy, the exact area could be successfully identified by transvaginal 3D ultrasound[19]. We diagnosed this anomaly at 12 weeks of amenorrhea in a fetus of 27 mm in length, showing two separated heads with joining at the level of the thorax. The 2D, 3D and power Doppler studies are shown in Figure 40.9. The fetal orientation remained unchanged despite manipulation with the transvaginal probe and prolonged scanning by multiple sonographers. An early diagnosis of conjoined twins requires detailed examination of the fetus in the sagittal, coronal and transverse sections. Avoiding this recommendation can result in missing the diagnosis, because the appearance of conjoined twins in the sagittal section can be almost normal, as shown in Figure 40.9a.

Development of a fetus-like mass inside a more mature fetus characterizes the fetus-*in-fetu* (FIF) malformation (see Chapter 43)[20,21]. The true incidence of FIF is unknown, although it has been estimated to be 2 per million births[22]. Jones and co-workers reported in 2001 the 3D sonographic imaging of a highly developed FIF with spontaneous movement of extremities[23]. Compared with the relatively easy diagnosis with 3D imaging, FIF even with an extraordinarily high degree of differentiation is very difficult to distinguish by 2D sonography. Nonetheless, an increasing number of studies use 2D sonographic examination which follows the minimal criteria for diagnosis proposed by Willis[24]. This includes the presence of an axial skeleton or fetus with metameric organization, skin coverage, encapsulation and a two-vessel cord[24]. Since 3D sonography is capable of generating a surface view of the structure encapsulated within a fluid-filled sac, it should be used for this purpose. With this technique, a highly fetiform shape and axialization can be recognized even by less experienced sonographers who could not envision FIF on the basis of 2D sonography.

Distinguishing between FIF and teratoma is sometimes problematic. Therefore, whenever a cystic mass is recognized at specific locations within a fetus, an additional 3D scan is recommended. The prenatal sonographic differentiation between FIF and teratoma is related to the degree of differentiation of the anomaly. In highly differentiated FIF, the presence of a fetus-like mass is essential. However, in a poorly differentiated FIF the diagnostic criterion is based on the presence of a rudimentary spinal architecture, which confirms embryonic development

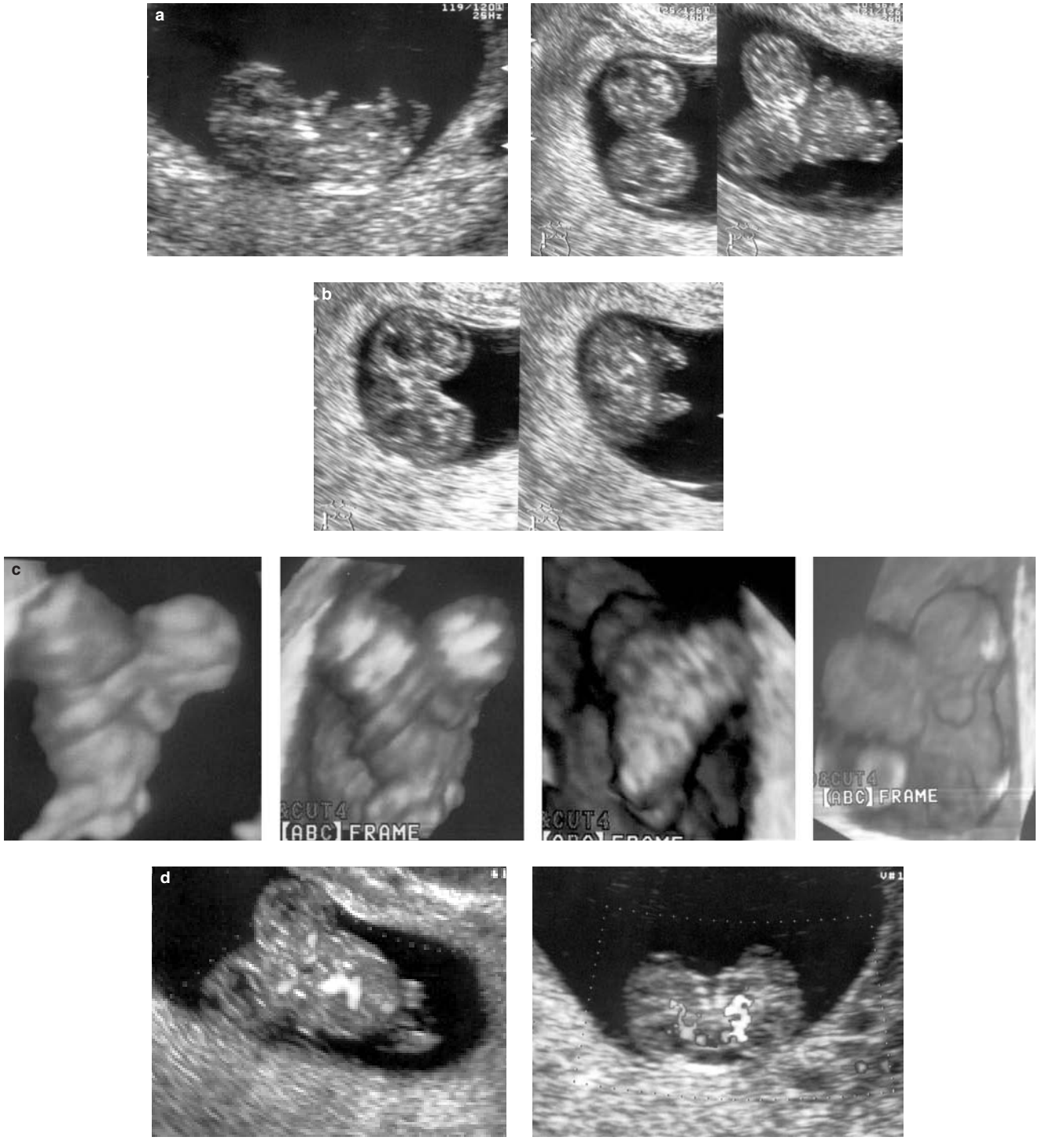


**Figure 40.9** (a) Conjoined twins at 12 weeks' gestation. 2D transvaginal sonography. Left image shows sagittal section through the conjoined twins, revealing an almost normal appearance. If one concludes on the basis of this section, the diagnosis of conjoined twins is missed. Middle image shows transverse sections through fetal heads which reveal two apparently normal heads adjacent to each other. Right image shows a coronal section which reveals a fetus with two heads and a single trunk, indicative of conjoined twins. (b) These images show transverse sections through the fetal head and abdomen which reveal two normal heads adjacent to each other. At the base of the head, the twins have a common thorax and abdomen. (c) 3D scan of same conjoined twins shown in a and b. Surface-rendered reconstruction of the conjoined twins is useful for the diagnosis of thoracophagus. Unfortunately, no information about the shared inner organs can be obtained due to limited visualization of superficial structures. (d) Conjoined twins at 12 weeks' gestation. 2D power Doppler. Power Doppler analysis can delineate the extent of organ sharing in the first trimester, an essential step for appropriate management of this anomaly. The coronal section (left) shows shared fetal circulation within a single heart. On transverse section (right) separated cerebral circulations are clearly visible

beyond the primitive-streak stage. This is in contrast to the classic embryonic concept which postulates that teratomas do not develop beyond the primitive-streak stage of 12–15 days[24].

Among malformations not unique for twins, 3D sonography can be advantageous for confirmation of suspected neural tube defects (NTDs). Twins may be concordant and discordant for congenital anomalies (see Chapter 43). Concordance for congenital malformations is defined as the presence of a concordant anomaly in both twins, whereas discordance for congenital malformations is characterized by the presence of an anomaly in only one of a twin pair. Monozygotic twins are at higher risk than dizygotic twins for such anomalies[25]. Under these circumstances, discordance for major malformation in a twin pair does not imply dizygotic or dichorionic status.

2D sonography is the primary modality for the detection of congenital anomalies. According to the Eurofetus Study, the sensitivity of routine 2D sonography for detection of a malformation in a singleton pregnancy is 61.4%[10]. On the other hand, the sensitivity in a multiple pregnancy has been reported to be between 39 and 87%[26,27]. Neural tube defects include: anencephaly, acrania, encephalocele and the various forms of spina bifida. Screening for these anomalies is recommended during the first trimester because reports document successful diagnosis in the embryonic period[28–30].

The morphologic anomalies of acrania and anencephaly can be confirmed even before 10 weeks of pregnancy. Bonilla-Musoles and colleagues reported two cases of anencephaly at 10 weeks of gestation using 2D sonography[28]. Takeuchi diagnosed acrania by conventional 2D sonography at 8 weeks and 5 days of amenorrhea in a fetus of 18 mm maximum length, showing an irregular shape of the head with neither cranium nor brain vesicle development[29]. A 3D surface-rendered image facilitated confirmation of this diagnosis because it showed characteristics of the anomaly more clearly. It is generally believed that absence of the cranial vault leads to disintegration of the exposed brain during the fetal period, resulting in clinical anencephaly. Bronshtein and Ornoy reported a case which detailed the progression from acrania to anencephaly[30]. Spina bifida is associated with anencephaly in 9–30% of cases[31]. Using 3D sonography, Bonilla-Musoles reported a diagnosis of spina bifida at 9 weeks[32]. Therefore, whenever anencephaly is found in the embryonic period, an additional 3D scan of the fetal spine is recommended. The multiplanar view is particularly useful in localizing spinal defects accurately in fetuses with spina bifida and in determination of the exact location of the extracranial mass and amount of extracranial tissue in fetuses with encephalocele[33].

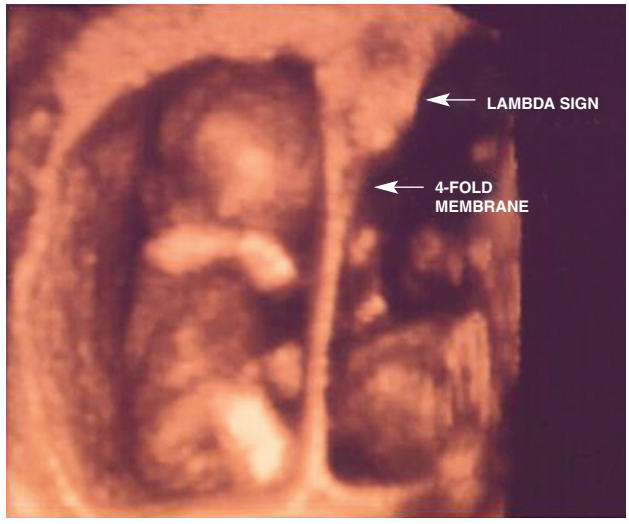


**Figure 40.10** 3D lambda ('twin peak') sign and intertwin membrane. Spatial reconstruction of the membrane's take-off site provides easier differentiation between dichorionic and monochorionic placentation. Furthermore, membrane thickness can be simultaneously evaluated

## CHORIONICITY ASSESSMENT

Using 2D ultrasound, membranes can be evaluated, counted and measured only when they are at 90° to the transducer (see Chapter 39). In other words, the orientation of the membranes must be positioned parallel with the transducer crystal array. In contrast, 3D ultrasound enables one to achieve a 'perfectly' oriented picture. Thus, chorionicity determinations should be ideal in the second and third trimesters using this technology (Figures 40.10 and 40.11). The most suitable area to study chorionicity and amnionicity is where the membranes change orientation from covering the placenta(s) or the uterine wall to meet each other and form the interfetal or intertwin membrane (the so-called 'take-off' area). Using 2D ultrasound, this means scanning at 90° to the plane of the intertwin membrane, and explains the potential advantage of 3D ultrasound in this analysis.

Membrane thickness depends on the membrane structure. In monochorionic–diamniotic placentation, the interfetal membrane consists of only two layers. Unfortunately, a thin intertwin membrane is usually not seen by the surface-rendered mode. Whenever the elusive intertwin membrane is not found, the examiner must consider a false-positive diagnosis of monoamniotic twins. In the situation of suspected monoamniotic twinning on 3D or 4D sonography, the use of 2D high-resolution sonography is recommended. Even when this happens, distinguishing between a monoamniotic and a diamniotic pregnancy is still difficult because of the low rate of visualizing a thin membrane (25%)[34].

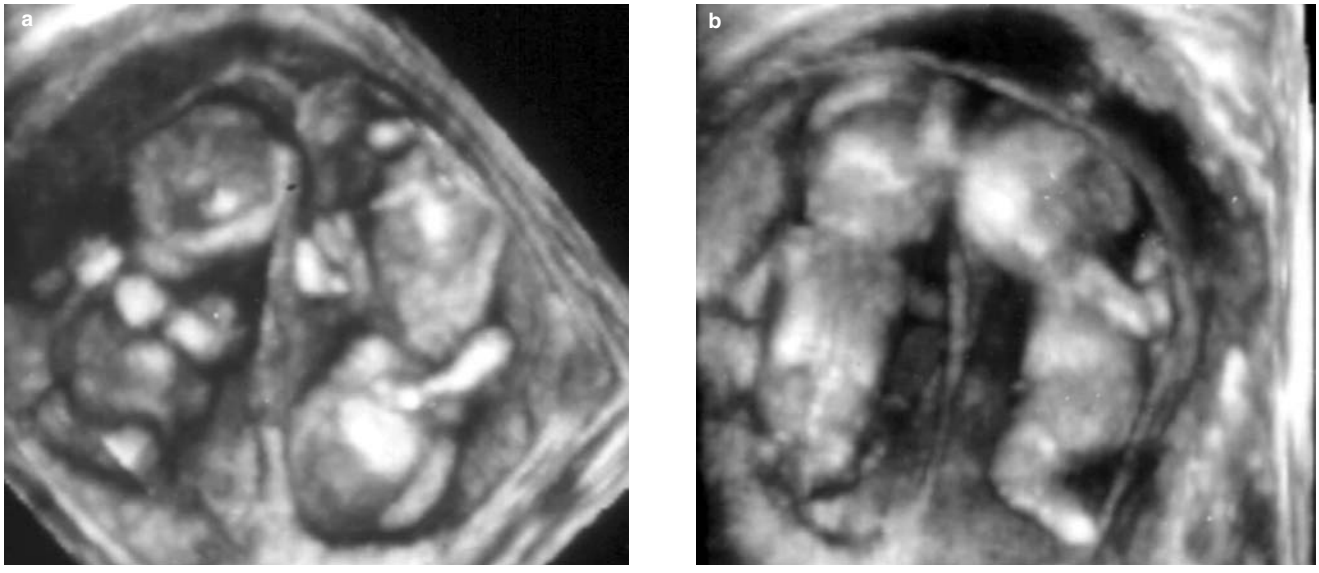


**Figure 40.11** 3D scan of dichorionic–diamniotic twins in the second trimester of gestation. With the 3D scan the same amount of detailed information is achieved in less time. Images (a) shows that both chorionicity and external frontal anatomy can be evaluated from a single image. Furthermore, orientation of one twin toward the other can be simultaneously assessed. (b) Twins seen from the back as well as the intertwin membrane

Unfortunately, the inability to recognize a separating membrane by sonography in the late second and third trimesters emphasizes the need for early chorionicity/amnionicity determination during the first and early second trimesters.

## THREE-DIMENSIONAL SPATIAL RECONSTRUCTION

Integration of data obtained by volume scanning can be used to depict 3D plastic (sculpture-like) reconstruction of the region of interest. 3D reconstruction can be presented in the surface mode, where only signals from the surface of the region of interest are extracted and displayed in a plastic appearance. Surface rendering provides additional information, by either confirming the normal anatomy or evaluating the extent of lesions, as exemplified in Figure 40.9. Surface rendering provides spatial reconstruction of the intertwin area, which may be useful in distinguishing between conjoined twins and monoamniotic twins positioned next to each other. At present, it is the best means to accomplish this distinction, as conjoined twins can be shown in three perpendicular 2D planes displayed simultaneously on the monitor. This procedure allows access to an almost infinite array of sections in any desired plane. At the same time, surface rendering enables assessment of the topographic orientation of conjoined twins, so that the exact area of fusion can be analyzed which can assist in planning postnatal management (Figure 40.9).

## VOLUMETRIC CALCULATIONS

Three-dimensional measurement of the organ volume (volumetry) is possible using sequential-step slicing measurements of areas through the volugram of the targeted organ. Whereas volume assessment by 2D sonography includes only an approximation of volume, based on the assumption that fetal organs have an ideal geometric shape, 3D volumetry is carried out in all three planes using the contour mode, in which the volume from the measured circumferences and the distances between them are computed by appropriate software. 3D volumetry of the first-trimester gestational sac volume (GSV) is superior to 2D volumetry in its estimation, but is without prognostic significance for outcome in a singleton pregnancy[35]. Despite this, our group considers comparison between volumes of each gestational sac in a multiple pregnancy an important parameter for confirmation of early concordant growth. The prognostic significance of early discordant growth in a multiple pregnancy is still a matter of controversy. Some authors report an association of early discordant growth with major anomalies and poor pregnancy outcome[36,37] but others do not[38]. Gassner and colleagues proposed using sonographic placental volumetry as a means of early detection of chromosomal anomaly in multiple pregnancy[39]. These authors described a growth-discordant dichorionic twin pregnancy with a distinctly small placental volume of the growth-restricted fetus at 12 weeks' gestation. These two markers were present before a severe heart defect and bilateral cleft lip and palate

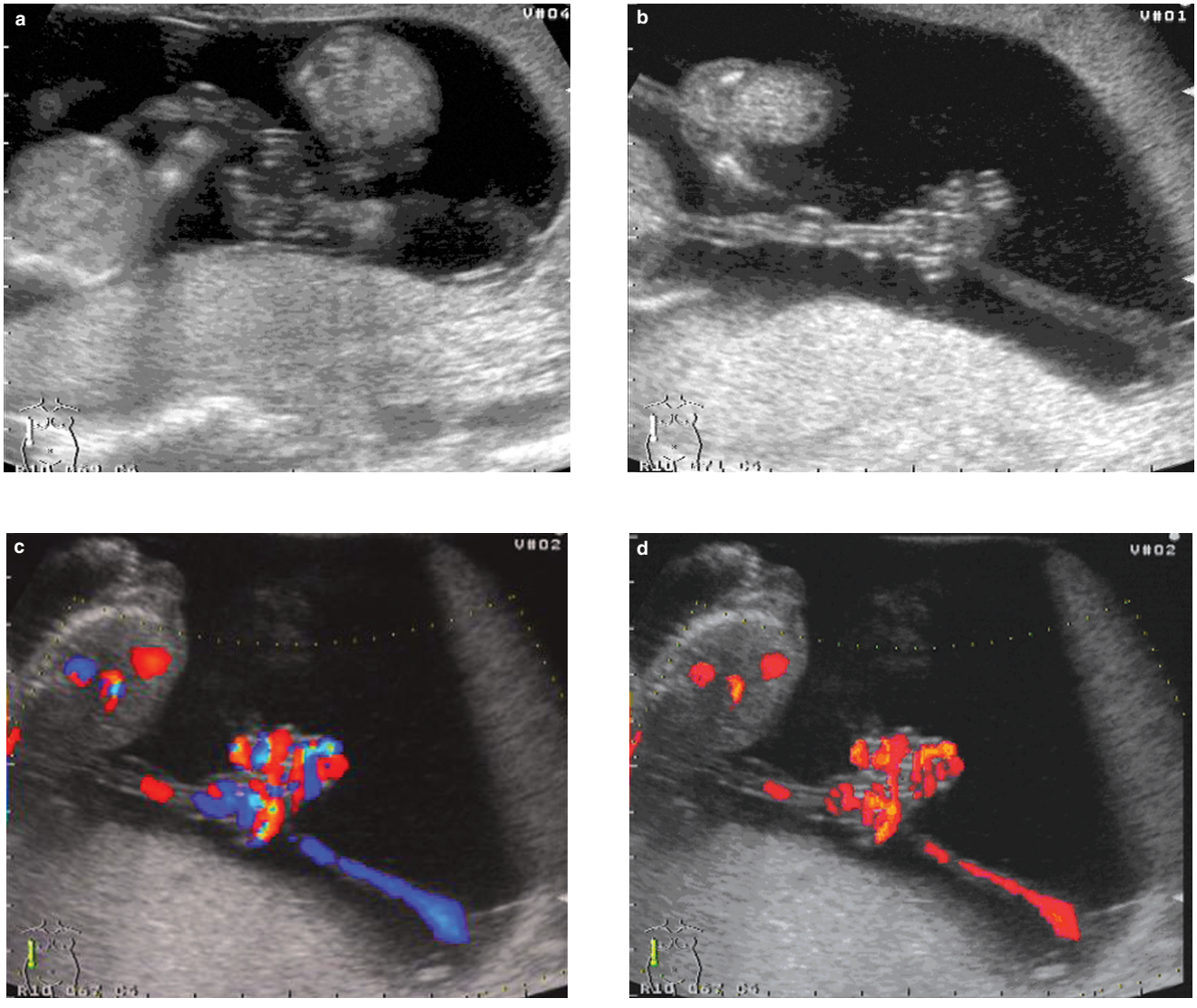


**Figure 40.12** (a) Monoamniotic twins. A single amniotic cavity, a single placenta and two umbilical cords closely inserted are criteria for diagnosis of monoamnionicity. (b) 2D image of cord entanglement in monoamniotic twins. 2D sonography is unable to distinguish between adjacent and entangled umbilical cords. (c) 2D color Doppler imaging of umbilical cord entanglement. (d) 2D power Doppler reconstruction of umbilical cord entanglement

were recognizable. It seems reasonable that placental volume should be the recommended criterion for distinguishing between pregnancies with or without risk for major anomalies and poor outcome in multiples[19]. Small placental volumes, in addition to growth restriction of one fetus early in the course of a twin pregnancy, could be an important early marker influencing the selection of chorionic villus sampling at 12 weeks instead of amniocentesis at 16 weeks, and could lead to an earlier selective pregnancy termination of a malformed twin, if indicated and desired.

Placental volumetry is easy to perform when the placentas are separate. Unfortunately, fusion of placentas often occurs during the second trimester in polychorionic pregnancies. Therefore, volumetry should be performed at the end of the first trimester or at the beginning of the second trimester.

## THREE-DIMENSIONAL ANGIO-MODE

3D angio-mode operates on the basis of high-energy powered Doppler. Its greater sensitivity is related to direction-independent scanning and better detection of smaller vessels. This mode provides optimal visualization and selective 3D reconstruction even of tortuous parts of vessels and blood flow arborization. More recently, 3D reconstruction of the vascular

**Figure 40.13** 3D power Doppler reconstruction of umbilical cord. This method provides the possibility to differentiate between false and true knots in polyamniotic pregnancies and between umbilical cord entanglement and adjacent cords in monoamniotic pregnancies

channels has been accomplished utilizing the Doppler amplitude mode[40,41]. The implementation of 3D power Doppler imaging permits the physician to investigate the anatomy and hemodynamic topography within the particular organ or region of interest.

Cord entanglement is a complication specific for monoamniotic twins. The diagnosis of cord entanglement with 2D real-time sonography usually requires a long examination period, and due to limited sectional imaging, the examination is informative only in terms of quality and number of loops (Figure 40.12). The main problem is distinguishing between adjacent and entangled cords. 3D power Doppler examination permits imaging of specific curvatures of the umbilical cord. Moreover, the number of loops involved in entanglement can be determined easily. Counting the number of the loops involved in entanglement provides a useful basis for longitudinal assessment of the effects of entanglement, i.e. tightening and subsequent fetal compromise (see Chapter 67).

It is currently possible to distinguish between true and false knots of the umbilical cord. A focal redundancy of the vessels, which sonographically appears as a vascular protuberance that does not persist in all scanning planes, characterizes a false umbilical cord knot[42]. This condition should be distinguished from a true umbilical cord knot which is a potentially life-threatening condition (Figure 40.13).

## FOUR-DIMENSIONAL SONOGRAPHY IN MULTIPLE PREGNANCY

Real-time 2D sonography enables visualization of spontaneous motor activity in the singleton pregnancy. Reinold was among the first to describe fetal activity using ultrasound, stressing the spontaneous character of early prenatal movements[43]. Two types of motor activity are defined in a multiple gestation: spontaneous and stimulated. Spontaneous motor activity is defined when each embryonic or fetal activity is not evoked by internal or external stimuli. On the other hand, activity evoked by intertwin contacts characterizes stimulated activity. Spontaneous motor activity precedes stimulated activity, in terms of gestational age of onset. The effect of prenatal reactions evoked by internal stimuli was the focus of interest of the systematic research initiated by the group of Arabin and associates[44]. These investigators used real-time 2D sonography to record and evaluate intertwin contacts. Due to sectional imaging, simultaneous visualization of both fetuses and assessment of their motor activity was impossible, however. Therefore, the motor activity of a single fetus provided only limited information. The same limitation applies to the intertwin area when it is tomographically visualized. Therefore, using this method to distinguish between spontaneous and stimulated motor activity is not only difficult, but sometimes impossible.

If, on the other hand, 3D sonography is used, the complete anatomy of both fetuses can be visualized simultaneously. In spite of this progress, the technology is not suitable for behavioral research because images are static. Moreover, fetal movements, the focus of interest for behavioral studies, cause significant artifacts in visualization.

All these problems are resolved by 4D sonography, which provides spatial visualization of the fetal anatomy and movements almost simultaneously with their appearance. Simultaneous visualization of the entire anatomy (head, body and extremities) of two or more fetuses along with their movements allows characterization of the type of movement, isolated movements of each fetus and intertwin contacts and interactions (Figure 40.14). Movement activity of each fetus can be determined in the first and early second trimesters[45] (Figures 40.15 and 40.16).

The Arabin group defined intertwin contacts for the first time[44]. According to this group, these movement patterns consist of initiations and reactions of both twins, which are sometimes difficult to distinguish

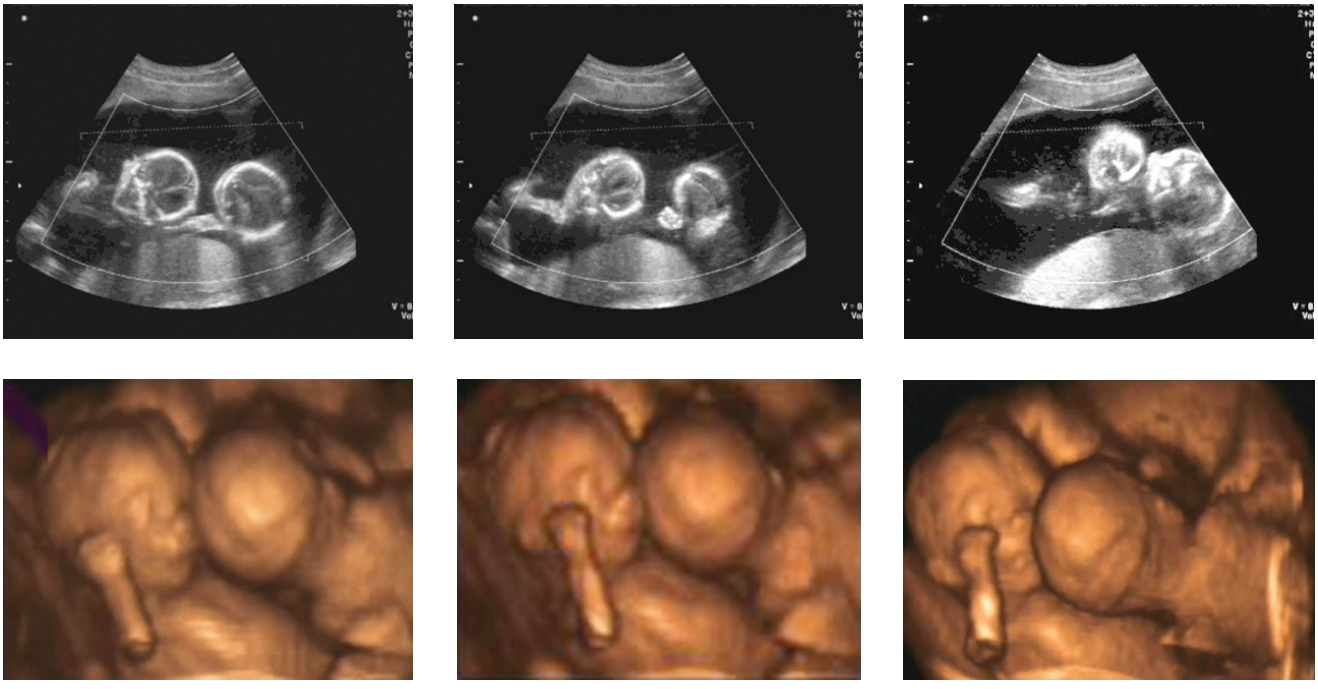

**Figure 40.14** Comparison between two techniques to evaluate fetal behavior. Using real-time 2D sonography (upper series), hand to head contact together with head to head intertwin contact can be recognized. Due to sectional imaging it is impossible to categorize hand to head contact. In the lower sequence of images, the advantages of spatial visualization are clear. Hand to head movement can be differentiated from hand to ear contact following movement of the right hand forward. Head to head intertwin contact can be determined in detail. The forehead of one twin contacts with the cheek of its co-twin. Furthermore, the facial expression of one twin is discernible

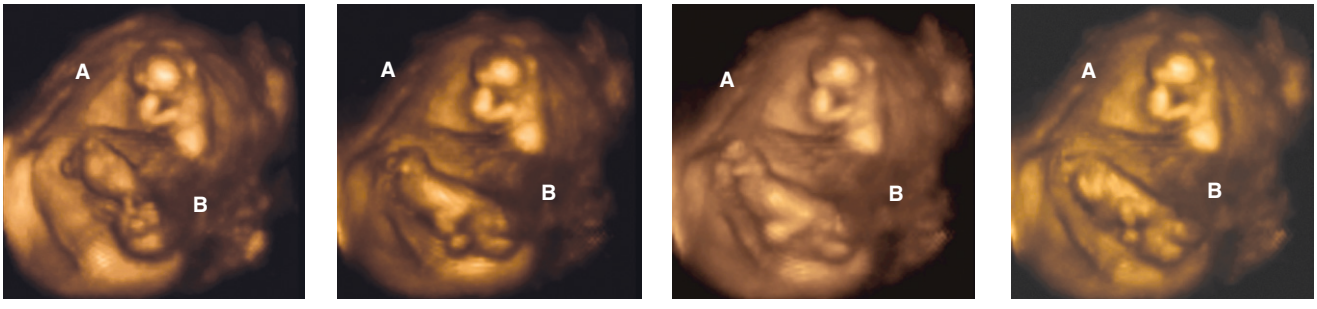


**Figure 40.15** Sequence illustrates reconstruction of fetal motor activity in twins at 13 weeks of pregnancy. In this sequence twin A is passive, whereas twin B is active. A change in position of twin B due to stretching movement pattern is seen, causing a change of posture. In the first image the fetal hand is positioned in front of the face. During the movement, the fetal hand moves from the central part of the face to the mouth region. It is visible that the legs participate in the movement pattern due to a change in their direction toward the uterine wall

by real-time 2D sonography as many last no longer than a few seconds. Using 4D scans, complex parts of these interactions can be analyzed for the first time. Furthermore, 4D sonography is useful in the evaluation of altered motor development in pathologic pregnancy[44]. The delay in activity pattern is described in twins with triploidy XXX, and some activities such as yawning and stretching are even absent[44].

## CONCLUSION

Along with the great progress achieved in many other areas of management of multiple pregnancy, the limitations of 2D sonography can be overcome by an additional 3D scan, because it provides more reliable or additional important information for management. 4D sonography has several advantages

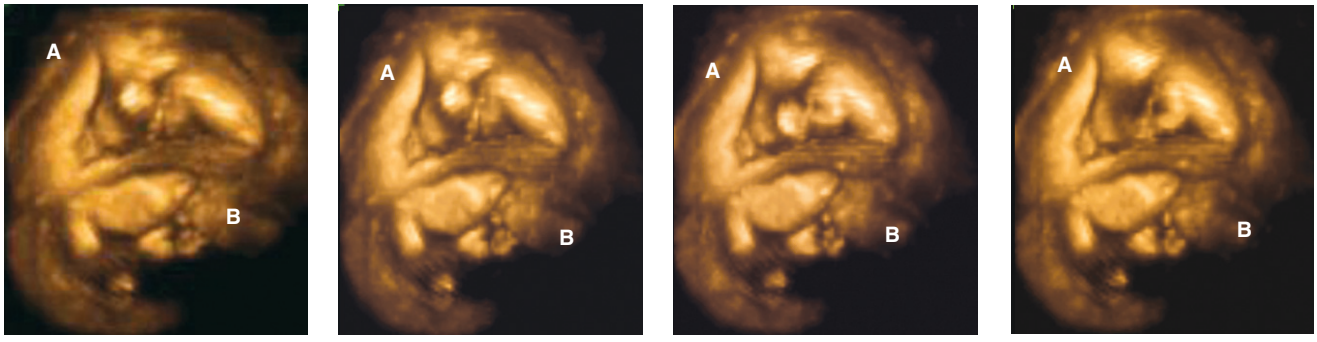


**Figure 40.16** Sequence of fetal motor activity in twins at 13 weeks of pregnancy. In this 4D sonography sequence twin A is active, whereas twin B is passive. One can see the change of position of the hand of twin A due to isolated hand movement. It seems as if this twin is trying to release itself from the umbilical cord around its neck. This may be indicative of the sensory maturation process at this gestational age. The umbilical cord causes tactile stimulus on the fetal skin which provokes the hand movement

over 3D imaging, including less scanning time, elimination of movement artifacts and visualization of fetal movement in three dimensions. Degradation in image quality of the surface-rendered or multiplanar view is compensated by other advantages. 4D sonography is undoubtedly a new, powerful imaging tool, whose scientific and clinical potential should be established in the coming decade.

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# The Role of Doppler Blood Flow Velocimetry

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41

GROWTH DISCORDANCE
INTRAUTERINE GROWTH RESTRICTION
ABNORMAL BLOOD FLOW IN UMBILICAL ARTERY
CEREBRAL CIRCULATION
UTERINE CIRCULATION
TWIN-TO-TWIN TRANSFUSION
TWIN REVERSED ARTERIAL PERFUSION SYNDROME
CORD ENTANGLEMENT

## GROWTH DISCORDANCE

Abnormal patterns of fetal growth are one of the most common complications of multiple pregnancies. It is believed that twins grow at the same rate as singletons until the 28th week of gestation, followed by a somewhat lower third-trimester rate (see Chapter 60 for details). The etiology of discordant fetal growth or growth restriction in multiple pregnancy is the same as that in singletons: placental insufficiency, early pregnancy infection and chromosomal, structural or constitutional anomalies[1,2]. A weight discordance in the absence of other pathological problems suggests either that one fetus is suffering from intrauterine growth restriction (IUGR) or has a chromosomal anomaly in the presence of a normal co-twin, or that both fetuses are normal in spite of the discordance, which merely reflects differences in their respective genetic potentials. It is also possible for both twins to be growth restricted and to exhibit concordant size.

Several studies suggest that discordance and growth restriction are associated with unequal or reduced redistribution of fetoplacental blood flow. The mechanism for growth restriction may be different in monozygotic (MZ) and dizygotic (DZ) twins. In DZ twins, local placental causes include umbilical cord abnormalities, infarction, placental abruption and local vascular abnormalities. In these pregnancies, increased resistance in the umbilical artery (UA) suggests downstream resistance to flow and placental insufficiency. In monochorionic (MC) pregnancies, on the other hand, two proposed mechanisms for growth restriction are possible. The first suggests insufficiency resulting from placental asymmetry; the second suggests the development of twin-to-twin transfusion syndrome (TTTS) due to placental anastomoses. Irrespective of the etiology of the growth restriction, the likelihood of less than ideal outcome is greater in MC compared with dichorionic (DC) twins.

Discordant growth is associated with a significant increase in perinatal morbidity and mortality[3]. Many parameters have been used in the identification of a discordant growth pattern, including intrapair differences in biparietal diameter (BPD), abdominal circumference (AC), femoral length (FL) and estimated fetal weight. The most common definitions of growth discordance are based on intertwin birth-weight difference expressed as a percentage of the larger twin weight[2]. The cut-off values for percentage difference of birth weight proposed in the literature vary from 15 to 40%[1,2]. Other commonly used values indicating abnormal discordant growth pattern include a difference in BPD > 6 mm[4], a difference in AC > 20 mm[5], a diference in FL > 5 mm[6], a difference in estimated fetal weight > 15%[1] and a difference in systole/diastole (S/D wave) ratio in the UA of more than 15%[1,4].

Numerous investigators report the use of UA velocimetry for the surveillance of twin pregnancies[7,8]. Abnormal UA velocity waveforms reflect unequal fetal–placental circulation, which is probably a major contributor to growth discordance in twin pregnancies. Saldana and colleagues found that a difference in S/D ratio in the UA has a better prediction of discordance than a difference in estimated fetal weight[8]. Farmakides and associates used a difference in S/D > 0.4 as a test for identification of discordant growth[7]. Similar results were obtained by Divon and Weiner applying a difference of S/D ratio > 15%[1]. Gerson and colleagues demonstrated in twins and triplets that discordance in S/D ratio was

present prior to the development of discordant ultrasound measurements[9]. Shah and co-workers reported that the S/D ratios for small discordant twins were significantly different from those of normal singleton pregnancies[10]. They found that discordant twin gestations with a small-for-gestational-age (SGA) fetus had a significant intrapair S/D difference as compared with concordant twins[7]. Degani and colleagues looked for the presence of SGA fetuses, and, by adding the use of the carotid internal artery to the UA pulsatility index (PI), increased the sensitivity of the diagnosis[11]. Seelbach-Gobel and colleagues, in a study of the pulsatility indices of the fetal aorta and the UA in twin pairs, noted a correlation between aortic and umbilical Doppler differences where there was a greater than 20% weight difference between the twins, and worst outcome with absent diastolic blood flow[12]. Kurmanavicius and associates, on the basis of UA Doppler velocimetry, were able to identify the twin with a reduced growth rate in 77.8% of cases[13].

Other researchers reported that the most useful method in the detection of twin discordance was B-mode ultrasound, and they did not recommend Doppler measurements in the management of unselected twin pregnancies. Faber and co-workers, in a prospective study, assessed the predictive value of Doppler measurements (PI in the UA, middle cerebral artery (MCA) and aorta) with regard to pregnancy outcome. The prediction of fetal distress (hypoxia, preterm birth, poor fetal growth, acidosis and disturbed neonatal adaptation) with Doppler had a sensitivity of 25% and a positive predictive value of 63%. These investigators concluded that Doppler screening might be useful even in unselected twin pregnancies[14]. Other authors reported two randomized trials of Doppler ultrasound including twins, and pointed out the usefulness of Doppler velocimetry in the prediction of adverse fetal outcome[15,16].

Triplet and quadruplet pregnancies are associated with a substantialy higher risk of perinatal and neonatal morbidity and mortality compared with singleton pregnancies. However, only a few studies evaluated the role of UA Doppler velocimetry in fetal surveillance of those pregnancies[17,18]. Gaziano and colleagues studied twins and triplets and found increased morbidity and mortality in twins when abnormal Doppler values were observed[18]. Prompeler and associates studied 16 sets of triplets and two sets of quadruplets and reported improved diagnosis of IUGR or discordant growth by combining pathological Doppler findings with biometry[19].

## INTRAUTERINE GROWTH RESTRICTION

Placental insufficiency induces a redistribution of fetal blood flow, with reduced impedance at the cerebral level and increased resistance at the level of peripheral vessels, resulting in preferential perfusion to the brain. Increased impedance in the UA may be a sign of impaired placental perfusion, and thus reduced diffusion of nutrients and oxygen through the placenta. Compromised fetuses suffer from low oxygen reserves. These fetuses with increased impedance in placental circulation will have little capacity to compensate decreased placental perfusion during uterine contractions. Under such circumstances, fetuses with very high impedance in the umbilical circulation frequently develop signs of distress. However, measurement of UA impedance is not a good test for acute fetal hypoxia. With progressive fetal compromise, cardiac function deteriorates, resulting in decreased peak velocity at the outflow tracts. As a consequence of a high pressure gradient in the right atrium secondary to the cardiac malfunction, the percentage of reverse flow in the inferior vena cava (IVC) increases and umbilical vein pulsations may occur.

Rizzo and colleagues evaluated Doppler-detectable differences in fetal circulation (PI values in the UA, MCA and aorta, and peak velocity from outflow tracts, percentage of reverse flow in the IVC) in discordant twin growth which resulted from either placental insufficiency or TTTS[20]. Serial recordings in the larger twin showed the absence of any differences, compared with singletons. Conversely, the smaller twin showed progressive changes in Doppler indices similar to those found in growth-restricted singletons secondary to placental insufficiency, characterized by a progressive increase in PI from the UA and descending aorta in the weeks preceding fetal distress, associated with a decrease in PI from the MCA[21].

It has been suggested that the absolute values of the Doppler indices in the smaller twin, or the intertwin difference between the smaller and the larger twin, may be used for fetal surveillance or for the prediction of fetal distress[20]. Vetter suggested that Doppler velocimetry is a good indicator of placental supply and function, allowing an insight into flow redistribution related to fetal stress[22]. Jensen correlated the intertwin difference in resistance index (RI) of the UA with the oxygen partial pressure difference[23] and demonstrated that the blood-gas exchange through the placenta is impaired when the impedance level in the UA surpasses a certain threshold value (RI ≥ 76%). He concluded that the absolute impedance level was superior to the difference in impedance between the fetuses. Joern and colleagues found that the results of Doppler sonography are better in predicting growth restriction than fetal outcome[24]. These investigators predicted a 'pathological outcome' on the basis of Doppler measurements of the fetal aorta, UA and MCA, and found low sensitivity and specificity values of 60% and 50%, respectively[24].

In summary, abnormal UA Doppler results are significantly associated with the birth of an SGA infant in multiple pregnancies[21,22,24,25]. The introduction of routine Doppler UA waveform assessment in twin pregnancy has been associated with a significant reduction in perinatal mortality and morbidity, particularly a reduction in fetal death. However, abnormal Doppler results may also lead to iatrogenic deliveries in some cases, especially if the decision is based only on abnormal Doppler tests. As in singletons, multiple parameter measurements and serial measurements are superior to individual values. Moreover, Doppler examinations supplement biometry and may increase the likelihood of detecting IUGR of multiples.

## EXTREMELY ABNORMAL BLOOD FLOW IN THE UMBILICAL ARTERY

Absent end-diastolic velocity (AEDV) in the UA is an uncommon finding, but, if present, the affected fetuses are at increased risk of adverse perinatal outcomes (Figure 41.1). End-diastolic velocities, a normal finding in early pregnancy, first begin to appear at 10 weeks' gestation and are always present by 15 weeks, but the absence of end-diastolic velocities is a pathological finding in the second and third trimesters when the majority of placentas show evidence of chronic insufficiency. When AEDV is present, it persists in the majority of cases; and occasionally deteriorates into a pattern of reversed end-diastolic velocity (REDV) flow, the most extreme form of increased vascular resistance in the placental bed. In the absence of intervention, this finding is usually followed by fetal distress and demise (Figure 41.1).

Hastie and colleagues evaluated 89 unselected twin pregnancies and found that persistent AEDV in the UA was associated with poor outcome[25], a finding that should alert the physician about the risk of fetal growth restriction or other adverse perinatal outcome. Ezra and associates analyzed abnormal Doppler waveforms from the UA in high-order multiples, comparing them with pregnancy outcome, and found that persistent AEDV was associated with a perinatal mortality rate of 50%[26]. In singleton pregnancies, persistent AEDV was associated with a perinatal mortality rate of 36%[27]. Rafla also reported increased morbidity in triplets when AEDV was documented[28]. Giles and co-workers found two stillbirths among 17 fetuses with AEDV in 20 triplet pregnancies[17].

The management of AEDV pregnancies has recently changed. In the past it was deemed necessary to perform immediate delivery, but nowadays a much less aggressive approach is advocated. However, even with careful fetal monitoring, it seems unlikely that the duration of pregnancy can be significantly prolonged.

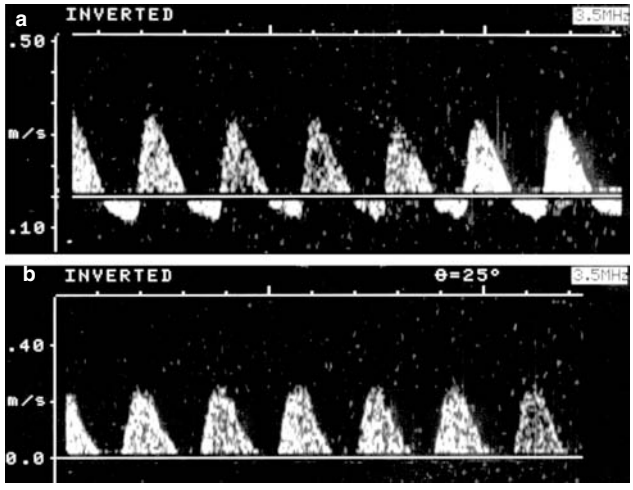


**Figure 41.1** Abnormal blood flow velocity waveforms in the umbilical artery. Note (a) the presence of reversed end-diastolic flow; and (b) the absence of end-diastolic flow in the growth-restricted twin

In spite of numerous articles on Doppler blood flow in the UA, data and opinions conflict regarding the role of UA Doppler assessment in pregnancy. There is a higher incidence of AEDV/REDV in multiple pregnancies[17,18,26,28], and most authors recommend monitoring with Doppler velocimetry in multiple gestations. Any intervention resulting from a discordant abnormal test carries ethical problems whereby the interest of the compromised fetus has to be weighed against that of the unaffected one.

## CEREBRAL CIRCULATION AND REDISTRIBUTION OF BLOOD

States of chronic fetal deprivation result in blood flow directed preferentially to the brain, myocardium and adrenal glands. Fetal stress is accompanied by an increase in PI values in the UA and a reduction of PI values in the MCA. A low PI in cerebral arteries indicates dilatation of downstream resistance vessels (Figure 41.2). The reduced PI in the MCA is thought to reflect the brain-sparing response to inadequate perfusion or oxygenation, and to represent an appropriate compensatory decrease in cerebrovascular impedance, as well as a redistribution of blood flow to the brain.

Akiyama and colleagues examined alterations in fetal vascular resistance of fetal peripheral arteries (the MCA, UA, aorta and splenic, renal and femoral arteries) with advancing gestation in appropriate-for-gestational-age singleton, twin and triplet pregnancies, and reported no significant differences for regional arterial vascular resistance, irrespective of plurality[29]. Gaziano and co-workers studied fetal growth and blood flow redistribution in MC–DA compared with DC–DA twins[30], finding the mean

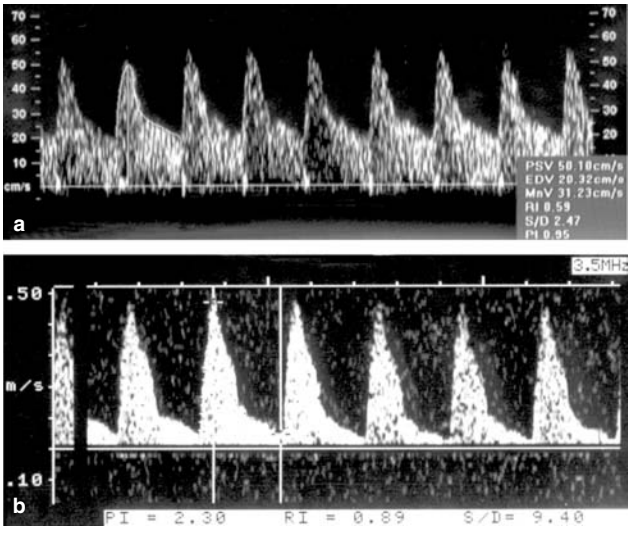


**Figure 41.2** Pulsed Doppler waveforms from the middle cerebral artery of a 35-week growth-restricted twin (a) with enhanced diastolic flow and a normally grown twin at 34 weeks' gestation with normal pattern of blood flow (b)

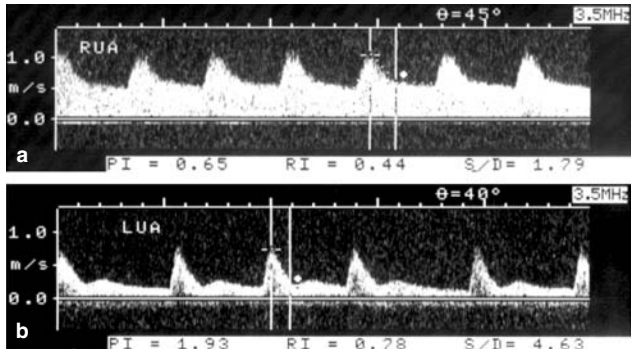


**Figure 41.3** Uterine artery flow velocity waveforms. (a) Normal multiple pregnancy, (b) high-impedance pattern with well-defined diastolic notch in twin pregnancy with growth discordance of 1000 g

cerebral/placental ratio lower in MC–DA than in DC–DA pairs, and indicating greater blood flow redistribution and brain-sparing effect in the former. Redistribution of fetal blood flow was also more common in growth-restricted MC–DA twins. This adaptation to fetal stress suggests the differential risk to MC fetuses.

MC twins exhibit blood flow redistribution more often, compared with DC twins[30]. Placental vascular connections and the attendant hemodynamic changes in MC fetuses probably account for this difference. Also, brain-sparing events commonly occurred without any clinical appearance of feto-fetal transfusion in this group[30].

## UTERINE CIRCULATION

Doppler blood flow velocimetry of the circulation in singleton pregnancies was able to predict some pregnancy complications such as IUGR, pregnancy-induced hypertension and pre-eclampsia. However, no clear evidence supports that Doppler velocimetry of the uterine arteries may be useful in the management of multiple pregnancies (Figure 41.3).

Rizzo and colleagues found that the RI from both uterine arteries decreases significantly with gestational age, and is lower in singleton pregnancies, suggesting a lower vascular resistance in the uterine circulation[31]. No significant differences were found when the RI in all patients with gestational hypertension or pre-eclampsia was compared with that of reference cases. The diagnostic efficacy of the uterine artery resistance index between 20 and 24 weeks of gestation to predict the development of hypertensive disorders was disappointingly low. Chen and associates studied the PI of uterine arteries over the course of pregnancy[32]. The mean values of PI were consistently lower in twins than in singleton pregnancies at any gestational age, declining more rapidly and reaching a plateau earlier in twins. Bower and co-workers reported changes in uterine circulation in TTTS treated by amnioreduction[33]. The resistance and pulsatility indices decreased after amnioreduction, suggesting an improved uteroplacental perfusion. Yu and colleagues reported that Doppler assessment of the uterine arteries at 23 weeks identified a large group of twins at risk of developing adverse outcomes due to placental insufficiency[34]. There were no significant differences in uterine artery PI or notching between MC and DC twins. This may indicate that total placental size may play an essential role in the development of adverse outcome.

In summary, gestational hypertension, pre-eclampsia and IUGR may occur in twin pregnancies despite normal uterine artery velocity waveforms. The vascular resistance in the uterine artery is lower in multiple pregnancies than in singleton pregnancies, probably owing to wider invasion of the uterine vessels by the trophoblastic cells originating from a larger placental implantation area. The overall sensitivity for the prediction of pre-eclampsia and IUGR in twins is lower than in singletons. The different physiological effects of multiple pregnancy on the maternoplacental circulation may affect the use of uterine artery Doppler velocimetry as a screening test. However, owing to the high prevalence of complications in multiples, Doppler measurements of uterine artery blood flow may identify pregnancies at high risk for severe and early-onset diseases.

## TWIN-TO-TWIN TRANSFUSION SYNDROME

The sonographic diagnosis of TTTS is discussed in Chapters 44 and 65. The pathophysiology of TTTS is related to the presence of vascular anastomoses between two fetal circulations (see Chapter 27). Abnormalities of MC placental symmetry have received considerably less attention than the presence of anastomoses, but they seem to be of equal importance. In the absence of anastomoses, unequal sharing is an important cause of growth discordance in MC twins. The vascular anastomoses place an MC twin with an inadequate placental share at risk for placental insufficiency. Conversely, the anastomoses may sustain a twin with a small share by supplementing the otherwise deficient nutrients.

### Fetal arterial Doppler studies

Studies concerning Doppler velocimetry in TTTS are not in agreement. On the one hand, some authors[17,20] report no or little difference in the indices of the UAs in TTTS, whereas others find various changes in vascular resistance[10,18,35,36]. Ohno and colleagues suggested that Doppler velocimetry in the UA might detect TTTS before the appearance of fetal hydrops. Also, Doppler was found to be useful in monitoring of the fetoplacental circulation and fetal condition, especially during treatment, but no benefit was shown regarding fetal outcome[35]. Rizzo and associates reported that Doppler studies seem to be of limited efficacy in early diagnosis of TTTS, as it demonstrated no evident intertwin differences in PI values in the UA and fetal vessels[20].

A cross-sectional study investigating the circulatory profile of co-twins in TTTS in mid-pregnancy was reported by Hecher and co-workers[36]. These investigators found an increased resistance to flow in the UAs of both donor and recipient, but beyond 21 weeks of gestation, the resistance was increased only in the recipient. They suggested that this high resistance could be a consequence of compression of placental vessels due to two possible mechanisms. The first could be increased intra-amniotic pressure in polyhydramnios, and the second placental edema resulting from hypervolemia-related heart failure. The increased resistance to flow in the donor's UA either may reflect a primary maldevelopment of the donor's placenta or may be caused by compression of the cord due to polyhydramnios of the recipient's sac. The donor fetus could be expected to have severe uteroplacental insufficiency with additional chronic hypovolemia. Doppler studies of the MCA showed a decreased PI in the recipient, whereas PI values in the donor varied within the normal range, but were occasionally lower or higher[36]. Hecher and co-workers speculated that the changes in blood flow in the recipient's MCA might be the consequence of hypervolemia-related congestive heart failure, and might represent vasodilatation in response to heart failure-related hypoxemia[36]. The Doppler values in the donor's MCA suggested the absence of redistribution in the fetal circulation. The increased PI values in some cases could also be the result of head compression by polyhydramnios of the recipient's sac, or as a result of reduction in the left ventricular output, suggesting decompensation of fetal cerebral circulation[36]. Thus, the best explanation for the Doppler findings is hypovolemia rather than anemia and hypoxemia, and in the recipient, hypervolemia and congestive heart failure might partly explain the observed changes.

Suzuki and colleagues studied the MCA and the UA Doppler waveforms in growth-restricted fetuses with and without TTTS, and found that the MCA PI values in the TTTS group, especially in fetuses with periventricular leukomalacia, were significantly higher than normal values[37]. This finding suggests an absence of blood flow redistribution, as observed in hypoxemic and IUGR fetuses due to placental insufficiency[37]. The UA PI values in the smaller twin were significantly higher in the TTTS group compared with the non-TTTS group. These values decreased after amnioreduction, and were associated with recovery of fetal circulation[38].

The variable UA Doppler findings for TTTS are probably a result of the complex pathophysiological features of this condition, for which there is no predictable pattern of vascular anastomoses and no uniform pattern of UA blood flow abnormalities. The literature does not agree on whether fetuses presenting signs of increased placental resistance may be fetuses with TTTS or rather fetuses suffering from placental insufficiency.

### Echocardiography and venous circulation

The advantages of fetal echocardiography in TTTS include an accurate assessment of cardiovascular adaptation to intertwin transfusion, early recognition of deterioration and evaluation of antenatal management. The majority of recipient twins develop a cardiac malfunction *in utero*, predominantly affecting the right ventricle and the pulmonary artery, which often results in increased neonatal morbidity and mortality. Recent studies revealed congenital congestive cardiac failure developing *in utero*[39,40]. This may have different manifestations, ranging from a mild transient dysfunction to severe cardiac disease. The echocardiographic details concerning cardiac impairment in TTTS are described in Chapter 42.

Assessment of the venous system appears to be of great importance. Gudmundson and colleagues

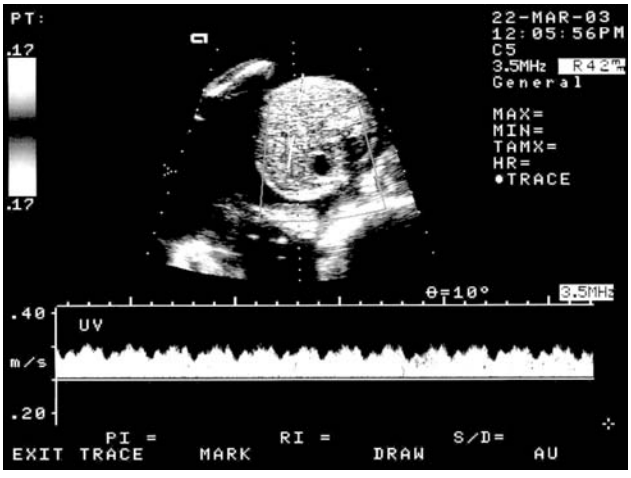


**Figure 41.4** Umbilical vein pulsations in the recipient with congestive heart failure at 29 weeks' gestation. Observe the unique and very peculiar line of pulsatility of blood flow

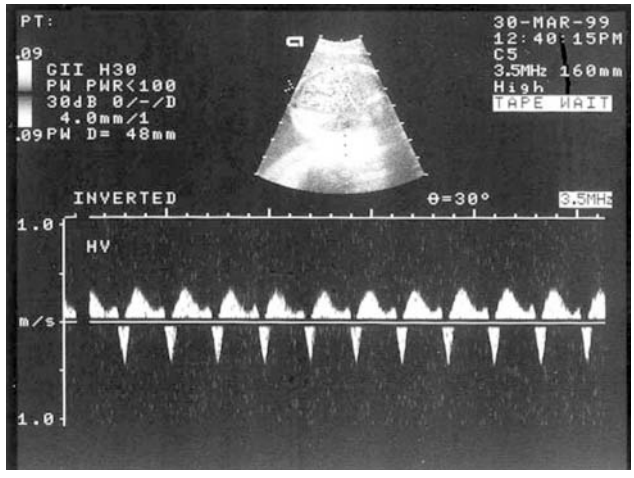


**Figure 41.5** Blood flow velocity waveforms from the hepatic vein in the recipient of twin-to-twin transfusion syndrome. Note the high percentage of reverse flow during atrial contractions in the hypervolemic twin

described umbilical venous pulsations as correlating with atrial contractions in six recipients[41] (Figure 41.4). These investigators also found an increased percentage of late diastolic reversed flow in the IVC compared with the forward flow during systole and early diastole (Figure 41.5). Umbilical venous pulsations have been shown to be a sign of fetal congestive heart failure in non-immune hydropic fetuses. These fetuses also present a decreased ventricular output and peak systolic velocities at the aortic and pulmonary valves[20]. Rizzo and colleagues observed changes in Doppler index values only at a time close to delivery in the majority of cases[20]. Such changes were present at the cardiac and venous levels, and were consistent with anemia in the smaller twin and massive blood transfusion in the larger twin[20].

Hecher and associates reported an interesting study of circulatory profile in both the recipient and the donor[42]. Most velocities in the IVC, the right hepatic vein and the ductus venosus (DV) were significantly reduced in both fetuses, and both indices describing waveform pulsatility were significantly increased in all three vessels of the recipient (Figure 41.6), whereas in the donor the increase was observed only in the DV. All fetuses with absent or reversed velocities during atrial contractions in the DV also showed umbilical vein pulsations. The majority of the recipients presented signs of tricuspid regurgitation. The authors suggested the existence of congestive heart failure in the recipient on the basis of abnormal waveforms in the studied veins and high incidence of tricuspid valve regurgitation. Two of the donors had abnormal DV waveforms and normal values of PI in the UA. The authors concluded that the possible explanation for this could be low umbilical

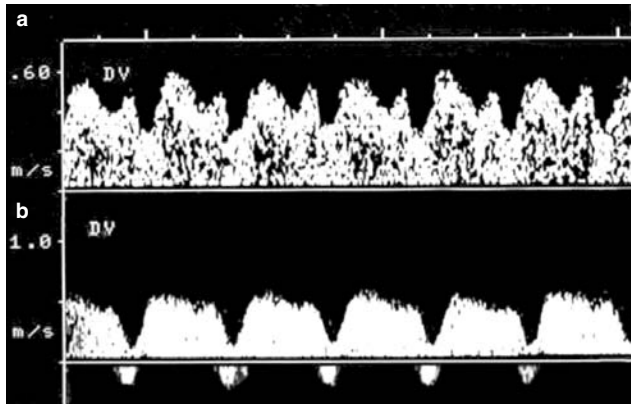


**Figure 41.6** Pulsed Doppler waveforms from the ductus venosus. (a) Normally grown twin characterized by forward flow throughout the cardiac cycle with high velocity during ventricular systole and diastole; and (b) recipient with signs of congestive heart failure in twin-to-twin transfusion syndrome. Note the presence of reversed blood flow during atrial contractions

venous pressure as a consequence of decreased umbilical venous return due to chronic TTTS[42].

The majority of investigators show the recipient's circulation as presenting signs of congestive heart failure due to hypervolemia. The increased end-diastolic ventricular pressure may be related to the significant decrease of diastolic venous flow velocities[42]. The donor's circulation is changed as result of hypovolemia, causing the decreased venous return[20,42], and the increased cardiac afterload results from an increased placental resistance[42].

The conflicting Doppler results in TTTS may be explained by different pathophysiological

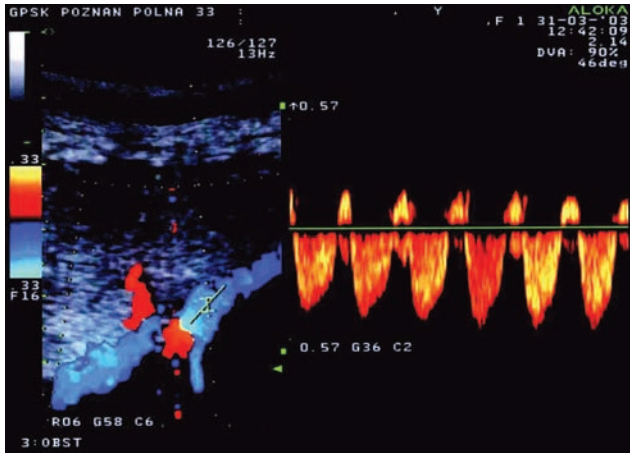


**Figure 41.7** Color flow mapping of arterio–arterial (A–A) anastomosis in twin-to-twin transfusion syndrome (left), and (right) pulsed Doppler waveforms obtained from superficial A–A anastomosis indicating bidirectional blood flow

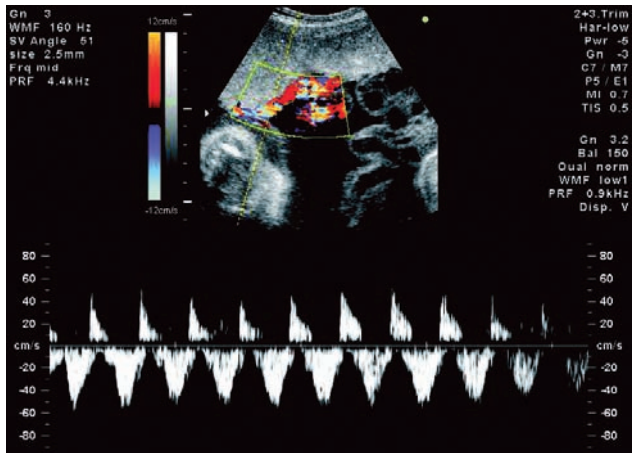


**Figure 41.8** Color flow mapping of arterio-arterial anastomosis with signs of turbulent flow (top) and blood flow velocity waveforms (bottom)

mechanisms and different stages of severity of the disease at the time of examination. Assessment of fetal cardiac function and better understanding of the pathophysiology of cardiac dysfunction in TTTS may help in determining the best therapeutic regimen and potentially improve the fetal outcome.

## Prenatal identification of anastomoses

Recently, color Doppler energy insonation of placental vasculature has been implemented. Arterio-arterial (A–A) anastomoses were recruited for an ultrasonographic survey of the chorionic plate using color Doppler energy, and were identified by their characteristic bidirectional interference pattern on spectral Doppler[43] (Figures 41.7 and 41.8). Antenatal demonstration of A–A anastomoses helps to diagnose monochorionicity. Because TTTS is associated with a paucity of superficial anastomoses, the presence or absence of functional A–A anastomoses may be a prognostic factor of TTTS development. Superficial anastomoses have been implicated in the hemodynamic sequel of co-twin death *in utero*, namely cerebral necrosis or intrauterine death. The visualization of superficial anastomoses by ultrasound may also have a role in monitoring therapy.

Even more recently, single reports demonstrated arterio-venous (A–V) anastomoses *in vivo* by color Doppler ultrasound[44,45]. An A–V anastomosis is characterized by termination of the chorionic artery near an unpaired chorionic vein, with blood continuing in the same direction as it flows towards the contralateral twin[44]. This technique allows identification of pregnancies at risk of TTTS and facilitates their treatment. Color Doppler ultrasound 'mapping' could make the endoscopic treatment of TTTS more selective and shorter, leading to less invasive techniques such as interstitial laser or focused ultrasound therapy[46].

Color Doppler sonography is unlikely to play a major role in assisting endoscopic laser in patients with acute polyhydramnios, as the communicating vessels cannot be identified in the majority of cases[36]. However, further prospective studies are indicated to determine the utility of color Doppler energy for those anastomoses in predicting risk in MC pregnancies.

## Is it possible to predict TTTS?

Alterations in cardiac hemodynamics might be indirectly shown by changes in venous blood flow waveforms. An abnormal pulsatile pattern of blood flow in the DV has been reported in fetuses with heart failure and growth restriction[47–49]. In TTTS, absent or reversed blood flow during atrial contractions has been described in the DV as a sign of congestive heart failure due to hypervolemia and increased preload from placental anastomotic transfusion[50]. Recently, reports of venous Doppler measurements in MC twins in early pregnancy suggested that early signs of cardiac impairment or defect might be manifested as increased nuchal translucency (NT) and abnormal blood flow in the DV[51]. Furthermore, the combination of discrepant intertwin NT and abnormal flow in the DV (Figure 41.9) in first-trimester MC twins was proposed as predictive of subsequent development of TTTS[52]. It is important to stress that

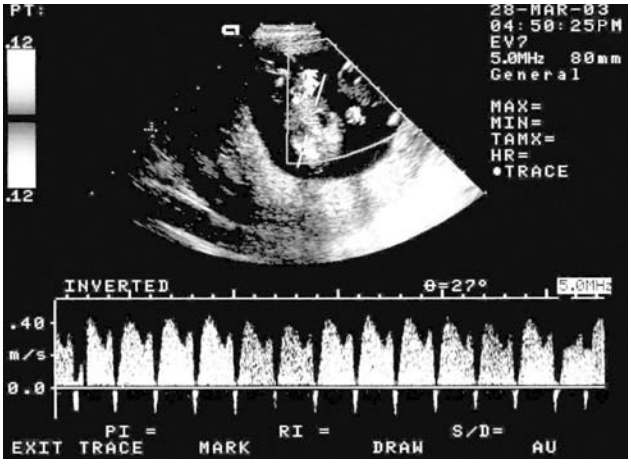


**Figure 41.9** Monochorionic–diamniotic twins at 12 weeks of gestation. The larger fetus presented reversed flow in the ductus venosus during atrial contractions in early pregnancy and signs of twin-to-twin transfusion syndrome at 28 weeks

increased NT in multiple pregnancy and abnormal blood flow in the DV seem to be related not only to chromosomal abnormalities or severe cardiac defects but also to specific complications of MC twins such as TTTS. Although this summary is possible, it should be remembered that these studies include small numbers of twin pairs.

## TWIN REVERSED ARTERIAL PERFUSION SYNDROME

Twin reversed arterial perfusion (TRAP) is a rare anomaly of multiple pregnancy (see also Chapter 71). Ultrasound imaging shows MC twins with inappropriate growth in one twin. The morphological evaluation reveals different malformations, with absence of the head and the thoracic organs in the most common forms. The TRAP sequence has been attributed to placental anastomoses which cause disruption of organogenesis and subsequent fetal acardia. This theory is supported by Doppler sonography which demonstrates reversed arterial blood flow from the placenta towards the acardiac twin[42,53].

Transvaginal color Doppler ultrasound is able to demonstrate the presence of retrograde perfusion in the UA of the abnormal twin in early pregnancy[54]. Moreover, it is essential to stress the role of echocardiography in the diagnosis of congestive heart failure in the 'pump twin' and in management strategy (see Chapter 42). Shih and colleagues used Doppler velocimetry to analyze the blood flow pattern in the UA[55]. Patterns were classified into one of three categories. The first, the so-called 'collision-summation', is characterized by a pattern of two independent pulsation rates of bidirectional flow (abnormal pulsatile heart in the malformed twin) with cyclic alterations of blood flow. The second, reported as 'twin pulse', shows the flow away from the acardiac twin (with the presence of a primitive heart) with absent diastolic velocity, and the flow pumped into the acardiac twin with a prominent diastolic component. In other words, both flows are constantly pumping in opposite directions and at different rates. The third, 'pump-in' pattern demonstrates pulsatile flow towards the acardiac mass in the reverse direction. It was suggested that the flow patterns of acardiac twins are determined by both the existence of a primitive heart and the nature of the vascular anastomosis[55].

Gembruch and colleagues presented a case of TTTS with death of a donor at 25 weeks of gestation and the development of TRAP sequence[56], observing reversed flow from the UAs through the aorta, left heart, right heart, IVC, DV and back to the placenta through the umbilical vein. This finding suggests that if one fetus dies in an MC pair, the falling blood pressure in the dying fetus may lead to a shift in the pressure gradient and cause an acute transfusion of blood from the surviving twin to the dying one through the superficial A–A or V–V anastomoses.

## CORD ENTANGLEMENT

The utility of color flow imaging and Doppler velocimetry in the diagnosis and management of monoamniotic (MA) twins is discussed in several articles[57–60]. The increased risk of perinatal morbidity and mortality in MC/MA twins is associated with cord accidents from entanglement of the two umbilical cords, a phenomenon which is now recognized to occur in virtually all instances by the 12th week[59,60] (see Chapter 67). Cord entanglement is usually visualized as a loop of entangled umbilical cords interposed between the ventral surface of the two fetuses or at the placental insertion. Most investigators reported diagnostic criteria such as knots or branching (Figure 41.10) of the umbilical vessels[57,61], high blood flow velocities[61] and demonstration of two different heart rates obtained from a single segment[59] (Figure 41.11). Doppler analysis of the blood flow pattern may reveal an abnormal S/D ratio, absent end-diastolic flow in the UA or even the presence of a notch in the UA waveform, reflecting the narrowing of the arterial lumen. In some cases high blood flow velocity and/or pulsatile blood flow in the umbilical vein may also appear. Several reports have recently documented the detection of umbilical cord entanglement in the first trimester[59,60].

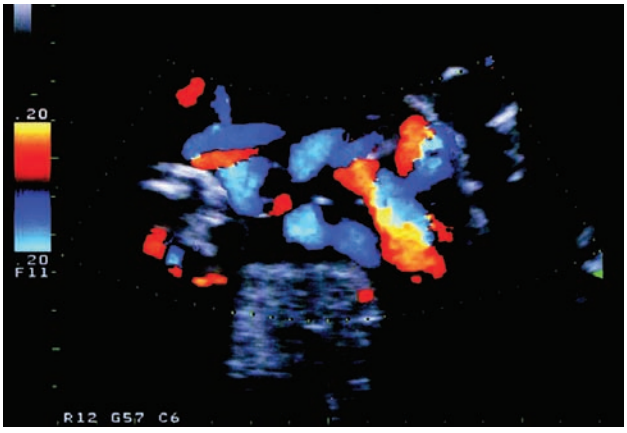


**Figure 41.10** Color flow mapping of umbilical vessels in transabdominal scan in monochorionic–monoamniotic pregnancy at 24 weeks of gestation. Note the overlapping vessels of the two crossing cords suggestive of 'branching' and cord entanglement

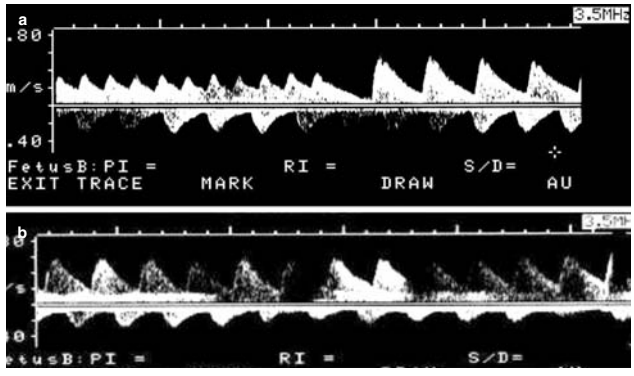


**Figure 41.11** Ultrasound scans of monochorionic–monoamniotic twins at 24 weeks. Blood flow waveforms obtained from the mass of cord vessels show two different heart rates, suggesting two various umbilical cords. This is especially evident in case (a) where one fetus presented signs of supraventricular tachycardia with periodic return to the normal rhythm

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# Fetal Echocardiography

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**42**

**FETAL ECHOCARDIOGRAPHY IN TWIN–TWIN TRANSFUSION SYNDROME**

**FETAL ECHOCARDIOGRAPHY IN TRAP SEQUENCE**

**CONGENITAL HEART DEFECTS**

**FETAL ARRYTHMIAS IN TWINS**

**FETAL ECHOCARDIOGRAPHY IN CONJOINED TWINS**

**FETAL CONGESTIVE HEART FAILURE**

## INTRODUCTION

Fetal echocardiography represents a major part of fetal cardiology, a new and exciting field of perinatal medicine. The use of echocardiography enables confirmation of normal heart anatomy and physiology, detection of structural malformations, follow-up of functional abnormalities and the monitoring of invasive therapeutic interventions. These diagnostic capabilities are not restricted to singleton gestations; fetal echocardiography also has specific goals when used in multiple pregnancies (Table 42.1). In the usual circumstance, multiple pregnancies are referred for targeted cardiac examination following an obstetric screening which detects a cardiac problem. However, there are also numerous maternal and fetal conditions (listed in Table 42.2) which indicate a comprehensive cardiac scan.

The examination duration is much longer in multiple pregnancy than the average 45 min required for a scan in singletons; more important, however, is the timing of the scan. In the first trimester when the size of the heart is 4–6 mm, fetal echocardiography can be misleading with respect to the intrinsic morphology (Figure 42.1). The optimal gestational age for fetal echocardiography is approximately 20 weeks, when the size of the heart is about 20 mm and large enough for clear and detailed visualization using a transabdominal

**Table 42.1** Goals of fetal echocardiography in multiple pregnancy

*General*
(1) Confirm normal heart anatomy
(2) Diagnose structural anomalies (congenital heart defect, or heart tumor)
(3) Relate neonatal prognosis with fetal cardiac defects
(4) Detect and evaluate functional anomalies such as valvular regurgitations
(5) Evaluate normal or abnormal cardiac rhythms
(6) Evaluate cardiomegaly (regardless of anatomy), myocarditis or cardiomyopathy
(7) Assess fetal congestive heart failure (imminent or fulminant)
(8) Identify extracardiac malformations
(9) Monitor fetal invasive therapy

*Specific to monochorionic twins*
(1) Evaluate the twin–twin transfusion syndrome
(2) Assess cardiac pathology in conjoined twins
(3) Assess cardiac function of the 'pump' twin in the TRAP sequence (acardiac twin)

TRAP, twin reversed arterial perfusion

**Table 42.2** Indications for fetal echocardiography

| |
|---|
| *Fetal* |
| Abnormal four-chamber view |
| Increased nuchal thickness |
| Abnormal heart rhythm |
| Ascites |
| Extracardiac malformation |
| Chromosomal abnormalities |
| Polyhydramnios |
| Oligohydramnios |
| Intrauterine growth restriction |
| Complicated twin gestation |
| Invasive fetal therapy |
| *Maternal* |
| Diabetes |
| Collagenosis |
| Epilepsy |
| Hyperthyroidism |
| Viral infection |
| Pharmacotherapy |
| Maternal age > 35 years |
| *Family history* |
| Congenital heart disease in the family |
| Chromosomal aberrations in the family |

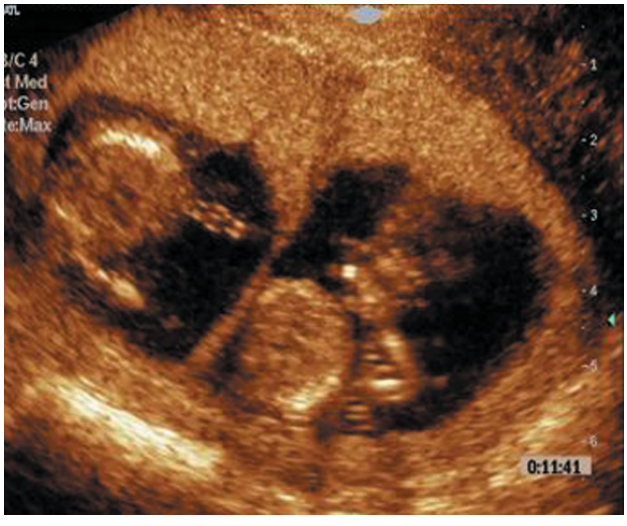


**Figure 42.1** Fetal heart at 12 weeks of gestation

approach (Figure 42.2), and, moreover, at this stage cardiac size should be similar in both twins (Figure 42.3).

After 30 weeks' gestation, however, when the size of the heart exceeds 30 mm, technical difficulties are more likely and interference with the image quality owing to fetal presentation and the well-developed rib cage, spine and lungs is a possibility.

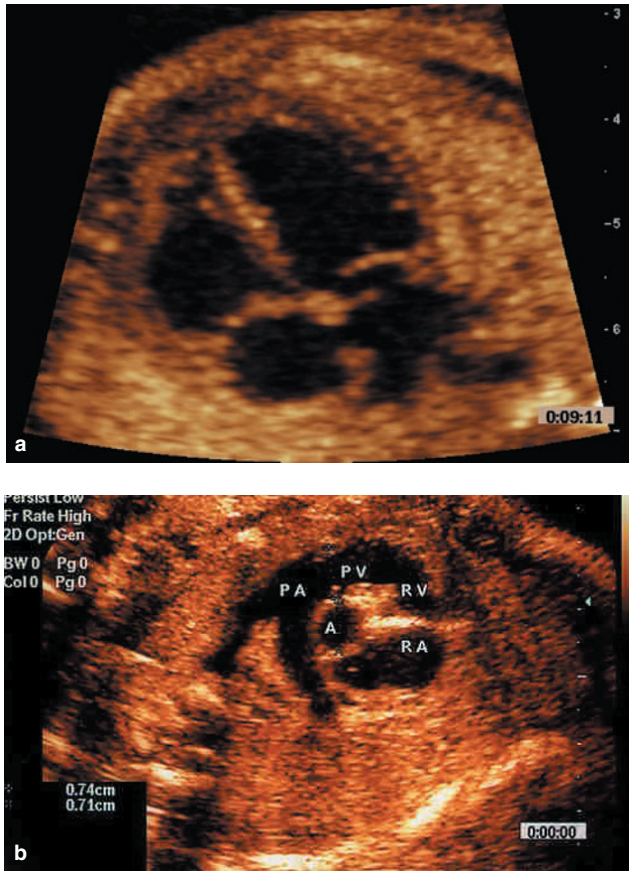


**Figure 42.2** (a) Normal four-chamber view of the fetal heart and (b) short-axis view of normal heart anatomy at 24 weeks' gestation. A, aorta; PA, pulmonary artery; PV, pulmonary vein; RA, right atrium; RV, right ventricle

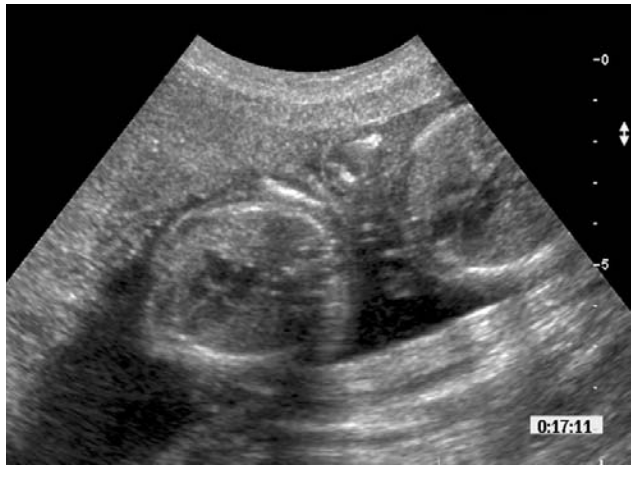


**Figure 42.3** Concordant size fetal hearts in normal twin gestation

Oligohydramnios and a thick maternal abdominal wall represent additional unfavorable conditions that make fetal late echocardiography time-consuming, difficult to perform, hard to interpret and, consequently, less reliable.

**Table 42.3** Echocardiographic characteristics of chronic twin–twin transfusion syndrome

| | *Donor* | *Recipient* |
|---|---|---|
| Heart size | normal | increased |
| Myocardium | normal | HKMP<br>R/LVOT obstruction |
| AV Doppler flow | normal (increased in anemia, decreased in end-stage) | increased<br>impaired systolic function<br>impaired diastolic function<br>tricuspid regurgitation<br>mitral regurgitation<br>pericardial effusion |
| Doppler studies | abnormal in UA, MCA | abnormal in IVC, DV, UV |
| Function | centralization | congestive heart failure |
| Hydrops | relatively rare | relatively common |

AV, atrioventricular valves; R/LVOT, right/left ventricular outflow tract; UA/UV, umbilical artery/vein; MCA, middle cerebral artery; IVC, inferior vena cava; DV, ductus venosus

## FETAL ECHOCARDIOGRAPHY IN THE TWIN–TWIN TRANSFUSION SYNDROME

### Cardiac pathophysiology

When the diagnosis of monochorionic twins is made in the first trimester, fetal echocardiography should be performed routinely at about 20 weeks in cases with concordant growth. However, in any case of discordant size or discrepant fluid volume, a fetal echocardiogram should be performed even earlier.

A detailed pathophysiological description of the twin–twin transfusion syndrome (TTTS) is provided in Chapter 65. TTTS is the result of an unbalanced circulation between a set of twins sharing the same chorion. Unidirectional net transfusion causes hypervolemia in the recipient and hypovolemia in the donor; however, hyper- and hypovolemia are not the only mechanism put forward to explain the syndrome, and other explanations including increased resistance due to primary placental malfunction and discordant oncotic pressures due to different protein levels have also been suggested (Chapter 65). Table 42.3 lists the echocardiographic characteristics when compensatory mechanisms fail to compensate for the increased preload and afterload of fetal hearts.

The recipient develops myocardial hypertrophy in either or both ventricles and in the septum, leading to outflow tract obstruction. Hypertrophy is probably caused by increased peripheral resistance and increased afterload. Bajoria and co-workers found increased levels of endothelin-1 in the recipient hydropic twin[1]. Endothelin-1 is a strong endothelium-derived vasodilator which, together with other vasoactive substances, remodels the myocardium and its vessels. Bajoria and co-workers also found a positive correlation between brain natriuretic peptide (BNP) levels and myocardial dysfunction. BNP increases in chronic congestive heart failure and causes diuresis and vasodilatation, and counteracts substances that remodel the heart (angiotensin II, endothelin-1, etc.). Hence, BNP is a sensitive biochemical marker of congestive heart failure in the recipient[2].

In the donor, but not in the recipient, high levels of renin–angiotensin protein are found in the kidneys as a result of to chronic ischemia, which may also increase arterial resistance and contribute to placental dysfunction and intrauterine growth restriction[3]. Hypertension in the recipient may be partly mediated by the transfer of the circulating renin produced by the donor. The major role of renin–angiotensin protein is stimulation of catecholamine and aldosterone, vasoconstriction and remodeling of the myocardium. This positive compensatory mechanism yields persistent increased overload, leading to myocardial ischemia and congestive heart failure. It follows that myocardial hypertrophy in the recipient, with the consequent impairment of cardiac function, can be partially explained by hormonal and vasoactive regulation of fetal circulation, and seems to be specific to the recipient. Moreover, the evolution of right ventricular hypertrophy and pulmonary stenosis are independent of treatment of TTTS[4]. In another report, Bajoria and colleagues[5] suggested that the recipient's increases in fetal urine output and polyhydramnios occur as a consequence of atrial natriuretic peptide.

Chronic hypovolemia and hypoxemia in the donor lead to insufficient tissue perfusion, stimulation of the renin–angiotensin system and permanent increase

in systemic resistance. Consequently, endothelial changes and fibrosis reduce arterial distensibility and cause systemic hypertension[6]. The donor's heart is usually of normal size, and lacks any functional abnormalities. However, Doppler studies may demonstrate increased maximal velocity at the level of the atrioventricular valve. For example, Lachapelle and colleagues[7] compared the cardiac index (cardiac output/body surface area) between donors and recipients, and found a lower index as well as lower cardiac output in donors. This may explain the observation that, in the hyperdynamic stage, maximal flow at the level of the atrioventricular valve increases in order to overcome hypovolemia, but decreases during the hypoxemic stage.

Fetal hydrops is unusual in the donor but may be induced by hypoproteinemia. Low angiotensin protein levels further induce hypovolemia and hypotension and decreased urine production. Hence, the fetal bladder is empty, and the donor is surrounded by oligohydramnios and later by ahydramnios.

## Echographic signs

### *First trimester*

The increased risk of developing TTTS in cases with increased nuchal translucency[8] is discussed in detail elsewhere (see Chapter 44). However, this association at least points to the possibility that increased nuchal thickness is an early manifestation of fetal congestive heart failure. Other signs such as discordant amniotic fluid volumes[9] and intertwin membrane folding[10] are discussed in Chapter 44.

### *Second and third trimesters*

The sonographic signs of chronic TTTS are described in detail in Chapter 44. In 1999, Quintero and colleagues proposed a method of TTTS staging, which did not include consideration of the fetal heart[11]. However, in the typical presentation of TTTS, differences are seen in the fetal heart (Figure 42.4a). Indeed, we have observed different functional cardiac anomalies as early as 18 weeks' gestation, strongly suggesting that cardiac malfunction is one of the first abnormalities of TTTS detectable by ultrasonography.

Our observation further suggests that the earliest symptom of fetal hypervolemia in the recipient is pulmonary regurgitation (Figure 42.4b), probably due to high pulmonary resistance at this stage of pulmonary vascular-bed development. This is followed by myocardial hypertrophy, an increase in size of the heart and leaking of the atrioventricular valve (Figure 42.4c and d). One should remember that myocardial hypertrophy mimics fetal cardiomyopathy, which usually affects the right heart[12], but rarely also the left[13].

Hecher and associates[14] reported that tricuspid regurgitation was present during systole in 40% of TTTS recipients. In six out of 19 cases, the E and A waves of the tricuspid valve fused during diastole (never noted in the donor), probably due to increased blood flow into the right ventricle. According to Karatza and co-workers[15], recipients had increased aortic and pulmonary flow velocities compared with their donor twins.

Cardiomyopathy in the newborn often results in impairment of both systolic and diastolic functions. Neonatal cardiomyopathy due to TTTS may also cause right ventricular outlet tract obstruction, mimicking (or causing) pulmonary stenosis, requiring treatment to maintain ductal-dependent circulation[16]. The neonate may also suffer from systemic hypertension. Among survivors, regression of cardiomyopathy, similar to that reported in infants of diabetic mothers, is observed during the early months (Figure 42.5).

The donor's heart is usually normal in echographic terms; however, blood flow velocity across the atrioventricular valves may be increased at the initial stage of hyperdynamic contractility. Lachapelle and colleagues[7] reported that the donor exhibits a hyperdynamic cardiac state, with significantly increased left ventricular shortening fractions and outputs. Hecher and associates[14], on the other hand, reported significantly decreased mean values of atrioventricular flow velocities.

Fetal hydrops in the donor is very rare, and its cause is unclear. It might be due to myocardial dysfunction and ischemia or redirected blood flow from the recipient to the donor. In contrast, hydrops in the donor after invasive laser therapy is not rare, and is present in 25% of cases[17]. It was postulated that a sudden increase in volume load after the procedure affected the donor, and that this clears a few days later in 90% of cases[17]. There are scant echocardiographic data on donor newborns. In one study, Fesslova and colleagues[13] found no abnormalities in these hearts.

Third-trimester and peripartum TTTS, without significant size discordance, may also occur. The acute type of TTTS results from blood shifts through the superficial anastomoses. The major problem is anemia and acute hypovelmia in the donor, and increased hematocrit and mild heart overload in the recipient. In such late or acute TTTS, the recipient newborn may present either with a moderate myocardial hypertrophy or without any echocardiographic abnormalities.

## Echocardiography after therapy

It is expected that more fetal cardiac hemodynamic abnormalities will be observed after laser therapy or

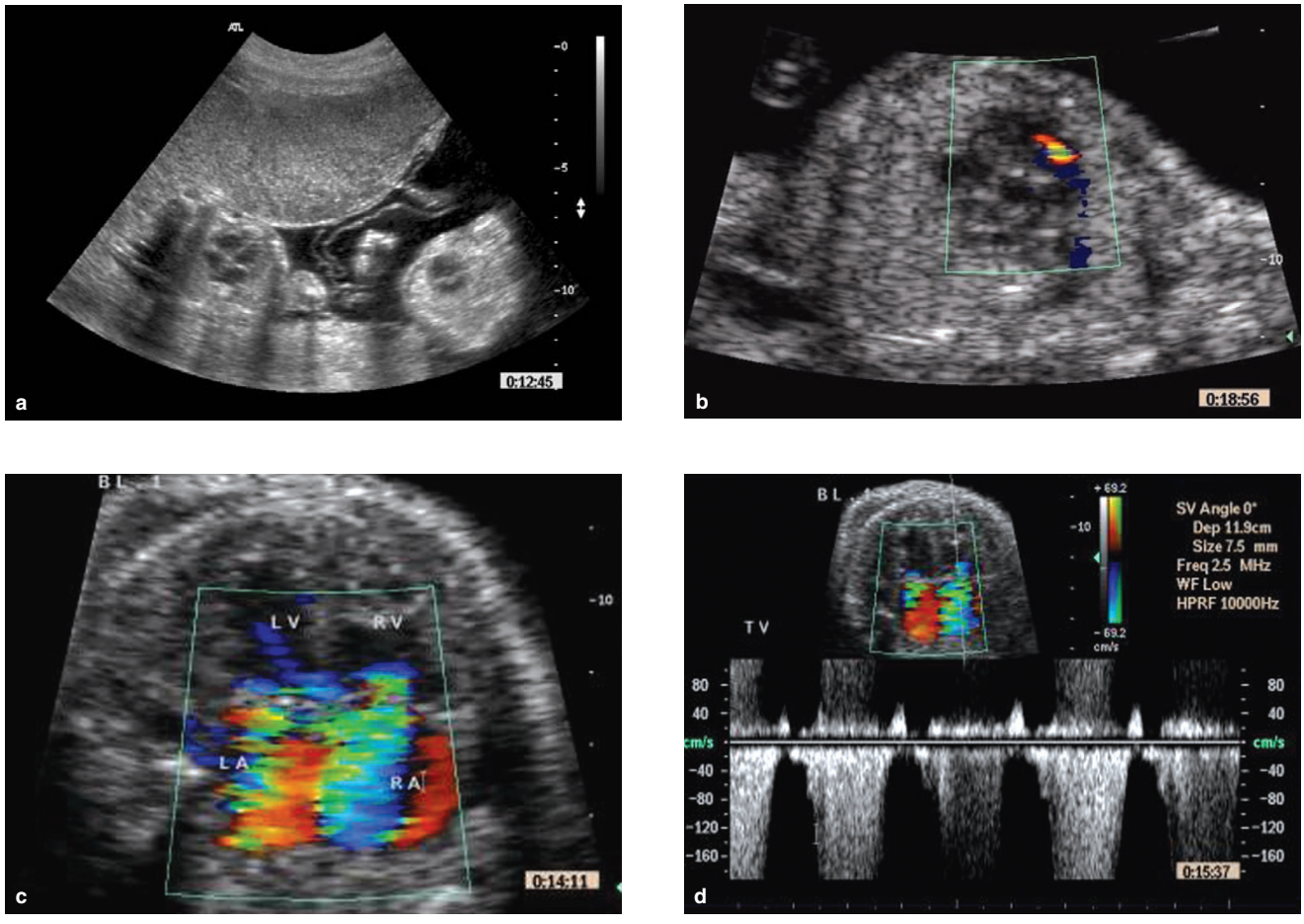


**Figure 42.4** (a) Discordant size fetal hearts suggestive of twin–twin transfusion syndrome (TTTS); (b) pulmonary regurgitation with normal heart anatomy: this is suggested as the first functional sign of TTTS due to blood volume overload in the recipient; (c) tricuspid and mitral regurgitation due to volume overload in the recipient: LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; (d) tricuspid valve holosystolic regurgitation (spectral Doppler tracing)

amniodrainage. Fetal hypertension in the ex-donor was suspected by Baud and associates[18] because of high systolic velocity through the tricuspid valve. Fetal systemic hypertension could occur either because of a dramatic increase in placental resistance in the area of the ex-donor twin or by reversal of the feto-fetal transfusion. Another cardiac abnormality after laser coagulation is temporary iatrogenic tricuspid atresia in the donor[14]. In the case of digoxin therapy, fetal echocardiography is the method of choice for close follow-up[19].

## Neonatal and post-neonatal sequelae

Cardiac complications beyond the neonatal period as a result of prenatal cardiac dysfunction can be transient, progressive or persistent[20]. Fesslova and colleagues[13] reported an improvement in cardiac

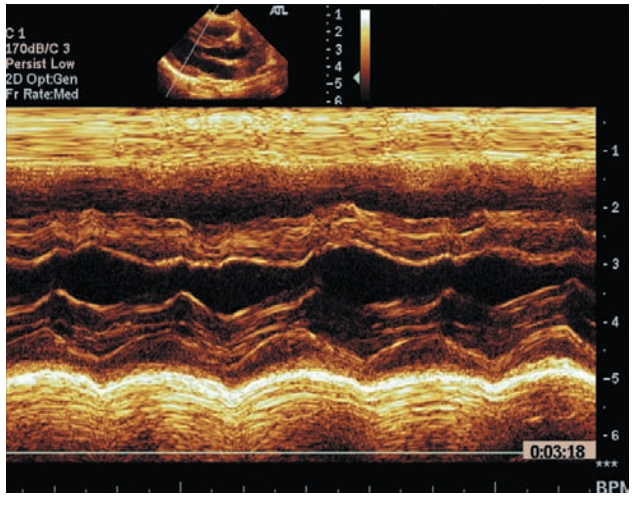


**Figure 42.5** Neonatal myocardial hypertrophy (in a recipient twin)

problems within 40 days to 6 months after birth in all surviving recipients; however, Zosmer's series[16] showed that one recipient died of endocardial fibroelastosis and infundibular pulmonary stenosis a week after delivery; two others needed balloon dilatation for pulmonary stenosis (one shortly after birth and one at 4 months); another twin had apical thickening of the right ventricle at 6 months of age. Pulmonary artery calcification in recipients, related to volume overload and endothelial injury, has also been reported as a postnatal complication of TTTS[21].

## FETAL ECHOCARDIOGRAPHY IN THE TWIN REVERSED ARTERIAL PERFUSION SEQUENCE

Chorioangiopagus parasiticus, the classic acardiac monster, is currently termed twin reversed arterial perfusion (TRAP) sequence (see Chapter 71). An acardiac twin is a rare complication that affects fewer than 1% of monochorionic multiple pregnancies or roughly one in 35 000 pregnancies[22]. In this anomaly, as the name implies, the heart is absent, and the circulation is maintained by vascular communications with the co-twin (the 'pump' twin). The 'pump' twin is structurally normal, but is at risk for *in utero* cardiac failure and fetal or neonatal demise.

Sonographic diagnosis of the TRAP sequence (see Chapters 39, 40 and 43) is confirmed by Doppler studies demonstrating retrograde perfusion in the umbilical cord of the abnormal twin. The final outcome and treatment modality, however, are based on frequent echocardiographic assessments[23]. The main issue is to detect early signs of *in utero* congestive heart failure of the 'pump' twin[24], because this complication may cause death in as many as in 50% of these otherwise normal co-twins. The surviving 'pump' twin may present with heart failure and persistent myocardial hypertrophy after birth, which may mimic hypertrophic cardiomyopathy. A typical presentation of an acardiac twin and 'normal' co-twin is shown in Figure 42.6a, and acardiac monster post-delivery in Figure 42.6b.

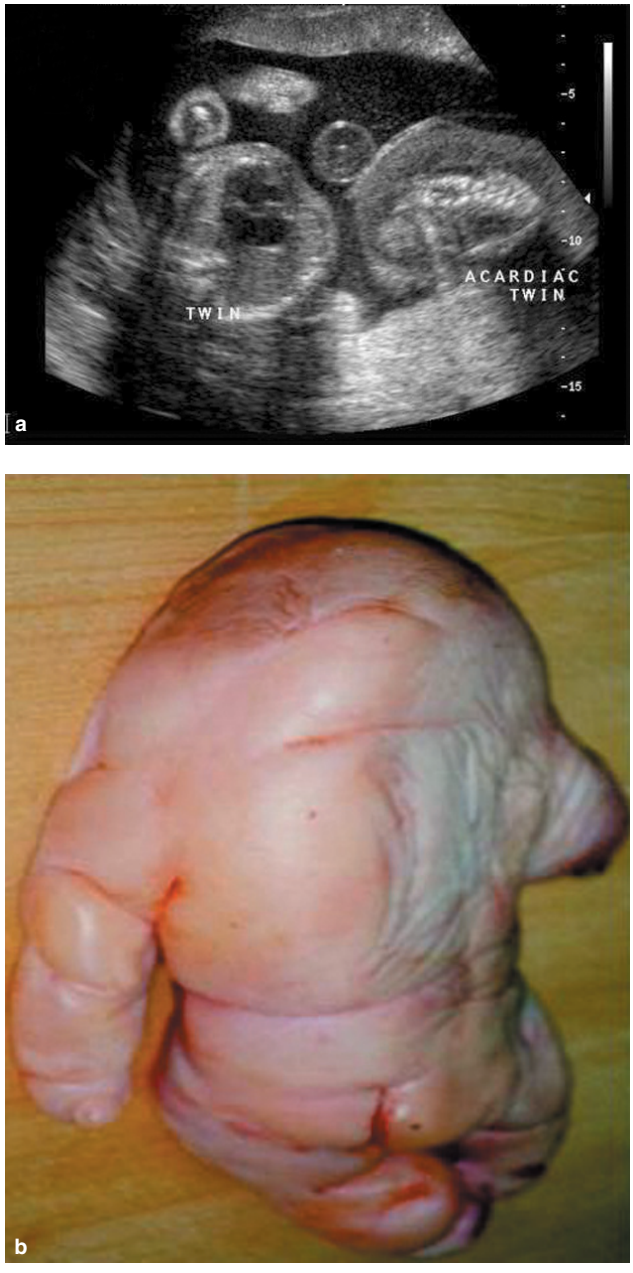


**Figure 42.6** (a) Twin pregnancy: normal fetus and acardiac monster, and (b) acardiac monster post-delivery

## CONGENITAL HEART DEFECTS IN MULTIPLE PREGNANCIES

The prevalence of structural malformations is increased in twin compared with singleton pregnancies (see Chapter 34). This axiom indicates careful examination of the fetal anatomy as an integral part of perinatal care. Twins may be discordant for a given anomaly (e.g. one twin with normal heart anatomy and the other with hypoplastic left heart) or both twins may have an anomaly, but of a different nature (e.g. one twin with a cardiac anomaly and the other with a central nervous system anomaly)[25].

In the majority of cases, structural heart defects present in dizygotic, dichorionic twins (for instance hypoplastic left heart syndrome or atrioventricular septal defect with normal heart anatomy in the co-twin) occur during heart embryogenesis. They should not be confused with 'acquired' structural defects in monozygotic, monochorionic twins, such as pulmonary stenosis which develops late during pregnancy. Discordant heart disease in a monochorionic set may mimic TTTS.

Koike and colleagues[26] reported hydrops fetalis due to Ebstein's anomaly at 22 weeks in one of

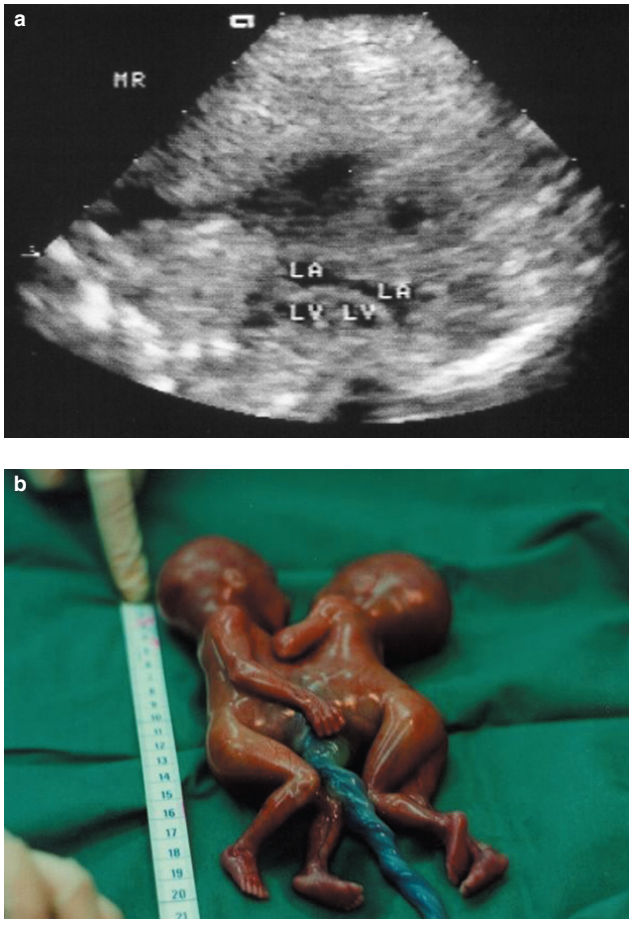


**Figure 42.7** (a) Conjoined hearts: LA, left atrium; LV, left ventricle; and (b) thoraco-omphalopagus after delivery at 22 weeks of gestation

monochorionic twins. The hydrops was treated with maternal digitalization and resolved by the 28th week of gestation. The twin with Ebstein's anomaly died 22 h after birth at 33 weeks; the non-affected twin survived, and was normal at 19 months of age. Needless to say, a cytogenetic work-up is often necessary when cardiac structural malformations are detected.

## FETAL ARRHYTHMIAS IN TWINS

The most common arrhythmias are premature atrial contractions, which are usually benign, require no pharmacological treatment and commonly resolve during pregnancy or during the first few days after delivery. However, the 'benign' nature of the arrhythmia should be carefully verified, because fetal premature atrial contractions can coexist with congenital heart defects such as ventricular septal defect (VSD) or transposition of the great arteries. Some types of fetal arrhythmias, in particular bradyarrhythmias, may be the first sign of neonatal myocarditis[27].

Supraventricular tachycardia in one twin requires special attention. Edwards and co-workers[28] reported good results with transplacental flecainide therapy in one such case, without evidence of maternal or fetal side-effects. However, such a situation may raise ethical and possible legal concerns regarding the best management option for this condition, which, at the same time, may cause complications in the co-twin and/or the mother.

## FETAL ECHOCARDIOGRAPHY IN CONJOINED TWINS

The most common form (52.4%) of conjoined twins is thoracopagus[29] (see Chapter 33). By definition, a conjoined heart is present, but the extent of sharing is variable. The hearts can be joined as a pericardial junction, minor venous/atrial connections or, more commonly (75%), an extensive conjunction with intermixing of chambers and valves. A typical example of conjoined hearts is shown in Figure 42.7a. Figure 42.7b is the same thoraco-omphalopagus after delivery at 22 weeks of gestation.

Clearly, the presence and extent of the cardiac union is a major determinant of the potential to separate the twins. According to Raffensperger[30], sharing of atrioventricular valves and ventricles virtually precludes successful separation, even if one twin is sacrificed.

Often a common atrium is present in conjoined twins, connecting with the inferior vena cava and the hepatic veins from each fetus. Anomalous pulmonary venous connection is common. Two or three ventricles are usually present. Single ventricles, one from each twin, are often joined and have one or more defects in the common wall, allowing communication between the chambers. Common or straddling atrioventricular valves often attach into the ventricular components from both twins. The right ventricles are often hypoplastic or rudimentary. Abnormal ventriculoarterial connections, including transposition or double-outlet right ventricle, are common in at least one twin. Abnormalities of the great arteries, including truncus arteriosus or interruption of the aortic arch, are also common[29]. Other reported defects include tricuspid atresia, mitral atresia, hypoplasia of either ventricle, tetralogy of Fallot and VSD. Very rarely, an acardiac twin is involved in the conjoined set[31].

The diagnosis of conjoined twins can be made as early as 8–10 weeks[32,33] (see Chapters 39 and 40). For those patients who decide to terminate pregnancy irrespective of the type of their conjoined twins, the sooner the diagnosis is made, the better. For those who consider continuation of the pregnancy, further fetal echocardiographic assessment is crucial. After completion of fetal echocardiographic evaluation at around 20 weeks' gestation, counseling

**Table 42.4** Treatment and outcome options in thoracopagi twins

| *Heart anatomy* | *Possible outcome* |
|---|---|
| Two separated hearts, both with normal anatomy | separation and survival possible for both twins |
| Two separated hearts: one with congenital heart defect, one normal | separation and survival possible for the twin with normal heart anatomy |
| Conjoined hearts | |
| at level of atria | single survivor after cardiac surgery |
| at level of ventricles | no survivors |

**Table 42.5** Etiology of fetal congestive heart failure

| | |
|---|---|
| (1) | Heart failure due to myocardial dysfunction (myocarditis, cardiomyopathy, volume overload) |
| (2) | Disorders of cardiac rhythm (tachycardia: FHR > 220/min, or persistent bradycardia) |
| (3) | High output failure due to anemia, arteriovenous fistula, Galen's malformation, sacrococcygeal teratoma, etc. |
| (4) | Abnormal peripheral impedance with fetal growth failure |
| (5) | Twin–twin transfusion syndrome or acardiac twin |
| (6) | Congenital heart defect and progressive valvular regurgitation and/or 'acquired' *in utero* myocarditis |

FHR, fetal heart rate

**Table 42.6** Fetal echocardiographic markers of congestive heart failure

| |
|---|
| Cardiomegaly: heart area/chest area ratio > 0.45 |
| Heart circumference/chest circumference ratio > 0.55 |
| Atrial enlargement |
| Holosystolic tricuspid valve regurgitation |
| Slow upstroke for tricuspid valve regurgitation (d*P*/d*t*) |
| Trivial and holosystolic mitral valve regurgitation |
| Pulmonary and aortic regurgitation |
| Decreased shortening fraction of right ventricle, left ventricle or both (normal values 28–40%) |
| Myocardial hypertrophy (wall thickness > 4 mm, sign of fetal hypertension) |
| Abnormal A/E ratio for mitral and/or tricuspid valve (in compromised fetus E = A, or E > A) |
| Dilatation of the inferior vena cava > 5 mm |
| Dilatation of the hepatic vein |
| Hepatomegaly |
| Reversal flow in ductus venosus |
| Abnormal pulsation in the inferior vena cava (A/S ratio > 0.15) |
| Pulsation in the umbilical vein |
| Ascites, pericardial effusion or hydrothorax |
| Polyhydramnios |
| Placentomegaly |

*P*, pressure; *t*, time

about the possible surgical procedures after birth can be offered. It should be remembered, however, that neonatal echocardiography is technically much more difficult and usually provides only screening information during the first examination.

When conjoined twins are diagnosed during the later stages of pregnancy, obstetric ultrasound as well as fetal echocardiography is much more difficult to perform, and sometimes three-dimensional and/or fast magnetic resonance imaging is necessary for better anatomical delineation of the twins. However, even if not all the anatomical details are clarified by fetal echocardiography, there is usually sufficient information to support a 'no resuscitation' decision after elective cesarean. Out of 11 cases of conjoined twins reported by Sanders[29], there were nine thoracopagi: six with conjoined hearts and three with shared pericardium. Survival is possible only in those with normal heart anatomy, as was the experience of Mackenzie and co-workers[34].

Based on fetal echocardiographic findings in conjoined twins, one may construct a follow-up scheme to confirm or rule out an option for successful separation (Table 42.4).

## FETAL CONGESTIVE HEART FAILURE

Fetal congestive heart failure (CHF) is defined as inadequate tissue perfusion, which results in a series of complex reflexes and adaptation to improve forward flow or redirect flow to vital organs. As well as TTTS, other conditions may lead to fetal CHF (Table 42.5). Although fetal CHF is a serious condition, it can be successfully managed with extensive co-operation between the obstetrician and fetal cardiologist[35].

Once the diagnosis is made and the fetuses have reached maturity, fetal CHF is an indication for elective cesarean section. Before this stage, fetal therapy such as maternal digoxin administration, dexamethasone or other drugs administered to the mother or directly to the fetus can be considered. Serial echocardiograms, focusing on specific markers of CHF (Table 42.6), would follow fetal response to treatment.

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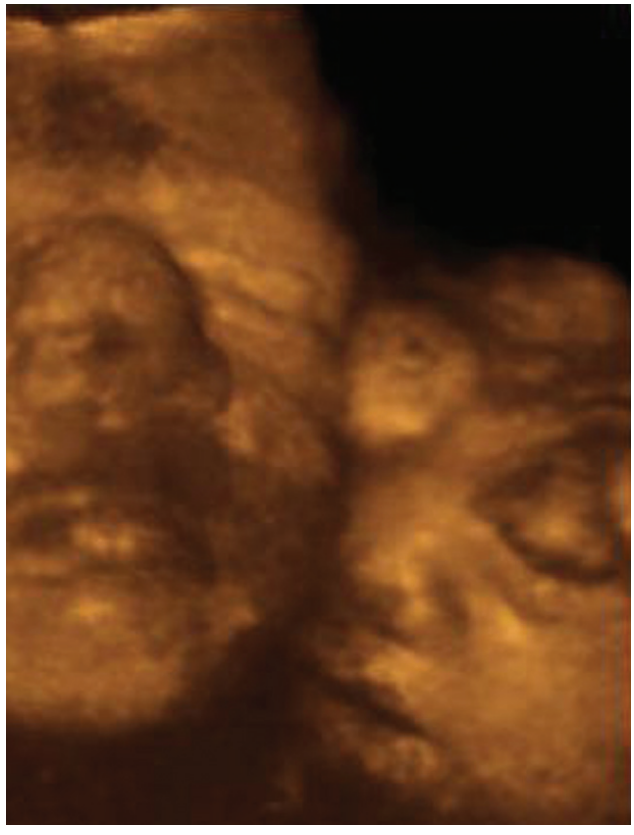
# Sonographic Assessment of Fetal Anomalies

*I. Meizner and R. Hackmon*

**43**





Normal (left) and anencepahlic (right) monochorionic twins. (3D image courtesy of B. Caspi)

## INCIDENCE AND ETIOLOGY OF FETAL ANOMALIES IN TWINS

The rate of multiple pregnancies, mainly twins, has increased significantly in the past three decades, owing mostly to the introduction of assisted reproductive technologies in developed countries[1]. Multiple pregnancies are associated with higher risks of preterm birth, fetal anomalies and intrauterine growth restriction[2,3]. Twin pregnancies result from the

fertilization of two ova (dizygotic twins, DZ) or a single ovum (monozygotic twins, MZ) (see Chapter 15). They can also be classified on the basis of chorionicity and amnionicity (see Chapter 24). All DZ twins are dichorionic–diamniotic, whereas MZ twins are dichorionic–diamniotic, monochorionic–diamniotic or monochorionic–monoamniotic, depending on the timing of zygote division[4]. Before the introduction of assisted reproductive technologies (ART), the estimated proportions in twin pregnancies are 80% dichorionic and 20% monochorionic[5].

In general, twins have a two- to three-fold higher rate of congenital malformations than that of singletons, mainly because of the higher incidence (by about 50%) of malformations in MZ compared with DZ twins[6,7]. The reasons for the higher morbidity and mortality in twins compared with singletons and in MZ compared with DZ twins remain unclear. However, the three leading theories are as follows[8,9]:

(1) Vascular theory: the hemodynamic imbalance caused by vascular anastomoses impairs normal organogenesis.

(2) Implantation theory: an unfavorable implantation site leads to abnormal blood supply to the fetuses, predisposing them to malformations. Indeed, marginal and velamentous cord insertions are commonly found in malformed twins.

(3) Two-hit theory: monozygosity *per se* is an imbalance in the genetic clock of the embryo. The consequence is a disadvantaged embryo susceptible to environmental agents that would not have any effect in singletons or in dizygotic twins[9].

Congenital defects in twins are classified into three main groups[10]:

(1) Unique to twins: such as twin-to-twin transfusion, conjoined twins, twin acardia and fetus-*in-fetu*.

(2) More common in twins than in singletons: such as anencephaly, hydrocephalus and congenital heart disease.

(3) Mechanical or vascular-related: such as congenital dislocation of the hip, clubfoot and skull asymmetry.

These anomalies are significant because of the much higher *in utero* mortality of twins than singletons (25% vs. 0.3%)[11]. Congenital defects may also be divided into major malformations, i.e. structural anomalies in the major anatomic systems (cardiovascular, nervous, gastrointestinal and urinary), and minor malformations. Concordant anomalies are those that occur in both twins simultaneously. Their incidence is 15% in MZ twins and lower in DZ twins[7].

In this chapter, we review the unique fetal anomalies in MZ twins and the prenatal ultrasound criteria for their diagnosis and assessment.

## FETAL ANOMALIES IN MONOZYGOTIC TWINS

The unique fetal anomalies in MZ twins include twin-to-twin transfusion syndrome (TTTS) (see Chapter 65), acardiac twin (see Chapter 71), fetus-*in-fetu* and conjoined twins (see Chapter 33). The first three are thought to derive from a vascular imbalance resulting from intraplacental anastomotic communications. As this type of imbalance is possible only in the presence of a single (i.e. monochorionic) placenta, these anomalies are seen only in MZ twins. They also occur more often in females[12,13]. Some authors suggest that the timing of twinning may be a factor in gender difference, with a female tendency for incomplete embryonic division. Female predominance may also be explained by the increased intrauterine survival of females compared with males, and findings that several phenotypic female twins are genotypic XO. Conjoining is due to division of the embryonic disk after more than 13 days of fertilization[14,15].

In view of the greater incidence of fetal anomalies in twin pregnancies (especially MZ), early ultrasonic evaluation of fetal anatomy is of crucial diagnostic importance. In the first and early mid-trimester, assessment should focus on six major factors: chorionicity at 5 weeks and amnionicity at 8 weeks (see Chapter 39)[16]; major structural defects; nuchal translucency (see Chapter 47); gender of both twins; placentation (see Chapter 39); and exclusion of bifid appearance of the embryonic pole.

In the middle–late second trimester and the third trimester, sonography should focus on the following features: fetal anatomy; estimated fetal weight; discordance between fetal weights; intertwin discrepancy in amniotic fluid; evidence of 'stuck twin'; presence of hydrops; and cord insertion sites (see Chapter 44). Doppler velocimetry, performed in early and late pregnancy, can often reduce perinatal mortality in twin pregnancies in selected cases (see Chapter 41)[17].

## TWIN-TO-TWIN TRANSFUSION SYNDROME

TTTS is discussed in detail in several chapters of this volume (see Chapters 27, 44 and 65). Within the context of this chapter, however, it should be stressed

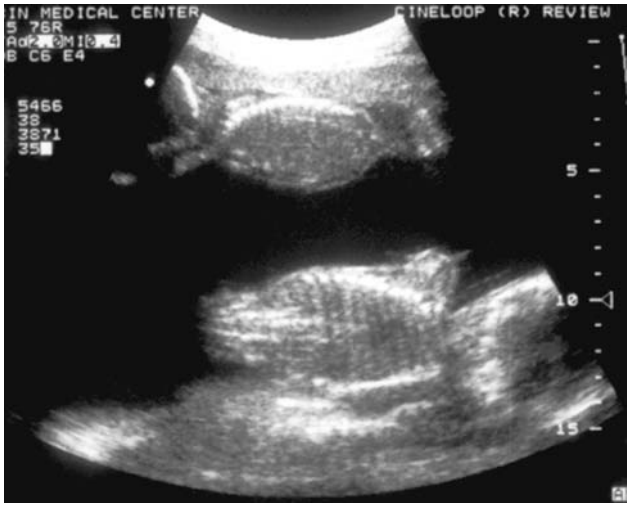



**Figure 43.1** Ultrasound image of the 'stuck twin' in twin-to-twin transfusion syndrome. The lower fetus is larger and is surrounded by polyhydramnios. The smaller (upper) fetus has no amniotic fluid at all

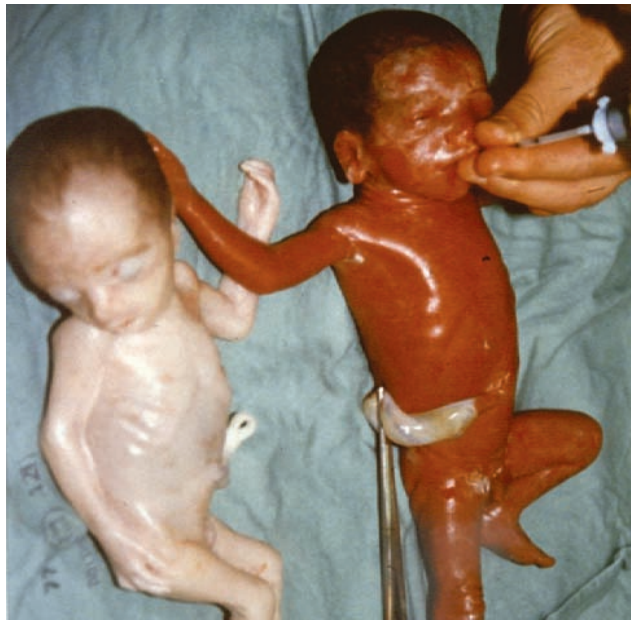


**Figure 43.2** Postpartum image of newborns with twin-to-twin transfusion syndrome. Note the larger plethoric newborn on the right and the smaller, anemic twin on the left

that the 'classical' sonographic findings of the so-called 'stuck twin'[18] (Figures 43.1 and 43.2) are not always seen. A related sonographic phenomenon is twin oligohydramnios/polyhydramnios sequence (TOPS). Its criteria include same-sex twins, single placenta, thin separating membrane, weight discordance of at least 20% of the weight of the larger twin and a major difference in amniotic fluid volume with severe oligohydramnios in one sac. This sequence is diagnosed in mid-gestation when the oligo–polyhydramnios becomes apparent as a consequence of variations in fetal urine production[19]. The earlier is its appearance, the graver is the outcome[20]. The differential diagnosis of TOPS includes rupture of the membranes of one twin, fetal renal disease of one twin or polyhydramnios of one twin (as in gastrointestinal obstructions). Such diagnoses require a very high index of suspicion, however, if the twins are of different sex or dichorionic, or when two distinct placentas are detected[21].

## ACARDIAC TWIN

The reported prevalence of acardiac twin is variable (see Chapter 71). A strong female predominance is seen[22,23]. Typically, the acardiac twin has a non-functioning heart, in addition to other characteristics, such as poorly developed or absent upper extremities or head[24] and severely malformed upper body with (variably) holoprosencephalus, anencephalus or other brain malformations, facial cleaving and large cystic hygroma, abnormality of the thoracic viscera, severe abnormality of the thoracic bone structure, or severe abnormality or absence of the upper abdomen (liver, pancreas and upper intestine). Less frequently, the lower half of the body is affected, resulting in abnormalities of the external genitalia[25], equinovarus and radial-ray deficiency, or abnormal or aberrant vasculature (single umbilical artery, persistent urachus, etc.). The 'normal' or 'pump' twin is usually also affected, and has functional abnormalities due to volume overload, such as cardiomegaly, polyhydramnios, heart failure and pleural and peritoneal effusion[25].

The leading developmental theory for the occurrence of this phenomenon suggests that acardiac twin results from imbalanced interfetal blood flow from a high- to a low-pressure placental artery, causing cardiac atrophy. The 'normal' twin thus supplies blood to the recipient acardiac twin through arterio-arterial or veno-venous placental anastomoses. The consequent reversed flow in the arterial cord blood of the recipient is termed twin-reversed arterial perfusion (TRAP) sequence (see Chapter 71). The low-pressure deoxygenated blood flows from the arterial cord blood via the hypogastric artery, so that the lower fetal body is better developed than the upper[7,23]. Half of all acardiac twins have an abnormal karyotype[24], considered to be a contributing factor to this anomaly[10].

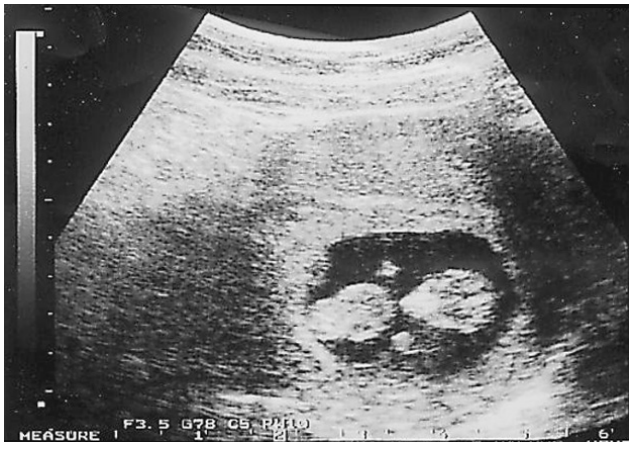
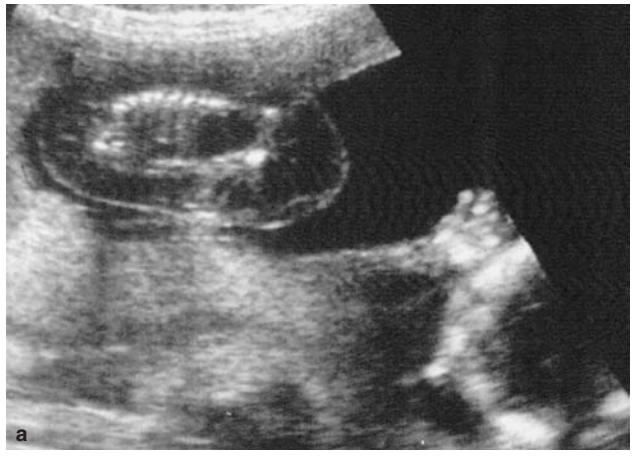



**Figure 43.3** First-trimester ultrasound image of monochorionic twins. The left structure was considered a missed twin. The diagnosis of acardiac twin was reached when the missed twin had increased in size on a subsequent scan. (Image courtesy of I. Blickstein)



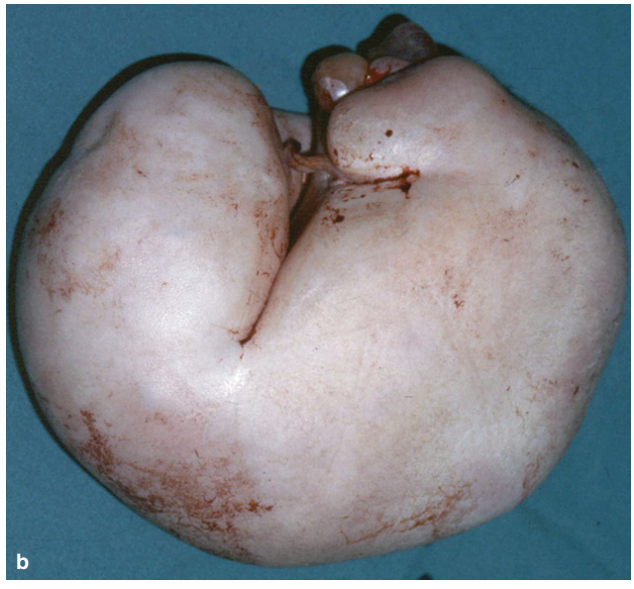




**Figure 43.4** Acardiac twin. (a) Ultrasound image of the amorphic acardiac fetus. Note part of the fetal skeleton. (b) Postnatal photograph of the same acardiac twin

The earliest reported gestational age for sonographic diagnosis of acardiac twin is 9 weeks. Figure 43.3 shows an early sonogram of MZ twins with one acardiac fetus erroneously diagnosed as a missed twin. However, sonographic prenatal diagnosis is easy in the second trimester (Figure 43.4a and b). The diagnosis should be suspected on detection of a severe malformation, such as an unidentifiable head, trunk or extremities, in a monochorionic pair[23]. Other sonographic criteria include the absence of cardiac pulsations in one twin, generalized subcutaneous edema, polyhydramnios and cystic masses in the upper fetal body (Figures 43.5–43.11). In rare instances, a heartbeat is noted in the acardiac twin, which may represent either a reflection of the pump twin's heartbeat or the presence of a rudimentary heart in the acardiac twin[10]. Sometimes serial sonographic examinations are required to rule out single fetal death within the pair. The diagnosis is confirmed by a finding of reversed blood flow in the acardiac twin on umbilical Doppler study. In addition, the arterial umbilical systolic/diastolic (S/D) ratio is significantly high[26–28].

The main sonographic differential diagnosis of acardiac twin is teratoma, wherein an amorphous trigeminal-layer mass is attached to a normal fetus. Teratoma can be differentiated by the completely disorganized nature of the tissue and the intrafunicular position[26]. In addition, the acardiac twin has a separate umbilical cord.

In a large retrospective review, Moore and colleagues[29] reported the outcome of 49 pump twins. Respective rates were: perinatal mortality 55%, premature delivery 35%, congestive heart failure 53%, polyhydramnios 46% and major structural anomalies 9%. These authors suggested that the proportion of weight of the acardiac twin related to the weight of the pump twin could serve as a prognostic indicator: the larger the recipient twin, the higher the overload on the pump twin (Figure 43.12a). A ratio of over 70% was associated with a preterm birth rate of 90%, polyhydramnios rate of 40% and a rate of congestive cardiac failure of 30% (Figure 43.12b), as opposed to 75%, 30% and 10%, respectively, for ratios lower than 70%. In view of the poor outcome of these pregnancies, several authors[30,31] suggest that when the diagnosis is made before 24 weeks or the twin weight ratio is more than 70%, parents should

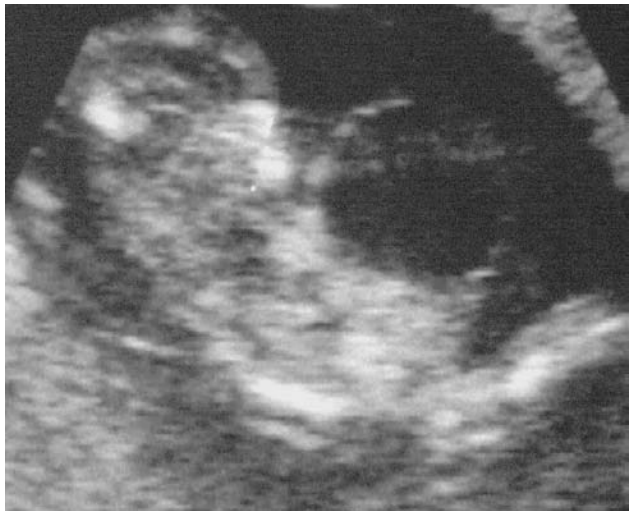


**Figure 43.5** Ultrasound image of another acardiac twin. Note the distended, fluid-filled abdomen

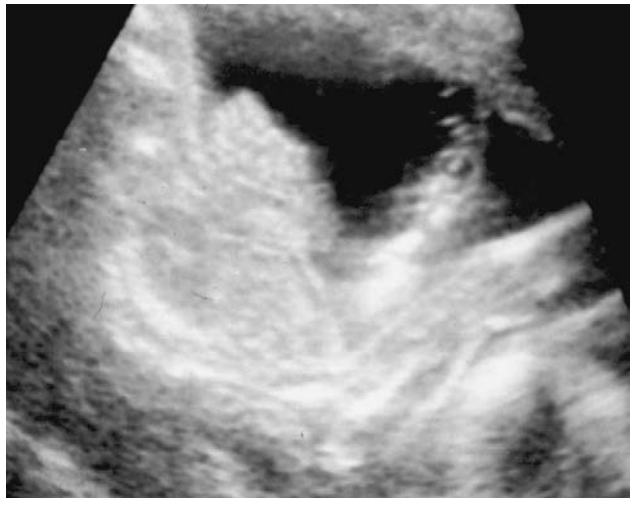


**Figure 43.7** Acardiac twin at 22 weeks of gestation. Note the grotesque and malformed structure of the fetus

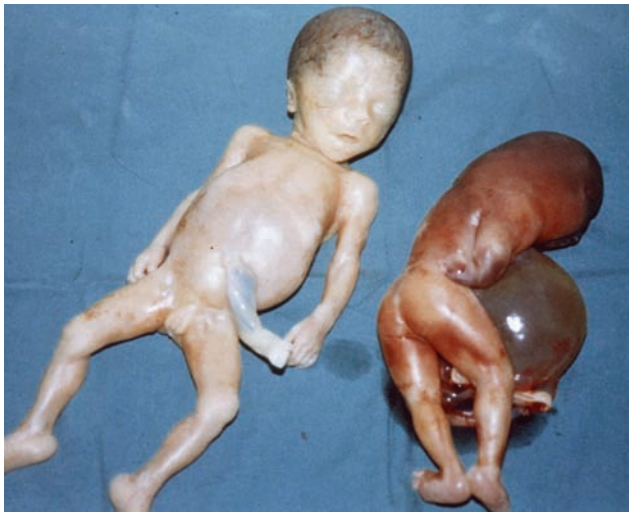


**Figure 43.6** Post-abortion image of the acardiac twin seen in Figure 43.5. Note the malformed acardiac abortus in relation to the normal abortus

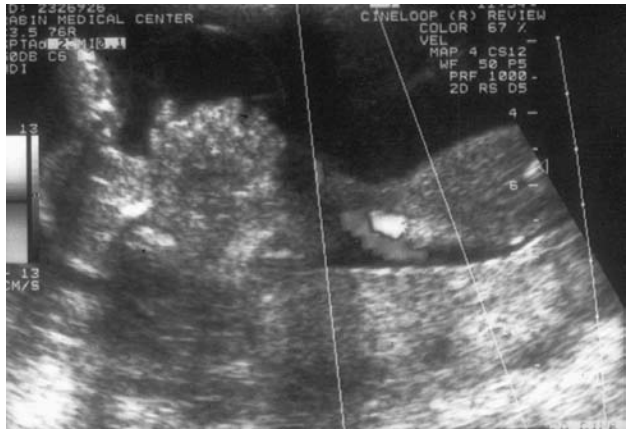



**Figure 43.8** Ultrasound image of the umbilical artery of the normal fetus

be counseled regarding elective termination of the pregnancy. Other options are genetic amniocentesis and medical treatment or invasive procedures, namely hysterotomy and selective delivery of the acardiac twin, coil occlusion of the acardiac umbilical cord or fetoscopic ligation of the acardiac umbilical cord[32–34]. However, the last procedure has been used only sporadically, and with partial success. When the twin weight ratio is less than 70%, expectant management with weekly sonographic evaluation is advised. Medical treatment, such as indomethacin to alleviate hydramnios or maternal digoxin to improve the hydrops, can be considered.

## FETUS-*IN-FETU*

This rare malformation consists of one MZ, monochorionic–diamniotic twin lying within or partially within the body of its sibling (Figure 43.13). The reported incidence in the older literature is one per 500 000 births[35]. The suspected etiology is similar to that of acardiac twin, that is, reversed umbilical flow and anastomoses of the vitelline vasculature[36]. Cardiac development in the affected twin is impaired, arresting its growth. The so-called

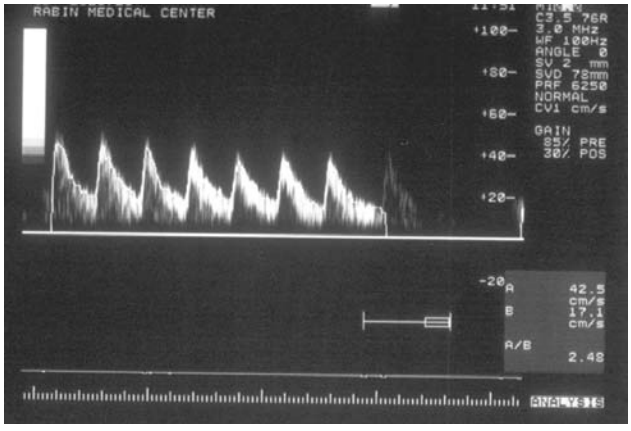



**Figure 43.9** Doppler signals obtained from the umbilical artery of the normal twin. Note normal pulsatile pattern

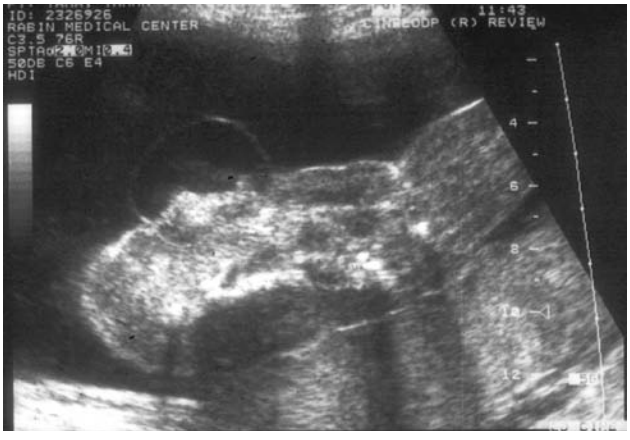



**Figure 43.10** Ultrasound image of the umbilical artery of the acardiac twin

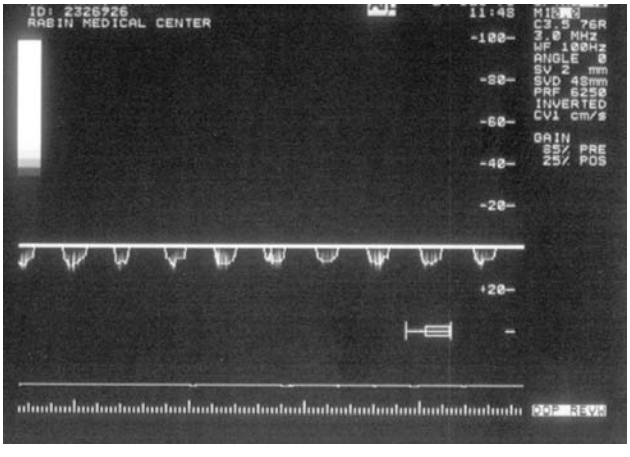



**Figure 43.11** Doppler signals detected in the acardiac umbilical artery. Note shallow amplitude and absent end diastolic flow

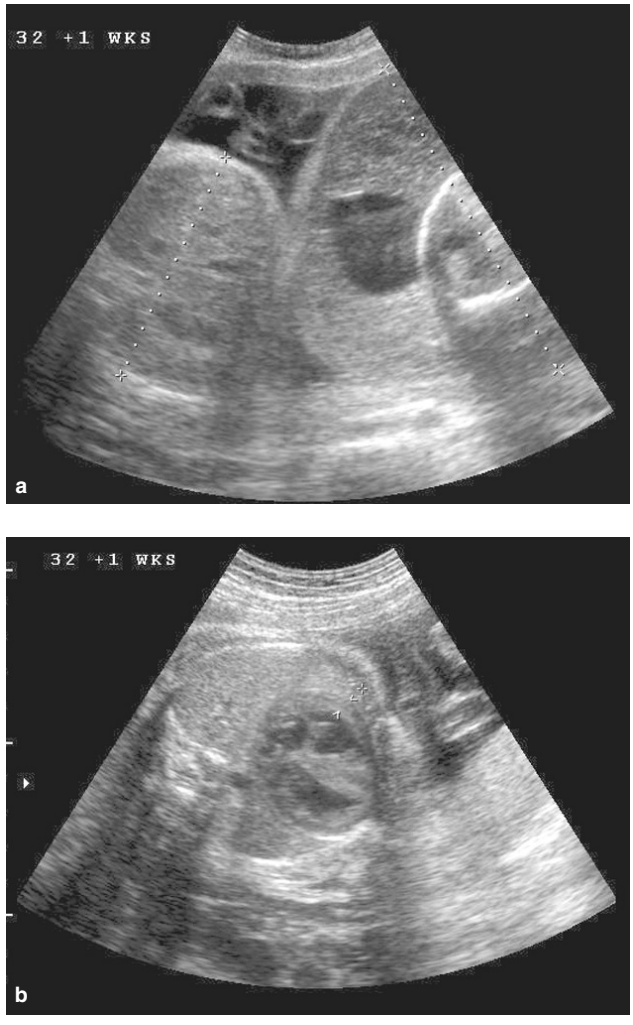



**Figure 43.12** (a) Comparison of abdominal perimeters of the normal (right) and acardiac (left) twins. (b) Measurement of cardiac wall hypertrophy of the 'pump' twin. (Images courtesy of B. Caspi)

normal twin grows so that, by the third week of gestation[37], it 'embeds' the growth-restricted partner.

In their contemporary review of 88 surviving children (and one original case), Hoeffel and colleagues[38] noted that most children born with a fetus-*in-fetu* did not survive beyond 18 months; there were ten exceptions: one at 20 months, two at 5 years, one at 7 years, two at 9 years, one at 10 years and three at more than 15 years. The male/female ratio was 47 : 35, with five undetermined genders. Abdominal pain was the main complaint in 70% of cases. The fetus was located retroperitoneally in 80% of cases. Other locations were the skull (six cases), sacrum (six cases), scrotum (one case) and mouth (one case), in addition to the central nervous system, gastrointestinal tract, gastrointestinal vessels and genitourinary tract, but rarely in the lungs, adrenals,

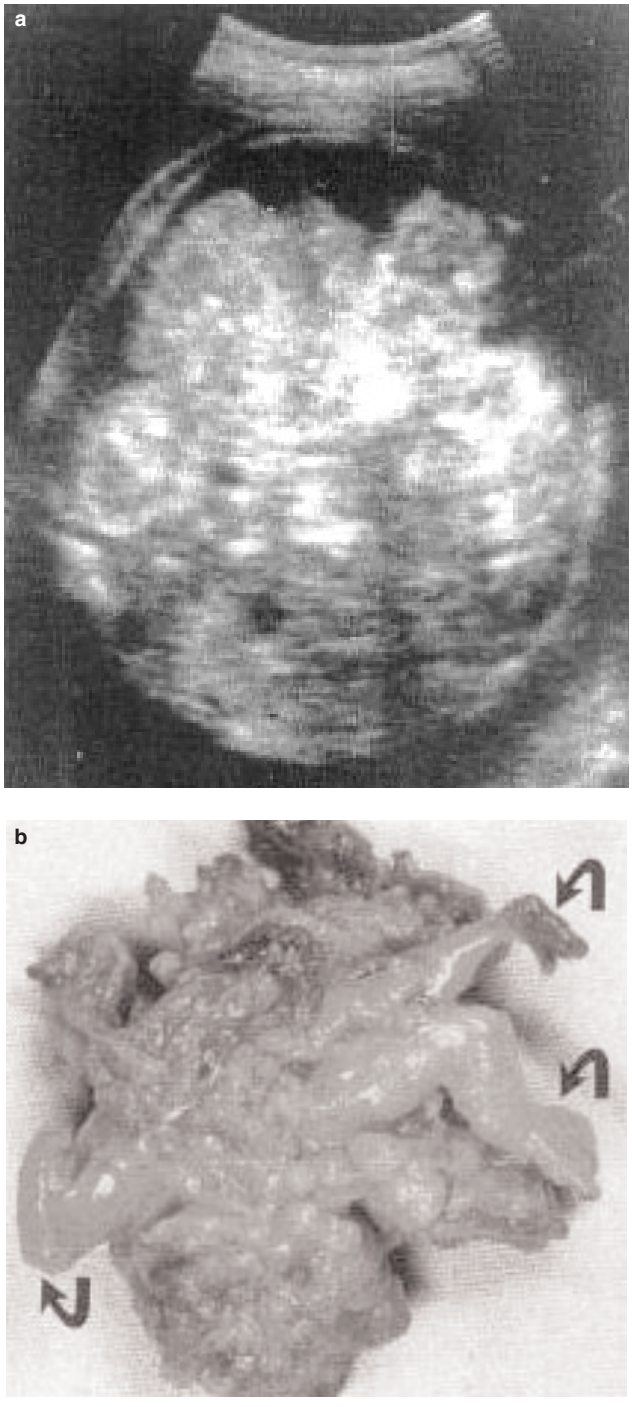



**Figure 43.13** Fetus-*in-fetu*. This case was found in a miscarriage of 24 weeks. The sonographic scan (a) shows a large-for-dates fetal head (biparietal diameter 12.4 cm. head circumference 42 cm), with a large intracranial hyperechogenic and amorphic mass. The pathologic examination (b) revealed an immature teratoma, including well-defined fetal limbs. Images courtesy of I. Solt MD and I. Goldstein MD. Reprinted from *Am J Obstet Gynecol* Vol. 175. Goldstein I, Jakobi P, Groisman G, Itskovitz-Eldor J. Intracraninal fetus-*in-fetu*, 1389–90 (1990), with permission from Elsevier

spleen, pancreas or lymph nodes. In 88% of cases, there was a single parasitic fetus; in the remainder ($n$ = 5), the number of fetuses ranged from two to five. Fetus size ranged from 4 to 24.5 cm, and weight from 1.2 g to 1.8 kg. The organs present in the fetus-*in-fetu* were as follows: vertebral column, 91%; limbs, 82.5%; central nervous system, 55.8%; gastrointestinal tract, 45%; vessels, 40%; and genitourinary tract, 26.5%. The *in situ* fetus was always anencephalic, and in almost all cases, the vertebral column and the limbs were present (91% and 82.5%, respectively). Lower limbs were more developed than upper, and the heart was very rarely found[38].

On prenatal ultrasound, fetus-*in-fetu* appears as a complex mass within the host twin. The mass is characteristically cystic with fluid (amniotic fluid), and contains a second, echogenic mass within it (fetus) suspended on a pedicle (cord). Most cases are described as pedunculated masses within a capsule containing fluid and a single umbilical artery[39,40]. A rudimentary spinal architecture may also be visualized. Other malformations such as anencephalus or omphalocele are common[41].

The differential radiologic and sonographic diagnosis includes teratoma and meconium pseudocyst, which also tend to be calcified. In most cases, fetus-*in-fetu* is differentiated by the presence of a spinal structure[41]. However, in 9% of cases, no vertebral column is found, even on pathologic examination. At least one author suggests that teratoma and fetus-*in-fetu* are the same phenomenon with a different appearance[42]. We, however, agree with others that teratoma is an accumulation of pluripotential cells that have not undergone organogenesis or vertebral segmentation[43].

The sibling twin is generally normal, and seldom has other malformations not directly related to the mass[16].

## CONJOINED TWINS

'Conjoined twins' is covered in Chapter 40.

## ASSISTED REPRODUCTIVE TECHNOLOGIES AND TWIN FETAL ANOMALIES

Of the 8319 live-born children conceived by intracytoplasmic sperm injection (ICSI) to date, 40% were multiples. Most multiples are twins, and 4.4% (in one survey 13.2%) are triplets. This substantial increase in multiple pregnancies must be considered the most important complication of assisted reproductive technologies. Having said this, the data on the malformation rate in children born after assisted reproductive technologies are unclear.

The few studies of ICSI fetal karyotype reveal that, compared with the general neonatal population, babies conceived by ICSI have a slight but significant increase in *de novo* sex chromosomal aneuploidy (0.6% vs. 0.2%) and structural autosomal abnormalities (0.4% vs. 0.07%), and an increased number of inherited (mostly from the infertile father) structural aberrations. Nevertheless, although the different percentages of major and minor congenital malformations cannot be compared, the large, reliable surveys thus far do not indicate a higher rate of malformations in ICSI than in naturally conceived children[44].

## ACKNOWLEDGMENT

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# Sonographic Diagnosis of Twin-To-Twin Transfusion Syndrome

*A. Matias and N. Montenegro*

**44**



*'… Two nations are in thy womb, and two manners of people shall be separated; and the one people shall be stronger than the other people; and the elder shall serve the younger…'*

*Genesis 36: 25*

## INTRODUCTION

Perinatal mortality among monochorionic (MC) twins is three- to five-fold higher than in dichorionic (DC) twins, especially before 24 weeks, when the perinatal loss in MC compared with DC pregnancies is 12.2% versus 1.8%, respectively[1].

A great part of this difference is because about 15% of MC twin pregnancies are complicated by twin-to-twin transfusion syndrome (TTTS)[1]. This syndrome accounts for 17% of perinatal mortality, nearly 12% of neonatal deaths and 8.4% of infant deaths in twins[1].

TTTS has long been recognized as a devastating complication of so-called identical twins, but approximately 400 years was required to understand its mechanisms, and this understanding is still subject to rapid and continual revision (Table 44.1). Although clinically devastating and easily identifiable with modern sonography, adequate and safe treatment remains elusive (see Chapters 65).

TTTS presents some of the greatest therapeutic challenges in perinatal medicine because:

(1) It affects *two* fetuses, both of which are completely structurally normal;

(2) Its basis lies in the *placenta*, not in either fetus;

(3) It causes *important perinatal morbidity* and *mortality* but is amenable to *treatment*.

Although the earliest possible diagnosis of MC twinning is highly desirable, it is seldom achieved in practice. Clearly, it is chorionicity rather than zygosity that determines several aspects of antenatal management and perinatal outcome (see Chapters 39 and 40). Zygosity refers to the type of conception, whereas chorionicity denotes the type of placentation. The type of placentation, depends on the time of splitting of the fertilized ovum.

**Table 44.1** Important milestones in the present-day understanding of twin-to-twin transfusion syndrome (TTTS)

| | |
|---|---|
| 1687 | description of vascular anastomoses in MC placentas |
| 1900 | description of anastomoses in TTTS (Schatz[7]) |
| 1941 | neonatal diagnosis of TTTS (Herlitz) |
| 1981 | antenatal diagnosis of TTTS (Wittmann *et al.*[2]) |
| 1990 | scoring for diagnosis of TTTS (Blickstein[3]) |
| 1995 | AV anastomoses architecture in MC placentas (Bajoria *et al.*[8]) |
| 1997 | antenatal prediction of TTTS (Sebire *et al.*[1], Matias *et al.*[4]) |
| 1999 | scoring for therapy of TTTS (Quintero *et al.*[5]) |
| 2001 | mathematical model for TTTS (Umur *et al.*[6]) |

MC, monochorionic; AV, arteriovenous

## TWINNING PROCESS: DOES IT MATTER?

Monozygotic (MZ) twinning occurs in one-third of twin pregnancies. The MC twin placenta is designed and built for a singleton fetus; hence, attempts to cater for the needs of twin fetuses are often suboptimal. Specifically, the fetal circulations of each twin are seldom separate, and intertwin vascular communications are commonly present. In addition, unequal sharing of the placental parenchyma is the rule rather than the exception. The intertwin vascular communications frequently, but not invariably, lead to a complication virtually unique to MZ twinning: TTTS[3].

In the most simple of terms, TTTS reflects a pathologic form of circulatory imbalance that develops chronically between hemodynamically connected MC twin fetuses. By way of intertwin vascular connections, blood is transfused from the donor, who becomes growth-restricted and develops high-output cardiac insufficiency and oligohydramnios, to the recipient, who develops circulatory overload with congestive heart failure and polyhydramnios (see Chapter 42).

## THE MONOCHORIONIC PLACENTA IS NOT A 'BLACK BOX'

The ubiquitous nature of the vascular anastomoses found invariably in virtually all MC placentas means that interfetal transfusion is a normal event in MC twin pregnancies. When the intertwin transfusion is balanced, clinical manifestations of TTTS do not occur; when it is not, TTTS becomes apparent, in forms that vary between mild and catastrophic. More than a century ago, Schatz[7] suggested that TTTS was due to discordant hemodynamics secondary to transfusional imbalance. Almost a century later, Bajoria and co-workers related TTTS to unbalanced intertwin transfusion mediated by one or more arteriovenous (AV) anastomoses in association with absent bidirectional superficial anastomoses[8]: those affected by TTTS had fewer arterio-arterial (AA) anastomoses than those without TTTS.

The relative paucity of AA anastomoses meant that these placentas were unable to compensate for the unidirectional flow in a 'causative' A+V anastomosis. Under this circumstance, the progressive nature of TTTS *in utero* is thought to be due to one twin (the donor) slowly pumping blood to the other (the recipient) through the causative anastomoses. The net result of transfusion between twins depends on:

(1) *Vascular anastomoses*: combination of type of connections (number, type and diameter) and direction of connections. In some cases, the normal transfusion from the donor's arterial to the recipient's venous circulation is not adequately compensated by oppositely directed flow by other deep or superficial anastomoses[8].

(2) *Placental sharing*: unequal placental sharing, either by discrepant size of placental territory or by velamentous insertion of the umbilical cord, augments changes caused by transfusion differences[9].

(3) *Asymmetry in the progressive reduction* of an initially large number of bidirectional anastomoses[10].

(4) *Unbalanced renin–angiotensin system (RAS)*: up-regulation of the RAS (donor) and down-regulation of the RAS (recipient) with transfer of angiotensin II may cause or contribute to the development of TTTS[11]. In the donor twin, the initial volume depletion may activate the renin–angiotensin cascade, resulting in the production of angiotensin II, a vasoconstrictive peptide, restoring extracellular volume and maintaining blood pressure. The initial adaptation then becomes noxious, since an excess of angiotensin II induces intrarenal vasoconstriction and decreases fetal diuresis, thus aggravating oligohydramnios. In the recipient, down-regulation of the RAS increases diuresis and causes polyhydramnios. This causes compression of the umbilical cord of the donor with consequent hypoperfusion and stimulation of the RAS in the donor, thereby increasing oligohydramnios. Extrarenal RAS activation may explain the occurrence of fetal hypertension and cardiomyopathy.

(5) *Incomplete remodeling* and *defective trophoblast invasion of maternal spiral arteries*.

In singleton pregnancies with intrauterine growth restriction, examination of the placental bed shows that vascular colonization and remodeling are incomplete, essentially in myometrial segments. In MC twins with TTTS, Matijevic and colleagues[12] demonstrated that in the smaller twin placenta there is defective trophoblast invasion of the myometrial component of the maternal spiral arteries, contributing to the interpair variation in birth weight.

The pathophysiology of TTTS is incompletely understood, and, although transfusion has been confirmed *in vivo*, TTTS pathophysiology clearly includes more than shunting of blood from the donor to the recipient. A vicious cycle of hypervolemia–polyuria–hyperosmolality is established, so that in about one-third of cases an acute polyhydramnios/oligohydramnios sequence develops in the second trimester of pregnancy, thus providing an additional insult to the fetuses who have already begun to deteriorate.

## DIAGNOSIS OF TWIN-TO-TWIN TRANSFUSION SYNDROME

In the past, diagnosis of the syndrome was made only after delivery of the affected twin pair and careful examination of the placenta. The standard neonatal criteria comprised: a difference in *cord hemoglobin*

concentrations of 5 g/dl or more; a difference in *birth weights* of 20% or more.

Danskin and Neilson[13] revisited the neonatal criteria for diagnosis of TTTS, finding that an intertwin hemoglobin disparity of 5 g/dl or more and birthweight differences of more than 20% were found in both MC and DC twins at similar rates. Wenstrom and colleagues[14] shortly thereafter also found that weight and hemoglobin level discordance were relatively common among MC twins without TTTS. With the publication of these two reports, it became clear that making a diagnosis of TTTS based solely on neonatal criteria was totally insufficient.

Fortunately for all concerned, sonographic criteria for antenatal diagnosis of TTTS were waiting in the wings[2,15–17]. Specifically, in 1981, Wittmann and associates[2] proposed as discriminating findings in the diagnosis of TTTS: discrepancy in the sizes of twins, as well as hydramnios surrounding the larger twin. One year later, and almost 400 years after the causative anastomoses were first described, Brennan and colleagues[15] added to these criteria: disparity in the size of vessels in the umbilical cords, same sex, single placenta showing different echogenicities of the cotyledons supplying the two cords, and evidence of hydrops in either twin or congestive heart failure in the recipient. It is clearly a credit to countless obstetric sonographers in diverse locations, having at their disposal increasingly sophisticated technology, that, at the present time, not only is the diagnosis ultrasonically based, but recently a composite of ultrasonographic features has been proposed to identify TTTS correctly and minimize false-positive errors (Table 44.2). The following paragraphs elaborate the steps listed in the table. Interested readers can refer to Chapters 27, 39 and 40 for further information.

## Determination of monozygosity and monochorionicity

TTTS is a syndrome peculiar to MC pregnancies. As such, the first step towards its diagnosis is the establishment of zygosity (if possible) and chorionicity (around 100% correct chorionic assignment is possible in the first trimester of pregnancy). Same sex and monoplacentation strongly suggest but do not prove monozygosity. In contrast, the concomitant appearance of several sonographic criteria assists in the correct diagnosis of chorionicity, the most determinant factor in terms of perinatal prognosis:

(1) One placenta with a paper-thin, reflective hair-like septum without a chorion between the two amnions (T-sign) at 10–14 weeks of gestation (Figure 44.1);

(2) Very thin septum of less than 2 mm;

(3) Same sex in the observed pair.

If, on the other hand, one finds two separate placentas (Figures 44.2 and 44.3) or two fetuses of unlike sex, and a lambda or twin-peak sign with chorion between each layer of amnion at 10–14 weeks of gestation, dichorionicity is strongly suggested (see Chapter 39) and TTTS can be ruled out because it is a complication of MC placentation.

## Discordance in size

Discordant growth is a common complication of twin pregnancies (see Chapter 61). The need for stricter sonographic criteria to define growth has resulted in a change in the so-called 'gold standard' of growth assessment over time. Considering that fetal weight estimations based on singleton growth charts vary with different populations and thus may be inadequate for twins, the abdominal circumference criterion was proposed as the most reproducible and meaningful for the sonographic diagnosis of divergent twin growth. Indeed, a 20-mm difference in abdominal circumference between twins indicates growth discordance of more than 20%[18].

## Discordance in amniotic fluid volume (oligohydramnios sequence)

In 1988, Chescheir and Seeds[19] described a powerful diagnostic clue for TTTS based on the fact that six out of seven twin pregnancies with MC placentas and this condition had concurrent polyhydramnios and oligohydramnios. This is not surprising when we consider that TTTS is a clinical manifestation of an intertwin hemodynamic imbalance[13]. As part of the

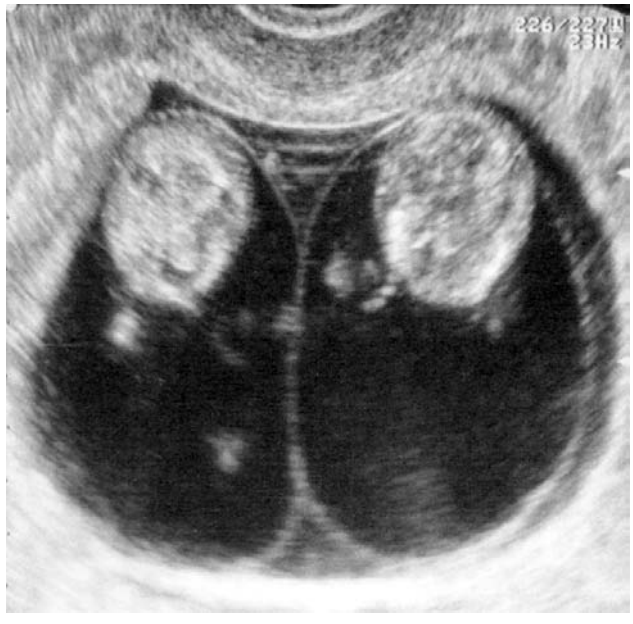

**Figure 44.1** Example of a monochorionic twin pregnancy at 11 weeks of gestation, showing a thin dividing membrane without chorion between the amnion layers

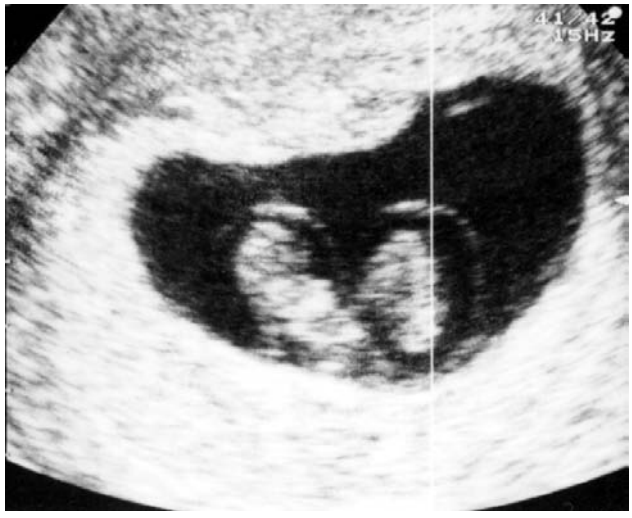

**Figure 44.2** Early scan at 9 weeks of gestation, showing a monochorionic twin pregnancy with two amniotic sacs

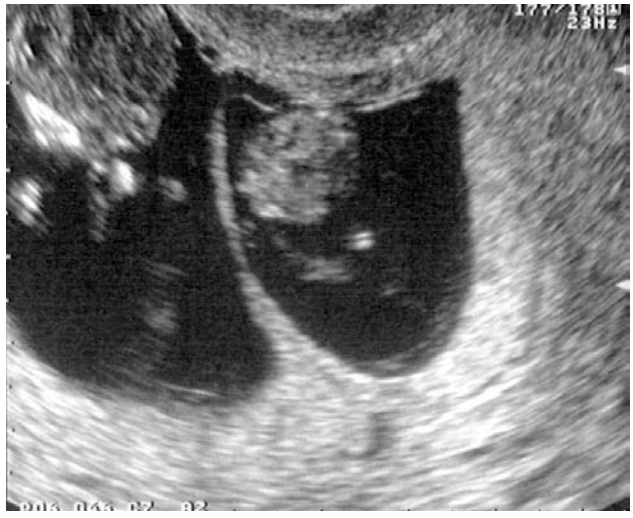

**Figure 44.3** Lambda sign at 12 weeks of gestation, depicting a thick layer of chorion between the two layers of amnion, and defining a dichorionic–diamniotic twin pregnancy

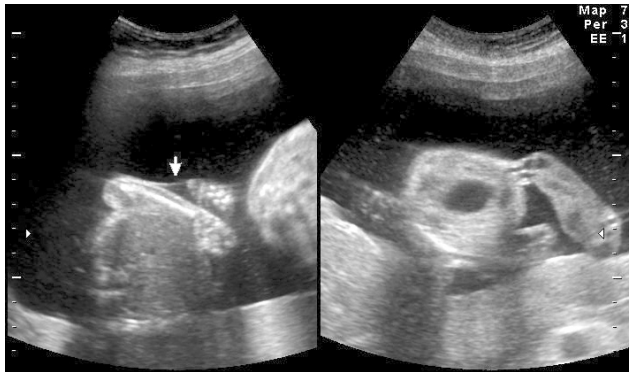

**Figure 44.4** 'Stuck twin'. The right image shows the recipient surrounded by severe polyhydramnios. The left image shows the donor entrapped in its membranes (arrow), surrounded by the severe polyhydramnios of the recipient. If the thin membrane is missed, the image could be erroneously diagnosed as monoamniotic twins. Image courtesy of B. Caspi, Kaplan Medical Center

hemodynamic imbalance, fetal renal perfusion is asymmetric, because hypervolemia in the recipient will overperfuse the kidneys, with consequent polyuria and an excess of amniotic fluid. At the same time, the hypovolemia in the donor causes inadequate perfusion of the kidneys, with a decrease in urinary output and oligohydramnios.

Recently, more uniform criteria have been proposed for a quantitative definition of the oligohydramnios sequence: deepest vertical pool in the donor sac < 2 cm, and > 8 cm in the recipient sac[20]. Not infrequently, the oligohydramnios becomes anhydramnios in the donor sac and results in it becoming 'stuck', that is, shrouded by the intertwin membrane, while, at the same time, the recipient sac becomes severely polyhydramniotic (Figure 44.4).

The importance of using all the criteria listed in Table 44.2 lies in the observation that, in the presence of discordant anomalies in twins that cause differences in amniotic fluid volume, i.e. esophageal atresia or renal agenesis, the oligohydramnios/anhydramnios sequence can also be present, albeit without the other diagnostic criteria. Other related confirmatory features include a small or non-visible bladder due to hypovolemia and renal hypoperfusion in the donor, along with a distended urinary bladder with resulting excessive micturition in the recipient. Two cases of 'prune-belly' syndrome have been reported in pairs with TTTS, one in the donor and one in the recipient[21]. Whether this anomaly was found coincidentally or was related to ascites and excessive micturition in the syndrome remains to be proven.

**Table 44.2** Step-by-step diagnosis of twin-to-twin transfusion syndrome (TTTS)

| | |
|---|---|
| Step 1 | look for chorionicity (preferably between 11 and 14 weeks) |
| Step 2 | look for discordance in amniotic fluid volume/bladder size |
| Step 3 | look for discordance in size between twins (abdominal circumference) |
| Step 4 | assess Doppler blood flow in fetal vessels (UA, DV, UV)/fetal heart (transtricuspid flow) |
| Step 5 | look for signs of fetal hydrops (echocardiography) |
| Step 6 | look for placental brightness or other ancillary signs |

UA, umbilical artery; DV, ductus venosus; UV, umbilical vein

### Abnormal Doppler findings

Alterations in cardiac hemodynamics are indirectly shown by alterations in venous blood flow waveforms. The abnormal pulsatile pattern consists of increased velocity of blood flow away from the heart during atrial contraction, and has been reported in the fetus with a failing heart. The most striking feature is the reduced or reversed flow during atrial contraction in the ductus venosus (DV) commonly found in fetuses with congenital heart defects[22,23], growth-restriction[24] and TTTS[4] (Figures 44.5 and 44.6) . In all these

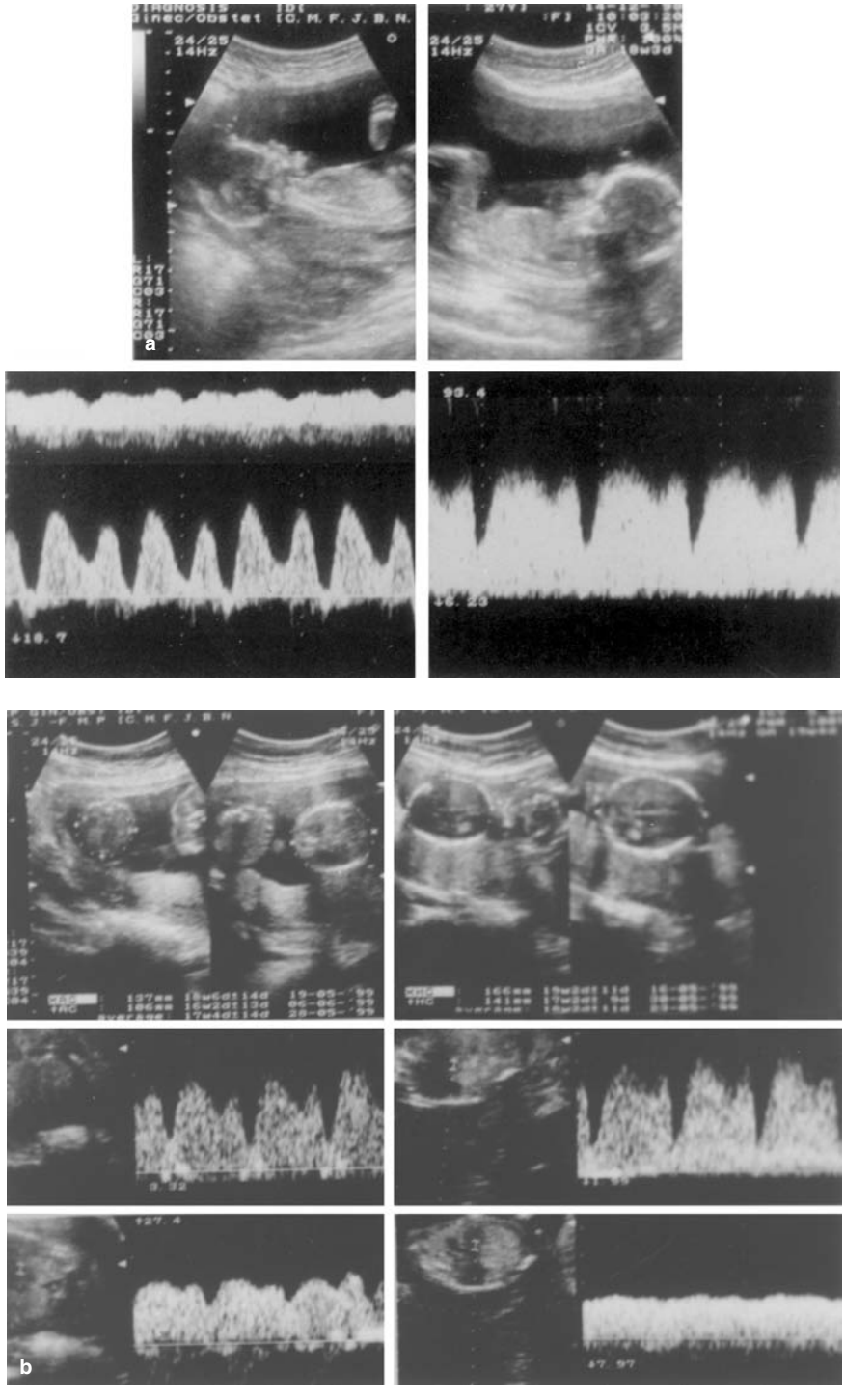


**Figure 44.5** (a) Doppler blood flow waveforms in the ductus venosus (DV) obtained in case 1 at 18 weeks of gestation, when twin-to-twin transfusion was detected. Abnormal flow in the DV (absent flow during atrial contraction) and umbilical vein (pulsatile flow) was recorded in the recipient. (b) Improvement DV waveforms in the recipient (case 1) 1 week after fetoscopic laser coagulation

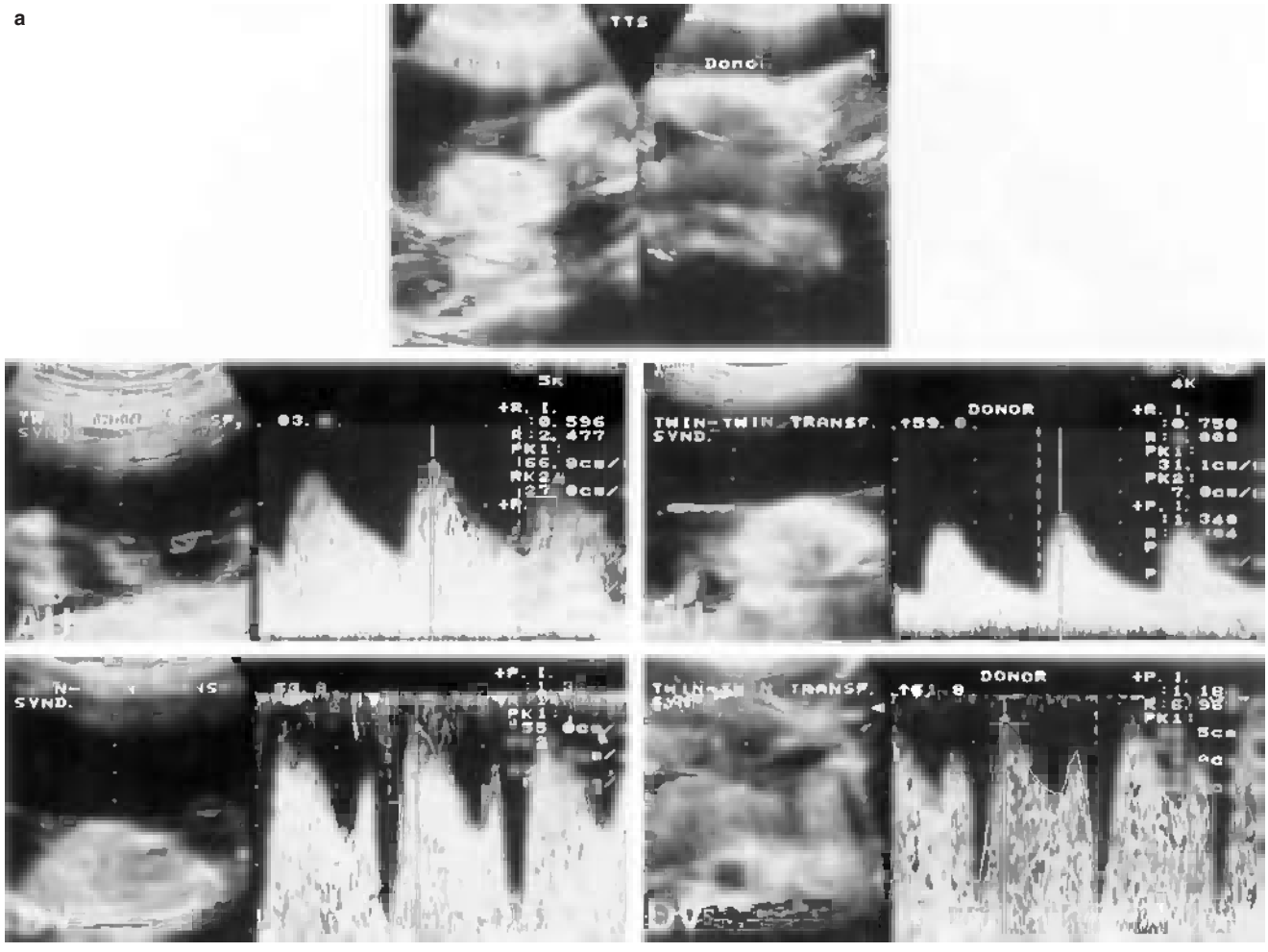


**Figure 44.6** (a) Doppler blood flow waveforms in the umbilical artery (AU) and ductus venosus (DV) obtained in case 3 at 17 weeks of gestation, when twin-to-twin transfusion was detected. In both fetuses, abnormal flow in the DV (decreased velocity during atrial contraction) was recorded. The umbilical artery showed normal blood flow waveforms. Note the 'stuck twin' with oligohydramnios (donor) and the polyhydramnios around the recipient. (b) *Opposite* Normal Doppler blood flow profiles (arterial and venous) obtained in both fetuses (case 3) 1 week after fetoscopic laser coagulation. MCA, middle cerebral artery; UA, umbilical artery; Ao, descending aorta; DV, ductus venosus; UV, umbilical vein. Reproduced with permission from reference 4

b

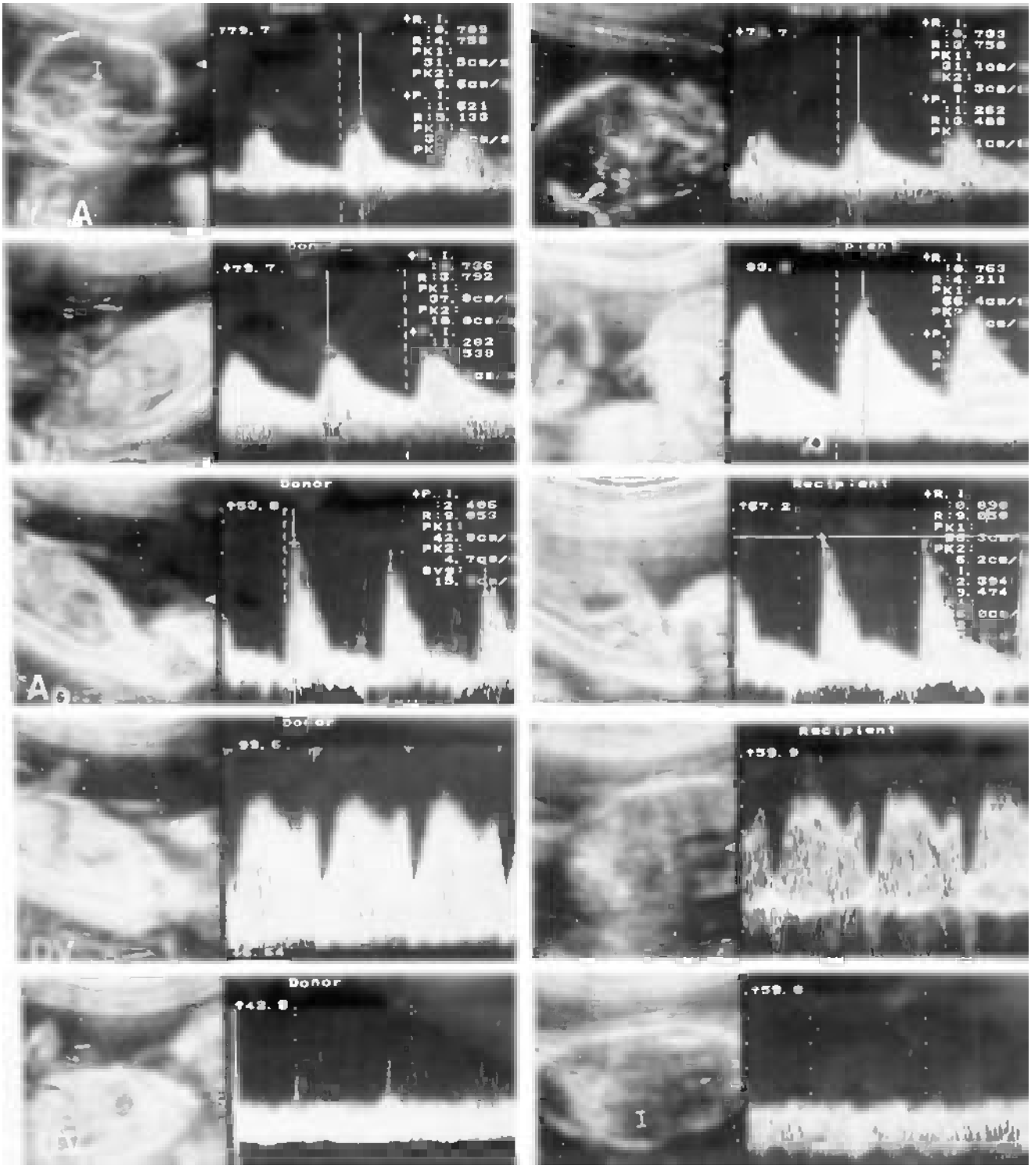


**Figure 44.6** *Continued*

clinical situations this particular hemodynamic alteration seems to reflect impaired cardiac performance and appears as a sign of dismal prognosis.

Hecher and co-workers[24] described highly pulsatile venous waveforms in the recipient with fully established TTTS. Umbilical vein pulsations and absent or reversed flow during atrial contraction in the DV are signs of congestive heart failure due to hypervolemia and increased preload from placental vascular anastomotic transfusion (Table 44.3). Zosmer and colleagues[25] showed that some surviving twins of TTTS had a persistent right ventricular hypertrophic cardiomyopathy, and proposed that cardiac dysfunction could be induced *in utero* by continued strain upon the heart by TTTS, predominantly affecting the right ventricle. The right ventricle is stiffer and more afterload-sensitive than is the left ventricle, mostly due to the redistribution of blood in the cerebral arteries, which decreases the left ventricular afterload. In contrast, the significant reduction of blood flow velocity in the umbilical artery recorded in the 'donor' is consistent with hypovolemia and increased placental resistance, increasing cardiac afterload and decreasing umbilical venous return (Table 44.3).

**Table 44.3** Sonographic characteristics of twin-to-twin transfusion syndrome and pathophysiology of hemodynamic imbalance between donor and recipient

| *Recipient* | *Donor* |
|---|---|
| Increased NT<br>Polyhydramnios<br>Large bladder<br>Polyuria | normal NT<br>oligohydramnios<br>non-visible bladder<br>oliguria |
| *Congestive heart failure* | *High-output heart failure* |
| Increased venous return; TR | decreased flow velocity in arteries and veins (hypovolemia) |
| Increased cardiac strain (hypervolemia)<br>Increased afterload | |
| Hypertrophic cardiomyopathy of RV | |

NT, nuchal translucency thickness; TR, tricuspid regurgitation; RV, right ventricle

## Echocardiography

Considering the hemodynamic imbalance between the circulations of the twins, involving some excess of blood flowing from the donor to the recipient fetus, cardiac involvement is logically expected. Echocardiography is a well-established tool for antenatal assessment of structural and functional heart disease, making it possible in TTTS to assess cardiovascular adaptation to intertwin transfusion, early recognition of deterioration and evaluation of antenatal management.

In one recent study, all recipient fetuses (17 pairs of MC twins with TTTS were evaluated) showed cardiac hypertrophy and dilatation, well-known compensatory mechanisms for blood volume overload and high cardiac output (Frank–Starling mechanism)[26]. The cardiac involvement in recipient twins was of variable severity, ranging from biventricular hypertrophy and dilatation to impaired contraction, with massive signs of tricuspid regurgitation and hydrops fetalis. A larger study of this possibility showed unquestionable functional changes but a lower prevalence (less than 80%) of hemodynamic abnormalities in the recipient[27].

That the ultrasound changes are real and persistent is demonstrated by the observation that, after birth, about half of the recipients show biventricular hypertrophy, with prevalent left ventricular hypertrophic cardiomyopathy. Of equal importance, a smaller subgroup will develop right ventricular tract obstruction (functional pulmonary stenosis) and pulmonary hypertension in the neonatal period[25], which may be aggravated by systolic right ventricular dysfunction. Diastolic abnormalities have also been described in the right ventricle, with abnormal filling patterns, prolonged isovolumic relaxation time and abnormal flow patterns in the inferior vena cava and DV.

The fetal abnormalities continue after birth, and problems of vascular distensibility have been described in survivors of TTTS in infancy[28]. The donor fetus shows evidence of chronic hypovolemia, resulting in activation of the RAS. This up-regulation initially attempts to correct volume depletion, and transfusion of increased concentrations of angiotensin II will probably cause increased vascular stiffness in the surviving donor in childhood.

## Other ultrasonographic findings

These include *identification of cord insertion*, specifically velamentous insertion of the cord.

Also, *funipuncture* may theoretically allow the antenatal assessment of intertwin hemoglobin difference, the degree of fetal anemia in the donor twin and the twins' zygosity through blood group studies. However, the possible benefit of this procedure seems to be very poor on clinical grounds, and the risks importantly outweigh the informative gain.

Other findings might include *signs of hydrops in the recipient twin*. In an advanced stage of TTTS the

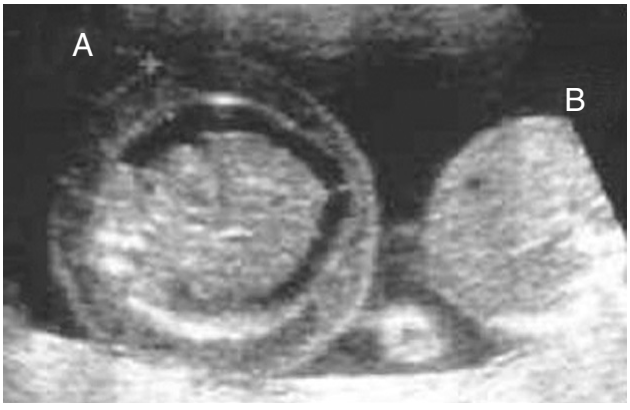


**Figure 44.7** Severe hydrops of the recipient twin (A) is seen on the left, with skin edema and liver floating in massive ascites. On the right is the donor twin (B). Image courtesy of B. Caspi, Kaplan Medical Center

recipient twin affected by congestive heart failure may present signs of serosa effusions, such as ascites, pleural effusion or subcutaneous edema (Figure 44.7).

### Placental brightness

There may be a *difference in color of the placentas*. Owing to blood transfusion from one twin to the other, the placenta of the donor twin tends to be whitish ('pale'), and the placenta of the recipient a denser color (excess of blood) (Figure 44.8). This can be both seen in the ultrasound scan by differences in the brightness of the placenta, and confirmed after birth by necropsy examination.

## PREDICTION OF TWIN-TO-TWIN TRANSFUSION SYNDROME

While accounting for only 2.5% of the population, twins are responsible for 12.6% of perinatal mortality. In the particular case of MC twinning the fetal loss rate is even more relevant, and there is an increased risk of adverse perinatal outcome. Therefore, targeted surveillance of MC twins at earlier stages of gestation could anticipate and provide timely management of the pregnancies at risk of one of the most devastating type-specific complications: TTTS.

### Nuchal translucency

Data gathered from the literature show that increased nuchal translucency thickness (NT) at 10–14 weeks of gestation was found twice as often in MC twins than in singleton pregnancies, and the likelihood ratio of developing TTTS in those twins with increased NT was 3.5[1,11] (see Chapter 47). Considering that MC pregnancies do not show a higher prevalence of chromosomal abnormalities,

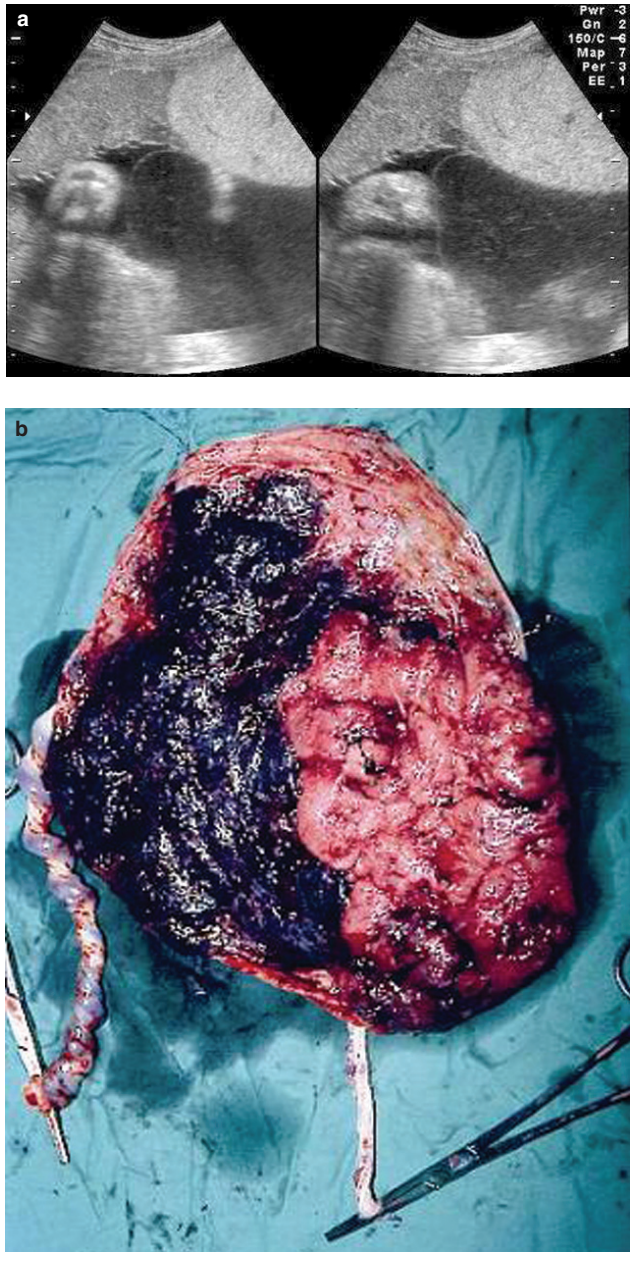


**Figure 44.8** (a) This case was diagnosed as a monochorionic twin pregnancy. However, the twins exhibited many signs of twin-to-twin transfusion syndrome, but both sacs showed polyhydramnios. At 32 weeks, a clear difference in echogenicity between the two parts of the placenta could be seen. After birth, an H-type tracheo-esophageal fistula was found in the donor, explaining the dual polyhydramnios. (b) The maternal surface of the placenta seen in (a). The dark color was due to congestion and the pale part due to blood depletion. Images courtesy of B. Caspi and I. Blickstein, Kaplan Medical Center

the higher prevalence of increased NT in those twins could be ascribed to cardiac dysfunction. With advancing gestation, this transient heart failure eventually resolves, with increased diuresis and ventricular compliance.

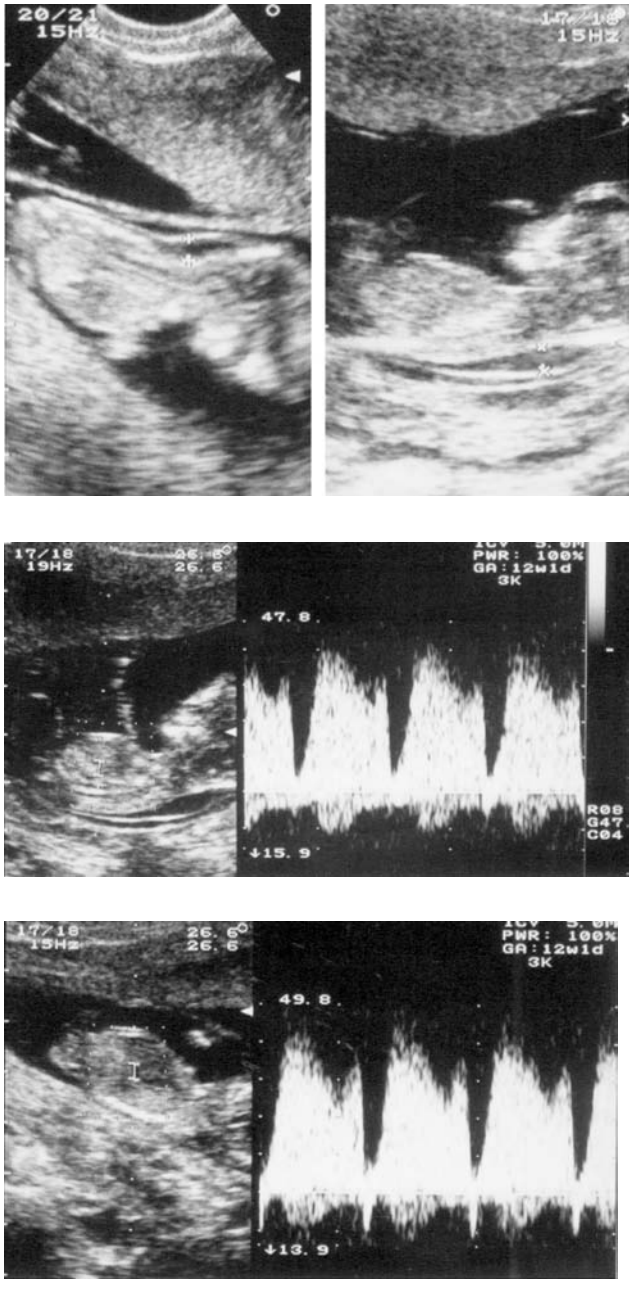


**Figure 44.9** A monochorionic–diamniotic twin pregnancy was established at 12 weeks of gestation (case 1). Doppler blood flow waveforms in both fetuses were obtained in the ductus venosus (DV). A discrete nuchal translucency (NT) discrepancy was noted (NT = 3.3/3.7 mm). The fetus with the highest NT showed an inverted A-wave in the DV and later developed signs of twin-to-twin transfusion syndrome at 18 weeks of gestation

### Ductus venosus flowmetry

Can the characteristic circulatory imbalance of TTTS, fully expressed later in pregnancy, disclose indirect signs of cardiac dysfunction in earlier stages of gestation, and can this dysfunction be shown on ultrasonography? In recent studies of vascular hemodynamics in fetuses with increased NT at 10–14 weeks, the abnormal flow in the DV more frequently recorded in fetuses with chromosomopathies, with or without cardiac defects, was related to heart strain[22,23]. These findings are in good agreement with the overt hemodynamic alterations found in TTTS later in pregnancy[16]. Therefore, accumulated evidence suggests that increased NT along with abnormal flow in the DV, even in the presence of a normal karyotype, may be early signs of cardiac impairment or defect[4,22,23] (Figures 44.6 and 44.7).

During a 4-year period, 45 MC–diamniotic pregnancies were identified in our Ultrasound Unit during routine ultrasonographic assessment at 11–14 weeks of gestation. NT and Doppler blood flow waveforms in the DV were recorded in both twins between 11 and 14 weeks of gestation. TTTS was recorded in those fetuses with combined increased NT and abnormal flow in the DV. To date, all cases with both discrepant NT and abnormal blood flow in the DV, TTTS eventually developed (Figures 44.9 and 44.10). In contrast, whenever NT was discrepant but with normal flow in the DV, no cases of TTTS were found.

### Arterio-arterial anastomoses

The search for AA anastomoses in the placental plate of MC placentas by color Doppler has, until now, mainly provided a negative value: only 5% of MC twins develop TTTS if AA anastomoses are present. In contrast, if absent, 58% will develop TTTS[4]. The studies of Taylor and co-workers[29] show the sensitivity and positive predictive value for absent AA anastomoses in predicting TTTS to be 74% and 61%, respectively. The major limitation to the use of absent AA anastomoses in predicting TTTS, however, is the difficulty in being sure that an AA anastomosis is really absent or simply not yet seen, as frequently happens before 18 weeks.

### Intertwin membrane folding

At 15–17 weeks of gestation, the disparity in amniotic fluid volume between the two amniotic sacs may cause membrane folding. If present, 28% of cases developed severe TTTS and 72% developed mild TTTS. If membrane folding was absent, no cases of TTTS were recorded[30].

## CONCLUSIONS

Until now, we have been able to diagnose fully established TTTS in MC pregnancies after 17 weeks only by identifying the disparities in fetal size and amniotic fluid volume between donor and recipient. However, perinatal morbidity and mortality rates might be

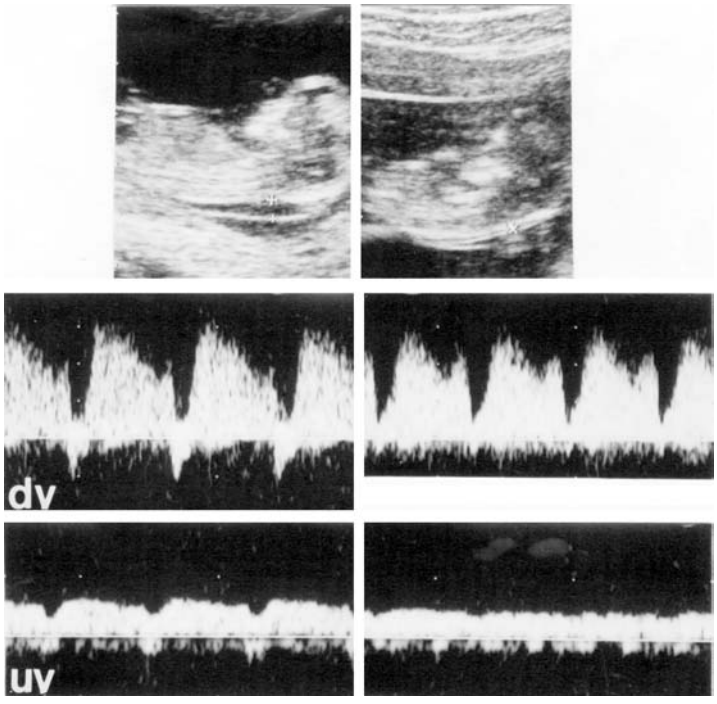


**Figure 44.10** A monochorionic–diamniotic twin pregnancy was established at 12 weeks of gestation (case 3). Doppler blood flow waveforms in both fetuses were obtained in the umbilical vein (uv) and ductus venosus (dv) in the same scan. A nuchal translucency (NT) discrepancy was noted (NT = 3.7/1.0 mm). The fetus with increased NT showed an inverted A-wave in the ductus venosus and dicrotic pulsatility in the umbilical vein. Twin-to-twin transfusion syndrome developed at 17 weeks and the patient was referred for laser ablation of anastomosis. Reproduced with permission from reference 4

dramatically decreased if TTTS could be identified at earlier stages of pregnancy. It may well be that the combination of discrepant NT and abnormal flow in the DV at 11–14 weeks of gestation in MC twins represents the alarm signal predictive of subsequent development of TTTS. Both first-trimester clues may anticipate the early development of heart dysfunction, and should motivate the sonographer to undertake closer monitoring of these twins more prone to develop TTTS.

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# Genetic Counseling: Overview

*Z. Appelman*

45



## INTRODUCTION

The goal of genetic counseling is to provide accurate, up-to-date and comprehensive information related to inherited diseases in patients, their offspring or family members. Such information should be given in a non-directive manner and in an empathic atmosphere using the simplest possible terminology. At the end of this process, the patient and the counselor should be able to reach mutual informed management decisions. To achieve this objective, relevant family, pregnancy and medical histories are initially obtained. Thereafter, appropriate genetic testing, other diagnostic modalities or therapeutic means, when indicated, should be offered to the patient. Although most genetic counselors act along these lines, it is still surprising how differently information given to the patient is actually conceived and how often, despite all efforts, significant parts of the information are either misunderstood, misinterpreted or forgotten.

The most common situations discussed in the context of multiple pregnancies are screening and diagnostic measures to detect aneuploidy, genetic counseling when a structural anomaly is detected and in circumstances with increased risk for specific inherited conditions. The basic rules of genetic counseling in singletons are applicable also in multiples; however, there are specific facets in multiple gestations that need special attention, which makes counseling more complex. Indeed, it is the combination of medical and ethical aspects that makes it so complicated. The basic difference between counseling singletons and multiples is the fact that, as opposed to singletons, any decision in multiples should take into consideration the implication of that decision for the other sib(s). This includes both diagnostic and therapeutic measures.

This volume contains detailed accounts of non-invasive and invasive genetic diagnosis in multiple pregnancies (see Chapters 46, 47 and 48). However, genetic counseling is often provided by a general obstetrician, who may benefit from a simplified approach. This chapter describes specific medical situations that require the attention of the genetic counselor.

## CHORIONICITY

Chorionicity is an important factor in genetic counseling in multiples. The diagnostic accuracy of chorionicity based on ultrasound approaches 100% in the first trimester (Figure 45.1). However, accuracy is reduced when chorionicity assessment is performed later in pregnancy. From the genetic point of view, monochorionic (MC) twins imply monozygosity and high genetic resemblance. On the other hand, only unlike-sexed dichorionic (DC) twins are 100% dizygotic (DZ), and zygosity is unknown in all like-sex DC twins. This uncertainty is even greater in iatrogenic conceptions because the proportion of DZ to monozygotic (MZ) twins (about 10 : 1), as well as the proportion of DC to MC in the subpopulation of MZ twins (proportion unknown), is different from that of spontaneous conceptions.

When chorionicity is unclear and management decisions might be altered by determination of zygosity, prenatal DNA studies should be considered. An example of the difficulty arising from inconclusive

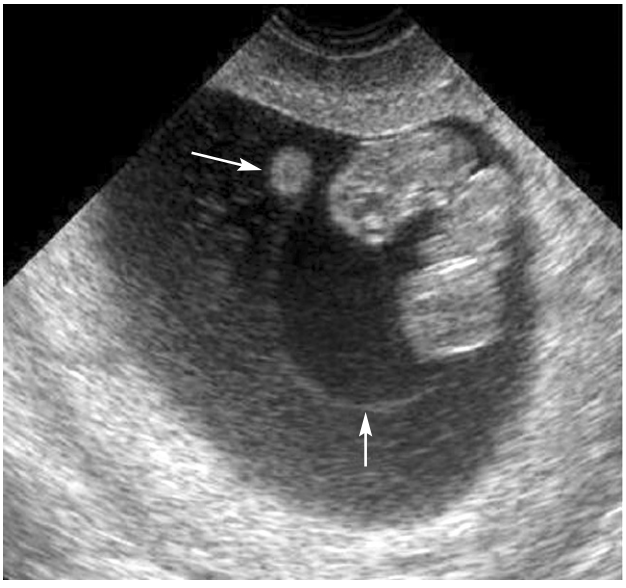

**Figure 45.1** A single yolk sac (upper arrow) and two fetuses were observed within a single amniotic sac (lower arrow). This sonographic scan at 9 weeks led to the diagnosis of monoamniotic twins. Image courtesy of B. Caspi, MD, Kaplan Medical Center, Israel

chorionicity determination in the later parts of pregnancy is presented in a case of twin pregnancy discordant for hydrocephaly and oligohydramnios, in which sonographic evaluation could not exclude MC twinning. Before considering selective feticide, blood samples from both fetuses were examined by DNA 'fingerprint' analysis. The different banding patterns of the blood samples established dizygosity[1]. Similarly, DNA zygosity studies were performed on amniocytes to guide management of four such pregnancies[2]. In this series, DNA zygosity analyses provided >99% likelihood of MZ twins in two cases, a fact that altered counseling regarding selective termination options[2]. In the other two cases, DNA studies were used to assess risk to the normal twin in the event of the co-twin's demise, based upon the differentiation of twin–twin transfusion syndrome (TTTS) from discordant severe intrauterine growth restriction (IUGR) and oligohydramnios[2].

## GENETIC COUNSELING IN MONOCHORIONIC TWINS

MZ twins have a 2–3-fold increased risk of structural anomalies (see Chapters 28 and 43). When a MC gestation comes to the attention of the genetic counselor, the patient should be informed about this risk, and should be referred for a comprehensive sonographic scan, including detailed echocardiography. When a discordant structural anomaly is found, discussion of management options should consider the vascular anastomoses between the circulations of the twins. This circumstance precludes termination of the anomalous twin by intracardiac KCl injection, which may lead to the so called 'embolization' syndrome. Selective termination of the malformed twin can be carried out by one of the cord occlusion techniques (see Chapter 64). Similarly, single fetal demise of a MC twin may indicate appropriate counseling regarding the potential damage to the survivor (see Chapters 69 and 70).

When a case of MC twins is referred early enough, nuchal translucency (NT) measurement is of clear benefit. Although NT assessment may be indicated in all twins in order to detect chromosomal aberrations and cardiac anomalies, an increased NT in MC twins may also be an early sign of TTTS (see Chapter 44). It should be noted, however, that the risk of TTTS is mainly associated with MC–diamniotic and is rarely seen in MC– monoamniotic twins.

The fact that utility of biochemical screening in twins is limited and practically not available in higher-order multiples (Chapter 46) only underscores the importance of performing NT measurements in all multiples (Figure 45.2a and b). It is currently unknown whether the absence of the fetal nasal bone (sign for trisomy 21) during NT measurements will significantly increase the screening efficacy of ultrasound (Figure 45.2)[3].

## GENETIC COUNSELING BEFORE REDUCTION PROCEDURES

The genetic counselor may be required to opine about issues related to prenatal diagnosis in cases scheduled for multifetal pregnancy reduction (MFPR) for elective or medical reasons. In the former case, the embryos/fetuses are considered at low risk for genetic problems, and MFPR is carried out only to reduce the risks associated with high-order multiple pregnancies. In the latter instance, on the other hand, the reduction is performed after the diagnosis of a problem in one or more of the sibs. Even so, the parents may request to know whether the remaining fetuses are also affected. When such a request is made, the most common diagnostic procedure in the second trimester is amniocentesis.

In contrast, when this question arises in the first trimester, or in relation to MFPR, the options are chorionic villus sampling (CVS) or early amniocentesis (performed at 11–14 weeks' gestation). We performed CVS in five triplet sets before MFPR for a variety of genetic reasons[4]. No sampling failure occurred. A chromosomal mosaic 46,XY/47,XXY was detected in one fetus; in another set, a 47/XXY (Klinefelter's syndrome) was found in one triplet,

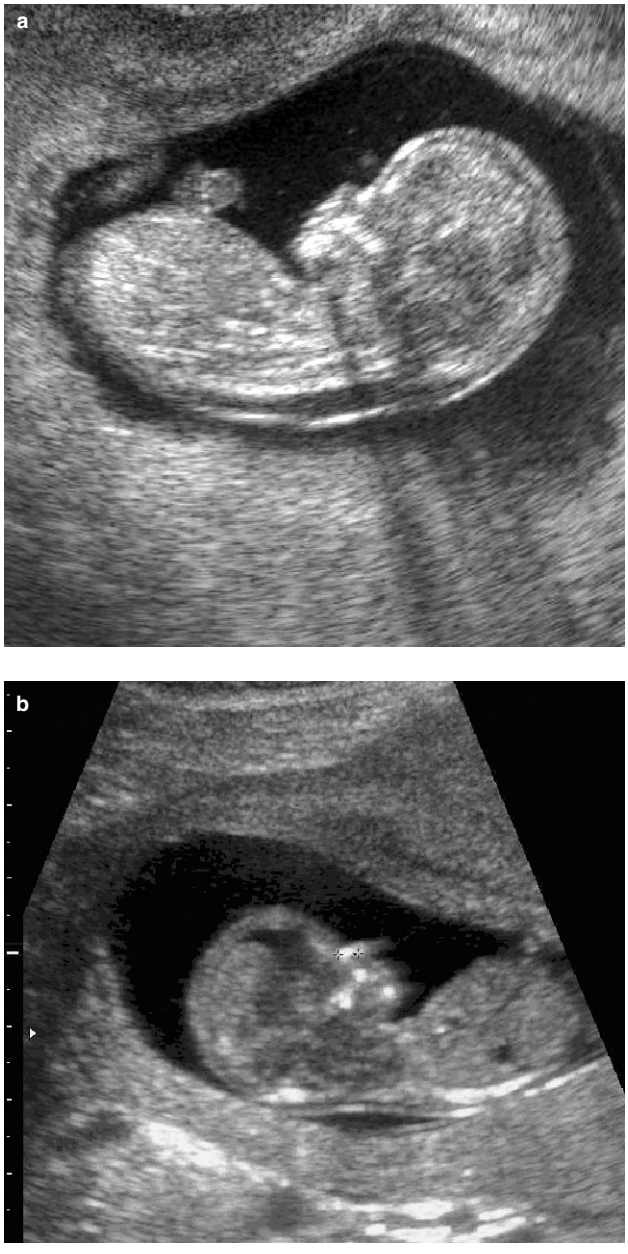


**Figure 45.2** Twins screened for nuchal translucency (NT) and the absence of a nasal bone. (a) Image showing an increased NT and absent nasal bone. (b) Image showing a normal NT and presence of a nasal bone (calipers). Images courtesy of B. Caspi, MD, Kaplan Medical Center, Israel

and in a third set, we diagnosed fragile X syndrome in one fetus. All these affected fetuses were selectively reduced. Brambatti and colleagues[5] offered genetic analysis before fetal reduction to both high- and low-risk pregnant women carrying two or more fetuses after ovulation induction. The use of short-term culture, the polymerase chain reaction (PCR) and fresh tissue enzymatic analyses enabled genetic diagnosis in a few days[5].

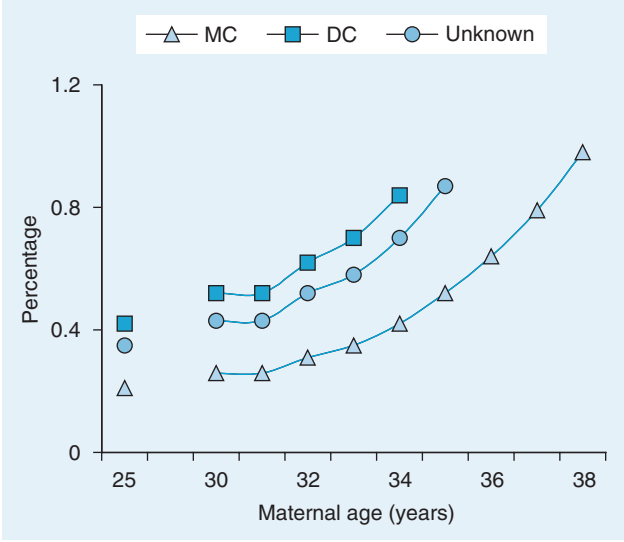


**Figure 45.3** The risk (percentage at term) in Caucasian women, of at least one chromosomally abnormal twin by maternal age and zygosity. MC, monochorionic; DC, dichorionic. (Adapted from Table 48.2)

The alternative to CVS, namely early amniocentesis, was evaluated in a recent randomized trial in a predominantly advanced-maternal-age population with singletons. The results show that amniocentesis at 13 weeks carries a significantly increased risk of talipes equinovarus compared with CVS, and also suggest an increase in early, unintended pregnancy loss[6]. These and other studies indicate that first-trimester CVS is a highly efficient, reliable and relatively safe approach for genetic diagnosis in multiple pregnancies. Although a precise relative risk of CVS compared with amniocentesis in multiples must await randomized controlled studies, the advantages of a first-trimester diagnosis to enable early decision-making about selective or numerical fetal reduction are obvious (see Chapters 63 and 64).

## COUNSELING THE OLDER PATIENT

The increased maternal age in multiple pregnancies observed worldwide has led to tailored approaches to such patients. On the one hand, the risk of aneuploidy is age-dependent, placing the older mother at increased risk (Figure 45.3). On the other, every invasive diagnostic test entails risks of miscarriage (up to 2% in twins), and very rarely infection and fetal injury. Given the fact that many of these pregnancies are considered 'premium' because of adverse prior maternal reproductive history, the reluctance for invasive testing in the older patients seems understandable. In these circumstances, and only in countries where late feticide is legally permissible,

late amniocentesis may be offered. In a study from Israel, elective third-trimester cytogenetic amniocentesis was performed in 14 women, including five with twin pregnancies[7]. There were no procedure-related complications, and all newborns weighed >2000 g and exhibited normal development. This study did not attempt to answer the moral and ethical questions surrounding the use of third-trimester (versus second-trimester) amniocentesis, but shows that the procedure (late amniocentesis) is safe and may constitute a good alternative for patients who are unwilling to accept the risks of early fetal karyotyping.

Calculations suggest that the risk of aneuploidy (mainly trisomy 21) in one of the fetuses in DZ twins should lower the maternal age at which amniocentesis is recommended in singletons (from 35 to about 32 years). This risk, however, has not been accepted as an indication for invasive genetic testing. A Belgian group recently collected 512 prenatal diagnoses (amniocentesis or CVS) from 278 twin pregnancies[8]. The most frequent indications were maternal age ≥35 years (38.8%), assisted procreation (12.3%) and suspicious ultrasound findings (7.2%). Autosomal chromosome aberrations were found in eight twin sets (2.9%): four inherited balanced rearrangements (two Robertsonian translocations and two paracentric inversions of chromosome 11) and four cases of trisomy 18. Surprisingly, the authors did not detect any trisomy 21 in this population[7].

An interesting issue is the case of pregnancies following use of donor oocytes. Intuitively, one may think that the donor's age should be used for aneuploidy risk assessment. However, the donor's age may not always be known or reliable. For example, in a series of established pregnancies from oocyte donation in women aged ≥50 years, the authors found one case of Down's syndrome in 23 infants[9]. Although this single case does not imply an increased risk in pregnancies following oocyte donation, it demands the same attention as all other multiples to markers of aneuploidy.

## 'REVERSED' CYTOGENETICS

'Reversed' cytogenetics refers to an indication for cytogenetic analysis following a suspected or a pathognomonic ultrasonographic finding. The literature is replete with such signs in singletons, but, regrettably, does not discuss extensively the value of these signs in multiples. It should be remembered that some findings, which indicate further assessment in singletons, are seen more frequently in twins (i.e. major anomalies such as cardiac malformations, or minor anomalies such as a single umbilical artery, intrauterine growth restriction, polyhydramnios, oligohydramnios, etc.). Regardless, the approach in such cases should be the same as in singletons with the same presentation.

## ETHICS

Genetic counseling frequently involves important ethical issues. In the antepartum period, a conflict may arise in the case of discordant anomalies, when any form of treatment of the anomalous twin may endanger the co-twin. For example, consider the possibility of a DC twin pregnancy with a suspected discordant chromosomal anomaly. Would it be ethical to perform an invasive procedure to reach a diagnosis, and, at the same time, put the co-twin at risk for potential adverse outcome? Moreover, in the context of multiple pregnancy, these issues are not restricted to prenatal diagnosis only. It may start postpartum with parental requests for zygosity diagnosis of their infants. In the absence of a medical indication, would it be ethical to perform any procedure to satisfy the curiosity of the parents to know if their twins are 'identical'? This may go on to adulthood, when one twin of an MZ set is diagnosed with a late-onset genetic disease. Is there an ethical obligation to reveal the patient's disease state to his/her co-MZ-twin? Finally, consider the situation when one twin wishes to know the results of her deceased mother's tests for BRCA1 mutations (increased risk for breast cancer) and the second twin objects to researchers making this information available[10]. Who is in the state to decide? Obviously, answers are not at hand, and for many cases called into question, the lines of ethical certainty become less clear[10]. Unfortunately, is seems that technical advances will always precede ethical dilemmas, and in this respect, especially in multiple pregnancies, the future does not seem to facilitate the ethical conflicts in genetic counseling.

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# Non-invasive Screening Tests

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**46**



## INTRODUCTION

This chapter deals first with the background to prenatal screening in general, and then with its specific application in multiple pregnancies.

Prenatal screening in the first or second trimester to identify pregnancies that may be complicated by neural tube defects (NTDs) or chromosomal abnormalities is an established part of obstetric practice in many parts of the world. Such programs aim to identify a subset of women within the general pregnant population, whose pregnancy may be at increased risk of being affected by such a problem. These women may then be offered a suitable diagnostic test. In the case of NTDs, the definitive diagnosis is usually accomplished with a detailed spinal ultrasound scan, which in most centers has superseded the invasive withdrawal of amniotic fluid and its subsequent biochemical analysis. However, fetal chromosomal abnormalities can only be diagnosed by fetal karyotyping from cultured amniotic fluid cells or chorionic villi, using either conventional techniques, or the recently advocated more rapid techniques of fluorescent *in situ* hybridization or quantitative polymerase chain reaction (Q-PCR). Thus, an invasive test is currently the only method of diagnosis for chromosomal abnormalities. Such procedures carried out in singleton pregnancies carry risks to both the fetus and the mother. In particular, the fetal loss rate post-amniocentesis is often quoted as 0.5–1.0% above the background rate, and that of chorionic villus sampling (CVS) some 1–2% above the background rate. As with all invasive procedures, the fetal loss rates vary tremendously between operators, based on skill, training and experience.

The incidence of twin pregnancy is increasing worldwide, partly as a result of the increased use of assisted reproductive techniques[1], and partly because as the maternal cohort ages the rate of spontaneous twinning increases, with women over 35 being three times more likely to conceive twins than women under the age of 20[2]. In the UK the incidence of twins rose from 0.97% in 1979 to 1.43% by 1999[3]. This trend has a significant impact on healthcare, since twin pregnancies are associated with a greater incidence of perinatal complications than are singletons, twice the risk for structural defects[4–6] and a higher risk for chromosomal abnormalities[7], although the evidence for the latter with respect to trisomy 21 is questionable[8].

The data on fetal loss in twin pregnancies after invasive diagnostic procedures is unclear. Some studies indicate no increased fetal loss for amniocentesis, whereas others indicate that it is double. In studies using single-needle insertion and a group of twin controls not undergoing amniocentesis, the fetal loss rates were 3.5% and 3.2%, respectively[9], but were twice as high in another series[10]. In a similar study of first-trimester CVS in twin pregnancy[11], the control group had twice the rate of fetal loss (6.9% vs. 3.4%), whereas a study comparing first-trimester CVS and second-trimester amniocentesis[12] showed almost no difference (3.2% vs. 2.9%). Although sampling accuracy in twin pregnancies is probably higher with amniocentesis, the method of choice for invasive diagnosis is probably best chosen in relation to the risk of an abnormality[13].

Several complex issues are associated with screening for chromosomal anomalies in twin pregnancies, namely: how to interpret the marker values, the

paucity of data in abnormally affected pregnancies when the fetuses are either concordant or discordant for an anomaly, the dilemmas regarding which invasive test to offer, the perceived increased risk of such a procedure in twins, the technical difficulties of ensuring fetal tissue is obtained from each fetus, the need to ensure each fetus can be clearly differentiated at a later date and, finally, the difficulties of clinical management of fetal reduction and the potential increased risk to the unaffected co-twin. These concerns form the basis of arguments that screening in twins poses such a serious clinical, ethical and moral dilemma[8,14] that it should be discouraged[15]. Despite such reservations, screening programs for twin pregnancies have been proposed and successfully implemented in both the second and first trimesters, in units that have links with specialized fetal medicine centers capable of dealing with the clinical management of invasive testing and selective fetal reduction in twin pregnancies.

Population-based non-invasive screening strategies for NTDs and for the major chromosomal abnormalities of trisomies 18 and 21 depend upon the measurement of one or more fetoplacental markers in the maternal serum during the second trimester between 15 and 20 weeks of gestation. Such procedures have been the standard pattern of care since the early 1990s in many countries. In recent years, an increasing interest in screening for the major trisomies 13, 18 and 21 earlier in pregnancy has followed, using either ultrasound alone or a combination of ultrasound and the measurement of placental markers in the maternal serum, during the first trimester between 11 and 14 weeks of gestation. At this time, it may also be possible to identify a significant proportion of fetuses with anencephaly (acrania), open spina bifida and abdominal wall defects using a high-quality 11–14-week ultrasound examination in the hands of trained individuals.

## SCREENING FOR NEURAL TUBE DEFECTS

The fetal skin barrier is breached in the presence of an open lesion of the neural tube (either anencephaly or open spina bifida), and fetal proteins pass into the amniotic fluid at an increased rate, thus increasing their concentrations. Elevated levels of α-fetoprotein (AFP) in the amniotic fluid of pregnancies with an open NTD were first demonstrated in 1972 by Brock and Sutcliffe[16], and Hino and colleagues[17] demonstrated a raised maternal serum AFP level in an anencephalic pregnancy in the same year. AFP is a 69-kDa single-chain glycoprotein produced initially in the embryonic yolk sac, and subsequently by the fetal gastrointestinal tract and liver. Nearly all AFP is synthesized in the liver by the end of the first trimester. AFP in fetal serum passes through the glomeruli intact, and is then reabsorbed in the renal tubules. Normally, only a small amount escapes and appears in fetal urine, and eventually, by micturition, in the amniotic fluid. Early in gestation, AFP also enters the amniotic fluid via transudation across the immature epithelium. Diffusion of AFP from the fetal to the maternal compartment is across the fetal membranes and at the placental level. As a consequence, the relative levels of AFP in the three compartments of fetal serum, amniotic fluid and maternal serum differ markedly, with levels in fetal serum reaching a peak of about 3000 ng/ml at around 13 weeks, followed by a decline. Levels in amniotic fluid have a similar pattern, with a peak concentration of about 30 ng/ml. In contrast, levels in maternal serum increase to a peak of about 1 ng/ml at around 32 weeks of gestation, falling slightly to delivery. Because concentrations of AFP in the fetal serum are approximately 100 000 times those in maternal serum in the second trimester, it is easy to understand how even small amounts of fetal blood may cause increased levels of amniotic fluid AFP and subsequently elevated levels in maternal serum.

Since AFP levels change with gestational age (in both amniotic fluid and maternal serum), accurate pregnancy dating is important for interpretation of the levels. AFP concentrations are usually expressed as the multiple of the normal median (MoM) for a gestation of the same duration. Thus, a value of 1.0 is normal, 2.0 is raised and a value of 0.5 is reduced, at any gestational age. The demonstration of increased levels of maternal serum AFP in two UK studies[18,19] raised the prospect of a screening test for NTDs, and led to the relationship between maternal serum AFP and fetal NTDs being comprehensively examined in a large collaborative study of 301 affected cases and 18 684 unaffected pregnancies[20]. This showed that, using a cut-off equal to or greater than 2.50 MoM in singleton pregnancies at 16–18 weeks, 88% of pregnancies with anencephaly and 79% of cases with open spina bifida would be identified, respectively, with a false-positive rate of 3%. These findings were used to form the basis of a screening program in which women with levels above 2.49 MoM could be offered amniocentesis and further testing of the amniotic fluid for AFP. The second report of the UK collaborative study[21] of 385 pregnancies with open NTD and 13 000 unaffected pregnancies provided the definitive diagnostic criteria. At 16–18 weeks, using a cut-off of 3.0 MoM, 99% of cases with anencephaly could be identified along with 95% of cases with open spina bifida, with a false-positive rate of 0.42%. The figures from this large trial have proved robust in routine practice,

and the predicted performance has been borne out or exceeded in prospective use.

Further improvements to the diagnostic accuracy were shown when amniotic fluid was examined electrophoretically for the presence of cerebrospinal fluid-derived acetylcholinesterase[22]. The benefits of acetylcholinesterase testing as a secondary test in cases with a high amniotic fluid AFP (> 3.0 MoM) were evaluated in two large collaborative studies. In the first, the additional test allowed the same level of detection but at a much reduced false-positive rate[23]. The second suggested that an AFP level of 2.0 MoM was a more appropriate cut-off to select for acetylcholinesterase measurement and, in such instances, the false-positive rate could be reduced to 0.14%[24]. However, since the early 1990s, detailed ultrasound scanning has largely replaced amniocentesis and biochemical analysis as the diagnostic test of choice, certainly amongst pregnancies known to be at high risk of an NTD through past history or an elevated maternal serum AFP. Anencephaly is detectable at 10–14 weeks of gestation as acrania[25,26], and indirect cranial or cerebellar markers of NTD such as the 'lemon' and 'banana' signs prominent in the second trimester[27] may also be present in the first trimester[28,29]. The reliability of ultrasound diagnosis in high-risk populations is said to be of the order of 97% sensitivity and 100% specificity[30]; however, when used as a primary screening test it is somewhat more variable, with results for spina bifida varying from 70 to 98%.

Maternal serum AFP is only useful as a marker for NTD after 14 weeks of gestation. The UK collaborative study[20] showed that the optimal time for detection of open spina bifida was 16–18 weeks, with a fall to 20% at 10–12 weeks. Aitken and colleagues[31] assessed a series of 14 cases with NTD in both the first and second trimesters. None of the cases had an AFP MoM above 2.0 in the first trimester, whereas all had elevated levels in the second trimester. Sebire and associates[32] found that AFP levels were increased in seven of nine cases with anencephaly, but were normal in two cases with spina bifida at 10–14 weeks.

## AFP in twin pregnancies

Maternal serum AFP levels in normal twin pregnancies are approximately twice those observed in normal singleton pregnancies. In a meta-analysis of 1892 published cases, the overall median MoM was 2.23[15]. When a further series of published cases is added to this series, the median MoM from 9959 cases is now 2.081, as summarized in Table 46.1.

Although monozygotic twin pregnancies are reported in small studies[33,39] to have higher levels of AFP, one large study[34] looking at chorionicity has found no difference in maternal serum AFP levels between monochorionic and dichorionic twin pregnancies in the second trimester.

**Table 46.1** Summary of the median multiple of the normal median (MoM) α-fetoprotein (AFP) in unaffected twin pregnancies in published series

| *Study* | *Twins (n)* | *Median AFP MoM* |
|---|---|---|
| Wald[15] | 1892 | 2.23 |
| Thom[33] | 100 | 1.9 |
| Crossley[35] | 81 | 1.91 |
| Raty[36] | 145 | 2.18 |
| Raty[36] | 30 | 2.3 |
| Muller[34] | 3043 | 2.1 |
| Barnabei[38] | 225 | 1.91 |
| O'Brien[37] | 4443 | 2.02 |
| Total | 9959 | 2.081 |

In second-trimester normal twin pregnancies, amniotic fluid AFP levels do not appear to be elevated[21] compared with singleton pregnancies. However, several reports show increased amniotic fluid AFP levels in cases with twins concordant or discordant for NTD[21,40], although diffusion of AFP and acetylcholinesterase between adjacent sacs in both normal and abnormal pregnancies makes the interpretation of amniotic fluid biochemistry difficult in cases when only one twin is affected[40,41].

In a proportion of twin pregnancies in which one or both twins are affected by NTD, maternal serum levels of AFP are elevated compared with the levels in normal, unaffected twins. In a report of 11 cases of twins discordant for an open NTD, Ghosh and colleagues[42] found maternal serum AFP levels over 5.00 MoM in each instance. In extending this series to 46 cases (22 with anencephaly, 24 with open spina bifida), Cuckle and co-workers[43] found that the median MoM in anencephalics was 7.50 times the MoM in unaffected singleton pregnancies, whereas that for open spina bifida was 4.40 times higher. To achieve a similar false-positive rate in twin pregnancies as for singleton pregnancies at 16–18 weeks, the cut-off level would need to be raised to 5.0 MoM (false-positive rate 3.3%); in this circumstance the detection rate for anencephaly would be 83% and that for open spina bifida 39%. This is a considerably lower detection rate for open spina bifida compared with the 79% in singleton pregnancies. To achieve a similar open spina bifida detection rate in twins, the cut-off level would need to be 3–3.5 MoM with the consequent increase in the false-positive rate to 15–20%.

## SCREENING FOR DOWN'S SYNDROME AND OTHER ANEUPLOIDIES

The natural frequency of chromosomal abnormalities at birth, in a population without any prenatal diagnosis, is estimated at 6/1000 births. The most common is trisomy 21 (Down's syndrome), with an often quoted birth prevalence of one in 800[44]. However, the risk of fetal trisomy 21 increases dramatically with advancing maternal age, and along with the shift over the past 20 years to women having babies at an older age, the general prevalence of trisomy 21 during the second trimester increased from one in 740 in 1974 to one in 504 by 1997 in the United States, for example[45]. The other common autosomal trisomies including trisomy 18 (Edwards' syndrome) and trisomy 13 (Patau syndrome) occur with birth incidences of one in 6500 and one in 12 500, respectively. There are numerous published rates of trisomy 21 at different maternal ages. One of the most commonly used in commercial software is that of Cuckle and associates[46], which provides regressed maternal age risks at individual maternal ages based on data from eight published surveys. This background risk is the starting point for calculating any posterior risk based on previous history or based on prenatal screening tests.

The first prenatal screening test for trisomy 21 was based on using a specific maternal age to select women for an invasive test such as amniocentesis. In the USA and UK during the 1970s and 1980s, a cut-off of 35 years was used to select women for amniocentesis, which would identify some 30% of cases for an invasive testing rate of around 6%. However, the predictive value of screening by maternal age alone is poor, with about one abnormal case being identified for every 125 invasive procedures. Furthermore, the uptake of amniocentesis amongst this group was low, and resulted in a much lower detection rate that the 30% predicted. The changing demographics of pregnant populations in the Western world show that the proportion of pregnant women over age 35 is now in excess of 15%. Using a maternal age cut-off of 35 in today's populations would identify some 50% of cases with a 15% false-positive rate. Assuming a fetal loss rate of 1% due to the invasive procedure, such screening would result in the loss of three normal, unaffected fetuses for every two cases with trisomy 21 identified – a loss rate that cannot be considered acceptable. Fortunately, the past two decades have seen dramatic advances in screening for aneuploidy, with the introduction of screening tests using maternal serum biochemical markers in the second trimester or a combination of maternal serum biochemical markers and ultrasonography in the first trimester.

### Maternal serum biochemistry in the second trimester

Merkatz and colleagues[47] first reported in 1984 an association between low second-trimester maternal serum AFP in pregnancies complicated with fetal aneuploidy. The significant reduction of AFP in cases with trisomy 21 and trisomy 18 was confirmed by Cuckle and colleagues[48] in the same year, and subsequently in many other studies. The initial screening proposal to use specific maternal age-related AFP MoM cut-offs to select women for amniocentesis revealed that AFP alone was a poor marker for trisomy 21[49]. This observation led to a search for other markers of fetal aneuploidy, and a large number of markers have now been investigated (Table 46.2), initially in the second trimester and, more recently, in the first trimester.

In what proved to be one of the key developments in these investigations, Bogart and colleagues[51] reported that levels of maternal serum human chorionic gonadotropin (hCG) and its free α subunit were altered in the late second trimester (18–25 weeks) in pregnancies complicated by fetal aneuploidy. Many subsequent studies confirmed that hCG levels are increased by approximately two-fold in cases with trisomy 21, and reduced in association with trisomy 18. For the free α subunit, other workers found only small but significant elevation in cases with trisomy 21. Assays for hCG have varying specificities and, broadly speaking, can be categorized into three types: those detecting intact or dimeric hCG, those detecting total hCG (i.e. dimeric hCG plus free β-hCG) and those detecting specifically free β-hCG only. In 1990 and 1991, Macri and associates[52] and Spencer[53], respectively, reported that second-trimester maternal serum levels of the free β subunit of hCG were elevated in cases with trisomy 21, and that the clinical separation between unaffected and trisomy 21 cases was greater than with intact or total hCG[54]. Many other studies confirm this, and in cases with trisomy 18, free β-hCG levels are also reduced[55].

In 1988, Canick and colleagues and Wald and coworkers[56,57] reported that second-trimester maternal serum unconjugated estriol levels were reduced in pregnancies with trisomy 21, as they are also in cases with trisomy 18. Although reduced levels of unconjugated estriol have been confirmed in many studies, the use of this marker in screening programs remains controversial[58–60].

The fourth major second-trimester marker for trisomy 21 is inhibin A. In the early 1990s, preliminary studies[61,62] showed that levels of immunoreactive inhibin were increased in pregnancies with trisomy 21. Inhibin is a dimer composed of an α subunit and one of two similar but distinguishable β subunits.

**Table 46.2** Meta-analysis of published maternal serum biochemical markers in cases with trisomies 21, 18 and 13 in the first and second trimesters. Modified from reference 50

| | *Second trimester* | | | | *First trimester* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *Trisomy 21* | | *Trisomy 18* | | *Trisomy 21* | | *Trisomy 18* | | *Trisomy 13* | |
| *Maternal serum marker* | *n* | *Median MoM* | *n* | *Median MoM* | *n* | *Median MoM* | *n* | *Median MoM* | *n* | *Median MoM* |
| AFP | 1328 | 0.75 | 519 | 0.65 | 611 | 0.80 | 53 | 0.91 | 42 | 0.92 |
| Total hCG | 907 | 2.06 | 347 | 0.32 | 625 | 1.33 | 53 | 0.38 | 42 | 0.74 |
| Unconjugated estriol | 733 | 0.72 | 263 | 0.42 | 210 | 0.71 | | | | |
| Free β-hCG | 562 | 2.20 | 145 | 0.33 | 846 | 1.98 | 126 | 0.27 | 45 | 0.51 |
| Inhibin A | 524 | 1.92 | 73 | 0.87 | 112 | 1.59 | 235 | 1.41 | 45 | 0.74 |
| SP-1 | 448 | 1.46 | 25 | 1.13 | 246 | 0.86 | | | | |
| Free α-hCG | 239 | 1.43 | 12 | 0.86 | 162 | 1.00 | | | | |
| CA125 | 187 | 1.01 | | | 34 | 1.14 | | | | |
| PAPP-A | 159 | 0.97 | 90 | 0.11 | 777 | 0.45 | 119 | 0.20 | 42 | 0.25 |
| Activin | 82 | 1.23 | | | 45 | 1.36 | 45 | 1.23 | | |
| HPL | 81 | 1.29 | 12 | 0.55 | | | | | | |

MoM, multiple of the normal median; AFP, α-fetoprotein; hCG, human chorionic gonadotropin; SP-1, Schwangerschafts protein 1; PAPP-A, pregnancy-associated plasma protein-A; HPL, human placental lactogen

Earlier assays for inhibin were non-specific, and measured all forms of inhibin containing the α subunit. More specific assays allowing the measurement of dimeric inhibin A were developed, and this is a useful second-trimester marker, where levels are increased in trisomy 21. There is a high correlation with inhibin A and hCG. However, this, coupled with an evolving assay methodology[63], variable standardization, lack of stable and robust commercially developed assays and poor comparability from center to center[64], has delayed the appearance of prospective data using this marker. In the first trimester the marker appears to have little if any clinical discrimination for trisomy 21.

## Maternal serum biochemistry in the first trimester

Two maternal serum biochemical markers are of value in screening for chromosomal anomalies in the first trimester. Free β-hCG levels in cases with trisomy 21 in the first trimester between 10 and 14 weeks are on average close to 2.00 MoM[65], being only slightly less than those seen in the second trimester[54]. Levels in trisomy 13 and trisomy 18 are also significantly reduced[66,67]. On the other hand, intact or total hCG are not significantly elevated in trisomy 21[68], although they are reduced in trisomy 18[69]. The second biochemical marker is pregnancy-associated plasma protein-A (PAPP-A), produced by the placenta. In cases with trisomy 21, 13 or 18 at 10–14 weeks, levels are reduced to around 0.45 MoM for trisomy 21[65] and to around 0.20 for trisomies 13[66] and 18[70]. In cases with trisomy 21 and possibly trisomy 18, the clinical discrimination with PAPP-A changes across the first trimester and into the second trimester[71–73]. In the case of trisomy 21, better clinical discrimination is achieved earlier (at around 8 weeks) and the clinical discrimination gets poorer as the gestation progresses, such that by the 17th week there is no difference in PAPP-A between normal pregnancies and those with trisomy 21[71]. In contrast, the clinical discrimination with free β-hCG prior to 10 weeks gets worse[71]. These balancing temporal changes mean that across the 9–14-week period, detection rates using these two biochemical markers remain relatively constant[72]. Table 46.2 summarizes a meta-analysis of the various biochemical markers that have been investigated in the first and second trimesters in cases with trisomies 21, 18 and 13.

## Ultrasound in the first trimester

The major marker of fetal aneuploidy is the first- trimester ultrasonographic marker of fetal nuchal translucency thickness (see Chapter 47). An echogenic area of fluid exists in all fetuses between the fetal skin and soft tissue overlying the cervical spine, and Nicolaides and colleagues[74] first used the term 'nuchal translucency' to describe this accumulation of fluid. Studies of high-risk populations in the first trimester identified a possible association

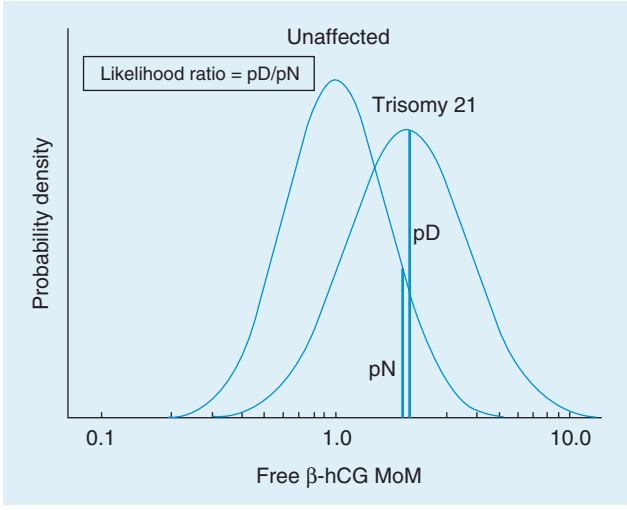


**Figure 46.1** Probability density distribution of free β-human chorionic gonadotropin (hCG) in unaffected and pregnancies with trisomy 21 (Down's syndrome). pD represents the probability of trisomy 21 and pN the probability of being unaffected at a given free β-hCG multiple of the normal median (MoM) level

between increased NT and the presence of a fetal chromosomal anomaly[74]. Pandya and associates[75] later proposed a protocol for the measurement of NT that has formed the basis of the Fetal Medicine Foundation (FMF) approach to training, certification and ongoing audit of sonographers and obstetricians in the 10–14-week scan[76].

## Calculation of risk

Many of the biochemical observations in pregnancy vary with duration of the pregnancy. To remove gestational age-variation effects, many biochemical parameters, in a screening context, are expressed as MoMs, i.e. the observed result expressed as a ratio of the median value observed in a normal pregnancy of the same gestational age. When expressed as MoMs, the majority of biochemical markers follow a Gaussian distribution in both the normal and affected populations only when the MoM is log-transformed. Figure 46.1 shows the distribution of free β-hCG in normal and trisomy 21-affected pregnancies. Unfortunately, there is a significant overlap of the two populations with all markers, so in order to use the marker information, Cuckle and colleagues[46] proposed the use of Gaussian statistics to derive a probability or likelihood ratio that a particular marker concentration was associated with an affected pregnancy. In Figure 46.1, the ratio of the heights of the distributions in the affected and unaffected pregnancies at a given marker MoM is the likelihood ratio of the result being from the trisomy 21 population. To calculate the patient-specific risk, the *a priori* maternal age risk is then multiplied by the likelihood ratio.

**Table 46.3** Mahalanobis distance of the prime candidate markers in second- or first-trimester screening for trisomy 21: the greater the value the more discriminatory

| *Marker* | *Second trimester* | *First trimester* |
|---|---|---|
| AFP | 0.69 | 0.23 |
| Unconjugated estriol | 1.20 | 0.68 |
| Intact/total hCG | 1.86 | 0.38 |
| Free β-hCG | 2.04 | 1.45 |
| Dimeric inhibin A | 1.65 | 0.35 |
| PAPP-A | 0.15 | 2.08 |
| NT | | 6.46 |

AFP, a-fetoprotein; hCG, human chorionic gonadotropin; PAPP-A, pregnancy-associated plasma protein-A; NT, nuchal translucency

Two important features of the marker distribution dictate how good the marker is in discriminating between unaffected and affected populations. These are the difference in the median values in the two populations, sometimes referred to as the median shift, and second, the width of the distributions or the standard deviations. These two features jointly define the extent of the overlap of the two populations. Expressing these features as the Mahalanobis distance, calculated from (mean [unaffected] – mean [affected]/SD [unaffected])$^2$, where the mean and standard deviation (SD) are in the log domain, allows markers to be ranked in a scale of clinical effectiveness. Table 46.3 indicates the Mahalanobis distance for the commonly used first- and second-trimester markers, indicating that the most effective markers in the first trimester are NT, PAPP A and free β-hCG, whereas in the second trimester free β-hCG, total hCG and dimeric inhibin A are the most effective.

No individual marker alone has sufficient clinical discrimination. A more efficient screening program can be obtained in practice by combining information from more than one marker. If markers have no interdependence then the likelihood ratios for each marker can simply be multiplied together to obtain the combined likelihood ratio. In practice, markers to a varying extent are correlated (i.e. providing similar information), and this needs to be corrected for. Examples of significant correlation are those between hCG and inhibin, and AFP and unconjugated estriol. The basis behind multimarker risk assessment is effectively an extension of that used for the single-marker, with the addition of marker correlation

**Table 46.4** Studies of nuchal translucency (NT) screening which have not used the Fetal Medicine Foundation (FMF) protocol

| Study | n | Gestation (weeks) | NT not measured (%) | NT cut-off | False-positive rate (%) | T21 detection rate |
|---|---|---|---|---|---|---|
| Bewley[88] | 1704 | 8–13 | 34 | 3.0 mm | 6.0 | 1 of 3 (33%) |
| Kornman[89] | 923 | 8–13 | 42 | 3.0 mm | 6.3 | 2 of 4 (50%) |
| Haddow[90] | 3991 | 9–15 | 17 | 95th centile | 5.0 | 18 of 58 (31%) |
| Crossley[91] | 17 229 | 10–14 | 27 | 95th centile | 5.0 | 20 of 37 (54%) |
| Wald[92] | 47 053 | 6–16 | 18 | 95th centile | 5.0 | 37 of 74 (50%) |

T21, trisomy 21

information. The detailed mathematics behind this approach is beyond the scope of this review, but has been outlined by Reynolds and Penney[77].

## Second-trimester combined biochemical screening

Expected screening performance using various marker combinations can be modeled from data obtained in retrospective case–control studies of samples from pregnancies affected by trisomy 21 or trisomy 18 (and trisomy 13 in the first trimester). Considerable disparity exists in estimates of detection and false-positive rates in various studies, possibly as a result of a variety of factors including variation in sample size, sample selection, assay methodology, analyte stability, risk calculation algorithms, estimation of gestational age, marker distribution, marker correlations, correction for co-variables and the underlying maternal age distribution of the population model used. In general terms, model predictions for second-trimester markers suggest detection rates of 65–70% for trisomy 21 using either two-marker protocols (AFP and free β-hCG or total hCG) or three-marker protocols (AFP, free β or total hCG and unconjugated estriol), whereas the addition of inhibin A in general is likely to increase the detection rate by a further 3–5%[78]. For trisomy 18, protocols using AFP and free β-hCG predict a 50% detection rate at a 1% false-positive rate[55], whereas those using AFP, total hCG and unconjugated estriol[79,80] predict 60% detection at a 0.3% false-positive rate. More recently, measurement of PAPP-A has been shown potentially to increase second-trimester detection rates for trisomy 18 to some 82% for a 0.1% false-positive rate, using a two-step screening protocol[73,81].

In over 20 prospective intervention studies, the modeled second-trimester screening performance described previously has been confirmed in large-scale studies over a considerable time period[82–85].

## First-trimester screening: nuchal translucency thickness

In studies using the FMF protocol, detection rates for trisomy 21 of the order of 70–75% with a 5% false-positive rate have been achieved in practice[86,87]. In studies which have not used the FMF protocol (Table 46.4), and with sonographers/obstetricians who are not FMF-trained, then detection rates have been much less – emphasizing that training, attention to detail, following the set protocol and ongoing audit are all of great importance. The FMF has developed a quality management system approach to first-trimester screening which involves setting standards for both ultrasonographic and biochemical measurement, training and certification of sonographers and prenatal screening laboratories, provision of software certified to FMF standards and incorporating the FMF algorithm for risk assessment, and a continuous audit and monitoring of the performance of NT and biochemical measurements from certified sonographers and screening centers (www.fetalmedicine.com).

## First-trimester screening: maternal serum biochemistry

Estimated detection rates for trisomy 21 at a fixed 5% false-positive rate are reported in a variety of studies using free β-hCG and PAPP-A, and are summarized in Table 46.5. Although the general consensus suggests a detection rate of the order of 65%, some variability is present because detection rates are highly dependent upon the gestational age of the pregnancies studied. Some of the earlier studies[93,96] incorporated PAPP-A assays that were polyclonal-based, and cross-reacted with a number of other serum components, whereas others used a very wide gestational age and did not take into account temporal changes in the marker values[94].

**Table 46.5** Modeled detection rates for a fixed 5% false-positive rate in various studies using free β-human chorionic gonadotropin, pregnancy-associated plasma protein-A in combination with maternal age

| *Study* | *Detection rate (%)* | *Cases (n)* | *Controls (n)* |
|---|---|---|---|
| Spencer[93] | 51 | 21 | 320 |
| Wald[94] | 62 | 77 | 383 |
| Krantz[95] | 63 | 22 | 483 |
| Berry[96] | 49 | 52 | 227 |
| Haddow[90] | 60 | 48 | 3169 |
| Spencer[65] | 67 | 210 | 946 |
| Cuckle[97] | 65 | meta-analysis (502) | |

Cuckle and van Lith[97] used a meta-analysis of published literature to provide parameters to model detection rates in the first trimester. Although this approach enables population parameters to be derived from a large group of affected cases, it is potentially flawed when used in the first trimester. First, it assumes that all of the assays for each analyte are comparable or that conversion to MoM removes any biases – a fact well established to be incorrect in the second trimester. Second, with respect to PAPP-A, some of the earlier published series used non-specific assays for PAPP-A, which could introduce bias. Another problem with the meta-analysis approach relates to the temporal changes occurring in marker levels across the first trimester[71,72]. As a result, grouping data from a wide gestational window is not appropriate, and will inevitably lead to errors in estimating the performance of the marker combinations. Although Cuckle and van Lith[97] made adjustments for changes in the median MoM in the trisomy 21 group for PAPP-A, they did not make adjustment for free β-hCG and neither did hey make adjustment for changing standard deviations.

It is important to make allowance for the inherent lethality of fetal aneuploidy when comparing detection rates between different time periods in pregnancy. Hence, a detection rate of 75% in the first trimester is actually worse than the same detection rate in the second trimester. Dunstan and Nix[98] provided a methodology to make this comparison, taking into account fetal loss. If one assumes that the fetal loss in women of all ages is best described in the studies of Morris and colleagues[99], a detection rate of 75% in the second trimester would need to be 3.5% higher in the first trimester for it to be statistically significantly higher[100]. In practice, such detection rates of around 80% cannot be achieved by first-trimester serum biochemistry or by fetal NT measurement alone, but can be achieved by combing the two.

## Combined first-trimester screening using ultrasound and maternal serum biochemistry

Combining maternal serum biochemistry and NT measurement in the first trimester is an effective screening procedure because the two modalities do not appear to be correlated[65]. A retrospective study of 210 cases of trisomy 21 and approximately 1000 controls showed that this combined approach could achieve 89% detection with a 5% false-positive rate[65]. Other studies[91,97,101,102] also found that such a combination can achieve detection rates in excess of 80%. In addition to identifying cases with trisomy 21, combined screening also identifies pregnancies complicated by trisomy 13[66], trisomy 18[67], Turner's syndrome, other sex aneuploidies[103] and triploidy types I and II[104]. In addition to detecting 89% of cases with trisomy 21, 90% of other chromosomal anomalies can be identified with an additional 1% false-positive rate.

In prospective screening using the combined approach, the modeled detection rates have been largely confirmed in larger series in which point-of-care screening used rapid immunoassay technology for the biochemical measurement[105]. In reporting the results of 3 years of screening in a one-stop clinic for assessment of risk (OSCAR), in which patients attend for a 1-h visit and have pretest counseling, ultrasound examination, maternal serum biochemistry testing and post-test counseling of the combined risk report, Spencer and colleagues[106,107] showed a detection rate of 92% for trisomy 21 with a 5.2% false-positive rate, as well as detection rates of 96% for all aneuploides, after screening over 12 000 women. Another OSCAR, screening 15 000 women, reported a detection rate for trisomy 21 of 91.5% with a 6.8% false-positive rate, and the detection of 88.5% of cases with other chromosomal anomalies[108]. The combined experience in prospective screening to date in these two centers is summarized in Table 46.6.

An alternative to the combined first-trimester screening approach was proposed by Wald and colleagues[109] based on multistage testing in the first and second trimesters. The approach, termed 'integrated screening', has modeled the theoretical performance of a test which includes the measurement of NT and PAPP-A in the first trimester. A risk based on these two parameters is not calculated (withheld from the patient), and further results for free β-hCG, AFP, unconjugated estriol and inhibin are combined after the 16–18-week second-trimester test. The theoretical detection rate predicted from such modeling

**Table 46.6** Prospective performance of combined ultrasound and maternal serum biochemical screening in two one-stop clinic for assessment of risk (OSCAR) centers over a 5-year period

| | *Spencer*[107] | | *Bindra*[108] | |
|---|---|---|---|---|
| | *3 Years* | *Years 4 and 5* | *3 Years* | *Total* |
| Screened (*n*) | 12 030 | 19 959 | 14 383 | 46 372 |
| At increased risk (*n*) | 577 (4.8%) | 767 (3.8%) | 1096 (7.6%) | 2440 (5.3%) |
| T21 detected/total | 23/25 (92%) | 47/52 (90%) | 75/82 (92%) | 145/159 (91%) |
| T18 detected (*n*) | 11 | 7 | 21 | 39 |
| T13 detected (*n*) | 4 | 6 | 10 | 20 |
| 45X detected (*n*) | 4 | 7 | 10 | 21 |
| Triploidy detected (*n*) | 5 | 4 | 7 | 16 |
| Others detected (*n*) | 2 | 3 | 6 | 11 |

T, trisomy

suggests 94% detection with a 5% false-positive rate. Although this modeled performance is a fraction higher than can be achieved routinely in the first trimester alone, the implementation of the integrated screening test as a method of population screening may be difficult in practice. First, it requires two visits by the patient, at the appropriate time, with the consequent additional cost and inconvenience (and likelihood of default). Second, women must wait and endure the additional anxiety associated with a 4–6-week delay for results, when 90% of cases could be detected at the first visit and a first-trimester termination offered. Additionally, some authors have seriously questioned the ethical and moral issues associated in withholding information after the first visit, and others have questioned the validity of the statistical model used[110–112].

One potentially new marker of trisomy 21 may also focus on screening solely in the first trimester. A new ultrasound marker has been described in which the nasal bone at 11–14 weeks was found to be absent in about 70% of fetuses with trisomy 21 and in 0.5% of chromosomally normal fetuses[113]. The findings of this preliminary study were confirmed in other smaller studies[114]. In extending their previous study, Cicero and colleagues[115] examined 3788 cases in which 430 cases had an abnormal karyotype; they confirmed that the nasal bone was absent in 67% of cases with trisomy 21 and in 2.8% of cases with a normal karyotype. Furthermore, they showed that the incidence of absent nasal bone in the normal pregnancy group varied with ethnic origin (2.8% in Caucasians, 10.4% in Afro-Caribbeans and 6.8% in Asians). Also, they showed that the incidence of absent nasal bone decreased with increasing crown–rump length and increased with increasing NT thickness. One way in which this marker may be used in the future if difficulties over technique and learning curves can be overcome[116] is to incorporate it into the existing first-trimester scan as part of the integrated ultrasound and biochemical screening performed at 11–14 weeks. Preliminary studies reveal that the absence of the nasal bone is not significantly correlated with free β-hCG or PAPP-A[117], and a combination of all of these markers would enable a detection rate of 97% with a 5% false-positive rate. If one wished to focus more on reducing the rate of invasive testing, then at a 0.5% false-positive rate, the detection rate would still be 90%. All of this could be achieved in a 1-h visit to a one-stop clinic, with screening and diagnosis by CVS and Q-PCR within a maximum of 48 h and prior to 13 weeks, giving the family the benefits of an early first-trimester termination of pregnancy if this is deemed necessary and wanted.

## Improving accuracy of individual risks: co-variables

Screening programs invariably quote population detection rates and false-positive rates to clients when counseling women, or in the literature made available to women. Often little attention is focused on the individual patient; for example, in second-trimester screening, detection rates of 75% may be achieved by a program with a 5% false-positive rate, but these numbers are totally inappropriate to quote to either a 20-year-old woman or indeed a 40-year-old woman. In a 20-year-old, the detection rate is much less (around 45%), and the false-positive rate much lower (around 3%), whereas in a 40-year-old detection rates are higher (around 92%) and false-positive rates higher (around 40%). Similarly, in first-trimester screening, detection rates fall to around 80% at age 20 (false-positive rates 2.5%) and increase to 96% at age 40 (false-positive rate 25%). As a result

**Table 46.7** Co-variables and factors influencing maternal serum marker levels or risk for trisomy 21

| *Co-variable* | *First trimester* | *Second trimester* |
|---|---|---|
| Gestational age | PAPP-A increased, free β-hCG decreased after 9 weeks | AFP, $UE_3$ increased, hCG decreased, inhibin little change |
| Maternal weight | all decreased with increasing weight | all decreased with increasing weight |
| Multiple pregnancy | 2 × higher in twins, 3 × higher in triplets | 2 × higher in twins, 3 × higher in triplets |
| IDDM | PAPP-A and free β-hCG (?) decreased | (?) AFP decreased related to level of control, $UE_3$ and hCG decreased, (?) inhibin |
| Fetal sex | free β-hCG and PAPP-A increased with female fetus | hCG increased and AFP decreased with female fetus |
| Assisted conception | free β-hCG increased, PAPP-A decreased | $UE_3$ decreased, hCG increased |
| Ethnicity | Afro-Caribbean and Asian both markers increased | AFP, hCG increased in Asian and Afro-Caribbean, inhibin lowered in Afro-Caribbean |
| Smoking | PAPP-A decreased | hCG, $UE_3$ decreased, AFP increased and inhibin very increased |
| Gravidity/parity | both markers increased with increasing number of pregnancies | hCG decreased with increasing pregnancies |
| Vaginal bleeding | unclear if any effect | AFP increased |
| Previous pregnancy | 2–3 times more likely to be high risk if previous pregnancy at high risk | 3–5 times more likely to be high risk if previous pregnancy at high risk |

IDDM, insulin-dependent diabetes mellitus; PAPP-A, pregnancy-associated plasma protein-A; hCG, human chorionic gonadotropin; (?), effect unclear; AFP, α-fetoprotein; $UE_3$, unconjugated estriol

of such variation, counseling needs to be tailored to the specific patient[118]. In a similar manner, other personal or individual factors may influence personal risk, and these need to be taken into account when calculating individual risks. Although correcting for many of these factors (or co-variables) in themselves has little impact on detection rates at the population level, they can be quite significant for the individual. Examples of such factors are summarized in Table 46.7. A more detailed description of these is found in reference 50.

## MULTIPLE PREGNANCY

One of the major factors that alters biochemical marker levels is the presence of more than one fetus. The preceding discussion has focused on singleton pregnancy in order to provide sufficient background for the reader to understand some of the complexities associated with screening in multiple pregnancy.

### Risk algorithms in twin pregnancy

#### *Background rates*

Age-specific trisomy 21 prevalence rates for twin pregnancies were derived by Rodis and colleagues[7], in which the authors made theoretical calculations of prevalence based not on direct observations but rather on the assumption that 80% of twins were dizygotic, and in such cases the trisomy 21 risk for each twin is that in a singleton. Myers and associates[119] updated these figures based on age-specific dizygosity rates. However, these theoretical rates do not match those observed in birth prevalence studies. A meta-analysis of 106 cases with trisomy 21 in twins showed that the prevalence was only 3% greater than for singletons[8]. Although it is possible that intrauterine lethality for affected twins may suppress birth prevalence, making first-trimester risk much higher, current thinking suggests that in the light of present knowledge, the safest assumption is that the prior risk in twins is the same as in singletons.

#### *Pseudo-risk*

Wald and colleagues[120] proposed that it should be possible to specify a screening policy for twins that would be expected to yield a false-positive rate similar to that in singleton pregnancies. These authors suggested that, since the width of the distribution of the maternal serum second-trimester biochemical markers was similar in both singleton and twin pregnancies, it should be possible to calculate a risk in twins by dividing the appropriate analyte MoM value by the corresponding median MoM value for

**Table 46.8** Published studies of maternal serum biochemical marker levels in unaffected twins in the second trimester

| | AFP | | Total hCG | | Free β-hCG | | Dimeric inhibin | | $UE_3$ | |
|---|---|---|---|---|---|---|---|---|---|---|
| Study | n | Median | n | Median | n | Median | n | Median | n | Median |
| Wald[15] | 1892 | 2.23 | 1211 | 2.01 | 619 | 2.08 | 199 | 1.99 | 739 | 1.65 |
| O'Brien[37] | 4443 | 2.02 | 2101 | 1.806 | | | | | 830 | 1.575 |
| Thom[33] | 100 | 1.90 | | | | | | | | |
| Crossley[35] | 81 | 1.91 | | | 81 | 1.85 | | | | |
| Raty[36] | 175 | 2.22 | | | 68 | 1.98 | | | | |
| Muller[34] | 3043 | 2.10 | | | 3043 | 2.11 | | | | |
| Barnabei[38] | 225 | 1.91 | | | 225 | 1.99 | | | | |
| Total | 9959 | 2.081 | 3312 | 1.878 | 4036 | 2.091 | 199 | 1.99 | 1569 | 1.610 |

AFP, α-fetoprotein; hCG, human chorionic gonadotropin; $UE_3$, unconjugated estriol

twin pregnancies, and treating the risk calculation as for a singleton pregnancy[120]. Table 46.8 is a meta-analysis summary of published cases of twins for which biochemical marker levels have been measured in the second trimester. A similar summary is given in Table 46.9 for the first-trimester biochemical markers. In the first trimester, the width of the marker distributions has been shown to be similar to that in singleton pregnancies[124,127].

The pseudo-risk approach was introduced because it was impossible to establish, by observation, the median MoM in cases of twins in which both were affected with trisomy 21, or indeed in cases of twins discordant for trisomy 21. In only one study have marker values been published, in eight cases discordant for trisomy 21[128], and this observation has recently been supported by 11 cases in which seven were discordant and four concordant for trisomy 21[34]. Detection rates have been modeled using the pseudo-risk approach for the double marker combination of AFP and free β-hCG[128]; with a 5% false-positive rate, a detection rate of 51% was expected in twins discordant for trisomy 21, some 15–20% lower than can be achieved in singleton pregnancies. For the triple marker approach, Neveux and colleagues[129] also found a similar detection rate of 53% with a false-positive rate of 5%, based on modeling after taking zygosity into account. However, other authors challenge the assumption that the pseudo-risk procedure is valid for estimating risks in twin pregnancies[37], because maternal serum levels are an integration of what is happening in both twins, and because in discordancy the altered marker levels expected in a trisomy 21 pregnancy are diluted or potentially masked by the marker output from the normal twin.

Very little prospective second-trimester screening performance has been published with respect to twins. One case of twins concordant for trisomy 21 was identified as a result of screening using the pseudo-risk approach[130]. The recently reported series of cases observed in second-trimester prospective screening[34], however, confirmed that if a pseudo-risk approach had been used with this two-marker (AFP and free β-hCG) protocol, then 54.5% of cases would have been identified with an 8% false-positive rate. Table 46.10 summarizes the values in a total of 20 published cases with trisomy 21 in the second trimester. The median MoM AFP in cases discordant for trisomy 21 appears to be higher than in singleton pregnancies (0.81 vs. 0.75), and the median free β-hCG lower than in singleton pregnancies (1.44 vs. 2.20). These observed values are very similar to what might be expected based on a normal fetus producing 1.00 MoM and an affected fetus

**Table 46.9** Published studies of maternal serum biochemical marker levels in unaffected twins in the first trimester

| | PAPP-A | | Free β-hCG | |
|---|---|---|---|---|
| Study | n | Median | n | Median |
| Spencer[121] | 159 | 1.87 | 159 | 2.11 |
| Niemimaa[122] | 67 | 2.36 | 67 | 1.85 |
| Orlandi[123] | 150 | 1.52 | 150 | 2.01 |
| Brambati[124] | 39 | 1.50 | 39 | 1.94 |
| Noble[125] | | | 136 | 1.94 |
| Bersinger[126] | 68 | 1.87 | | |
| Berry[96] | | | 50 | 1.97 |
| Spencer[127] | 224 | 1.98 | 224 | 2.15 |
| Total | 707 | 1.826 | 825 | 2.035 |

PAPP-A, pregnancy-associated plasma protein-A; hCG, human chorionic gonadotropin

**Table 46.10** Summary of second-trimester marker levels in published cases of twins affected by trisomy 21 (T21)

| *Case (study)* | *Author-stated chorionicity or zygosity* | *AFP MoM* | *Free β-hCG MoM* | *AFP twin-corrected MoM* | *Free β-hCG twin-corrected MoM* | *T21-affected (n)* |
|---|---|---|---|---|---|---|
| 1[128] | dizygotic | 2.01 | 2.92 | 0.88 | 1.35 | 1 |
| 2[128] | dizygotic | 0.79 | 5.26 | 0.35 | 2.44 | 1 |
| 3[128] | dizygotic | 0.71 | 3.97 | 0.31 | 1.84 | 1 |
| 4[128] | dizygotic | 1.42 | 2.74 | 0.62 | 1.27 | 1 |
| 5[128] | dizygotic | 1.96 | 2.89 | 0.86 | 1.34 | 1 |
| 6[128] | dizygotic | 1.85 | 2.02 | 0.81 | 0.94 | 1 |
| 7[128] | dizygotic | 1.19 | 3.75 | 0.52 | 1.74 | 1 |
| 8[128] | dizygotic | 1.81 | 4.62 | 0.79 | 2.14 | 1 |
| 9[34] | dichorionic | 2.04 | 30.1 | 0.97 | 14.27 | 1 |
| 10[34] | dichorionic | 2.06 | 1.57 | 0.98 | 0.74 | 1 |
| 11[34] | dichorionic | 2.18 | 3.00 | 1.04 | 1.42 | 1 |
| 12[34] | dichorionic | 1.78 | 2.36 | 0.85 | 1.12 | 1 |
| 13[34] | dichorionic | 0.99 | 3.04 | 0.47 | 1.44 | 1 |
| 14[34] | dichorionic | 1.51 | 15.25 | 0.72 | 7.23 | 1 |
| 15[34] | dichorionic | 1.99 | 5.86 | 0.95 | 2.78 | 1 |
| 16[34] | dichorionic | 2.31 | 4.20 | 1.10 | 1.99 | 2 |
| 17[34] | monochorionic | 1.97 | 1.14 | 0.94 | 0.54 | 2 |
| 18[34] | monochorionic | 1.85 | 16.22 | 0.88 | 7.69 | 2 |
| 19[34] | monochorionic | 2.10 | 3.69 | 1.00 | 1.75 | 2 |
| 20[130] | monochorionic | 1.66 | 0.72 | 6.05 | 2.80 | 2 |
| Median discordant | | 1.81 | 3.04 | 0.81 | 1.44 | 1 |
| Log mean | | 0.1855 | 0.6124 | –0.1560 | 0.2830 | 1 |
| SD | | 0.1588 | 0.3329 | 0.1659 | 0.3345 | 1 |

SD, standard deviation; AFP, α-fetoprotein; MoM, multiple of the normal median; hCG, human chorionic gonadotropin

producing the expected median in a singleton pregnancy, and the measured value being an average of the two. The standard deviations of the twin-corrected log MoM are very similar to those observed in singleton pregnancies, with perhaps the free β-hCG MoM being slightly more widely dispersed than in singleton pregnancies.

Screening in twins clearly results in a lower detection rate than in singletons. However, such detection rates are better than using maternal age alone, and should provide women with twins some chance of determining whether their pregnancy is complicated by trisomy 21. Whether improvements can be made to detection rates by taking into account some observed difference in marker levels based on zygosity or chorionicity remains to be seen, as currently scant data exist to make a satisfactory conclusion. Wald and colleagues[39] showed significantly higher MoM levels of AFP in monozygotic twins (2.57) compared with dizygotic twins (2.06). On the other hand, in a much larger study with respect to chorionicity, Muller and associates[34] found no difference in AFP MoMs between mono- (2.10) and dichorionic (2.10) twins, although they did find significant difference for free β-hCG (monochorionic 2.16, dichorionic 2.07).

In the first trimester, NT measurements are not affected by the problems encountered in serum screening, and some authors argue that first-trimester ultrasound should be the method of choice for screening chromosomal anomalies in twin pregnancies. This approach is based on the observation that the distribution of NT measurements in twin fetuses with trisomy 21 is similar to that in singletons[131–133]. In a study of 896 unaffected twin pregnancies, the NT was above the 95th centile for singletons in 7.3% of cases, and in seven out of eight with trisomy 21[132]. The prevalence of increased NT was higher in monochorionic fetuses (8.4%) compared with dichorionic fetuses (6.9%), suggesting that false-positive rates would be higher in monochorionic twins[132]. In calculating risk, essentially each co-twin is treated as a separate singleton and its risk calculated using the singleton distribution parameters. Thus, biophysical markers can be used to identify the fetus potentially at risk, and it has

**Table 46.11** Summary of first-trimester marker levels in published cases of twins affected by trisomy 21 (T21)

| *Study* | *n* | *Median twin-corrected free β-hCG MoM* | *Median twin-corrected PAPP-A MoM* | *Concordant for T21* | *Discordant for T21* |
|---|---|---|---|---|---|
| Noble[125] | 12 | 1.46 | | 2 | 10 |
| Spencer[127] | 4 | 1.27 | 0.595 | 0 | 4 |
| Brambati[124] | 3 | 1.28 | 0.69 | 0 | 3 |
| Bersinger[126] | 6 | | 0.693 | 0 | 6 |
| Bersinger[126] | 4 | | 0.335 | 4 | 0 |
| Total | 19 (17) | 1.39 | 0.56 | | |

hCG, human chorionic gonadotropin; MoM, multiple of the normal median; PAPP-A, pregnancy-associated plasma protein-A; total *n* 19 (free beta), 17 (PAPP-A)

been suggested that the risk based on the NT and maternal age can be used as the basis for making decisions regarding the appropriate diagnostic procedure to be followed in such circumstances[133].

Whereas maternal serum biochemistry alone cannot specifically identify the fetus at risk in the presence of twins discordant for an anomaly, it may be possible for the combination of the two to improve the detection rate, yet still retain the benefits of using NT to identify the fetus[121]. A screening protocol in twins based on the calculation of pseudo-risk from NT and maternal serum biochemistry was proposed by Spencer[121]. In this modeled study, it was expected that maternal serum biochemistry would add a further 5% to the detection rate using NT alone, thus bringing the detection rate up to 80% compared with the 90% in singleton pregnancies. As was the case in the second trimester, first-trimester biochemical distribution data on twins concordant or discordant for trisomy 21 are rare. Noble and colleagues[125] published a series of 12 twin pregnancies (ten discordant and two concordant for trisomy 21), along with free β-hCG levels. Brambati and associates[124] published three cases discordant for trisomy 21, along with both PAPP-A and free β-hCG levels. A further four cases were observed in prospective screening[127,134] using combined ultrasound and biochemical screening. Bersinger and co-workers[126] also published PAPP-A levels in a further ten cases (six discordant and four concordant for trisomy 21). Table 46.11 summarizes the overall median in the published cases.

In prospective screening in the first trimester using combined ultrasound and biochemical screening over a 3-year period, Spencer and Nicolaides[127] offered screening to 230 women with twins, and in 97% of cases screening was accepted. This uptake is very similar to that reported by Spencer and colleagues[107] in screening of singleton pregnancies. In this group of women, four cases were observed with twins discordant for trisomy 21, and in three cases combined screening identified the affected pregnancy. In all three instances, fetal reduction of the affected twin was selected, and the normal co-twin was delivered at term. A risk for trisomy 21 was calculated for each fetus based on the individual NT and the maternal serum biochemistry corrected for twin pregnancies. Of the twin fetuses screened, 6.8% had risks greater than the cut-off, and 9.2% of pregnancies had at least one fetus with an increased risk. After counseling, 37% of women declined invasive testing. Of the 63% remaining, CVS was the procedure chosen by the majority (83%). The uptake of invasive testing was lower than the 77% experienced in singleton pregnancies[107], reflecting both the added risk and the complexity of the invasive procedure in twins. This study concluded that NT should be the predominant factor by which women presenting with increased risk should be counseled regarding invasive testing.

As was the case in the second trimester, further studies need to be made of chorionicity and its impact on marker levels. Spencer[135] showed that PAPP-A in monochorionic twins may be lower (0.89 vs. 1.01) than in dichorionic twins after applying the twin correction, whereas free β-hCG levels were not different.

Wald and colleagues[136] recently suggested that it is more appropriate to calculate a pregnancy-specific risk estimate rather than calculate individual fetus-specific risks in the first trimester, arguing that since it is standard clinical practice to sample amniotic fluid or fetal material from both twins, a woman should not be expected to make two separate decisions on whether to have an invasive test with respect to each fetus. For a DZ pregnancy, the risk of trisomy

21 for each fetus is independent of the risk for the other, whereas in MZ twins the risk for one fetus is the same as for the other. These authors propose that in DZ pregnancies the pregnancy-specific risk should be calculated by summing the individual risk estimates for each fetus. In MZ twins, on other hand, the risk can be calculated based on the geometric mean of both NT measurements. Whether this is an acceptable or a desirable procedure remains to be seen, however, as the detection rates modeled using this procedure showed a rate 10% lower than that in singleton pregnancies, as was previously shown by Spencer[121] using the conventional approach.

## CONCLUSIONS

First- or second-trimester screening in twin pregnancies is feasible using either a combination of ultrasound and maternal serum biochemistry in the first trimester or maternal serum biochemistry in the second trimester. Retrospective modeling studies suggest that detection rates will be of the order of 50–55% in the second trimester, some 20% lower than in singleton pregnancies. Limited prospective data suggest that these modeling figures are realistic. In the first trimester, combined screening appears to achieve detection rates of around 80% using modeling, and in limited prospective practice this has been achieved. Nevertheless, detection rates are some 10% lower than in singletons.

For higher-order multiples, such as triplets, scant data exist by which to examine marker distributions in normal pregnancies, let alone in cases with chromosomal anomalies. In the second trimester, Barnabei and colleagues[38] published a series of 39 cases with a median AFP of 2.68 and a median free β-hCG of 2.78. Spencer and associates[128] showed an AFP median of 3.77 and a median free β-hCG of 3.75 in 19 cases. The combined series of 57 cases produced a median AFP MoM of 2.997 and of 3.066 for free β-hCG. Brambati and co-workers[124] showed a median MoM for free β-hCG of 2.77 and of 2.22 for PAPP-A in a series of 17 cases in the first trimester. In a similar series (Spencer, 2003, unpublished) of 17 cases, the median MoM for free β-hCG was 2.74 and was 3.26 for PAPP-A. The combined series of 34 cases suggests that the median MoM for free β-hCG is 2.755, and for PAPP-A is 2.744. Much larger studies are required before such data could be used in triplet pregnancy screening. At present, the best approach would be to use NT alone in higher-order multiple pregnancies.

Until more data are available on the distribution of markers in concordant or discordant twins, the pseudo-risk approach is a satisfactory procedure for use in screening twin pregnancies in either the first or the second trimester.

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# Nuchal Translucency Measurement

*R. Maymon and A. Herman*

47

DOWN'S SYNDROME SCREENING USING MID-GESTATION SERUM SCREENING

DOWN'S SYNDROME SCREENING USING NUCHAL TRANSLUCENCY MEASUREMENT

SCREENING BEFORE MULTIFETAL PREGNANCY REDUCTION

## INTRODUCTION

Routine multimarker screening for Down's syndrome (DS) is now an established practice in many areas of the world. In the second trimester, the most common markers include maternal serum human chorionic gonadotropin (hCG) or its free β subunit (Fβ-hCG), α-fetoprotein (AFP) and unconjugated estriol ($uE_3$). Large studies using combinations of hCG (or Fβ-hCG) and either or both of the other markers confirm model predictions that about two-thirds of DS-affected pregnancies can be detected with a false-positive rate (FPR) of about 5%[1]. In the first trimester, the combination of maternal serum pregnancy-associated placental protein-A (PAPP-A) and Fβ-hCG can achieve similar performance[2].

Another approach to the detection of fetal trisomies utilizes the ultrasonographic finding of nuchal translucency, an echo-free area at the back of the fetal neck, as this marker is associated with fetal chromosomal abnormalities[3,4]. Wald and Hackshaw[5] in 1997 proposed combining ultrasound with first-trimester biochemical serum markers in a single screening test. Such a combination allows an 85% DS detection rate with a 5% FPR[5,6], a significant improvement over other DS screening tests.

During the past decade, the increasing maternal age at which pregnancy is desirable and acceptable and the widespread use of a variety of assisted reproductive technologies (ART) and medications affected obstetric practice worldwide[7,8]. The resultant changes were followed by increasing understanding of the use of all mid-gestation serum markers. Mainly affected was the appreciation of serum hCG levels, which are increased in ART pregnancies, leading to a higher FPR in singletons[9–14] and in twins as well[15,16].

Spencer and Nicolaides[17] suggested that adding maternal serum biochemistry to NT measurement could improve DS detection in twins.

Clearly, the artificial production of large numbers of high-order multiple gestations was followed by an urgent need to screen for DS among these pregnancies, many of which occurred in older women, and the subsequent recognition of the complexity of such procedures. This chapter discusses proposed management protocols to achieve the best estimation of DS risk in this population.

## DOWN'S SYNDROME SCREENING IN HIGH-ORDER MULTIPLE GESTATION USING MID-GESTATION SERUM SCREENING

Triplet pregnancies are primarily iatrogenic conceptions following successful infertility therapy[18]. In the United States, 6000 babies were born during 1996 in sets of triplets or more[19]. In such a selected population, serum screening is not widely applicable, although studies have been published[20]. Furthermore, the use of fetal reduction, which parallels the widespread use of assisted conception[18,21], complicates the screening algorithm, mainly because elevated mid-gestation maternal serum AFP levels are present after first-trimester fetal reduction. Grau and co-workers[22] reviewed maternal serum and amniotic fluid levels of AFP from 40 women who underwent fetal reduction at approximately 12 weeks of gestation. Respectively, 95% and 25% of the patients who had mid-gestation AFP measured in maternal serum and amniotic fluid had elevated values. Fortunately, none of those abnormal levels were associated with neural tube defects, although two structural defects were detected by other means.

The difference between serum and amniotic fluid AFP was attributed to either one or several mechanisms. All pregnancies were reduced to twins and one to triplets, and it is not uncommon to find elevated maternal serum AFP in such pregnancies. Alternatively, fetal AFP could have been released from the dead fetuses because of autolysis[23]. In such circumstances, the transport of AFP across fetal membranes and the placenta may be enhanced by the remaining live co-twin(s)[22]. Lynch and Berkowitz[23] reported similar findings, and concluded that mid-gestation maternal serum AFP is always elevated after multifetal pregnancy reduction, and thus is not necessarily indicative of fetal defects. In contrast, Groutz and colleagues[24] found elevated AFP maternal serum in only two of 28 studied cases, both having adverse perinatal outcomes: severe pre-eclampsia in one, and exomphalos in the other.

Other groups[24–26] studied the effect of first-trimester fetal reduction on triple test results (AFP, $uE_3$ and hCG), and confirmed the elevation of maternal serum AFP. Recently, Rotmensch and associates[27] reported mid-gestation triple serum screening results from 27 high-order multiple gestations reduced to twins. About 90% of women exhibited maternal serum AFP levels > 2 multiples of the median (MoM), but only one of the newborns had structural anomalies. In their experience, this marker did not correlate with either the number of reduced fetuses or adverse obstetric outcome. In this study, however, the mean hCG and $uE_3$ serum levels were slightly increased as well ($1.22 \pm 0.49$ MoM, $1.15 \pm 0.31$ MoM, respectively). Although previous studies found that both hCG and $E_3$ were not altered[25,26], the effect of first-trimester reduction on DS screening efficacy remains undetermined[24–27], and amniocentesis is not indicated in these cases. Moreover, ultrasonography for evaluation of fetal anatomy should be considered, mainly because maternal serum AFP cannot be used in these patients to screen for fetal abnormalities[23].

## DOWN'S SYNDROME SCREENING IN HIGH ORDER OF MULTIPLICITY USING NUCHAL TRANSLUCENCY MEASUREMENT

It is currently accepted that ultrasound can identify and measure subcutaneous fluid collections between the soft tissue covering the fetal spine and the overlying skin during the late first trimester[3,4,28]. The thickness of this hypoechoic ultrasonographic feature, defined as nuchal translucency (NT), is associated with chromosomal abnormalities[3,4,28] and cardiac and other structural defects[29,30], as well as an increased risk of spontaneous abortion[29,31]. Nicolaides and his group[3,4,29] emphasize the importance of proper image technique, and describe measurement on a mid-sagittal section as the 'maximum thickness of the subcutaneous translucency between the skin and the soft tissue overlying the cervical spine'. In reports emanating from this group, readers were referred to specific images in order to pinpoint placement of the calipers on the nuchal lines adjacent to the translucent area.

In light of the currently available statistical models for assessment of DS risk, the need for a clearly defined and reproducible measurement is obvious. Accordingly, the size of each image should be magnified until the fetus occupies at least 75% of the screen. The maximum NT thickness is achieved and recorded by measuring it in the true mid-sagittal plane, with calipers placed on the inner surface of the nuchal membranes (on-to-on measurement). At least three measurements should be obtained, and the largest used for purposes of counseling. Special attention is given to observe fetal movement, so that the fetal skin and amnion are adequately discriminated. Only fetuses with a crown–rump length (CRL) between 38 and 84 mm should be included[3,4,29], because this size corresponds to a gestational age of between 10 and 3/7 weeks and 13 and 6/7 weeks.

Because NT is perceived as a valuable marker for detecting fetal abnormalities and complications, its importance is clear-cut for multiple pregnancies in which biochemical screening is of limited value. In twin pregnancies, first-trimester ultrasound screening for chromosomal abnormalities is both reliable and feasible[32]. NT screening in twins is the predominant factor underlying the provision of counseling regarding further invasive testing[17]. Moreover, NT measurement may provide additional data about twin pathophysiology, such as underlying hemodynamic changes associated with early onset of twin-to-twin transfusion syndrome in monochorionic twins[33].

Caution is appropriate, however, as evidenced by Berkowitz and colleagues[34], who reported that among 200 patients who underwent fetal reduction, six of the remaining fetuses had either anatomical ($n = 4$) or chromosomal ($n = 2$) abnormalities. Based on this observation, pre-procedure genetic counseling and careful scanning was proposed, especially for those patients with an increased risk of karyotype abnormalities[34]. To overcome such problems, first-trimester ultrasound screening using NT measurement appears to be the best option.

Our group assessed pregnant patients who conceived following assisted reproduction and were carrying ≥ 3 fetuses[35]. Each fetus (Figures 47.1 and 47.2) was ultrasonographically assessed by measuring the CRL and NT thickness using a published protocol[3,4]. Prior to the test, women were provided with a leaflet explaining the nature and implications

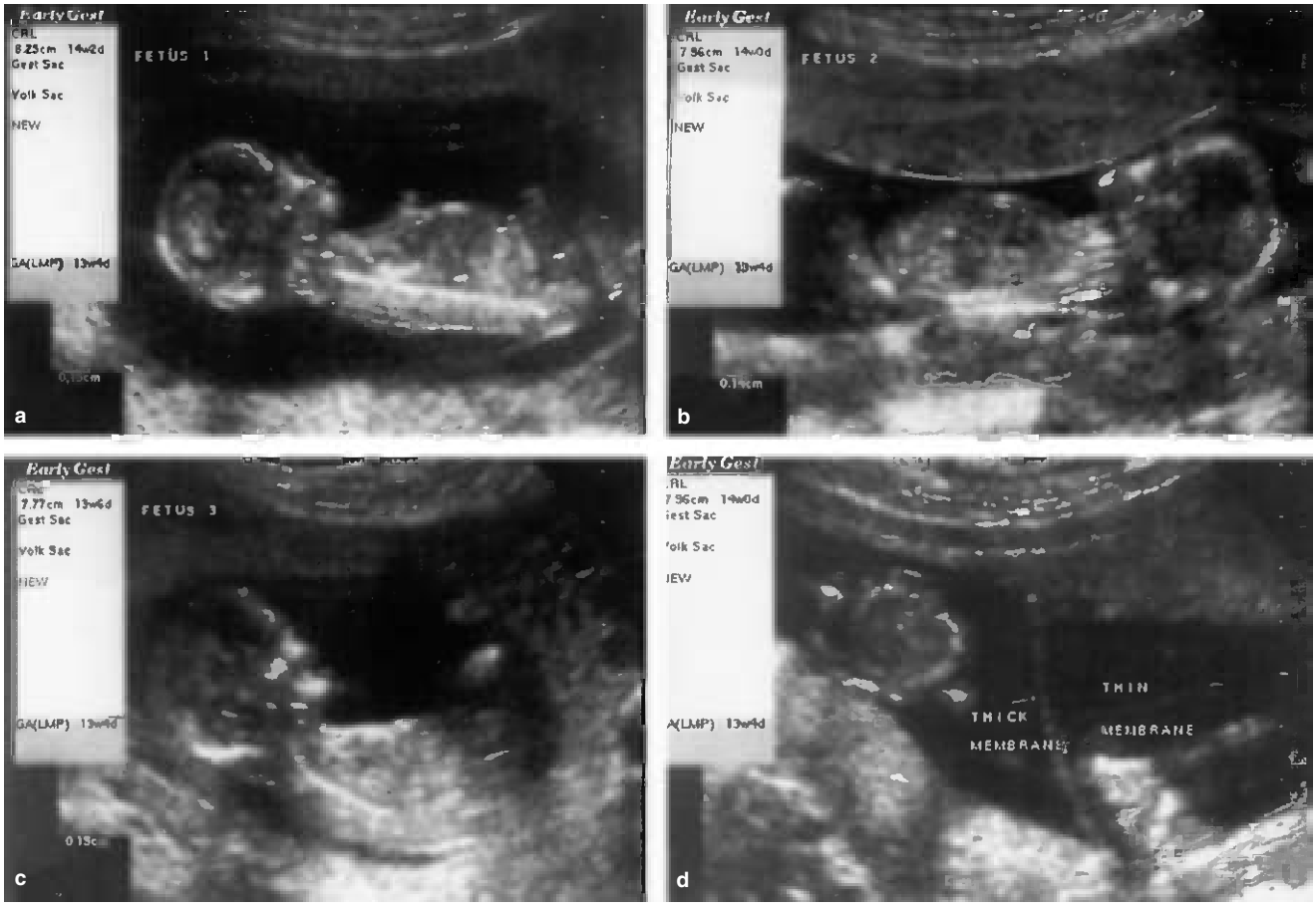


**Figure 47.1** Transabdominal nuchal translucency measurement in a dichorionic triplet pregnancy: biamniotic in one chorionic sac and the third triplet in the other chorionic sac. (a, b, c) Adequate nuchal translucency measurements are illustrated. Each fetus is in the mid-sagittal plane, occupying about 75% of the image. The calipers are placed on the inner borders of the hypoechoic area behind the fetal neck (nuchal translucency). The bichorionic triplet pregnancy is demonstrated by a thick membrane of one sac and thin membrane in the monochorionic other sac (d)

of the test. Upon completion of the scanning, they were counseled regarding risks, and asked to sign a written NT-informed consent form.

The study group were scanned by two examiners who showed intraobserver repeatability coefficients of 0.34 mm and 0.28 mm, respectively, and an inter-observer repeatability coefficient of 0.36 mm[36]. Individual sonographer's and the unit measurements were subject to regular internal audit to check quality control of standardization and distribution of measurements and performance[36,37]. With results that corresponded well with previous reports[38], they are used for counseling prior to any invasive procedure.

Twenty-four pregnant patients, initially carrying 79 fetuses aged between 10 and 14 weeks of gestation, were compared with consecutively matched, singleton controls[35]. NT measurements were feasible for both study and control fetuses, which exhibited similar NT measurements for the 5th, 50th and 95th centiles. Also, mean NT thicknesses (mm or MoM) were similar for both groups (1.41 ± 0.41 mm and 1.35 ± 0.39 mm, respectively and 0.87 ± 0.23 MoM and 0.83 ± 0.25 MoM, respectively). No instances of chromosomal abnormalities were detected in either group, and of those infants who had no karyotyping, no traits were observed postnatally that warranted chromosomal analysis. As there is no other effective screening modality for these pregnancies, it is reasonable to recommend NT measurement for antenatal screening services for higher-order multiple gestations[8,35]. Moreover, in contrast with others who reported obtaining an NT thickness in only about 83% of assessed singletons[2], we succeeded in measuring it in all of our cases[35]. Regardless, it is premature to draw any conclusions concerning the sensitivity and FPR of the method, as our series is too small, and no other series exist in the English literature.

We believe that our observations[35] validate the use of NT measurements obtained originally in singletons[3,4] and twins[32,39,40] in higher-order multiple

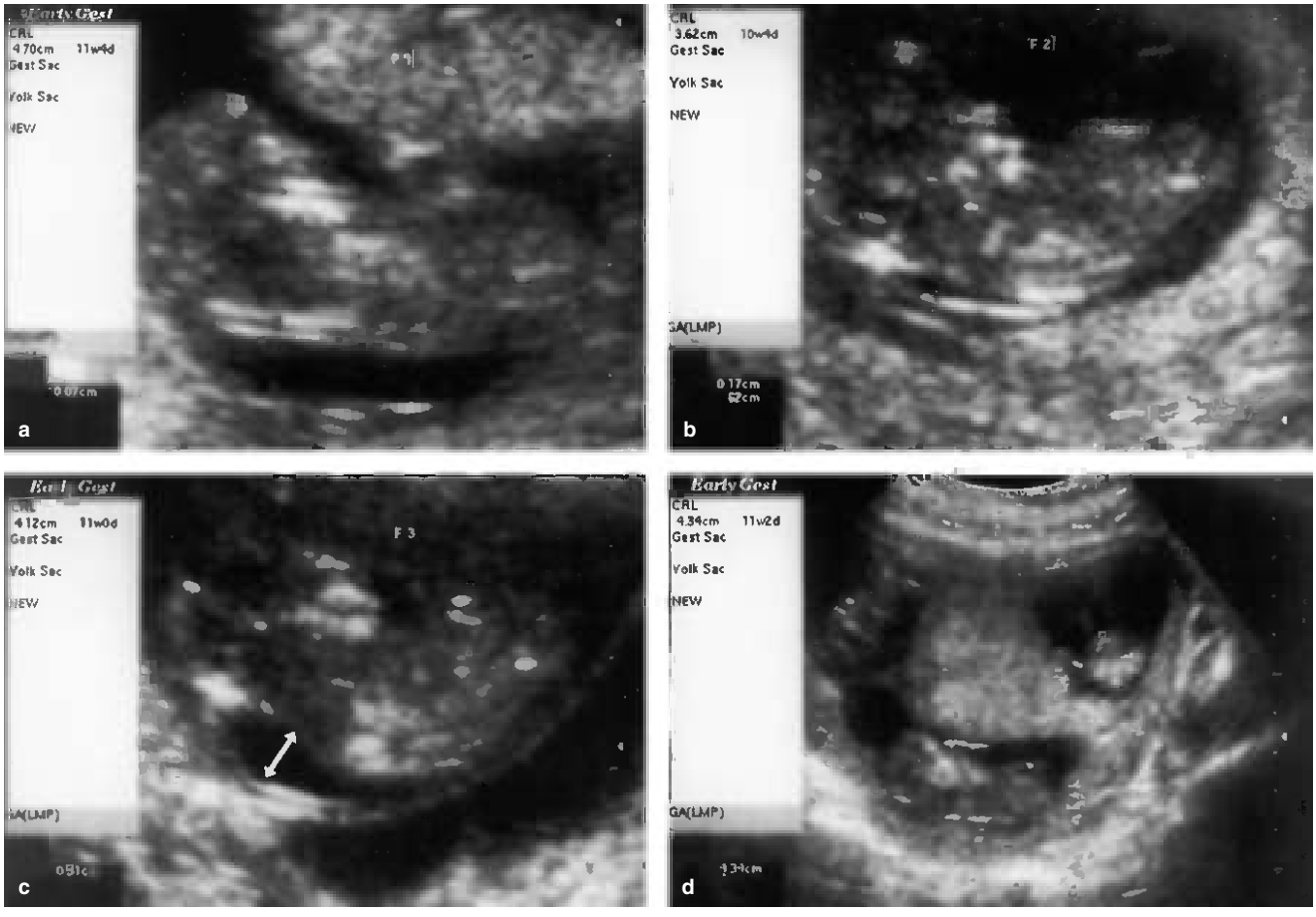


**Figure 47.2** Transabdominal nuchal translucency measurement in a triplet pregnancy. (a, b) Adequate nuchal translucency measurements are illustrated (same as in Figure 47.1). Increased nuchal translucency (marked by the arrow heads) in the third fetus is presented (c). This fetus was chosen for reduction because of the increased nuchal area. The three fetuses in three separate sacs are presented (d)

gestations. Furthermore, this sonographic screening method provides additional data for the identification of an abnormal fetus[29], thus lowering the complications of leaving an abnormal one after reduction[34].

## SCREENING BEFORE MULTIFETAL PREGNANCY REDUCTION

A critical problem of higher-order multiple gestation management protocols is that of fetal reduction. Most authorities agree that reducing multifetal pregnancies to twins improves both pregnancy and perinatal outcome[18,41]. Moreover, this possibility offers an alternative, apart from terminating the entire pregnancy, to those women carrying either a higher number of fetuses than desired or an affected fetus[21].

Fetal reduction is generally carried out at the end of the first trimester, using transabdominal intrathoracic introduction of a fine needle under ultrasound guidance, and injection of concentrated potassium chloride solution[18,34]. Whereas agreement exists as to the number of fetuses to be left (twin pregnancies having the best outcome[18,34])[42], the choice as to which fetuses to terminate is governed by a number of variables. Thus, before feticide, careful ultrasonographic assessment of the entire pregnancy is recommended to determine the actual number of living fetuses, their location, the placentation for monochorionic twins[43] (Figure 47.1), presence of visible fetal anomalies (Figure 47.3) or fetal discordancy[21,44], as well as slower fetal heart rate[45]. The above parameters may indicate an anomaly or poor prognosis for the survival of a particular fetus[44,45]. Additionally, it seems important to offer pre-procedure, non-invasive genetic testing and careful scanning, especially for those patients with a significantly increased risk of karyotypic abnormalities by virtue of their age[34]. In this respect, first-trimester ultrasound screening using NT measurement seems to be a most promising option.

Lipitz and colleagues[46] recommend performance of fetal reduction in triplets at 13–14 weeks' gestation rather than at 11–12 weeks, as this allows a more

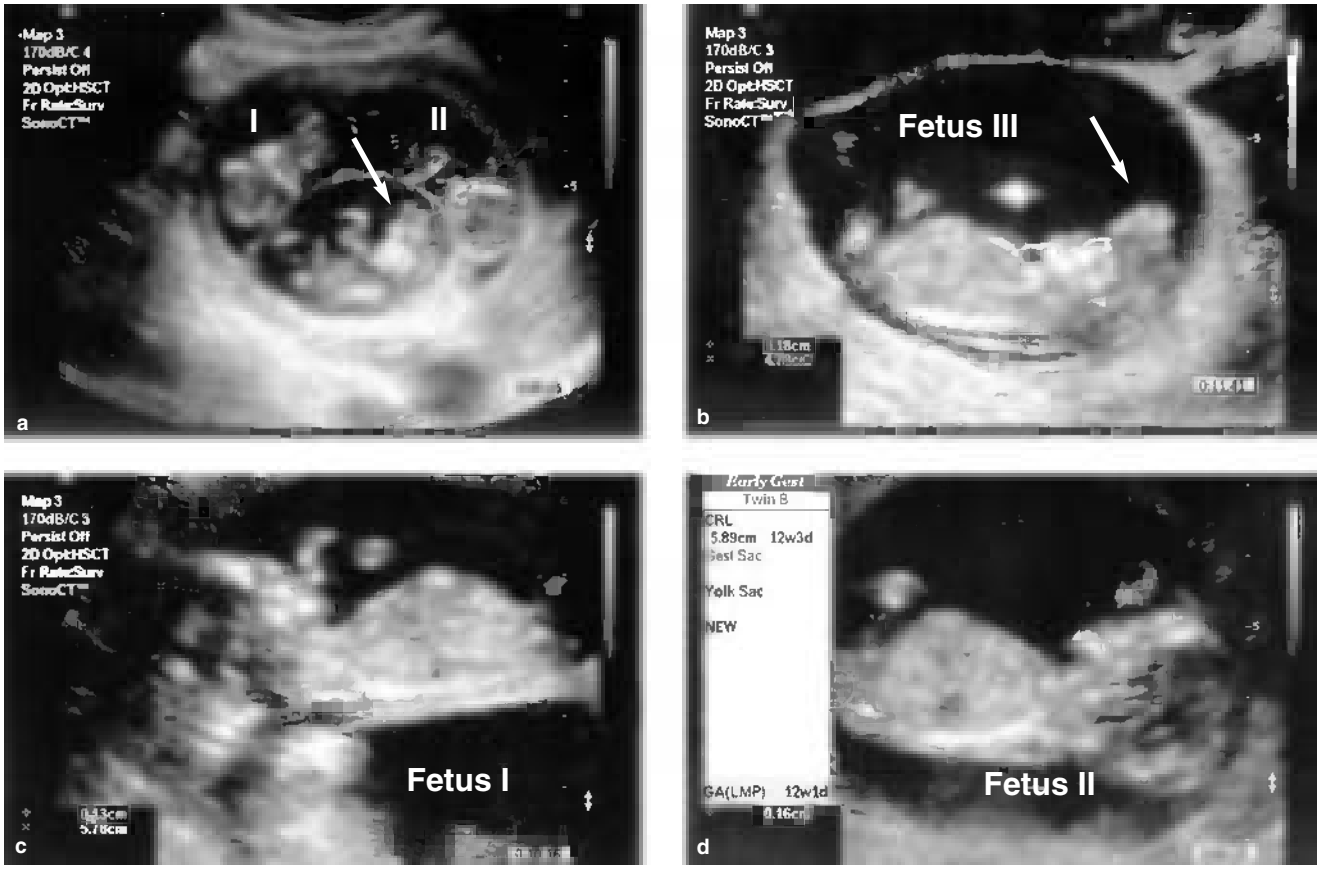


**Figure 47.3** Transabdominal nuchal translucency measurement in a triplet pregnancy. (a) A triplet gestation. The arrow head is pointing to a fetus with acrania; (b) an image magnification. This fetus was chosen for reduction because of the severe brain defect. (c, d) Adequate nuchal translucency measurements are illustrated

detailed anomaly scan at a slightly more advanced gestational age. According to their experience, pregnancy loss is similar (about 4%) in either group. They conclude that screening before fetal reduction at 13–14 weeks should include NT measurement and ruling out relative intrauterine growth restriction and structural anomalies. At this gestational age, the sex of the fetus can also be determined, a factor which may be of clinical importance for families at risk for chromosomal X-linked disorders[46]. In triplet pregnancies, such an early detailed fetal anomaly scan requires a very experienced sonographer and a modern ultrasound machine with high resolution.

Since transvaginal sonography provides a better picture of the lower fetus, combined transvaginal and transabdominal scan may be required[46]. With such high scanning performance, it seems reasonable to consider additional sonographic markers, or fetal biometric measurements such as the fetal nasal bone (NB), at the time of an NT scan[47]. For singletons, the corresponding predicted DS detection rate for a 5% FPR is 86% for such a sonographic combination (NB + NT)[48]. Additional studies are needed to determine the most efficient screening combination by means of ultrasound for the subgroup of high-order multiple gestation.

Brambati and colleagues[49] and Eddleman and co-workers[50] reported performing chorionic villous sampling (CVS) before multifetal pregnancy reduction. The message from these two studies is that in high-risk groups for chromosomal aneuploidy, CVS should be offered before embryo reduction is employed. Eddleman and co-workers[50] further supported their management protocol, stating that 'rarely, there is a visible anomaly or a smaller than expected crown–rump length that influences the decision about which fetus to remove'. According to their report, however, CVS procedures alone were associated with 1.2% sampling errors, which is actually the primary risk for aneuploidy in this group.

Although pre-reduction CVS has its advantages, primarily in older patients, the following disadvantages hinder the widespread use of this practice: the risk of abortion; the objective difficulty in carrying out villocentesis in multiple pregnancies; the difficulty in identifying ill fetuses to be eliminated within a few

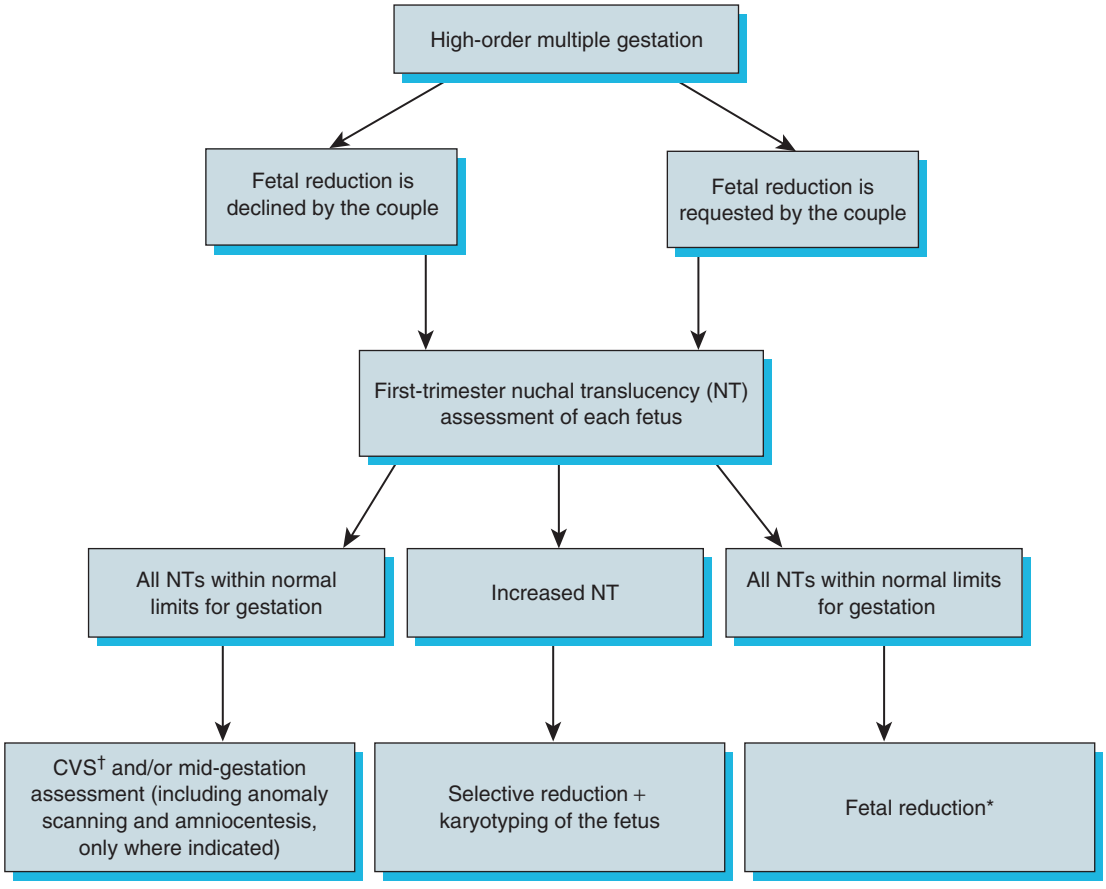


**Figure 47.4** Flow chart of first-trimester screening for chromosomal abnormalities in high-order multiple gestation. *Reduction could be postponed until after detailed anomaly scan (around 14 weeks' gestation); †chorionic villous sampling (CVS) is reserved for only very high-risk cases, such as carriers of a single gene disorder or balanced translocation

days of taking the sample; and the higher stress level in patients caused by the two invasive procedures carried out within a few days of each other[51].

The gestational age at which multifetal pregnancy reduction is optimally carried out overlaps with the proper timing for fetal NT measurement[29]. Therefore, during the past few years, our group[35,52] as well as others[51] have routinely used NT measurement prior to multifetal pregnancy reduction as the criterion for selecting fetuses at high risk for chromosomal pathology (Figure 47.2). We also showed that screening by NT measurement is feasible and accurate in high-order multiple gestation[35]. It is our intention to suggest the following approach, which includes NT measurement as part of pre-procedure non-invasive genetic testing, before any embryo reduction. This is followed by reducing the fetus exhibiting the highest risk, once detected, and thereby lowering the probability of leaving an affected fetus after the procedure[34]. Using this policy we encountered a triplet pregnancy in which one fetus exhibited an NT of 3 mm (> 95th centile for CRL[29,52]). The other two fetuses had NTs within the normal limit for gestation[52]. Before reducing that fetus and using the same fine needle, a few milliliters of amniotic fluid were aspirated for chromosomal analysis. This test revealed a fetus affected with trisomy 13. Mid-gestation amniocentesis performed later confirmed euploid karyotype of the remaining fetuses. Similar experience was reported by Monni and colleagues[51]. Our current policy[34,52] is:

(1) Routine NT measurement before any multifetal pregnancy reduction. Patients could be offered postponement of reduction until around 14 weeks, after a detailed anomaly scan;

(2) Reduction and karyotyping of the high-risk fetus (Figure 47.2) and/or the malformed fetus (Figure 47.3);

(3) Performance of mid-gestation amniocentesis, where indicated. The performance of genetic amniocentesis after multifetal pregnancy reduction does not increase the risk of pregnancy loss over that observed in association with the reduction itself[53] (Figure 47.4). We believe that

CVS should be reserved for only highly selected instances, including parents with balance translocations or carriers of a single gene disorder in which prenatal diagnosis is available.

In summary, women who conceive a multifetal pregnancy after assisted conception are naturally wary of any invasive prenatal diagnostic procedure. As they receive careful antenatal care from the start of their pregnancies, and because their serum markers are less discriminative for chromosomal screening, it seem reasonable to offer them ultrasound assessment including NT measurement, which currently is the only available and highly efficient screening method. This valuable information can contribute to overall management if fetal reduction is planned, and as a screening modality for other structural anomalies associated with increased NT.

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# Diagnostic Genetic Testing

*E. Pergament*

**48**



## DIAGNOSTIC GENETIC TESTING IN MULTIPLE GESTATIONS

Diagnostic genetic testing in multiple gestations presents unique and unmatched challenges compared with singleton pregnancies. To accomplish genetic diagnoses prenatally, an invasive procedure such as first-trimester chorionic villus sampling or mid-trimester amniocentesis is necessary. Obtaining a sample of cells from each fetus in a multiple gestation is more complex and poses greater obstetric risks. Not only are two or more fetuses involved, but multiple gestations typically occur in older women who are at increased risk for aneuploidy. In addition, each fetus from a multiple gestation may also be at increased risk for congenital malformations compared with a singleton pregnancy. The genetic problems and counseling issues posed by multiple gestations are acutely dramatized in the case of the successful application of assisted reproductive technologies whereby the common practice of transferring two or more embryos increases the likelihood of multiple gestations[1], previously infertile couples having become pregnant may now not only have to consider undergoing invasive genetic testing with all of its attendant risks including pregnancy loss, but also must be counseled concerning the unique ethical and moral issues engendered if only one fetus in a set of multiples is found to be genetically abnormal.

This chapter reviews prenatal genetic diagnosis in multiple gestations and describes the risks, benefits and consequences of diagnostic genetic testing in multiple gestations from a genetic perspective.

## CHORIONICITY

Knowledge of chorionicity must be considered an essential prerequisite prior to undertaking prenatal genetic diagnosis in multiple gestations, as it is invaluable in assessing the overall risks for chromosome abnormalities and mendelian (single gene) mutations. Risk assessments for chromosome abnormalities and mendelian disorders in multiple gestations must consider a number of confounding factors. First, the different mechanisms of twinning result in genotypic differences existing between dizygotic twins but not monozygotic twins. Second, the rate of dizygotic twinning increases with advancing maternal age. And, third, significant racial and geographic variations exist in the rate of dizygotic twinning. Thus, African women have a higher rate of dizygotic pregnancy than Caucasians and Asians have a lower rate[2].

If zygosity has not as yet been established by the time of the initial genetic counseling session, a crude risk assessment can be made by assuming that approximately one-third of naturally occurring twin pregnancies will be monozygotic and two-thirds will be dizygotic. Higher-numbered gestations, e.g. triplets or quadruplets, present additional complications because of the different possibilities and combinations of monozygotic and dizygotic twinning in the set.

First-trimester ultrasound is a very reliable method of chorionicity determination and is recognized as the most accurate approach. Misdiagnosis of chorionicity should be a relatively rare occurrence[3]. Despite the availability of first-trimester ultrasound, most patients with multiple gestations appear not to

know the chorionicity of their pregnancy, reflecting the lack of application of ultrasound determination on the part of their obstetrician.

## GENETIC COUNSELING IN MULTIPLE GESTATIONS

Before any prenatal diagnostic procedure is performed, profound medical, emotional and moral issues must be addressed with parents with multiple gestations. There must be a favorable cost : benefit ratio, i.e. the reproductive risk of a genetic disorder in one or more fetuses must significantly exceed the risk of serious obstetric complications of the diagnostic procedure, particularly the loss of one or more fetuses as a direct consequence of the procedure itself. As part of the genetic counseling, prospective parents must be informed that no cures are available for genetic disorders, and if a genetic abnormality is detected, there are only two choices: either to continue the pregnancy recognizing that one or more infants will be compromised physically and functionally for their entire life, or to terminate the pregnancy. In the case where only one fetus is genetically affected, selective termination with all of its medical, emotional and ethical implications must be discussed as an option. It is recommended that no diagnostic procedure should be performed if a multiple gestation is observed during the course of an ultrasound examination prior to an anticipated singleton prenatal diagnostic procedure[2]. Rather, the patient should be removed from the examining room and undergo, along with her partner, additional genetic counseling pertinent to all aspects of diagnostic testing in the case of multiple gestations. Both patient and partner should be given sufficient time to process the additional information such that an informed decision for which they share responsibility can be reached by the prospective parents.

## INDICATIONS FOR PRENATAL DIAGNOSIS IN MULTIPLE GESTATIONS

Indications for prenatal diagnostic genetic testing are now established as standard, routine and applicable to both single and multiple gestations. These indications include:

(1) Advanced maternal age;

(2) A previous offspring with a chromosome abnormality;

(3) A family history of a chromosome abnormality or known carriers of a mendelian mutation;

(4) A previous offspring with an open neural tube defect;

(5) A family history of a congenital malformation;

(6) Structural abnormalities identified in the course of ultrasound examination.

### Advanced maternal age and the risk of aneuploidy in multiple gestations

The most common indication for prenatal genetic diagnosis is advanced maternal age. The well-recognized association of advancing maternal age with increased risk of having a conception with trisomy 21 (Down's) or other autosomal trisomies immediately distinguishes mothers with multiple gestations. In a multiple gestation, the overall risk of an aneuploid fetus is directly determined by zygosity. The theoretic risks of fetal aneuploidy in a twin gestation are listed in Table 48.1. Four risk combinations are presented:

(1) The risk of *both* fetuses being simultaneously chromosomally abnormal;

(2) The risk of *only one* chromosomally abnormal fetus;

(3) The risk of *at least one* chromosomally abnormal fetus;

(4) The risk of *both* fetuses being chromosomally normal.

The risk of *both* fetuses being simultaneously abnormal in monozygotic twins is the same as the age-related risk for a singleton, ignoring the rare occurrence of discordant chromosome constitutions due to post-zygotic mitotic non-disjunction (see Chapters 32 and 94). For dizygotic twins, as each fetus has an independent risk of an abnormal chromosome constitution, the probability of both fetuses being chromosomally abnormal is the product of their separate probabilities, i.e. this risk is relatively small except for women 45 years of age or older. And, therefore, the risk of both fetuses being chromosomally abnormal for twins of unknown zygosity approximates that of monozygotic twins.

The risk of *only one* affected fetus in the case of a monozygotic pregnancy is essentially zero, with exceptions due to post-zygotic mitotic non-disjunction. In a dizygotic pregnancy, twin A may be chromosomally abnormal (X) and twin B normal (1 – X) or vice versa; therefore, the probabilities are added to determine the likelihood of either occurrence. In clinical practice, the risk of only one affected fetus in a dizygotic pregnancy or a

**Table 48.1** Maternal age-related risks of fetal chromosome abnormalities in twin gestations (derived in part from reference 4)

| | *Monozygotic pregnancy* | *Dizygotic pregnancy* | *Zygosity unknown* |
|---|---|---|---|
| Risk of both fetuses affected | X | $(X)(X) = X^2$ | $X + X^2 \approx X$ |
| Risk of only one affected fetus | 0 | $X(1 - X) + (1 - X)X = 2X - 2X^2$ | approximately same as risk for dizygotic pregnancy |
| Risk of at least one affected fetus | X | $2X - X^2 \approx 2X$ | $1/3X + 2/3(2X) = 5/3X$ |
| Risk of both unaffected | $1 - X$ | $1 - X^2$ | $(1 - X) + (1 - X^2)$ |

X, age-related risk of chromosome abnormality; 1 – X, age-related risk of normal karyotype

pregnancy of unknown zygosity is approximately two times the age-related risk of a singleton pregnancy, since the contribution of the component $-2X^2$ is negligible.

The risk of *at least one* chromosomally abnormal fetus is the same as the probability of having both fetuses affected or having one affected. For monozygotic twins, this risk is the same as the risk of both fetuses being affected. For dizygotic twins, this risk is approximately two times the risk of the age-related risk of a singleton pregnancy, as the component $X^2$ will be insignificant and can essentially be ignored, with the possible exception of women 45 years of age or older. For twins of unknown zygosity, the general assumption is that one-third of twin gestations are monozygotic and two-thirds are dizygotic, and therefore the best overall estimate of having *at least one* chromosomally abnormal fetus is five-thirds of X. However, this last ratio will vary according to: race, e.g. African women have a higher risk of dizygotic pregnancies and Asian women a lower probability than Caucasian[2]; maternal age, e.g. the rate of dizygotic pregnancies increases with maternal age; and form of conception, e.g. monozygosity occurs at higher rates than expected in cases where multiple gestations result from the application of artificial reproductive technologies[1].

The clinical significance of these calculations is illustrated in the choice of maternal age to offer prenatal invasive testing for chromosome aberrations in the case of multiple gestations. There is no internationally accepted, standard criterion for determining at what age a mother with a singleton pregnancy should be offered the option of an invasive prenatal diagnostic test for fetal chromosome analysis. For example, in the United States, this option is generally offered to women 35 years of age and older, whereas in the United Kingdom and France, chorionic villus sampling and amniocentesis are available to women 37 years of age and older. This choice is further complicated by the fact that risk figures at the time of first-trimester chorionic villus sampling, mid-trimester amniocentesis and delivery differ remarkably because a subset of pregnancies with chromosome abnormalities are spontaneously lost during each of the three trimesters of pregnancy. The risks of at least one chromosomally abnormal twin at these three periods of gestation are listed in Table 48.2. In general, this table indicates that *diagnostic genetic testing should proceed 3 years earlier* in twin gestations when compared with the maternal entry age in a singleton pregnancy, regardless of which entry age is applied, 35, 37 or 38 years, regardless of what type of zygosity is present and regardless of what gestational age is used as the entry age, i.e. risk at first-trimester chorionic villus sampling, at amniocentesis or at term.

The theoretic calculations presented above, however, may be misleading, particularly when rates at birth are applied because of high intrauterine mortality[6]. For example, the birth prevalence of Down's syndrome in twins was estimated by meta-analysis of five cohort studies including a total of 106 Down's syndrome twins[7,8]. The estimate was only 3% higher than the prevalence in singletons. None of the studies was stratified for maternal age, and the chance of having twins increases with age. Therefore, the observed small increase in the crude Down's syndrome prevalence rate among twins implies a reduction in the age-specific prevalence. However, until there is a more precise estimate of these rates, it may be reasonable to assume no difference from singletons[6]. Clearly a multicenter study is needed that documents the actual rates of chromosome aberrations at the time of first-trimester chorionic villus sampling and compare such rates with those at mid-trimester amniocentesis and term. For example, the concordance for Down's syndrome at birth is relatively low, 12% in one study[9], indicating either a selection pressure against monozygotic Down's syndrome twins over dizygotic Down's syndrome twins during gestation or that the

**Table 48.2** Risk of at least one chromosomally abnormal twin by maternal age and zygosity for Caucasian women (derived in part from reference 1)

| Maternal age (years) | *Chorionic villus sampling (10–12 weeks)* | | | *Amniocentesis (~16 weeks)* | | | *Term* | | |
|---|---|---|---|---|---|---|---|---|---|
| | *Mono* | *Di* | *Unkn* | *Mono* | *Di* | *Unkn* | *Mono* | *Di* | *Unkn* |
| 25 | | | | 1/1533 | 1/767 | 1/920 | 1/476 | 1/238 | 1/285 |
| 30 | | | | 1/455 | 1/228 | 1/273 | 1/385 | **1/193** | 1/231 |
| 31 | | | | 1/357 | 1/179 | 1/214 | 1/385 | **1/193** | 1/231 |
| 32 | | | | 1/280 | **1/140** | 1/168 | 1/322 | 1/161 | |
| **1/193** | | | | | | | | | |
| 33 | | | | 1/219 | 1/110 | **1/131** | 1/286 | 1/143 | 1/171 |
| 34 | | | | 1/172 | **1/86** | 1/103 | 1/238 | **1/119** | 1/142 |
| 35 | **1/113*** | 1/57 | **1/68** | **1/135** | **1/68** | **1/81** | **1/192** | **1/96** | |
| **1/115** | | | | | | | | | |
| 36 | 1/87 | 1/44 | **1/52** | 1/106 | | **1/63** | 1/156 | | **1/93** |
| 37 | **1/66** | 1/33 | 1/40 | **1/83** | | | **1/127** | | |
| 38 | **1/50** | 1/25 | 1/30 | **1/65** | | | **1/102** | | |

*Bold numbers indicate entry age of 35, 37 or 38 years for singleton pregnancy undergoing diagnostic genetic testing; Mono, monozygotic; Di, dizygotic; Unkn, unknown

**Table 48.3** Maternal age-related risks of chromosome abnormalities in triplet gestations

| | *Monozygotic pregnancy* | *Dizygotic pregnancy* | *Zygosity unknown* |
|---|---|---|---|
| Risk of all three fetuses affected | X | $(X)(X)(X) = X^3$ | $X + X^2 \approx X$ |
| Risk of only one affected fetus | 0 | $3X(1 - X)^2$ | $3X(1 - X)^2$ |
| Risk of two affected fetuses | 0 | $3(1 - X)X^3$ | $3(1 - X)X^3$ |
| Risk of all three fetuses unaffected | $1 - X$ | $1 - X^3$ | $(1 - X) + (1 - X^3)$ |

X, age-related risk of chromosome abnormality; 1 – X, age-related risk of normal karyotype

approximation that one-third of pregnancies are monozygotic is in fact an overestimate.

Theoretic risk calculations for karyotypic anomalies in triplet pregnancies warrant consideration, given the increasing number of multiple gestations beyond twinning particularly as a consequence of *in vitro* fertilization. The theoretic risks of chromosome abnormalities in a triplet gestation are listed in Table 48.3. Four theoretic risk combinations are presented:

(1) The risk of *all three* fetuses being chromosomally abnormal;

(2) The risk of *one* chromosomally abnormal fetus and two unaffected fetuses;

(3) The risk of *two* chromosomally abnormal fetuses and one unaffected fetus;

(4) The risk of *all three* fetuses being chromosomally normal.

At the time of amniocentesis, the risk of one chromosomally abnormal fetus for a 30-year-old woman with a triplet pregnancy is the same as the risk for a 35-year-old with a singleton pregnancy. Thus, the general rule in triplet gestations is that *diagnostic genetic testing should proceed 5 years earlier* when compared with the maternal entry age in a singleton pregnancy.

### Previous child with a chromosome abnormality

A series of recurrence risk estimates are available for couples who have had a child with Down's syndrome due to non-disjunction. For women less than 35 years of age, the risk for a subsequent trisomic Down's syndrome singleton pregnancy is usually given as the mother's age-related risk plus 0.5%; and, the risk of a subsequent pregnancy for all chromosome abnormalities is usually given as the mother's age-related risk plus 1.0%. Above the age of 35 years, the risk appears to be little different from the general population age-specific risk. For twin and triplet pregnancies, the estimates listed in Tables 48.1–48.3 should be adjusted accordingly for a couple who have one trisomic Down's syndrome child and

**Table 48.4** Genetic risks in twin pregnancies* for mendelian mutations (derived in part from reference 10)

| | *Autosomal dominant* | *Autosomal recessive* | *X-linked (fetal sexing only)* | *X-linked (specific diagnostic test)* |
|---|---|---|---|---|
| Risk for singleton pregnancy | — | 1/4 | 1/2 | — |
| Risk of at least one twin being affected | 2/3 | 3/8 | 2/3 | 3/8 |
| Risk of both twins being affected | 1/3 | 1/8 | 1/3 | 1/8 |
| Twin A normal; risk of only twin B being affected | 1/3 | 1/6 | 1/3 | 1/6 |

*Assumes one-third of twin pregnancies are monozygotic

presumably for other aneuploidies as well, although the latter has not been established.

### A family history of a chromosome abnormality or known carriers of a mendelian mutation

Familial chromosome rearrangements such as Robertsonian and reciprocal translocations and inversions carry their own specific risk of recurrence, depending on a variety of factors including the chromosome(s) involved, the breakpoints and the sex of the parent carrying the chromosome rearrangement. Once defined for singleton pregnancies, risks for familial chromosome rearrangements can therefore be easily calculated for multiple gestations by substituting in Tables 48.1 and 48.3, for twin and triplet pregnancies, respectively, the age of the mother (X) for the risk of recurrence for any specific chromosome rearrangement. Such risk calculations can be applied to all aspects of the reproductive risks, e.g. the risk of a spontaneous abortion or the risk of a newborn with congenital malformations as a consequence of an unbalanced chromosome constitution, as well as the risk of an unaffected newborn.

For known carriers of a mendelian mutation, the risk in twin pregnancies will depend on whether the mutation is expressed as autosomal dominant, autosomal recessive, X-linked for fetal sexing or X-linked recessive (Table 48.4).

### X-linked disorders

If only fetal sexing is applied in X-linked disorders, the risk of at least one twin being affected, if both males, is approximately two times higher (66%) than if specific testing is applied (36%) (Table 48.4). Similarly, the risk of both twins being affected is approximately one-third lower if diagnostic testing is applied in known sex (12%), in comparison with the risk when only fetal testing is performed (33%).

### Autosomal recessive disorders

In the case of an autosomal recessive trait, the overall risk of at least one twin being clinically affected is 36%, compared with the established 25% recurrence risk for singleton pregnancies (Table 48.4). On the other hand, the risk of only one twin being affected (16%) is less than the risk of recurrence in a singleton pregnancy. In comparison with most other genetic patterns of inheritance, however, the recurrence risk that both twins would be clinically affected with an autosomal recessive disorder is considered high because the risk exceeds 10%.

### Autosomal dominant disorders

The recurrence risk figures for an autosomal dominant disorder are the same as those for X-linked disorders when only fetal sexing is performed (Table 48.4). Since the recurrence risk to a singleton pregnancy is extremely high, the recurrence risk of at least one twin being affected is strikingly elevated, 66%, as is the risk of both twins being affected (33%), when zygosity is undetermined.

### A previous offspring with an open neural tube defect

The occurrence of an open neural tube defect is based on the interaction of a genetic predisposition, environmental factors (e.g. reduced folic acid intake and geography) and time, i.e. 18–27 days postfertilization. Hence, open neural tube defects are described as multifactorial in their pattern of inheritance, involving several genes (polygenic) interacting with various environmental factors at a specific time during embryogenesis. The risk of recurrence after an affected conception with an open neural tube defect, therefore, varies between 1 and 4% depending on geography. Table 48.5 lists the genetic risk for an open neural tube defect based on a recurrence risk of either 1 or 4%. The risk of at least one twin being affected with an open neural tube defect is approximately two times that of a singleton

**Table 48.5** Genetic risk of recurrence in twin pregnancies for an open neural tube defect based upon geography (derived in part from reference 10)

| | *Recurrence risk 1%* | *Recurrence risk 4%* |
|---|---|---|
| Risk for singleton pregnancy | 1/100 | 1/25 |
| Risk for at least one twin being affected | 1/50 | 2/25 |
| Risk of both twins being affected | < 1/100 | < 1/100 |
| Risk of only one twin being affected | 1/100 | 1/25 |

pregnancy, whereas the risk of only one twin being affected, if one twin is normal, is the same as the risk to a singleton pregnancy.

### A family history of a congenital malformation

Diagnostic testing in the case of a family history of a congenital malformation is determined on the basis of genetic etiology. The issue to be resolved is whether a specific test is available for the diagnosis of the congenital malformation, and this can take the form of karyotyping for a chromosome analysis, FISH (fluorescence *in situ* hybridization) for specific deletions or duplications of genetic material, a DNA molecular analysis for single gene mutations as well as chromosomal duplications and deletions, or biochemical analysis for inborn errors of metabolism, to list the major laboratory technologies. Each of these technologies has very high efficiencies and accuracies, and therefore the focus of the genetic counseling relates to recurrence risks as outlined in Tables 48.1–48.5.

For those birth defects for which the etiology is unknown, multifactorial inheritance is usually invoked. Recurrence risks for multifactorial disorders are influenced by the disease severity, the degree of relationship to the index case, the number of affected close relatives and, if there is a higher incidence in one particular sex, the sex of the index case. In general, if the empiric recurrence risk for a singleton pregnancy has been determined, then it is possible to utilize the formulae listed in Tables 48.1 and 48.3, substituting the estimated recurrence risk for that of maternal age.

### Structural abnormalities identified in the course of ultrasound examination

The application of genetic testing for multiple gestations in the case of structural abnormalities identified in the course of ultrasound examination is also dependent on the availability of specific laboratory technologies that can appropriately address the issue of differential diagnosis and etiology. Structural abnormalities identified on ultrasound evaluation may be associated with an increased risk for a chromosome aberration, for example, and, since accurate assessment of the increased risk for a chromosome aberration is available for many anomalies detected on ultrasound in the case of singleton pregnancies, it should be readily possible to determine the level of risk in the case of multiple gestations, using the approaches outlined in Tables 48.1 and 48.3.

## AMNIOCENTESIS AND CHORIONIC VILLUS SAMPLING

Diagnostic genetic testing in multiple gestations necessitates some form of invasive procedure. Any technique for prenatal genetic diagnosis in multiple gestations must be safe and accurate and ensure that the sample represents the fetal genotype in all cases. The standard, conventional approaches involve either second-trimester amniocentesis or first-trimester chorionic villus sampling (CVS). The technical skills demanded in performing these procedures in the case of multiple gestations are not a simple extension of those skills required in the case of singleton pregnancies. This becomes an important consideration, since multiple gestations have been regarded at increased risk for both spontaneous and procedure-related loss when compared with singleton pregnancies. Knowledge of the background risk of pregnancy loss in multiple gestations and of the procedural risks following amniocentesis or CVS is essential, if prospective patients, as well as their health providers, are to make informed decisions concerning diagnostic genetic testing. The descriptions of the techniques of amniocentesis and CVS that follow are premised on the basis that the experience and technical skills of the operator who performs these procedures in multiple gestations is paramount, and not the different techniques *per se*.

### The techniques of amniocentesis in multiple gestations

Ultrasound evaluation is first undertaken to determine for each gestation fetal age, position, anatomy

**Table 48.6** Loss rates following amniocentesis in twin pregnancies based on studies reported since 1991

| Study | Single-needle technique (*n*) | Double-needle technique (*n*) | Loss to 20 weeks (%) | Loss to 28 weeks (%) |
|---|---|---|---|---|
| Pruggmayer *et al.*[17] | — | 529 | 2.3 | 3.7 |
| Wapner *et al.*[12] | — | 72 | 1.4 | 2.8 |
| Ghidini *et al.*[13] | — | 101 | 0 | 3.0 |
| Sebire *et al.*[18] | 176 | — | 1.1 | 2.3 |
| Buscaglia *et al.*[19] | 55 | — | 0 | 0 |
| van Vugt *et al.*[20] | 27 | — | 0 | 0 |

and gender; placental sites; and, the presence, locations and characteristics of the dividing membranes. Meticulous written documentation including diagrams of each of these characteristics is essential followed by similar painstaking attention to correct labeling of samples. Failure to sample or label correctly has potentially catastrophic consequences if selective reduction should follow diagnostic genetic testing. Amniocentesis is routinely performed after 15 weeks' gestation, based on the first day of the last menstrual period.

In performing amniocentesis in multiple gestations, the standard approach is to sample each amniotic sac separately and sequentially. A 22-gauge spinal needle is guided under continuous ultrasound visualization to the amniotic sac and 20 ml of amniotic fluid is aspirated; this procedure is then repeated depending on the number of fetuses present. A variant of this approach, and limited in application to twin pregnancies, is to introduce needles separately but then simultaneously visualize on either side of the septum to document correct sampling of each sac; this approach requires not only more than one operator but correct positioning of the septum. Although a single-needle ultrasound-guided technique has been applied, this approach is also essentially limited to twin pregnancies, and its use worldwide has been rather limited. With the single-needle technique, there is the real possibility of fetal cell contamination as well as cord entanglement through the creation of pseudo-monoamniotic twins, and, although no instance of either possibility has been reported in three series, the number of twin pregnancies undergoing the single-needle technique only totaled 251 (Table 48.6).

In the past, following amniocentesis of one sac, dye or sterile air was injected to ensure accurate sampling of the remaining sacs. This is no longer recommended. Besides the theoretic possibility of introducing infective agents, injections of methylene-blue dye have been associated with a marked increase in intestinal atresia and fetal death; the use of an alternative dye, indigo carmine, is counterindicated because of its vasoconstrictive properties. Given the resolution qualities of current ultrasound technology combined with an experienced operator, the use of any dye, or injecting sterile air, should be unnecessary and avoided. Nevertheless, in experienced centers, misdiagnoses have been reported, with inadvertent sampling of the same sac as high as 3.5%[11], and consequently some centers continue to employ such dyes as indigo carmine unless the amniotic sacs are clearly distinguishable from each other and there is no doubt of separate samplings.

## Loss rates following amniocentesis in multiple gestations

No randomized control trials concern the safety and efficacy of amniocentesis performed in the case of multiple gestations. And, it is extremely unlikely that such a trial will ever be conducted. Therefore, any evaluation of the procedural risks of amniocentesis performed in multiple gestations must rely on a series of reports of individual operators, and, which in describing their experiences and clinical outcomes, may in fact have no relevance in assessing any other operator. Worldwide, quality assurance in the performance of prenatal genetic diagnosis in the case of multiple gestations is virtually unheard of, unregulated and unknown. This then emphasizes the need for procedures such as amniocentesis and CVS in the case of multiple gestations to be performed in a tertiary referral or academic medical center with specific and documented experience.

A limited number of studies report pregnancy loss rates following amniocentesis in twin pregnancies. Whereas in several series on twin gestations passing mention is made of higher-order multiples, publications specifically relevant to gestations beyond twinning are non-existent. In the past decade, there have been just six publications on the pregnancy loss rate following amniocentesis in multiple gestations, one comparing amniocentesis and CVS[12] and one

**Table 48.7** Loss rates following chorionic villus sampling (CVS) in twin pregnancies based on studies published since 1991

| *Study* | *n* | *Loss to 20 weeks (%)* | *Loss to 28 weeks (%)* | *Fetal–fetal cell contamination (%)* |
|---|---|---|---|---|
| Brambati *et al.*[14] | 65 | — | 1.7 | 11.2 |
| Pergament *et al.*[16] | 128 | 2.3 | 3.1 | 3.2 |
| Wapner *et al.*[12] | 161 | 3.1 | 3.1 | 3.8 |
| De Catte *et al.*[21] | 104 | 2.9 | — | 3.8 |

case–control study comparing 101 twin amniocenteses with a control group of unsampled twin pregnancies recruited in the second trimester[13] (Table 48.6). Pregnancy loss rates in these studies ranged from 0 to 2.3% up to 20 weeks and from 0 to 3.7% up to 28 weeks. In the case–control study by Ghidini and colleagues[13], no significant difference was present in loss rates up to 28 weeks between cases and controls, 3.0% and 2.8%, respectively. Based upon the statistics listed in Table 48.6, it would appear that the rate of procedure-related pregnancy loss after amniocentesis in twin pregnancies was not different from that after amniocentesis performed in singleton pregnancies, empirically, approximately 1%. Although the number of studies is small and the procedures performed by experienced operators, the data certainly suggest that it is the background risk of loss that is increased in twin pregnancies, and not the procedure-related loss after amniocentesis.

## The techniques of chorionic villus sampling in multiple gestations

Ultrasound evaluation prior to performing CVS in the case of multiple gestations must be more comprehensive and detailed, in comparison with amniocentesis. The ultrasound evaluation must be undertaken to determine fetal age, as an accepted standard of care is to perform CVS after 10 weeks' gestation based on crown–rump length, because of the purported increased risk of limb reduction defects when CVS is performed earlier. Also, a critical assessment is that of the site of placental implantation for each fetus. The site of placental implantation and uterine version directly influence which of the two CVS methods, transcervical or transabdominal, is the approach that optimizes the conduction and safety of the procedure for each gestation. Therefore, CVS is routinely offered after 10 weeks' gestation and before the beginning of the 13th week of gestation. This window of time allows the operator to choose which of the two approaches offers the safest and most effective sampling of the placenta, which is based primarily on placental location. Zygosity is another extremely useful parameter affecting the overall safety of CVS performed in the case of multiple gestations; monozygosity, if certain, should only require a single invasive procedure, whereas in the case of di- and trizygosity, more than one invasive procedure would be necessary. Performing CVS in the case of multiple gestations also demands meticulous written documentation, including diagrams of each of these characteristics, followed by similar painstaking attention to correct labeling of samples.

A major concern when performing CVS in multiple gestations is the failure to sample correctly the genotype of each fetus. In one study[14], fetal–fetal cell contamination was reported to be greater than 10% in twin gestations, but subsequent studies report rates of less than 4% (Table 48.7). Nevertheless, in the limited number of series published since 1991 and involving a total of 458 cases of twin pregnancies, i.e. 916 chorionic villus samplings, there were no instances where fetal–fetal cell contamination had a negative clinical consequence, nor was the number of such pregnancies recommended to undergo a mid-trimester amniocentesis different from that of singleton pregnancies undergoing CVS. Several strategies have been proposed to minimize that possibility, including sampling at the margin of a placenta furthest from all other placentas present, or sampling nearest the insertion of major blood vessels. Otherwise, performing CVS in the case of multiple gestations is basically similar to sampling in singleton pregnancies, with attention being given to the specific ultrasound evaluations listed in the previous paragraph.

One study compared the diagnostic accuracy of amniocentesis and CVS in twins and triplets[15]. In the case of CVS performed in 163 twin pregnancies, uncertain results were present in seven CVS samples, five of which related to the presence of confined placental mosaicism. In the case of amniocentesis performed in 297 women with twins, no uncertain results were present but one incorrect

result was, probably a consequence of re-sampling of a single sac. In 15 triplet pregnancies undergoing prenatal genetic diagnosis, four by CVS and 11 by amniocentesis, two (one from each procedure) required a second amniocentesis for abnormal results. The authors[15] concluded that clinical diagnostic questions involving fetal–fetal cell contamination and confined placental mosaicism can be kept to a minimum with CVS.

### Loss rates following CVS in multiple gestations

CVS has been shown to be a safe and efficacious approach to prenatal genetic diagnoses in multiple gestations. First-trimester CVS in multiple gestations appears to have pregnancy loss rates no greater than that following amniocentesis; in the four series reported since 1991, the pregnancy loss rates ranged from 2.3 to 3.1% to 20 weeks' gestation and from 1.7 to 3.1% to 28 weeks' gestation (Table 48.7). Furthermore, these rates are not dissimilar to those in singleton samplings of the chorionic villi. Only one study compared the procedure-related loss rates of first-trimester CVS with second-trimester amniocentesis[12]. In that study, was present no difference was present in the overall risk of pregnancy loss, 3.2% for CVS and 2.9% for amniocentesis. The study, however, found that there was an increased risk of losing at least one fetus in the group sampled by amniocentesis, 4.9% for CVS and 9.3% for amniocentesis. A similar conclusion was reached when the experiences of several centers performing CVS in twin gestations were compared with published studies on pregnancy loss rates following amniocentesis[16]. This suggests that for prenatal genetic diagnoses in the case of multiple gestations, first-trimester CVS should be preferred over second-trimester amniocentesis for the following reasons: not only is CVS performed earlier, but, if an abnormal genotype is identified, selective reduction performed in the first trimester has lower procedure-related pregnancy loss rates and the medical and psychologic difficulties encountered with selective termination can be better addressed and minimized, when compared with the second trimester.

## CONCLUSIONS

Genetic diagnoses in multiple gestations present unique features both in genetic counseling and in estimations of occurrence and recurrence risks. The genetic counseling session for multiple gestations must include an assessment of the genetic risks, the risks of the procedure and the potential for selective termination. Diagnostic genetic testing in the case of multiple gestations involves the same laboratory technologies as applied to singleton pregnancies, and therefore can be considered accurate and efficacious when performed by those experienced in cytogenetics, biochemical analyses and recombinant DNA technologies.

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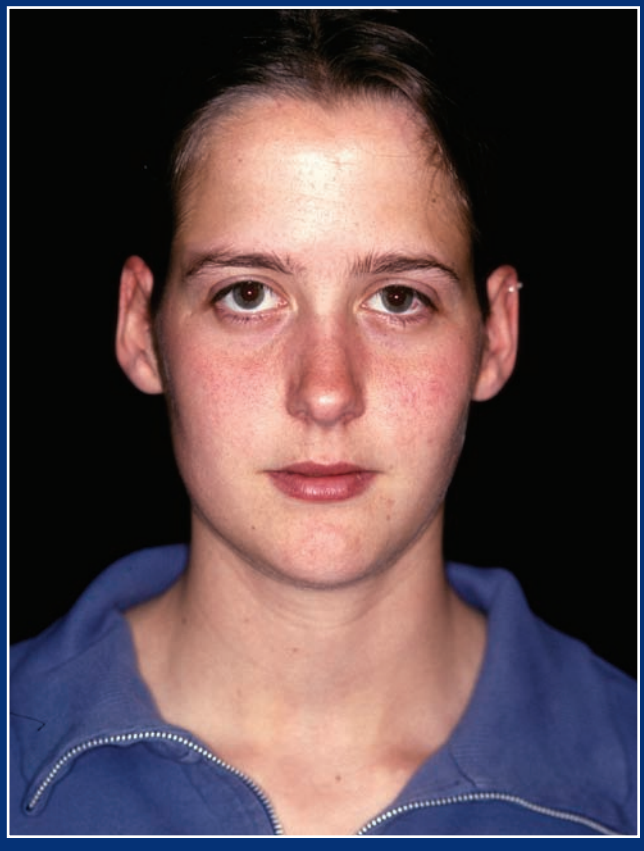
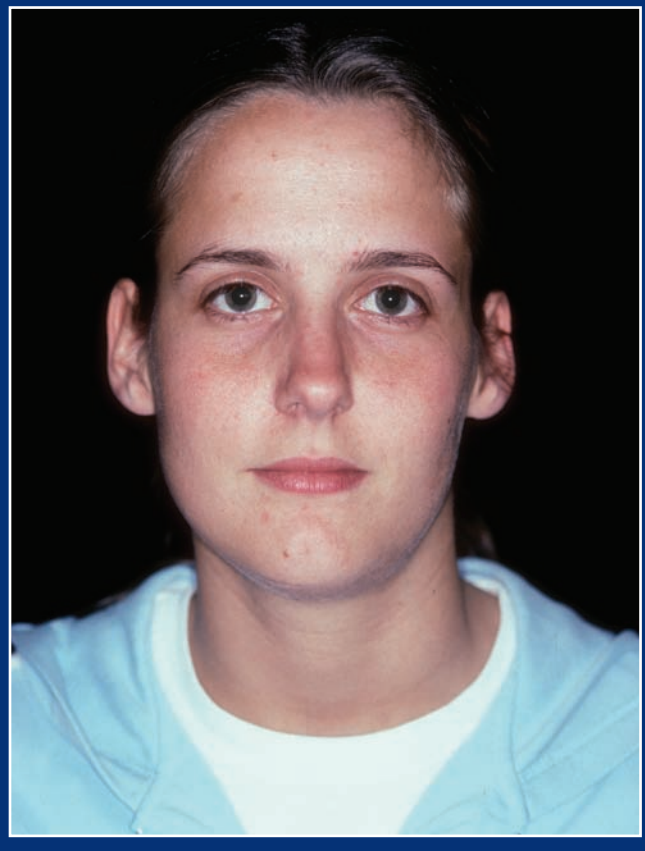
## SECTION IV

# PREGNANCY MANAGEMENT: MATERNAL





**22-year-old female monozygotic, monochorionic, non-mirror twins, Belgium, 2004.**

Participants since birth in the East Flanders Prospective Twin Study. Twin A left, Twin B right.

The mold-made fertility figurine, over three millennia in age, tells us how much has changed and how much has remained the same over time. If one looks at the woman, one realizes that, as opposed to many idols that could have been chosen for the purpose, this woman does not look quite young. Indeed, it seems that even at the time of antiquity, the significant change in the age of the mothers of multiples may have been anticipated.

If one looks at the contour of the womb, created by the woman's arms, one appreciates that it is large enough to accommodate twins. However, most peculiarly, the twins nurse from the mother's breasts *in utero*, suggesting that even 3000 years ago, intrauterine nurture of multiples was taken as a primary objective of the pregnant uterus. It goes without saying that
multiplicity was a sign of fertility, in the past, as well as nowadays. It is also clear that such a stance, whereby the hands open the mother's vagina to enable a safe delivery has the same meaning now as it had in ancient times.

This section is dedicated to all pregnant women with multiples. It first describes the tremendous maternal adaptation to the multiple pregnancy and then continues with a discussion of disease states that are more
frequently found in multiple gestations.

*I.B. and L.G.K.*

Mold-made fertility figurine found near Eqron, Israel.
The Israel Museum, Jerusalem.

# Contents of Section IV

# Routine Antepartum Care of Twins

*R. B. Newman*

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## INTRODUCTION

This chapter describes the components of routine antepartum care for mothers of twins. Given the increasing numbers of twin births worldwide and the disproportionate contribution they make to perinatal morbidity and mortality, the quality of prenatal care for multiples becomes a matter of community-wide concern. Twin pregnancies are one of the most common high-risk conditions encountered by practicing obstetricians. Unfortunately, antepartum care for these challenging pregnancies is poorly studied and highly individualized, as in any other area of medicine lacking an intensive evidence-based foundation.

This lack of definitive evidence-based outcomes, however, does not imply that the issue of antepartum care for twins lacks vitality. Specialized antepartum clinics and management protocols established for twin gestations report uniformly successful perinatal outcome data[1–4]. Although the design of these interventions makes it difficult to identify the specific components of antenatal care responsible for such improvements, the consistent reductions in early preterm birth, preterm premature rupture of the membranes (PROM), very-low-birth-weight (VLBW) delivery and perinatal mortality underscore the importance of their purpose and function.

This chapter provides gestational age-specific practice guidelines for the antepartum care of twins. When strong evidence-based support for specific management recommendations is available, it is presented. When lacking, recommendations are based on more limited non-randomized cohort studies, extrapolations from smaller case series, the judgment of qualified experts and clinical experience. In the end, it is hoped that the reader will be convinced of the potential benefit of a comprehensive and intensive approach to antepartum care for twins.

## PRIOR TO 12 WEEKS' GESTATION

### Early diagnosis

Specialized antepartum care for twins has, as its prerequisite, early diagnosis. Numerous clinical indices suggest twin gestation; most commonly, a fundal height greater than expected for dates, or conception as a result of ovulation induction or other assisted reproductive technologies. Despite these clinical clues, the early diagnosis of twins was the exception rather than the rule prior to the emergence of obstetric ultrasonography. In a 20-year review published in 1973, twins were not diagnosed until the onset of labor in almost 60% of cases, and in 31% the second twin was not diagnosed until after delivery of the first[5].

The widespread availability of diagnostic ultrasound has dramatically affected the early diagnosis of multiples. In the Routine Antenatal Diagnostic Imaging with Ultrasound (RADIUS) trial, twins were diagnosed more consistently at earlier gestational ages in the group receiving routine ultrasonography[6]. In the selective ultrasound group, more than a third of the twins were not diagnosed until after 26 weeks' gestation and almost 10% were not diagnosed until the onset of labor. Although the RADIUS trial was not powered to identify significant differences in the multiple gestation subgroup, it revealed an almost 50% reduction in the incidence of all adverse perinatal outcomes among the twins routinely screened[7]. A decade-long European study involving over 22 000 singleton and 249 multiple gestations also

demonstrated improvements in perinatal outcome with earlier detection made possible by routine ultrasonography[8].

Identification of the viable fetal number in the first trimester is also important. For patients with triplets or higher-order multiples, a discussion of multifetal pregnancy reduction is appropriate. The risks versus benefits of this technique are discussed in detail elsewhere in this volume (see Chapter 63). However, the procedure is most safely performed between 10 and 12 weeks of gestation, making an early diagnosis is crucial. A surprisingly large percentage of multiple gestations identified in the first trimester are lost either by spontaneous abortion of all fetuses or by spontaneous loss and reabsorption of at least one of the multiples. This latter event is referred to as the 'vanishing twin phenomenon' and is discussed in broader detail in Chapter 17. When a 'vanishing twin' is diagnosed, maternal reassurance is appropriate. In most cases, the twin is silently reabsorbed, albeit with a small amount of vaginal bleeding in some cases. It has been estimated that, of all patients with first-trimester vaginal bleeding, as many as 5% might be experiencing a vanishing twin[9].

## Confirming placentation

Early ultrasonic evaluation of twins assists with early diagnosis, determination of the viable fetal number and establishment of accurate dating parameters. One of ultrasound's most important roles, however, is to make an early determination of amnionicity and chorionicity (see Chapters 39 and 40).

Monochorionic placentation is associated with substantially higher risks of spontaneous abortion, congenital anomaly, intrauterine growth restriction (IUGR), vascular anomalies including twin-to-twin transfusion syndrome and intrauterine fetal demise. Approximately 1% of monochorionic gestations are also complicated by monoamnionicity. Despite monoamnionicity being rare, it is associated with an extreme risk of perinatal mortality as a consequence of cord entanglement and conjoining. Rodis and colleagues demonstrated that prenatal diagnosis followed by intensive surveillance and aggressive management results in significant improvements in the anticipated outcome for monoamniotic twins[10].

The ultrasonic characteristics associated with the determination of amnionicity and chorionicity are detailed elsewhere in this volume, but are most accurately assessed in the first trimester. With advancing gestation, the dividing membrane progressively thins, the yolk sacs are no longer visible, the likelihood of placental fusion increases, and fetal growth obscures visualization. Using a composite of available ultrasonographic findings, both chorionicity and amnionicity can be accurately identified in well over 90% of cases[11].

## Patient education

At some point early in gestation, the patient should be educated regarding the risks confronting women carrying twins. Such education appropriately begins with a discussion of prematurity, the leading cause of morbidity and mortality in multifetal gestations. Preterm birth is typically a result of premature labor or preterm PROM, but may also be a consequence of other maternal/fetal complications, such as vaginal bleeding, pre-eclampsia, abnormalities of fetal growth or uteroplacental insufficiency. Both neonatal and longer-term sequelae of preterm birth should be discussed in detail so that patients can appreciate the magnitude of the risk they face and the need for careful attention to antepartum care recommendations.

Potential interventions that might be used to reduce the risk of preterm birth should be reviewed and their relative efficacy described. Whereas a few of these interventions are generally accepted as beneficial, i.e. enhanced maternal nutrition, frequent cervical assessment, corticosteroid administration and multifetal pregnancy reduction in higher-order gestations, the majority are controversial in terms of their effect. Parents should be informed of your practice's view toward the use of interventions such as restricted maternal activities, endovaginal cervical sonography, fetal fibronectin, home uterine activity monitoring (HUAM) and tocolytic therapy. Parents should also be informed of the lack of benefit associated with the routine use of prophylactic interventions such as cerclage, tocolysis or hospitalization.

In addition to prematurity, other fetal and newborn complications encountered more commonly in twins, such as IUGR and congenital anomaly, need to be mentioned, as well as complications unique to multiples. Finally, both the mother and father should be apprised of potential common complications, such as gestational diabetes, pre-eclampsia, pruritic urticarial plaques and papules of pregnancy as well as potentially life-threatening complications, such as thromboembolic disease, peripartum cardiomyopathy and acute fatty liver of pregnancy.

The extent of this educational effort and the need for documentation is such that a separate consultation visit is often useful, as are prepared educational materials and/or checklists. Consideration should also be given to a second and a later educational visit to address issues such as third-trimester fetal surveillance, and timing and route of delivery.

## 12–20 WEEKS' GESTATION

### Anatomic evaluation

Congenital anomalies occur twice as often in twins compared with singletons. Although the majority of this increase occurs among monozygotic gestations, twins are concordant for fetal anomaly in only 15% of cases. Monozygotic twinning is associated with midline structural defects, such as holoprosencephaly, neural tube defects, cloacal exstrophy, sirenomelia and conjoining. Monozygotic and monochorionic twins are also at risk for anomalies associated with vascular exchange. Classic examples of this would be the acardiac monster, and various developmental abnormalities found in the surviving co-twin following a fetal death *in utero* (see Chapters 70 and 71). A detailed ultrasonographic evaluation of fetal anatomy is recommended for every twin gestation between 18 and 20 weeks.

In a single-center series of 245 consecutive twin gestations, 21 of 24 anomalous fetuses were detected (88% sensitivity; 4.4% anomaly rate) with a specificity and positive predictive value of 100% and a negative predictive value of 99%[12]. Accurate identification of congenital anomalies must precede any therapeutic intervention(s). Despite the fact that fetal therapy and surgery are disciplines still in their infancy, continued progress is being made. In addition, anticipating the presence of a fetal anomaly allows for increased fetal surveillance, a potential change in the timing, location or mode of delivery, consultation with pediatric subspecialists and, in some cases, the option of selective fetal termination.

### Prenatal diagnosis

The increase in older mothers spontaneously conceiving or successfully undergoing assisted reproductive therapy has made prenatal genetic screening and diagnosis even more important in twin gestations. The association between increasing maternal age and the risk of fetal trisomies is well known, but frequently overlooked is the impact of multiple fetuses on the probability that at least one of the fetuses will be affected (see Chapter 46).

No clear evidence confirms that the risk of chromosomal aneuploidy is inherently increased in multiples. Studies which had suggested this possibility failed to appreciate the differences in maternal age distribution between the twin and singleton pregnancies. In monozygotic twins, all fetuses have identical karyotypes, and the aneuploidy risk is the same as the maternal age-related risk. However, in dizygotic twins, each fetus has an independent risk of chromosomal abnormality, and thus the pregnancy risk will be additive. For example, a woman with an age-related risk of one in 100 for a singleton Down's syndrome birth would carry that same risk if she were pregnant with monozygotic twins. If she were pregnant with dizygotic twins, her risk of having at least one affected child would be the sum of the individual risks, or one in 50 (one in 100 plus one in 100). The risk that both dizygotic fetuses would be affected is the product of the individual risks, and therefore dramatically less (one in 100 multiplied by one in 100, or one in 10 000).

Even in cases where zygosity cannot be determined, the empiric risk of aneuploidy can be determined based on the known population distribution of monozygotic versus dizygotic twins using the following formula: 1/3 ($X$) (monozygotic risk) + 2/3 ($2X$) (dizygotic risk) = 5/3, where one-third of twin gestations are monozygotic and two-thirds are dizygotic. Using this formula, the empiric risk of aneuploidy in a twin gestation with unknown zygosity is about 5/3 that of the singleton age-related risk. Practically speaking, the risk of aneuploidy in a woman carrying twins is about the same as that in a woman 2 years older carrying a singleton. Therefore, prenatal diagnosis should be offered to women carrying twins at 33 years of age.

Prenatal diagnosis by amniocentesis or chorionic villus sampling (CVS) in twin gestations requires an experienced operator and sophisticated, high-resolution ultrasound capabilities. In such hands, both techniques can reliably sample each fetus, provide accurate karyotypes along with other genetic information and be acceptably safe. In addition to the operator's technical skill, other important aspects of the amniocentesis or CVS procedure are differentiating dichorionic from monochorionic placentation and mapping the location of each fetus in case one were to prove to be abnormal.

Professional prenatal diagnosis also requires the input of an experienced genetic counselor. This counselor must be fully informed, be experienced in dealing with multiple gestations and possess knowledge of the impact of chorionicity and zygosity on risk assessment. These genetic counselors should also understand the increased technical risks associated with prenatal diagnosis in multiples, and appreciate the qualitatively more difficult counseling required with identification of twins discordant for a particular abnormality, including the consideration of selective termination. The presence of more than one fetus complicates prenatal diagnosis as it does most other aspects of prenatal care. Fortunately, such diagnosis can still be reliably and safely performed in almost all cases as long as the unique requirements of the twin gestation are appreciated.

**Table 49.1** Body mass index (BMI)-specific dietary recommendations for twin gestations. Adapted from references 4 and 18

| | | | Twins | | | |
|---|---|---|---|---|---|---|
| | *Non-pregnant* | *Singletons* | *Underweight (< 19.8 kg/m²)* | *Normal weight (19.8–26.0 kg/m²)* | *Overweight (26.1–29.0 kg/m²)* | *Obese (> 29.0 kg/m²)* |
| Calories (kcal) | 2200 | 2500 | 4000 | 3500 | 3250 | 3000 |
| Protein (g) | 110 | 126 | 200 | 175 | 163 | 150 |
| Carbohydrate (g) | 220 | 248 | 400 | 350 | 325 | 300 |
| Fat (g) | 98 | 112 | 178 | 156 | 144 | 133 |

## Determining cervical status

Prophylactic cerclage placement has been evaluated in two prospective randomized trials including 50 and 74 twin sets, respectively[13,14]. The procedure failed to prolong gestation or improve perinatal outcome. Although both studies lacked substantial power owing to small sample sizes, they suggested an increased risk of preterm PROM as well as maternal infection in addition to a probable lack of efficacy.

Endovaginal sonography to measure cervical length is currently considered useful to identify functional cervical insufficiency and predict the risk of spontaneous preterm delivery. A large multicentered study sponsored by the National Institute of Child Health and Human Development (NICHD) including 147 twin pregnancies demonstrated that a cervical length of ≤ 25 mm at 24 weeks' gestation was the most powerful predictor of spontaneous preterm delivery before 32 weeks[15]. Similar results were reported from England by Souka and colleagues, among a cohort of more than 200 twins evaluated at 23 weeks' gestation[16]. Based on this powerful association, some investigators have proposed that identification of mid-trimester dilatation of the internal cervical os, prolapse of the membranes into the endocervical canal and shortening of the distal cervical length are changes synonymous with functional cervical insufficiency. Incorporation of an endovaginal cervical length measurement into the screening ultrasound performed between 18 and 20 weeks is recommended as an opportunity to identify this relative cervical insufficiency.

When such findings are identified, the optimal intervention is currently unknown. In our hands, cerclage placement was unable to improve obstetric outcome significantly among a cohort of twin gestations with a mid-trimester cervical length of ≤ 25 mm[17]. Further investigation will be necessary to determine the relative efficacy of bedrest or the potential usefulness of cerclage with more profound degrees of cervical shortening. At present, we continue too strongly to consider cerclage placement when confronted with a mid-trimester cervical length of ≤ 15 mm in women with twins (see also Chapter 73).

## Nutritional enhancement

The beneficial impact of nutrition on pregnancy outcome should not be underestimated. The nutritional demands of pregnancy are magnified by the presence of multiple fetuses. The accelerated depletion of maternal nutritional reserves has been associated with alterations in fetal growth as well as shortening of gestational length. Most of the studies evaluating the impact of maternal nutrition on obstetric outcome have involved singleton gestations. However, the emerging body of evidence in multiple gestations similarly demonstrates the role of maternal nutrition as an important and modifiable intervention. The 'constrained pattern of growth' experienced by multiple gestations creates a situation where modifiable factors such as nutrition have a greater opportunity to influence pregnancy outcome positively compared with singleton gestations.

Maternal nutrient requirements are increased in twins. The proportionately greater expansion of blood volume, increases in maternal tissues and doubling of the fetal mass require significant alterations in nutritional recommendations. While no national guidelines exist, an estimate of individual nutrient needs for twins is provided in Table 49.1. These recommendations are based on the non-pregnant and the singleton recommended dietary allowances (RDAs) published by the Food and Nutrition Board of the National Research Council, and body mass index (BMI)-specific extrapolations for twin gestations published by Luke and co-workers[4,18]. The recommended caloric intake is divided between protein (20%), carbohydrates (40%) and fat (40%). This represents a slightly lower percentage of calories from carbohydrates and a slightly higher percentage from fat than is usually recommended, to provide extra calories with less bulk.

Increased protein is also essential in twin gestations. Inadequate protein can occur secondary to insufficient intake (vegan diet), intake of poor-quality protein or inadequate caloric intake, which results in dietary protein being diverted to meet energy needs. The availability of amino acids from maternal protein intake is essential for the maintenance of normal fetal growth. Reduced amino acid availability not only affects fetal growth but may also have a restrictive effect on placental growth, thus further compounding the impact of protein deficiency.

Clinically, the rate and pattern of maternal weight gain has been used as a measure of adequate nutrition. Literature involving singleton gestations demonstrates that a progressive increase in maternal weight gain is associated with an increase in mean birth weight and a reduction in the incidence of low birth weight. This literature also establishes that a lower maternal pregravid weight and/or a low maternal weight gain is associated with an increased risk of premature birth, whereas a higher pregravid weight diminishes the effect of weight gain on either birth weight or length of gestation. As a result of such considerations, the Institute of Medicine issued pregravid BMI-specific weight gain guidelines for singleton pregnancies in 1990[18]. In the same report, the Institute of Medicine recommended a range of maternal weight gain of 35–45 lb (16–20 kg) for term twin pregnancies, albeit based on significantly fewer data. Two issues not addressed in that report are gestational age and BMI-specific recommendations for twins.

Whereas the increase in fetal weight is greatest during the third trimester, it appears that early and mid-gestation maternal weight gains have the greatest ultimate effect on twin birth weight. Optimal twin birth weights (> 2500 g) are associated with maternal weight gains of 24 lb by 24 weeks and total weight gains of 40–45 lb among women with normal pregravid weights[19]. Even when there was good catch-up weight gain after 24 weeks, a low rate of weight gain before 24 weeks (< 0.85 lb per week) was strongly associated with poor intrauterine growth and adverse outcomes[19].

A series of studies evaluating maternal weight gain before 20 weeks, at 20–28 weeks and after 28 weeks demonstrates a ripple effect of maternal weight gain on fetal growth. Early maternal weight gain (< 20 weeks) and mid-pregnancy weight gain (20–28 weeks) significantly enhanced the rates of fetal growth between 20 and 28 weeks and from 28 weeks until birth, in a study involving 1564 twin pregnancies[20]. The influence of early maternal weight gain on subsequent fetal growth was most pronounced in underweight women. These findings strongly suggest that early weight gain results in improved maternal nutrient stores that become important later in pregnancy as a nutrient reserve when fetal demands are increasing. Alternatively, or in addition, better early maternal weight gain might contribute to improved placental growth, which helps to sustain the twins later in gestation.

Weight gain recommendations for twins need to be modified based on maternal BMI just as they are for singletons. Using ultrasonographic measures of fetal growth and twin birth weights, BMI-specific weight gain guidelines have been developed for the gestational periods of 0–20 weeks (early), 20–28 weeks (mid-gestational) and after 28 weeks (late)[21]. As would be expected, optimal rates of fetal growth and birth weight at 36–38 weeks (2700–2800 g) were achieved with lesser weight gains among obese and overweight women, but required greater weight gains in underweight or normal-weight women (Figure 49.1).

Studies which have evaluated maternal iron stores in twins report lower hemoglobin levels in the first and second trimesters, higher rates of iron-deficiency anemia and residual iron-deficiency anemia in the infants up to 6 months of age. The frequency of maternal anemia is related to overall nutritional status, which underscores the need for adequate dietary sources of iron. Heme-iron rich sources, such as red meat, pork, poultry, fish and eggs, are emphasized because of both their better iron absorption and the higher quality and quantity of protein and other nutrients they offer. Non-heme-iron sources, such as iron-fortified breads, leafy green vegetables and nuts should be encouraged as well, for their iron content and for their folate, whose deficiency can also contribute to maternal anemia. As opposed to routine supplementation, we provide extra elemental iron (60 mg per day) or folic acid (1 mg per day) based only on documented deficiencies. Other nutrients often lacking in the diets of women include calcium, magnesium and zinc. Although no trials of supplementation with these specific minerals in twins are available, it is recommended by some, based on a desire to avoid their further depletion and from studies in singleton pregnancies suggesting reductions in the rate of preterm birth (calcium), pregnancy-induced hypertension (calcium), neuroprotection (magnesium), improved birth weight (zinc) and longer length of gestation (zinc).

In recognition of the critical role that nutrition plays in perinatal outcome in twins, we advise all patients to have a consultation with a nutritionist. The content of these visits should include in-depth counseling and patient education regarding fetal growth, diet and nutritional assessment, the role of mineral supplementation, individualized and BMI-specific weight gain recommendations, avoidance of smoking, drugs and alcohol, and follow-up. Time constraints associated with traditional obstetric visits limit the opportunity for patient education by

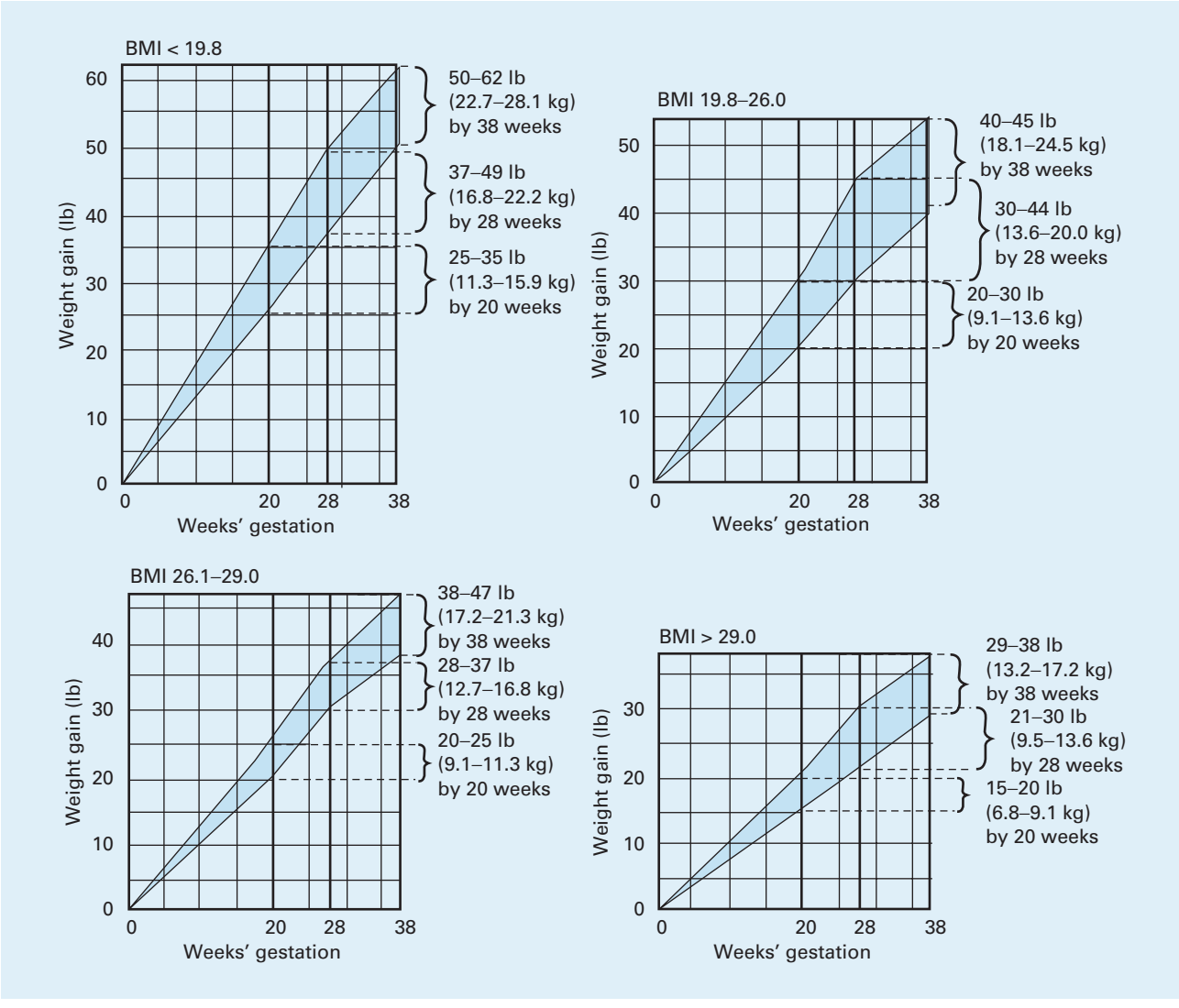


**Figure 49.1** Body mass index (BMI)-specific weight gain recommendations for twin pregnancies. Reprinted with permission from reference 19

the obstetric provider. Surveys of women with twins indicate that more than 25% receive no advice regarding weight gain, and among those who receive counseling regarding nutrition, the advice is often inappropriate[22,23]. In a study of 928 twin gestations, those women who consultated a registered dietician had higher maternal weight gains and were less likely to have a VLBW infant (2% versus 12% for women not receiving consultation with a registered dietician)[22] (see also Chapter 51).

## 20–26 WEEKS' GESTATION

### Preterm birth risk assessment

#### *Cervical length*

As previously described, a shortened cervical length in the mid-trimester correlates powerfully with the risk of preterm delivery in twins[15]. Souka and colleagues demonstrated that a cervical length of ≤25 mm at 23 weeks' gestation had a sensitivity of 100%, 80% and 47% for spontaneous preterm birth at <28, <30 and <32 weeks' gestation, respectively[16]. Alternatively, Imseis and colleagues performed a retrospective analysis of 85 twin gestations that underwent cervical length evaluation between 24 and 26 weeks. These authors found that only 3% of twins with a cervical length of >35 mm delivered prior to 34 weeks' gestation[24]. In our practice, we found that approximately 15% of twins associated with a mid-trimester cervical length of >38 mm delivered at 34 weeks' gestation or earlier, underscoring the importance of continued preterm labor surveillance even with above-average cervical length measurements[17]. In order to assess the risk of spontaneous preterm delivery, we obtain endovaginal cervical

**Table 49.2** Duration in weeks from the first occurrence of a specific 'cervical score' and spontaneous labor onset in two cohorts of twin gestations. Values are expressed as mean ± SD. Adapted from references 26 and 27

| | *Cervical score* | | | | | |
|---|---|---|---|---|---|---|
| | *+2* | *+1* | *0* | *–1* | *–2* | *–3* |
| Newman *et al.*[26] (*n* = 78) | 8.8 ± 4.2 | 7.0 ± 3.5 | 3.7 ± 1.7 | 3.2 ± 2.3 | 2.0 ± 1.3 | 1.5 ± 0.8 |
| Neilson *et al.*[27] (*n* = 223) | 7.9 ± 4.1 | 4.8 ± 2.5 | 3.6 ± 2.2 | 2.8 ± 2.1 | 1.8 ± 1.4 | 1.3 ± 1.1 |

length measurements at the time of our 18-week fetal anatomic survey and then repeat the evaluation between 22 and 24 weeks (see also Chapter 55).

### *Digital cervical examination*

The value of digital cervical examination lies in its ability to provide ongoing risk assessment, and it is performed at each antepartum visit after 20 weeks. The cervix is evaluated using the 'cervical score'. The 'cervical score' is calculated as follows: cervical length (cm) minus cervical dilatation (cm) at the internal os. A cervix that is 2 cm long and closed gives a score of +2. A cervix that is 1 cm long and dilated 1 cm at the internal os gives a score of 0. A cervix that is 1 cm long with an internal os dilated 3 cm gives a score of –2.

The calculation of a 'cervical score' effectively predicts preterm delivery in twins. Houlton demonstrated that a 'cervical score' of ≤0 on any examination predicted preterm labor within 14 days in 69% of their twins[25]. As the 'cervical score' decreases, the mean time until delivery shortens (Table 49.2). A cervical score of ≤ 0 on or before 34 weeks was associated with a positive predictive value of 75% and a four-fold increased relative risk of preterm delivery[26]. Neilson and colleagues found a similar positive predictive value with a 'cervical score' of ≤–2 among parous African women carrying twins[27]. The earlier in gestation that a 'cervical score' of ≤0 is detected, the greater is the positive predictive value that can be ascribed to it.

Although a 'cervical score' of ≤0 is a marker of increased preterm delivery risk, those women who maintain a 'cervical score' of >0 are excellent candidates for continued observation without obstetric intervention. In our series, only two of 78 multiples experienced spontaneous preterm labor or preterm PROM within 1 week of a 'cervical score' >0[26]. In Neilson's series of 223 twins, none delivered within 1 week of a 'cervical score' >0[27]. Whereas the digital examination lacks the objectivity of sonographic measurement, the human hand is still a relatively sensitive instrument for examining the cervix. This sensitivity can be further enhanced by the use of a consistent examiner. Admittedly, the digital examination lacks the ability of ultrasound to identify early cervical changes involving the internal cervical os. However, it remains a simple, safe and effective technique for assessing preterm delivery risk as pregnancy progresses. Moreover, it costs nothing and does not entail an additional visit.

### *Fetal fibronectin*

Fetal fibronectin is a high-molecular-weight extra cellular matrix glycoprotein normally found in fetal membranes, placental tissues and amniotic fluid. Numerous large trials involving singleton pregnancies demonstrate that cervical/vaginal fetal fibronectin at concentrations over 50 ng/ml after 20 weeks' gestation is abnormal, and associated with impending preterm delivery. Several observational studies find similar results in twins[15,28–30]. In brief, a single positive fetal fibronectin is associated with a relatively modest risk of preterm delivery that increases substantially with serial positive samples. Positive predictive values for twins with a positive mid-trimester fetal fibronectin range from 38 to 53%. Fetal fibronectin also has a high negative predictive value, which can be of value when evaluating a woman with early cervical change or worrisome symptoms. In the NICHD Preterm Prediction Study, however, the association of fetal fibronectin with preterm delivery in twins was no longer significant after controlling for cervical length[15]. Alterations in clinical management based on fetal fibronectin are currently being evaluated, and evidence of improved pregnancy outcomes for twins has not yet been demonstrated (see also Chaper 56).

## Work, activity and lifestyle modifications

Reduced activity and increased rest might be the most commonly prescribed intervention among twins, despite a paucity of any evidence supporting its efficacy. Existing data are all retrospective in

**Table 49.3** Meta-analysis of the obstetric outcomes in prospective randomized trials of routine hospitalization of twin gestations. Adapted from data presented in reference 32

| *Obstetric outcome* | *Treatment (n)* | *Control (n)* | *OR* | *95% CI* |
|---|---|---|---|---|
| Stillbirth | 12/528 | 15/568 | 0.82 | 0.38–1.77 |
| Early neonatal death* | 11/528 | 4/568 | 2.84 | 1.02–7.87 |
| Perinatal death | 23/528 | 19/568 | 1.31 | 0.70–2.43 |
| Delivery < 37 weeks | 117/264 | 108/284 | 1.31 | 0.92–1.89 |
| Delivery < 34 weeks* | 33/127 | 21/132 | 1.84 | 1.01–3.34 |
| LBW (< 2500 g) | 240/528 | 280/568 | 0.83 | 0.65–1.06 |
| VLBW (< 1500 g)* | 29/528 | 17/568 | 1.93 | 1.05–3.53 |
| Preterm PROM | 20/127 | 14/132 | 1.57 | 0.76–3.23 |
| Cesarean delivery | 47/127 | 49/132 | 1.00 | 0.58–1.72 |
| Apgar < 7 at 5 min | 14/254 | 18/264 | 0.79 | 0.39–1.63 |
| NICU admission | 72/254 | 69/264 | 1.12 | 0.76–1.66 |
| Maternal hypertension* | 19/264 | 36/284 | 0.55 | 0.32–0.97 |

*Significant difference between hospitalized cohort and control groups; OR, odds ratio; CI, confidence interval; LBW, low birth weight; VLBW, very low birth weight; PROM, premature rupture of the membranes; NICU, neonatal intensive-care unit

nature and dated. Many studies were biased by the indication for bedrest, and confounded by the fact that in many instances, those mothers allowed 'unrestricted' activity were, in reality, simply undiagnosed twin pregnancies.

Despite the absence of prospective randomized trials, there are other reasons to endorse restrictions of strenuous activity and increased rest in multiples. Studies using home tocodynamometry have shown that maternal rest is associated with a reduction in uterine contraction frequency in singleton gestations. A meta-analysis of over 160 000 singleton pregnancies in 29 studies demonstrated that physically demanding work significantly increases a woman's risk of adverse pregnancy outcome[31]. Preterm birth was also significantly associated with prolonged standing, shift- and night-work and a high cumulative work fatigue score (odds ratio 1.22–1.63)[31]. The National Institutes of Health (NIH)-sponsored Preterm Prediction Study associated maternal stress and occupational fatigue with both preterm birth and preterm PROM, respectively[32,33]. Although these studies involve singleton gestations, it would be naive to assume that a similar if not magnified effect did not occur in multiples.

Further research is needed to define the impact of restricted activity and increased rest on both the duration of pregnancy and fetal growth. In the meantime, we recommend that our mothers of twins reduce strenuous exercise, physically demanding work, tiring housework or lengthy travel after 20 weeks. We also advise against prolonged standing (> 3 h) and night-shift work whenever possible. Ongoing assessment of maternal symptoms, 'cervical score' and endovaginal cervical length measurements are used to guide further restrictions. Avoidance of sexual intercourse is advised if it is uncomfortable, associated with bleeding, pain or prolonged contractions, if there is a history of prior preterm birth or if the woman is carrying more than two fetuses.

Having said this, hospitalization of twins does not improve perinatal outcome as a routine intervention. Four prospective randomized trials of routine hospitalization of twins have been performed, and a meta-analysis of their results has not demonstrated a prolongation of pregnancy or any other consistent benefit (Table 49.3)[34]. Disturbingly, significantly more infants were VLBW and delivered prior to 34 weeks' gestation among the hospitalized cohort, which resulted in a higher rate of early neonatal demise in this group. Hospitalized mothers did experience a lower incidence of maternal hypertension, however. Although hospitalization of twins is frequently required for appropriate obstetric or medical indications, there is no obvious benefit associated with the routine use of this intervention.

## 26–32 WEEKS' GESTATION

By 26 weeks' gestation, twins are usually being seen on a weekly basis, and preterm birth risk assessment and modification of maternal activities initiated between 20 and 26 weeks are still ongoing. However, the majority of the clinically significant preterm births among twins occur between 26 and 32 weeks' gestation. Therefore, this section focuses on techniques to

prevent or ameliorate the maternal and newborn hazards associated with extreme prematurity.

## Preterm birth prevention

### *Home uterine activity monitoring*

HUAM was introduced in the 1980s with the promise of identifying preterm labor in women earlier than they would be able to identify it themselves. However, even with objective daily monitoring of uterine contraction frequency, HUAM has not proved itself superior to other forms of intensive surveillance. In a large multicentered investigation by Dyson and colleagues, 2422 pregnant women including 844 twins were educated in techniques of self-detection of preterm labor[35]. Following this educational program, all women were prospectively randomized to weekly contact with a perinatal nurse, daily contact with a perinatal nurse and daily contact with a perinatal nurse supplemented by daily HUAM. Ultimately, there were no differences in the frequency of preterm birth prior to 35 weeks' gestation between those women receiving weekly contact (22%), daily contact (24%) or daily contact with HUAM (24%). Similarly, there were no differences in mean cervical dilatation at the time of preterm labor diagnosis, the frequency of low-birth-weight (LBW) or VLBW infants, number of days gained with tocolysis or number of unscheduled visits[35].

Despite these findings, other investigators report more favorable outcomes in patients receiving HUAM, especially when the control group receives more standard care. In a small study, Knuppel and colleagues randomized 45 twins to either HUAM and perinatal nursing contact or to standard care. Preterm labor was diagnosed at earlier states of cervical dilatation in the HUAM group, which also experienced significantly fewer preterm births[36]. In an earlier publication, Dyson and colleagues prospectively randomized high-risk pregnancies including 189 twins to one of three intervention groups[37]. Group 1 was educated regarding the signs and symptoms of preterm labor but thereafter received only standard care. Group 2 received the same education and performed sham HUAM but they were contacted at least five times per week by a perinatal nurse. Group 3 received the same education and performed daily HUAM with perinatal nursing contact. The frequency of preterm birth prior to 36 weeks' gestation was significantly decreased in group 2 (29.8%; $p < 0.05$) and markedly decreased in group 3 (23.1%; $p < 0.01$), compared with the standard-care group 1 (46.3%). The infants from the HUAM group 3 were significantly less likely to be VLBW and be admitted to the neonatal intensive-care unit (NICU) and had shorter hospital stays, compared with neonatal outcomes in the other two groups[37].

At present, the benefit of HUAM in twin gestations remains controversial and investigational. HUAM has been associated with benefit in two prospective randomized trials with standard-care control groups but no benefit when compared with control groups receiving more intensive perinatal surveillance.

### *Tocolytic therapy*

Although widely used, tocolytic therapy has been associated with only limited benefit in twin gestations. A meta-analysis of seven prospective randomized trials failed to demonstrate any consistent effect on the risk of preterm birth, birth weight or neonatal mortality when tocolysis was used prophylactically[38]. A variety of different beta-mimetics and dosages were used, but none suggested benefit. Neither prostaglandin inhibitors nor calcium channel blockers have been studied as a prophylactic tocolytic in twins.

As a therapeutic intervention, tocolytic therapy has yielded mixed and relatively inconclusive results. Most of the literature regarding tocolytic treatment of preterm labor reveals only a short-term prolongation of pregnancy[39,40]. Short-term prolongations may be of value, however, in assisting with tertiary-care transport, or allowing the administration of antenatal corticosteroids. Reports from uncontrolled series of multiple gestations offer more favorable findings with substantially longer periods of successful tocolysis[41,42]. When used, the potential risks associated with tocolytic therapy must be respected. Women with twins are at higher risk for tocolytic-related complications, most notably pulmonary edema. This risk is highest when tocolytic therapy, corticosteroids and intravenous fluids are administered concomitantly. Other concerns, particularly with beta-mimetics, are increased risk of myocardial ischemia and cardiac arrhythmias, maternal cardiomyopathy and even evidence of fetal myocardial necrosis, with prolonged administration[43]. Both beta-mimetic agents and corticosteroids increase maternal glucose levels, aggravating either overt or gestational diabetes.

### *Corticosteroids*

Administration of antenatal corticosteroids significantly reduces the incidence of respiratory distress syndrome, interventricular hemorrhage and other complications of prematurity in singleton gestations. As a consequence, the NIH recommend that antenatal corticosteroids be administered to women

with preterm labor prior to 34 weeks and to women with preterm PROM at < 30–32 weeks, regardless of plurality[44]. This recommendation currently represents the standard of care, despite relatively few data confirming the benefit of corticosteroids administered specifically in multiples.

## Assessment of fetal growth

Along with prematurity, abnormalities of fetal growth contribute substantially to perinatal morbidity and mortality in twins. Up to a third of twin gestations are growth-restricted by 36 weeks' gestation. The impact of multiple fetuses competing for limited maternal nutritional resources has already been discussed. However, another major contributor is abnormal placentation. Abnormalities of vascular exchange in monochorionic placentas, suboptimal placental implantation and abnormalities of the umbilical cord, such as marginal or velamentous insertion or a single umbilical artery, are all more common in twin gestations (see Chapter 60).

It has been postulated that slowing of fetal growth in multiples is an adaptive mechanism, and that LBW twins do better than singletons of similar birth weights. However, this low birth-weight advantage cannot be confirmed in studies of perinatal outcome. In fact, growth-restricted preterm infants, regardless of plurality, have a significantly higher risk of both neonatal morbidity and mortality as well as long-term neurodevelopmental deficit, compared with appropriately grown infants of the same gestational age.

In addition to concordant growth restriction, twins are also at risk for the development of discordant fetal growth. While much of this discordance is constitutional (genetic dissimilarity of dizygotic twins), more severe degrees may be associated with twin-to-twin transfusion syndrome, fetal anomalies, genetic syndromes and local placental factors. In various studies, birth-weight discordance ranging between 20 and 30% is associated with IUGR, preterm delivery, cesarean birth, umbilical artery pH < 7.1, admission to the NICU, respiratory distress syndrome, stillbirth and early neonatal death[45,46]. The precise threshold at which discordant growth becomes a threat to the fetus and/or the newborn remains controversial. Even large degrees of discordance may be tolerated as long as both fetuses remain appropriately grown for gestational age[47–50].

No prospective randomized studies have explored the value of serial ultrasound assessment of fetal growth or even the appropriate interval for these ultrasounds. Nevertheless, serial sonographic evaluation of twins in the latter half of pregnancy has become the standard of care. The importance of ultrasound can be easily inferred. IUGR is three times more common among twins compared with singletons, and ultrasound is the only available technique for assessing individual fetal growth. The presumption is that ultrasound allows identification of twins with growth restriction, indicating the need for either antenatal surveillance or early delivery in order to improve perinatal outcome. Reviews of national trends in twin births reveal that the frequency of preterm birth is increasing, coinciding with a reduction in IUGR at term and an increase in preterm growth-restriction.

Most obstetricians repeat ultrasound examinations on a monthly basis, although this is purely empiric. The interval can likely be extended if prior examinations have demonstrated appropriate growth, particularly in dichorionic gestations, or shortened if abnormalities of growth, amniotic fluid, umbilical cord morphology, umbilical artery blood flow or placentation is discovered. The management of specific ultrasonographic abnormalities, such as IUGR, discordant growth, twin-to-twin transfusion syndrome or umbilical cord abnormalities, is discussed elsewhere in this volume (see Chapters 61 and 65).

## Screening for gestational diabetes

Gestational diabetes is believed to be a relative insulin insufficiency brought to light by the diabetogenic effect of anti-insulin placental hormones, human placental lactogen (HPL), progesterone and cortisol. All are proportionately increased by the larger placental mass associated with multiples. Consequently, the incidence of gestational diabetes is increased in multiples. In a series of 95 twins and 26 triplets, Roach and colleagues reported an incidence of gestational diabetes between 3 and 6%, and estimated that each additional fetus increases the risk by a factor of 1.8[51]. Current American College of Obstetricians and Gynecologists guidelines recommend that all pregnant women, including multiples, be screened for gestational diabetes between 24 and 28 weeks using the 1-h 50-g glucose load test. A standardized 3-h oral glucose tolerance test is used if the 1-h glucose load test results are > 140 mg/dl (see also Chapter 54).

Once diagnosed, the management of gestational diabetes in women with twins has not been well defined. Balancing the requirement for intensified maternal nutrition and the high caloric intake recommended for twins with the desire to maintain good glycemic control is a clinical challenge. The necessary number of daily calories, the optimal weight gain, the appropriate fasting and postprandial blood glucose targets, the value of insulin therapy, the fetal surveillance needs and the impact on the timing of delivery are all unknown. Although

macrosomia and being large for gestational age are not going to be a concern in twins, there is evidence to suggest that hyperglycemia may be associated with placental inflammation and an increased risk of premature delivery.

In twin gestations complicated by gestational diabetes, consultation with a nutritionist, careful assessment of fetal growth and antenatal fetal heart rate monitoring in the third trimester are prudent recommendations.

## AFTER 32 WEEKS

Most of the goals established for earlier gestational-age windows continue to be valid and important in later stages of pregnancy as well. Maternal education should be continued, although the focus in later pregnancy may change from prematurity prevention and nutrition to topics such as maternal complications, fetal well-being and the timing and mode of delivery. Digital cervical examination for preterm birth risk assessment and efforts to prevent preterm birth continue, as do serial assessments of fetal growth by ultrasonography. Weekly assessment of maternal weight gain, symptomatology, follow-up testing for maternal anemia and iron reserves and ongoing clinical evaluation of maternal–fetal health continue until delivery.

### Surveillance for gestational hypertension/pre-eclampsia

Twins are at approximately 2.5-fold higher risk of either gestational hypertension and/or pre-eclampsia compared with singletons, with reported frequencies ranging from 13 to 37%[52–54]. In addition to being more common, pre-eclampsia frequently occurs earlier and is more likely to be severe[52,55]. Krotz and colleagues reported that early-onset gestational hypertension (< 35 weeks' gestation), early-onset pre-eclampsia and severe hypertension (diastolic blood pressure > 110 mmHg) occur 12.4, 6.7 and 2.2 times more often in twins compared with singletons[55].

The management of hypertensive complications in twins is not fundamentally different than for singletons. Severe pre-eclampsia by standard criteria, chronic hypertension with superimposed severe pre-eclampsia and HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome would be indications for delivery regardless of gestational age. Mild pre-eclampsia after 35 weeks' gestation would also be an indication for delivery in our practice. Prior to 35 weeks' gestation, transfer to a tertiary-care facility and administration of antenatal corticosteroids likely improves ultimate outcome. Another hypertensive complication is placental abruption, which occurs with a 3–8-fold increased frequency in twins[54,55] (see Chapters 82 and 83).

### Surveillance of fetal well-being

The risk of stillbirth in twins is higher than the risk in singletons at each week of gestation[56]. Although no prospective randomized trials endorse the routine use of antenatal fetal surveillance, we nevertheless institute fetal testing between 32 and 34 weeks' gestation. Both the non-stress test (NST) and the biophysical profile are as reliable for twin gestations as they are for singletons in terms of identifying the infant at risk for hypoxic/asphyxic injury. In a retrospective cohort study, 230 twins who received third-trimester fetal testing with the NST were compared with 435 twins who did not. Although the differences were not statistically significant, the single stillbirth in the NST group stands in sharp contrast to the nine in the non-NST group[57].

The routine use of antepartum fetal testing among uncomplicated twins is questioned by some, but is certainly indicated in those pregnancies at higher risk for uteroplacental insufficiency. Twin pregnancies complicated by IUGR, severe discordance, twin-to-twin transfusion syndrome, pre-eclampsia, monoamnionicity, anomalies or abnormal amniotic fluid volumes are examples of those at such risk. The majority of these indications require ultrasonography for their identification. The inability of ultrasound to diagnose either IUGR or growth discordancy reliably among twins would be the major reason for some clinicians to recommend routine surveillance of all multiples.

When instituted, antepartum fetal surveillance using either the NST or the biophysical profile can be supported by fetal-kick counting, the vibroacoustic stimulation test and umbilical artery Doppler velocimetry. The contraction stress test is relatively contraindicated owing to the risk of preterm delivery, although a spontaneously negative contraction stress test is also a reliable measure of fetal well-being. Generally, fetal testing is performed on a weekly basis except in the presence of severe IUGR, abnormal Doppler studies or monoamnionicity, which might necessitate either twice-weekly or more frequent testing.

### Determining timing of delivery

The ideal time for delivery of the uncomplicated twin gestation is uncertain, but is an important issue to achieve optimal perinatal outcomes. The nadir of fetal mortality for twins occurs between 36 and

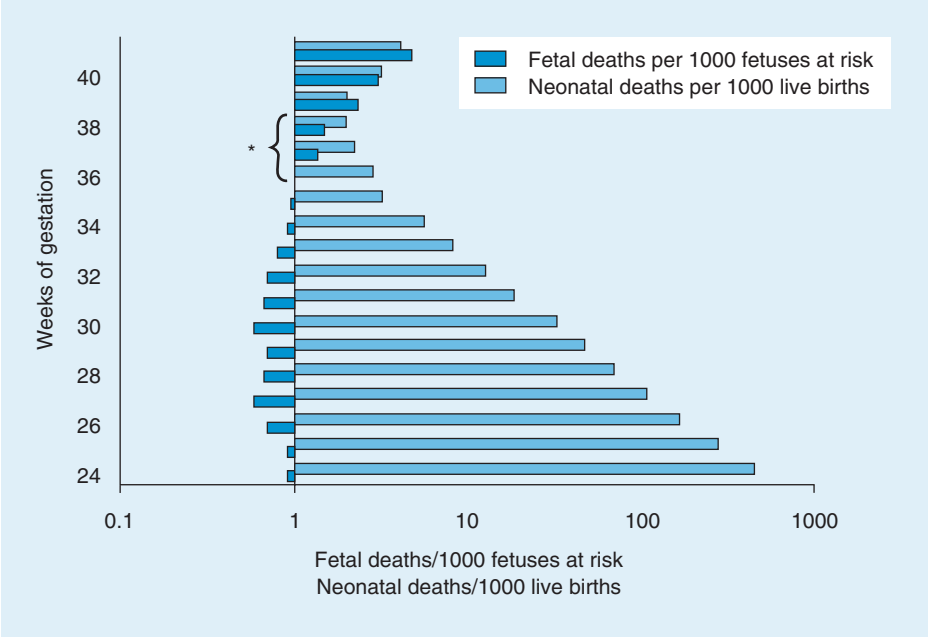


**Figure 49.2** Frequency of stillbirths per 1000 fetuses and frequency of early neonatal deaths (within 1 week of birth) per 1000 live births, based on 88 936 infants born of multifetal pregnancies in Japan between 1989 and 1993. *Optimal delivery interval. Reprinted with permission from reference 59

37 weeks' gestation with birth weights between 2500 and 2800 g[58]. Both fetal and neonatal mortality rates begin to rise in twins extended beyond 38 weeks (Figure 49.2)[60]. Most of this increased fetal and early neonatal mortality at late gestational ages is associated with IUGR. A recent United States population-based analysis looked at the intersection between neonatal and fetal mortality rates in twins[61]. The intersection between a falling neonatal mortality rate and a rising stillbirth rate occurs at 38 weeks' gestation (Figure 49.3).

Unfortunately, to date, the hypothesis that elective delivery of twins at 37–38 weeks improves overall perinatal outcome has not been subjected to prospective analysis. However, given the population-based data described above, it is clear that prolongation of a twin pregnancy beyond 37–38 weeks' gestation requires continuing evidence of appropriate fetal growth, normal amniotic fluid volumes and reassuring fetal testing. In addition, maternal status should not be compromised in an effort further to prolong pregnancy once these gestational ages have been achieved. The identification of IUGR, significant discordance, oligohydramnios, pre-eclampsia or any other significant alteration in the maternal–fetal condition would all mandate delivery once this window of 37–38 weeks' gestation (the nadir of perinatal mortality) has been achieved. These same indices are appropriate indications for even earlier delivery if they are severe.

Fetal lung maturity testing is of value in determining the appropriateness of delivery in twins complicated by preterm labor, preterm PROM, late prenatal care, diabetes or a desire for earlier elective preterm delivery. Most investigators report that twins develop evidence of fetal lung maturity earlier in gestation than do their singleton counterparts. This accelerated fetal lung maturity may occur as early as 31–32 weeks' gestation. In the majority of cases, fetal lung maturity develops congruently, but asynchronous pulmonary maturity occurs in over 5% of twins, regardless of gender or size[62]. Therefore, if technically feasible, sampling each gestational sac for maturity testing would be recommended. If sampling both sacs is not technically possible, we recommend sampling the sac with the normal amniotic fluid volume if the co-twin is oligohydramniotic; the larger fetus if there is more than a 20% estimated fetal weight discordance; or the non-presenting twin if all else is equal.

## SUMMARY

Institution of a comprehensive management protocol for twin gestations as outlined in the preceding sections (Figure 49.4) will result in improved perinatal

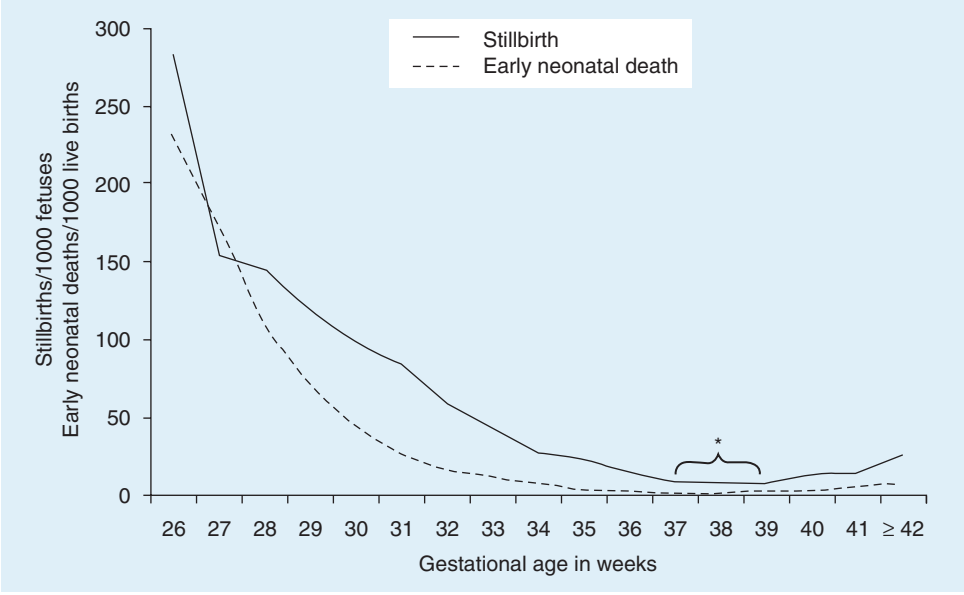


**Figure 49.3** Intersection of the fetal and neonatal death rates for twins based on 297 622 twin births between 1995 and 1998 reported to the National Center for Health Statistics (linked birth and death files). *Optimal delivery interval. Reprinted with permission from reference 54

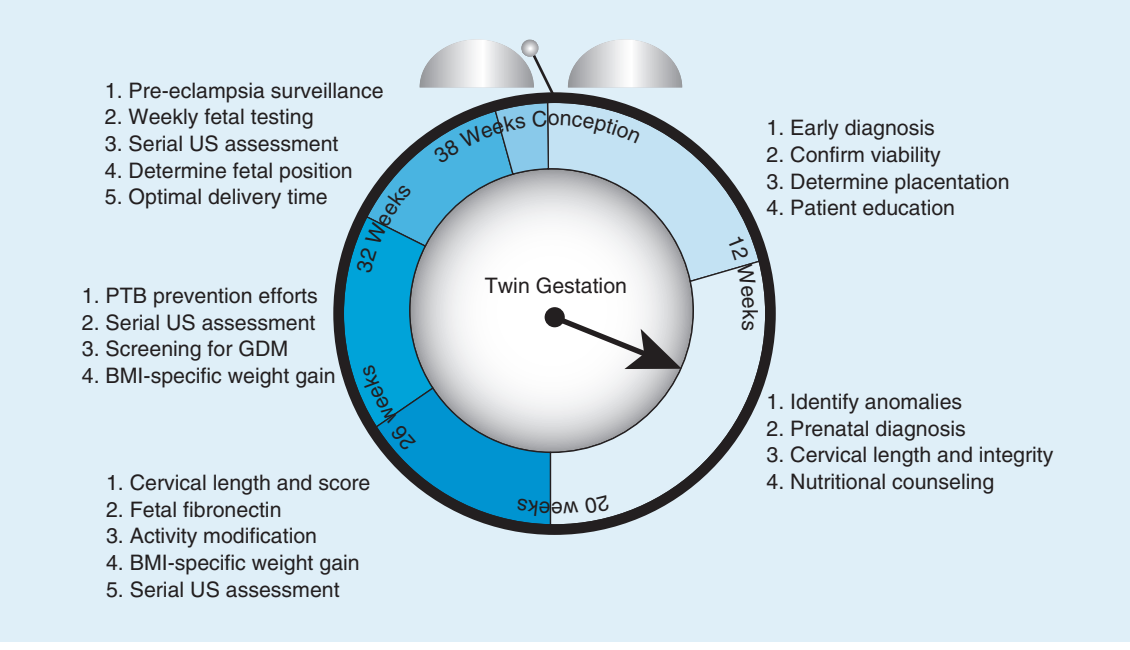


**Figure 49.4** A comprehensive management protocol for twin gestations. US, ultrasound; PTB, preterm birth; GDM, gestational diabetes mellitus; BMI, body mass index. Artwork by Ginny Canady

outcomes. An intensive and proactive approach to antepartum care for twins will reduce the risk of early preterm birth, preterm PROM, VLBW delivery and, ultimately, perinatal mortality. Anticipation of the complications which frequently affect multiples and the experience to manage them successfully result from the development of a specialized antepartum program for multiples.

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# Routine Antepartum Care of Triplets and More

*J. P. Elliott*

**50**



## INTRODUCTION

Routine antepartum care for high-order multiple (HOM) pregnancy ideally should begin in the preconception period. Appropriate monitoring and follow-up of these patients by their fertility specialists should result in early diagnosis of pregnancy as well as high-order multiple pregnancy before the first visit to the obstetrician. In addition, numerous medical and lifestyle issues can and should be addressed at this time, including medical conditions that may affect pregnancy such as diabetes mellitus, hypertension and hypo- or hyperthyroidism. Maternal obesity can also be addressed with a weight-reduction program of diet combined with exercise, which will allow the woman to become pregnant in the best possible condition to respond to the challenges of a potential HOM gestation. Anemia, hemoglobinopathy, rubella immunity and hepatitis B status can be assessed and appropriately managed if need be, and unique genetic risks can be assessed and evaluated, such as carrier states for sickle cell disease, Tay–Sachs disease, Canavan's disease or cystic fibrosis.

Lifestyle issues should also be addressed preconceptually, if possible. Risk for toxoplasmosis is present if there is a household cat, or if raw meat is ingested. Although not routine, screening for prior cytomegalovirus infection may be indicated in women who work in high-risk jobs (day-care centers, teachers or neonatal intensive-care unit (NICU) nurses) who are concerned about that risk. Drug usage should be assessed with emphasis on diminished consumption or elimination of legal drugs (cigarettes, alcohol and over-the-counter medications) as well as illegal drugs (marijuana, cocaine, amphetamines, etc). Cigarette smoking should be strongly discouraged in all pregnant patients because of the associated reduction in fetal weight and increased risk of premature ruptured membranes, both of which are potentially disastrous in a HOM gestation. Alcohol consumption should be limited when pregnancy is possible and stopped when it is confirmed.

All patients of reproductive age, especially if they are actively trying to become pregnant, should supplement their diet with folic acid. The Centers for Disease Control and Prevention (CDC) recommend that all women capable of becoming pregnant should take 0.4 mg of folic acid daily, which is easiest to achieve in a prepared supplement. Prenatal vitamins normally contain this amount and should be prescribed for all infertility patients. Czeizel and Dudas demonstrated a significant reduction in neural tube defects in women taking 0.8 mg of folic acid in a prospective trial[1]. In contrast, patients with a prior history of a child with a neural tube defect should take 4 mg of folic acid a day to reduce the recurrence risk[2].

## EARLY PRENATAL CARE FOR HIGH-ORDER MULTIPLE GESTATIONS

Most HOM gestations will be recognized early in the first trimester by ultrasound assessment following a positive pregnancy test. The diagnosis of three or more gestational sacs or embryos is always a shock to parents, and frequently a shock to the reproductive specialist. The pure joy that the couple experience with the positive pregnancy test is now tempered by the challenging and dangerous discovery that there are three or more embryos developing in the mother's uterus. Whereas some infertile patients actually hope for twins and are not overwhelmed if they

are found, a HOM gestation is not usually considered an immediate blessing by most couples. The 'reality' of the risks versus the rewards of a HOM gestation need considerable time for processing. The reproductive specialist plays a critical role in how a couple 'survives' this unexpected reality. Ethically, the physician should be caring but unbiased in his/her interaction with the couple. A HOM gestation is neither inherently 'good' nor 'bad'. The reproductive specialist should be well informed about the risks and benefits of a triplet or quadruplet pregnancy. The parents are typically overwhelmed by the initial news, and really cannot adequately comprehend recommendations by the physician. It is not appropriate for the physician to 'recommend' selective reduction. The parents should be encouraged to get as much information as possible about HOM pregnancies. Prompt consultation with a perinatologist who is experienced in caring for HOM pregnancies should occur within a few days. This physician can provide realistic obstetric risk and neonatal outcome information to the couple. Networking with other parents who have dealt with these issues is especially important. Two outstanding national support groups are available by phone or online. The Triplet Connection (www.tripletconnection.org; phone 209-474-0885) and Mothers of Supertwins (MOST) (Info@mostonline.org; phone 631-859-1110) have an abundance of printed information available, and names of parents in a particular area that the patient can speak with about issues or concerns. Each support group also has a scientific advisory board of physicians, nurses and dieticians who are available to answer questions.

After considering the medical/obstetric/neonatal risks and the psychosocial/economic impact on their family, each couple must decide on carrying the HOM gestation or selective reduction, usually to twins. Whatever the decision might be, it should be supported by the reproductive specialist, because that individual is very important in this woman's life not only because he/she helped the woman to become pregnant but also because the psychologic support of that person is substantial.

The next step in the process is referral of the couple to a maternal–fetal medicine specialist (perinatologist). A HOM pregnancy inherently carries a 100% risk of preterm delivery, which has a risk of morbidity and mortality for each of the babies. Ideally, care should be provided by the perinatologist in a level III hospital, although a variety of circumstances may make this a difficult logistic problem.

## THE INITIAL VISIT

The first prenatal visit is extremely important for a number of reasons, the most important of which is the ultrasound (US) assessment (see Chapter 39). This examination confirms the true number of embryos developing normally, because prognosis depends on the number of 'live' babies in the uterus. In general, each live fetus above one takes 3.5 weeks from the mean gestational age of delivery of the multiple gestation (see Table 50.1). The death of any fetus in a multiple gestation results in the pregnancy delivering at the expected mean gestational age of the number of live fetuses. For example, in a report by Collins and Bleyl on the outcome of 71 quadruplet pregnancies, the mean gestational age at delivery was given as 31.4 weeks, but if all pregnancies that did not have four live babies delivered were removed from the analysis, the mean gestational age at delivery was 29.7 weeks[3]. The other pregnancies delivered at a mean that corresponded to the number of live babies. One or more fetuses that are smaller than expected for the known gestational age in the first trimester or that have slow heart rates are at risk of fetal demise.

**Table 50.1** Mean gestational age at delivery

| *Number of fetuses* | *Gestational age at delivery* (mean weeks) |
|---|---|
| 1 | 40.0 |
| 2 | 36.5 |
| 2 (reduced) | 35.5 |
| 3 | 33.0 |
| 4 | 29.5 |
| 5 | 28.0 |

It is very important to establish the number of placentas (chorions) and sacs (amnions), because obstetric complications and management differ based on the nature of the placentas and sacs (see Chapter 39). Monochorionic placentation results when a single embryo splits into twins between day 4 and day 8. Twinning after day 9 and before day 14 results in monochorionic and monoamniotic placentation. Interestingly, monochorionic twinning is increased in assisted reproductive manipulations, and newer techniques of blastocyst implantation (day 5) insure that any twinning that occurs will result in monochorionic placentation. It is safest to have one chorion and one amnion for each baby. Monochorionic placentation presents the potential risk of twin–twin transfusion syndrome (TTTS), which occurs in 5–30% of monochorionic twin pregnancies (see Chapter 65). The resultant polyhydramnios/oligohydramnios can cause fetal morbidity/mortality and preterm delivery.

Signs of dichorionicity include separate placentas, fetuses of different gender, 'thick' membrane and 'twin peak' or lambda sign[4]. The twin peak sign is an

ultrasound finding of a triangular projection of placental tissue between the layers of the dividing membrane at the junction of the two placentas (see Chapter 39). Early ultrasound evaluation correctly identifies placentation in over 90% of multiple gestations. The case of monoamniotic twins adds increased risk of fetal death from cord entanglement to the risks of the HOM gestation. Assessment of the uterus for the location of the lowest placenta is important. A perception that placenta previa (PP) is more common in multiple gestation, but Francois and colleagues showed no statistical difference in the incidence of PP in singleton 55/29 268 (0.19%), twin 3/766 (0.39%) or triplet and quadruplet 1/140 (0.71%) pregnancies[5].

The remainder of the first prenatal visit establishes the general background of specific risks for this HOM pregnancy. Some are unique to this individual woman and others are related to the HOM gestation she is carrying. Basic 'routine' antepartum assessment of the woman is performed. Obstetric history is important, although in our experience over 90% of HOM pregnancies are nulliparous. Some patients may have had a number of unsuccessful pregnancies which ended in miscarriage with or without dilatation and curettage (D&C).

Patients with prior successful pregnancies have an advantage when carrying a HOM gestation. In a study of quadruplets, Elliott and Radin reported that parous patients delivered at a greater gestational age than nulliparas[6]. Ron-El and colleagues[7] reported that parous patients delivered 2 weeks later than nulliparas. Other reports support this association[8–10]. Maternal height also affects the outcome of HOM gestation. Blickstein and associates reported that nulliparous women who were taller than 165 cm delivered significantly heavier triplets and were at significantly lower risk of delivering very-low-birth-weight triplets[11].

Risk assessment is extended from the routine prenatal issues which include cigarette smoking, alcohol or recreational drugs. Some prescription medications have possible adverse consequences in pregnancy, such as antiepileptic medications, angiotensin-converting enzyme (ACE) inhibitors and coumadin. Other areas of inquiry include questions regarding domestic violence, which may involve up to 8% of pregnant women, and genetic risks need to be assessed in addition to the age-related risk of chromosomal abnormalities. Biochemical assessment of genetic risk is not practical for triplets or quadruplets (see Chapter 46). First-trimester nuchal thickness should not differ from singleton assessment, and prenatal invasive testing should be offered for fetuses with abnormal measurements (see Chapter 47). Second-trimester ultrasound genetic assessment for minor markers associated with aneuploidy may also allow selective sampling of individual fetuses if invasive procedures (chorionic villus sampling (CVS) or amniocentesis) are to be avoided (see Chapter 48). The risk of doing three or four amniocenteses is currently not known, but twin-amnio carries a greater than 1% risk of miscarriage.

The final risk assessment relates to stress factors, including heavy work, prolonged standing, high emotional or intellectual stress, heavy lifting or straining, or perhaps caring for one or two young children in the home. As these activities often precede preterm labor, it is important to reduce or eliminate the majority of them wherever possible. In addition, the mother should eliminate activities that cause fatigue, minimize standing, lifting and bending, and plan increased periods of rest. Because the commute to/from work may be stressful, working at home may help if that is possible. Sexual activity is permissible up to 20 weeks, and beyond if the couple desire to continue. However, the male ejaculate contains prostaglandin compounds that may initiate contractions, so it is wise to use a condom after 20 weeks to reduce any possible stimulation of contractions.

A thorough medical history should reveal underlying medical problems that will need to be managed concurrently with the HOM gestation. Given the older age of many women with HOM pregnancies, chronic hypertension and diabetes mellitus are the most common medical problems that require ongoing care. A physical examination, including careful cervical assessment and cultures for *Chlamydia* and gonorrhea and a screen for bacterial vaginosis, precede other routine assessments such as urinalysis and culture if appropriate, hemoglobin/hematocrit, blood type and antibody screen, and human immunodeficiency virus (HIV) screening.

A frank and honest discussion of the risks of prematurity is an important part of the first prenatal visit. Practice-specific information is most appropriate as it will provide the patient and her husband with accurate data on the local outcome with triplets or quadruplets. A general discussion of viability starting at 24 weeks with mortality and morbidity numbers at various gestational ages should be provided. Figure 50.1 shows data for survival and major morbidity at representative gestational ages.

It is also appropriate to approximate the patient's chances of delivery at various gestational ages. I usually divide the pregnancy into meaningful time periods. The first is from 13 to 24 weeks (roughly the second trimester), in which there is about a 3% risk of delivery of a HOM gestation, and the mortality risk is essentially 100%. The next interval is from viability (24 weeks) to 30 weeks. This represents the

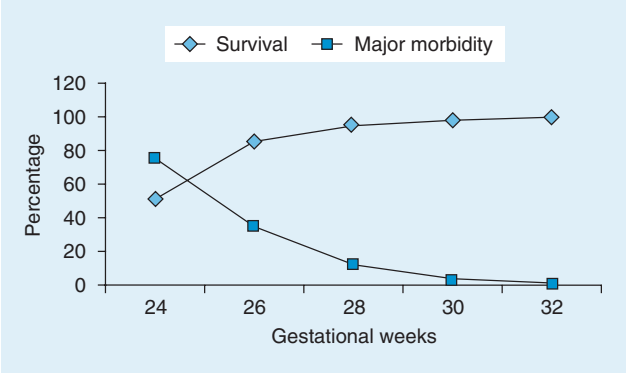


**Figure 50.1** Outcome of delivery at selected weeks of gestation. Data from Pediatrix Medical Group Inc. from 15 989 non-anomalous neonates 2001–02. Source www.pediatrix.com

time period of extreme prematurity in which neonatal outcome is uncertain. In a report detailing the outcome of 32 sets of quadruplets from our practice, 20% were delivered between 24 and 30 weeks and another 20% were delivered between 30 and 32 weeks, with 50% delivery between 32 and 34 weeks[12]. A similar distribution of triplet deliveries occurred in our population of HOM pregnancies. In a report of 55 triplet pregnancies from one institution, Malone and colleagues noted: 7% delivered at 20–24 weeks; 9% delivered between 24 and 27 weeks; 31% delivered between 28 and 31 weeks; and 53% delivered at greater than or equal to 32 weeks[13]. Although patients generally do not want to dwell on these risks, they appreciate a frank discussion of them.

The next aspect of information-sharing involves a discussion of the physiological and psychological stresses of a HOM pregnancy. Every organ system in the mother's body will be affected by the physiologic changes of her special pregnancy. She may already be experiencing the nausea and vomiting frequently encountered in HOM gestations, although true hyperemesis gravidarium occurs in only about 10% of cases, and the need for parenteral nutrition is infrequent[14]. General recommendations include avoiding greasy or spicy foods, small frequent feedings with a protein snack at night and crackers when nausea occurs, and sucking on hard candies along with sips of ginger ale. Occasionally antiemetic medications such as phenergan, compazine, thorazine, Reglan® and Zofran®, and vitamin $B_6$ (50–100 mg), are required.

Uterine distention occurs early and becomes extreme beyond 30 weeks. Backache, pressure, heartburn, constipation, hemorrhoids, headaches, leg cramps, constant fetal movement, pelvic pressure and urinary frequency often make the mother miserable. Psychological stresses also take their toll on the mother as well as her partner and children if any are in the home. Anxiety about the risk to her babies, guilt about not carrying her share of the household chores (other children, cleaning, cooking, washing, working), depression, sleep deprivation and physical stresses are all extreme in HOM gestations. These eventualities must be discussed with the patient early on so that preparations can be made to minimize their effects. Contact details of local support groups and the national groups, MOST and the Triplet Connection, should be offered to the parents (see 'Early prenatal care' section above).

The next part of the first prenatal visit should then shift to describing the proactive approach that the physician will take to give the patient the best possible chance for a good outcome. It is not appropriate to be passive in caring for a triplet or quadruplet gestation. The most important and frequent risks include: preterm labor which occurs in 76–90% of HOM gestations[13,14], pregnancy-induced hypertension (PIH) in 35% of triplets[13] and 72% of quadruplets[14], preterm premature rupture of the membranes (PPROM) 20%[13,14], anemia 25%[13,14] gestational diabetes (7% triplets, 19% in quads)[13,14] and incompetent cervix 14%[3]. Small for gestational age (birth weight < 10th centile for a singleton gestation) and intrauterine growth restriction (IUGR) (birth weight < 3rd centile for a singleton gestation) occur, respectively, in about 20% and 9% of triplets[15], and 10% and 1% of quads[14]. Our proactive approach includes aggressive weight gain, modified bed-rest at 20 weeks (which usually means stopping work), cervical length assessments every 1–2 weeks from 18–24 weeks, fetal fibronectin testing (fFN) starting at 24 weeks, home uterine activity monitoring (HUAM) at 20 weeks, office visits every 1–2 weeks, monitoring for PIH, ultrasound follow-up of fetal growth and biophysical profile assessment of fetal acid–base status. The purpose of each of these interventions is explained to the patient initially and then re-explained in detail when they are instituted.

Certain medications are prescribed routinely in our practice. Prenatal vitamins once a day and folic acid 1 mg/day are continued from preconception. Ferrous sulfate 325 mg/day is started after the first trimester. Baby aspirin 81 mg/day and calcium supplementation 2000 mg/day (four Tums® have 2000 mg of calcium) are started at about week 15, as they may lessen the risk of PIH developing. Colace® is started at 100 mg (once or twice a day) for stool softening. We also recommend magnesium supplementation at 1.2 g/day and zinc supplementation at 45 mg/day, as preterm labor is associated with a low serum magnesium level and zinc levels may be related to PROM.

Patients are also given general recommendations to maximize pregnancy outcome. The patient is

counseled to empty her bladder every 2 h while awake. This reduces the tendency of a full bladder to cause uterine contractions. The family is encouraged to be prepared for bed-rest at 20 weeks and the possibility of prolonged hospitalization. Travel, home remodeling, baby showers or moving to a new home, etc. should be accomplished ideally before 20 weeks. Another important early event (before 20 weeks) is a neonatal consultation and tour of the NICU. The patient and her family will all benefit from a reality check that familiarizes them with a very scary place, as viewing preterm infants on ventilators certainly creates a scene that the patient is motivated to avoid. As the neonatologist can reassure the family about what they do to care for fragile premature babies, meeting the neonatal team is very important in the continuum of care. It is never appropriate to maintain or lose weight in a HOM gestation, and thus the patient needs to gain weight even if she is overweight at the onset of pregnancy. The patient needs to maintain her fluid balance by keeping hydrated. Although water consumption is encouraged, it contains no calories, so other liquids can be used both to maintain hydration and to add important calories. Milk is ideal as a liquid, but fruit juices or sports drinks may also be used.

## FOLLOW-UP CARE

The second office visit should be scheduled 2 weeks later. This gives the patient time to digest (or at least consider thoroughly) all the information that has been given to her. Most mothers have numerous questions that they did not address at the initial visit. In addition, this is the time to begin education about general pregnancy changes and specific changes related to HOM gestation. Fetal heart tones (FHTs) are confirmed by ultrasound. In an otherwise uncomplicated HOM gestation, the patient should be seen in the office every 2–3 weeks until 18 weeks. The content of these visits includes assessment of weight gain: 2–3 lb a week is required in order to achieve the ideal weight gain of 50–75 lb for a triplet pregnancy, and 75–100 lb for a quadruplet pregnancy. It is crucial to stress that 75% of that weight should be achieved by 24–26 weeks, as preterm delivery is virtually assured and there will be no time 'later on'. Consultation should be arranged with a dietician who is familiar with pregnancy nutrition and hopefully with the specific dietary requirements of HOM gestation. A good resource for patients and dieticians alike is *When You're Expecting Twins, Triplets, or Quads* by Luke and Eberlein[16]. Blood pressure is assessed, as is urine for protein and glucose. FHTs are assessed by ultrasound. The patient is encouraged to discuss any issues she may have.

At 18 weeks the patient should have a targeted ultrasound examination to assess carefully the anatomy of each fetus to determine whether any identifiable malformations exist that may present special needs for intervention, either *in utero* or in the NICU. Careful attention should also be paid to the cervix. A vaginal ultrasound examination should be performed to assess cervical length and any evidence of funneling (see Chapter 55). Even nulliparous patients with a HOM gestation are at risk of a 'functionally incompetent' cervix. This is probably due to increased levels of relaxin, a hormone that causes softening and dilatation of the cervix[17], as well as downward pressure from the expanding uterine contents. The two circumstances producing the highest levels of relaxin in pregnancy are multifetal pregnancy and ovarian stimulation to cause multiple follicles to mature. Such infertility manipulations are frequent in HOM gestations. Follow-up cervical length ultrasound examinations should be performed every 2 weeks (between 18 and 24 weeks) if cervical length is greater than 3 cm or more frequently if it is less than 3 cm. Cervical shortening should prompt careful assessment for uterine contractions. If contractions are documented, treatment should be initiated with tocolytic drugs, preferably with a terbutaline pump for continuous parenteral administration of the drug[18] (see Chapter 55). If uterine activity is not occurring, strong consideration should be given to cervical cerclage (see Chapter 65).

Further ultrasound assessments are routinely indicated for fetal growth every 3–4 weeks. Routine assessment of fetal well-being in all HOM pregnancies is indicated beginning at the 32nd week. It is difficult at best and often impossible to use electronic FHR monitoring to assess fetal status, so biophysical profile (BPP) testing is equally appropriate. Elliott and Finberg reported on the utility of BPP testing in HOM pregnancies, and recommended routine testing twice a week starting at 32 weeks for normally progressing pregnancies[19]. BPP should be started earlier if there is a small-for-gestational-age fetus or if PIH is diagnosed.

Abnormal placentation affects the need for ultrasound assessment in multiple gestation, including HOM pregnancies. In particular, monochorionic twins, or less commonly monochorionic triplets, are at risk of developing acute, severe twin–twin transfusion syndrome (TTTS) (see Chapter 65). This complication occurs most frequently in the second trimester when discordant fetal size and extremes of amniotic fluid volume (polyhydramnios in the recipient sac and oligohydramnios in the donor sac) can develop very quickly (10 days–2 weeks)[20]. Making the diagnosis in a timely manner allows appropriate intervention to be initiated (see Chapter 74).

Treatments that improve outcome in TTTS include aggressive therapeutic amniocentesis[21] and laser ablation of anastomotic vessels on the chorionic plate[22]. It is important that fetal size and amniotic fluid volume be assessed every 2 weeks from 16 to 26 weeks in pregnancies containing one or more monochorionic placentas. After 26 weeks, assessment can be every 3–4 weeks.

Office visits should be every 2 weeks after 18 weeks. At ≥ 20 weeks a digital cervical examination is added at each visit to assess for cervical dilatation, which is difficult to assess with ultrasound. The patient is also asked about signs/symptoms of preterm labor. These would include: cramping, pelvic pressure, backache, contractions, change in vaginal discharge, pressure sensation in the inner thighs, or a feeling that things are just not right.

## ROUTINE INTERVENTION

The benefit of bed-rest is very difficult to establish. Goldenberg and colleagues reviewed the literature and concluded that bed-rest is of no benefit in any obstetric circumstance[23]; others agree (see Chapter 74). It is my belief that whereas bed-rest alone will not prevent preterm delivery, it may decrease the frequency of uterine contractions. It is widely appreciated that the more contractions that are occurring the greater is the possibility that preterm labor (PTL) will occur. Garite and co-workers demonstrated an increase in contractions 48 h prior to PTL to a mean of 3.5/h, and further to 5.5/h in the 24 h prior to the onset of PTL[24]. In our patients with HOM gestations, administration of betamethasone caused PTL in those patients whose background uterine activity was ≥ 3.5 contractions/h, although it did not initiate PTL if the contractions were less than 3.5/h when the steroids were given[25]. We believe that 3.5 contractions/h represents a threshold value that increases the likelihood of PTL. In our practice, modified bed-rest is prescribed to lower the background contraction frequency to reduce the likelihood of PTL. Modified bed-rest includes time spent recumbent in bed, on a couch, on a recliner chair or outdoors in a chaise-longue. The patient can go to the bathroom ad libitum and shower once a day. Mild ambulation for 15–30 min can be added for individual patients. Tocolysis may also be needed to keep the background contractions fewer than 3.5/h[18].

The role of contraction monitoring in the management of patients at risk of PTL remains controversial. In theory, detection of uterine contractions is important in attempting to detect PTL early. If a patient calls her physician with a complaint of cramping or contractions, the initial evaluation includes placing the patient on a contraction monitor in the hospital. However, the use of a more sensitive tocodynamometer in the out-patient setting evokes intense feelings in practitioners about the clinical utility of the same technology that is used in the hospital. In either event, the monitor will not prevent preterm delivery (PTD), whereas it might allow detection of PTL at an earlier stage to allow appropriate intervention possibly to prevent PTD[26]. The vast majority of articles evaluating home uterine activity monitoring (HUAM) support the concept that daily interaction with the patient by a specially trained nurse with or without a tocodynamometer affords better outcomes than typical standard management with weekly office evaluations. In HOM gestations, it is important to keep background uterine contractions to ≤ 3.5/h. The HUAM can be utilized to assess this background activity, in addition to picking up active PTL in a more timely manner. Out-patient management of HOM gestations is not only appropriate but is psychologically beneficial for the patient and her family[27–29].

Fetal fibronectin testing is a useful laboratory test to predict risk of PTD in patients at risk (see Chapter 56). In singleton pregnancies at risk of PTD, Peaceman and colleagues demonstrated a PTD rate of less than 1% within 2 weeks of a negative fFN test[30]. This is very reassuring. A positive fFN is associated with approximately a 17% risk of PTD in the ensuing 2 weeks. The significance of fFN in HOM gestations is less well understood. In unpublished data for our practice, a negative fFN in a HOM gestation is associated with a 6% risk of PTD in the next 2 weeks, whereas a positive test has almost a 50% risk of delivery in the next 2 weeks. A positive fFN should prompt closer monitoring of contractions, steroid administration if that has not yet been given and weekly office visits. Aggressive tocolysis should be initiated when labor occurs.

Another routine recommendation in our practice is the use of hydrotherapy. The patient is encouraged to stand in a swimming pool (if available) for 20–30 min a day. A spa or jacuzzi is also appropriate, with the legs as deep as possible. The water is very soothing, both physically and psychologically, especially as the mother gets into the third trimester. The physiologic benefits of hydrotherapy include a beneficial effect on peripheral edema which occurs in almost all HOM gestations. Head-out immersion is useful in increasing the intravascular volume, which in turn increases blood flow to the placentas. This therapy can also increase amniotic fluid volume in placental insufficiency[31].

## SUMMARY

Prenatal care of the patient with a triplet or quadruplet gestation is anything but ‘routine’. It incorporates

care that is provided to all pregnancies, but also has many features that are specific to HOM gestations. All the routine interventions are recommended to extend the pregnancy to the fullest extent possible prior to delivery. It is our goal with every pregnancy to have the woman admitted from her home for elective delivery at 35 weeks for triplets and 34 weeks for quadruplets. It is very important for the patient to embrace the prenatal program psychologically and intellectually. The patient needs to feel empowered by this program of care so that she is confident that she will succeed in her quest to deliver her babies as safely as possible with the least risk to them of morbidity and mortality. This psychologic confidence of the mother contributes to stress reduction and ultimately to a better outcome. Having a plan for prenatal care inspires that confidence in the patient and her family. The benefit cannot be calculated.

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# Nutritional Adaptation

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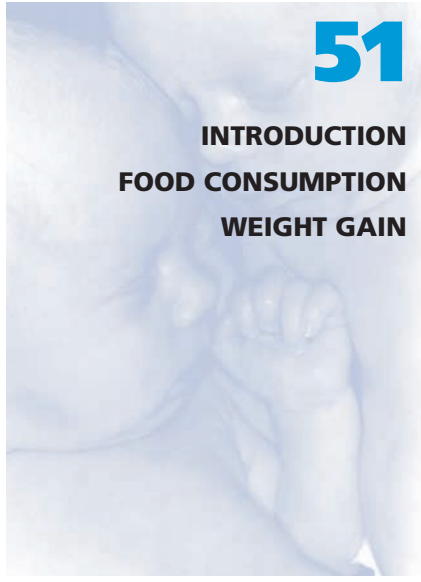


## INTRODUCTION

Nutrition plays an important role in optimizing positive outcomes for the mother and her fetus in singleton and multifetal pregnancies. Although extant literature examining singleton gestations does not extrapolate readily into specific guidelines for multifetal pregnancies, data on multifetal pregnancies are slowly being accumulated, providing a more accurate picture of nutritional demands. Despite this, further research is required to understand fully the influence of plurality on maternal physiological changes and in order to generate strategies for improved maternal and neonatal outcomes. Improved management and education on nutritional aspects of preconceptional and prenatal care may help reduce the fetal morbidity and mortality that currently is disproportionately ascribed to multiple gestations.

Complications of multifetal pregnancies are numerous and described throughout this book[1,2]. It is reasonable to surmise that adequate and appropriate nutrition can help circumvent these problems and potentially reduce maternal and neonatal morbidity. It is important to remember that multifetal pregnancies can exacerbate existing nutritional deficiencies in women already at risk for preterm delivery, especially in those who are underweight or have a low pre-pregnancy body mass index, low socioeconomic status or a history of preterm birth[3]. The importance of metabolic adaptations, pre-gravid body mass index, types and benefits of micronutrient supplementation, and amount and pattern of weight gain in multifetal pregnancies are addressed in this chapter.

### Physiology

Alterations in hormone levels, energy expenditure, micronutrient status and dietary intake all contribute to the physiologic nutritional adaptations of pregnancy[4]. Metabolic changes, including increased plasma volume, basal metabolic rate and carbohydrate intolerance, are more pronounced in multiple gestations than in singleton gestations[5,6] (see Chapter 49). These changes partly account for the at least two-fold increased incidence of gestational diabetes seen in multiple gestations.

### Gestational diabetes

Gestational diabetes in multiple pregnancies[7–12] is discussed in Chapter 54.

According to the American Diabetes Association (ADA), a non-pregnant diabetic diet follows a calorie distribution of: 20% protein, 30% fat and 50% carbohydrates[11,13]. Ahn and Phalan recommended an additional 300 kcal/day in twins for a total of 2400 kcal/day in a 60-kg woman of ideal body weight[14]. Luke and co-workers[15,16] studied the effects on multiple gestations of a diet composed of 20% protein, 40% fat and 40% carbohydrates and reported improved glycemic control with that regimen[11]. Luke and colleagues[15] as well as Dubois and associates[17] recommend a diet for twins that is 1000 kcal/day above that of singletons, for a total caloric goal of

**Table 51.1** Institute of Medicine's prenatal weight gain recommendations for singleton* pregnancies based on body mass index (BMI). Adapted from reference 26

| | *Underweight* | *Normal* | *Overweight* | *Obese* |
|---|---|---|---|---|
| BMI (kg/m$^2$) | <19.8 | 19.8–26.0 | 26.1–29.0 | >29.0 |
| *Recommended weight gain* | | | | |
| kg | 12.5–18 | 11.5–16 | 1–11.5 | >7.0 |
| lb | 28–40 | 25–35 | 15–25 | >15 |
| *Weight gain per week after 12 weeks* | | | | |
| kg | 0.5 | 0.4 | 0.3 | — |
| lb | ~1 | — | — | — |

*The Institute of Medicine recommends 35–45 pound weight gain for twin pregnancies

3000–4000 kcal/day. Although exercise ameliorates glycemic control, patients with multifetal pregnancies should be cautious, especially if at risk for premature delivery[18].

Treatment goals of gestational diabetes mellitus (GDM) in multiple pregnancies include prevention of macrosomia, fetal hypoxia and acidemia, and possible uterine contractility. Macrosomia is rarely encountered as the fetal growth patterns of multiple gestations lag behind those of singletons during the third-trimester period of maximum fetal growth[19]. The increased metabolism and energy expenditure resulting from hyperinsulinemia can lead to fetal hypoxia and acidemia[20]. In animal models, hypoglycemia was associated with increased uterine contractility through formation of prostaglandin $F_{2\alpha}$[21–23]. Therefore, recognizing and managing GDM in multiple pregnancies in a manner designed to achieve euglycemia is paramount.

## FOOD CONSUMPTION

### Diet

The ideal pregnancy diet avoids drastic maternal and fetal glucose fluctuations while maintaining healthy maternal and fetal nutrition. The ADA recommends, for singleton pregnancies with GDM, consumption of 35 kcal/kg/day, using pregnant weight[13]. Initially composed of 50–60% carbohydrates, this diet unfortunately caused unwanted weight gain and postprandial hyperglycemia in singleton diabetic pregnancies. Not surprisingly, 50% of patients required insulin therapy[24]. Jovanovic-Peterson and Peterson adjusted the ADA recommendation of kcal/kg/day based on pre-pregnancy weight and mild carbohydrate restriction[24]. In 1990, the Institute of Medicine published recommendations for singleton pregnancies, suggesting 30 kcal/kg/day for women of normal weight, 35 kcal/kg for underweight women, 24 kcal/kg for overweight women and 12 kcal/kg for morbidly obese women[12,15,24–26] (Table 51.1).

Luke and co-workers modified the singleton ADA diet and applied it to all twin and triplet pregnancies[11,15,16]. They successfully achieved euglycemia with the following modifications: 40% carbohydrates, 20% protein, 40% fat. Fewer carbohydrates facilitated normoglycemia, whereas greater fat allowed efficient delivery of more calories[11]. In addition, these investigators adopted the ADA diet plan of three meals and three snacks a day. Using the Institute of Medicine (IOM) designations of weight status by body mass index[25], they devised dietary recommendations for twin pregnancies (Figure 51.1).

### Protein

Increased calorie and protein intake in multiple-gestation pregnancies has been widely recommended based on positive results from observational studies. However, there is insufficient evidence from randomized controlled trials to support fully this practice[27]. In a review of randomized controlled trials in singleton pregnancies, protein and energy supplementation did encourage greater maternal weight gain and fetal growth[28]. As the morbidity and mortality of twins decrease with increasing birth weight, the association of increased calories and protein with greater fetal growth is promising[26].

No consensus exists on the amount of supplemental protein that optimizes the fetal growth of twins. A singleton pregnancy should have approximately 60 g of protein a day[29]. Some authors recommend an additional 50 g[17] to 115 g[15] of protein daily for twin pregnancies (Figure 51.1). Protein intake provides essential and non-essential amino acids for the mother and fetuses. However, similar maternal concentrations of amino acids have been described

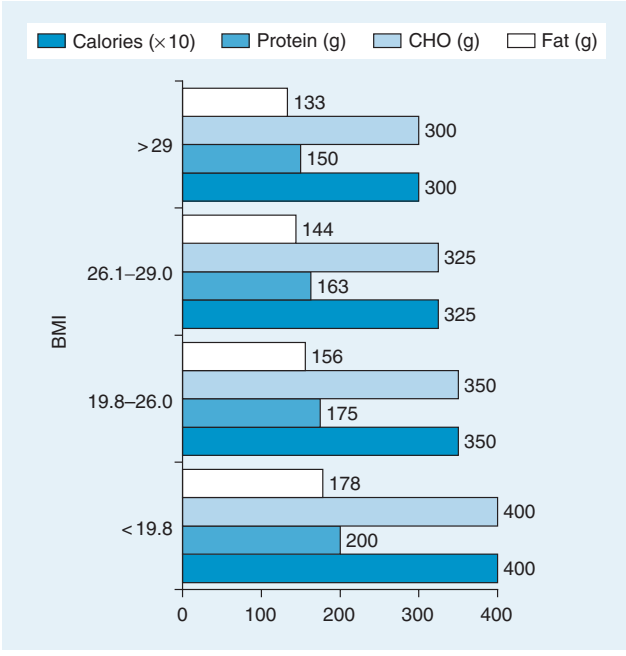


**Figure 51.1** Body mass index (BMI)-specific dietary recommendations for twin pregnancies. Adapted from reference 15. CHO, carbohydrates

in concordant and discordant twin pregnancies. Specifically, amino acid concentrations were similar in the concordant fetuses while the discordant twin sets had significant differences in amino acid concentrations. Impaired or unequal placental transport of nutrients contributes to the development of growth restriction in singletons and multifetal pregnancies[30].

## Nutrients

Healthy food choices and diet ideally should commence in the preconception period. With burgeoning usage of assisted reproductive technologies, this presents an opportune time for nutritional intervention in potential multifetal pregnancies. The IOM recommends nutrient supplementation for women of reproductive age who may become pregnant. The American Dietetic Association recommends a healthy diet and daily prenatal vitamin[25]. Given insufficient evidence to establish beneficial and non-toxic levels of multivitamin and multinutrient supplementation in multifetal pregnancies, it is advisable to follow the recommendation of the IOM[2] (Table 51.2). The US Food and Drug Administration (FDA) put forth several recommendations for singleton pregnancies and during lactation[31] (Table 51.3). Luke suggests that a 50–100% increase over the recommended daily allowance for singleton gestations is reasonable for multifetal pregnancies[32].

**Table 51.2** Daily nutrient supplementation for multiple gestations after 12 menstrual weeks. Adapted from reference 26

| | |
|---|---|
| *Minerals* | |
| Iron | 30 mg |
| Zinc | 15 mg |
| Copper | 2 mg |
| Calcium | 250 mg |
| *Vitamins* | |
| Vitamin B6 | 2 mg |
| Folate | 300 µg |
| Vitamin C | 50 mg |
| Vitamin D | 5 µg, 200 IU |

Guidelines for a healthy diet in singleton pregnancies combine increased calories with nutritious foods to meet the energy demands of the mother and growing fetus (Figure 51.1)[25]. Similar guidelines were tested in multifetal pregnancies and demonstrated that adjunct care, in which a dietician creates individualized diets, can not only better meet both maternal and fetal needs but also improve neonatal outcomes[15,17]. The Higgins Nutritional Intervention Program, for example, affected gestational age prolongation by providing antenatal nutrition support in twin pregnancies[17]. Whereas the Higgins Program reduced the preterm delivery rate by 15%[17], the Program Pregnancies intervention of the University of Michigan Multiples Clinic reduced preterm deliveries by 23%[15]. Such results are worthy of widespread recognition and duplication, as they clearly support the integral role of professional nutrition support during multifetal pregnancies.

## Essential fatty acids

Nutrients such as essential fatty acids (EFAs), vitamin B12 and folate play crucial roles in fetal central nervous system development. Reduced essential fatty acid levels in multifetal pregnancies could possibly affect neurologic outcomes of multifetal pregnancies[33]. Increasing the maternal intake of EFAs may be logical, but studies do not clearly demonstrate a benefit or harm. Dietary sources of linoleic and linolenic fatty acids include sunflower, safflower, canola, corn and soybean oils, egg yolk and meat[2].

## Folate

As folic acid plays an integral role in critical first-trimester events such as DNA synthesis, neural tube closure and hemopoiesis, there is universal agreement that maternal stores must be adequate prior to conception[34]. At present, the American College of Obstetricians and Gynecologists recommends folic acid and iron supplementation for

**Table 51.3** Recommended daily dietary allowances for pregnant and lactating women. Adapted from reference 31

| | | *Lactating* | |
|---|---|---|---|
| | *Pregnant* | *0–6 months* | *7–12 months* |
| *Protein* (g) | 60 | 65 | 62 |
| *Fat-soluble vitamins* | | | |
| Vitamin A (μg) | 800 | 1300 | 1300 |
| Vitamin D (μg) | 10 | 10 | 10 |
| Vitamin E (mg) | 10 | 12 | 11 |
| Vitamin K (μg) | 65 | 65 | 65 |
| *Water-soluble vitamins* | | | |
| Vitamin C (mg) | 70 | 95 | 90 |
| Thiamine (mg) | 1.5 | 1.6 | 1.6 |
| Riboflavin (mg) | 1.6 | 1.8 | 1.7 |
| Niacin (mg) | 17 | 20 | 20 |
| Vitamin B6 (mg) | 2.2 | 2.1 | 2.1 |
| Folate (μg) | 400 | 280 | 260 |
| *Minerals* | | | |
| Calcium (mg) | 1200 | 1200 | 1200 |
| Phosphorus (mg) | 1200 | 1200 | 1200 |
| Magnesium (mg) | 320 | 355 | 340 |
| Iron (mg) | 30 | 15 | 15 |
| Zinc (mg) | 15 | 19 | 16 |
| Iodine (μg) | 175 | 200 | 200 |

multifetal pregnancies but fails to provide an amount for either[35]. The IOM suggests a supplemental 300 μg per day of folate for multifetal gestations[6], but there are data to support that the daily folic acid requirement in pregnancy increases to approximately 800–1000 μg from 400 μg outside of pregnancy[36,37]. Folic acid deficiency may result in megaloblastic anemia, the second most common nutritional anemia of pregnancy. Most cases occur in the third trimester, with many occurring concomitant with iron deficiency anemia[36]. The primary reason to insist on folic acid supplementation is that intake of at least 400 μg prior to conception reduces the incidence of neural tube defects by 26%[38].

## Iron

Adverse maternal and neonatal outcomes are associated with iron deficiency anemia even though iron supplementation has not been proven to be unequivocally beneficial[33,34]. Maternal effects of anemia include increased mortality and reduced immunity. Neonatal effects include premature birth, lower birth weight and delayed psychomotor development[33]. Due to the high prevalence of iron deficiency in menstruating women and inadequate iron intake, 30 mg supplemental iron is recommended for all pregnant women[26,33,39]. This amount is generally available in most prenatal multivitamin supplements. The increased iron absorption in pregnancy provides minimal assistance in preventing the development of iron deficiency anemia, especially in multifetal pregnancies where iron stores are depleted by a large fetal erythrocyte mass. Periodic assessment of iron status to diagnose anemia or to monitor hematinic therapeutic response is warranted in all pregnancies[39]. A low hemoglobin value with low serum ferritin levels, $< 15$ μg/l, diagnoses iron deficiency anemia with a specificity of 98%. Successful hematinic treatment of iron deficiency anemia with 60–120 mg elemental iron increases hemoglobin values by 1 g/dl in 4 weeks. Non-responders should be evaluated for compliance and for hemoglobinopathies such as thalassemia[39].

## Calcium

Increased calcium absorption and decreased excretion in pregnancy facilitates meeting the fetuses' growing skeletal demands[25,33]. However, with multiple gestations, this demand is further increased. Accordingly, the American College of Obstetricians and Gynecologists recommends calcium supplementation in pregnancy[35]. In 1997, the IOM indicated that adequate calcium intake consisted of 1300 mg and 1000 mg for adolescents and adults of reproductive age, respectively, with an upper limit of total dietary calcium intake of 2500 mg. The 1997 statement also

indicated that this amount did not differ from the non-pregnant state, i.e. irrespective of either pregnancy or lactation[40]. In an earlier, 1990, statement, the IOM recommended a lesser dose of 250 mg of daily supplemental calcium after 12 weeks' gestation[26]. This amount did not affect maternal bone mineral density, but did seem to increase neonatal bone mineral density[40]. In spite of its dietary value, there is currently inconsistent evidence to support the role of calcium supplementation in reducing the incidence of either pre-eclampsia[11,25] or preterm delivery[11].

## WEIGHT GAIN

The Institute of Medicine (IOM) published *Nutrition during pregnancy* in 1990, which put forth the following recommendation:

> *'Total weight gain of 16–20.5 kg (35 to 45 lb) is consistent with a favorable outcome of a full-term twin pregnancy. This suggests that a woman who is pregnant with twins should aim for a weekly weight gain of approximately 0.75 kg (1.5 lb) during the second and third trimesters of pregnancy'*[26].

The Maternal Weight Gain Expert Work Group organized in 1996 by the Maternal and Child Health Bureau supported the IOM's 1990 findings[41]. These recommendations evolved from observational as well as retrospective studies of multiple gestations. The IOM categorized women by their pre-pregnancy weight status, using their body mass index (BMI), to develop specific weight gain recommendations for singleton pregnancies.

The lack of prospective controlled studies of large numbers of multiple pregnancies hinders the development of accurate weight gain recommendations for multifetal gestations. Many retrospective studies analyzed effects of maternal weight on fetal growth, birth weight and length of gestation in multifetal pregnancies. An epidemiologic approach to establish the 'ideal twin pregnancy' retrospectively determined that the individual twin birth-weight range of 2000–2500 g and gestational age at delivery of 35–38 weeks reduced the incidence of adverse neonatal outcomes[42–44]. These studies also confirmed the association with increased maternal weight gain, especially early and late in gestation, and increased birth weight[42–44].

Fetal growth lags sooner in multiple gestations with increasing plurality in a dose–response relationship[45–47]. Teleologic reasons for this pattern of fetal growth require further elucidation to focus efforts on optimizing outcomes prospectively in multifetal pregnancies[45]. Although a healthy birth weight is desirable for healthy outcomes, increased length of gestation is often inherent to increased birth weight[26] and multiparity. Factors that promote prolongation of the gestational period to allow for chronological maturation of the fetus and the systematic contribution of parity are yet to be determined for BMI categories other than for underweight. With current nutritional interventions, birth weight is more amenable to enhancement than is prolongation of gestational age in women who are not underweight.

The *FDA Consumer* published in April 1990 correctly expressed the opinion 'that the fetus is not a perfect parasite. The fetus is sometimes more affected than the mother by lack of nourishment, and there is a relationship between maternal weight gain and growth and development of the fetus'[48]. Underweight women who gain weight according to a pattern that promotes fetal growth in addition to a specific total weight gain goal achieve the greatest impact in terms of optimal fetal outcomes[33,49].

There appears little doubt that the total amount and pattern of maternal weight gain are important contributors to fetal growth and birth weight[50]. Maternal weight gain positively influences birth weight in a linear fashion. In other words, mothers with twin gestations who gain greater total weight produce heavier children. However, this benefit diminishes proportionately with increasing pregravid maternal weight status[51]. Brown and Schloesser[51] evaluated 922 twin gestations at term, with the lowest perinatal mortality with each neonate weighing between 3001 and 3500 g. The mean total maternal weight gains that achieved these outcomes in underweight and normal-weight women were $44.2 \pm 12.4$ pounds and $40.9 \pm 11.3$ pounds, respectively. Mothers who gained less weight had children who weighed less[51]. Pederson and colleagues[52] investigated desirable weight gain in 'optimum' twin pregnancies, defined as live births of both twins at $\geq 37$ gestational weeks, each twin weighing at least 2500 g and with a 5-min Apgar score $\geq 7$. The mean total weight gain associated with this 'optimum' outcome was 44 lb (20 kg), whereas those who gained 37 lb (16.8 kg) with low gain after 30 weeks had smaller babies[52]. Luke and Leurgans surveyed mothers of twins regarding weight gain and birth weight[53]. They concluded that a significant difference exists between advised and actual weight gain in twin pregnancies. The actual weight gain was greater, with ideal and non-ideal outcome pregnancies gaining a mean of $44.8 \pm 12.6$ lb versus $41.1 \pm 15.2$ lb, $p = 0.005$, respectively. Twins delivered between 35 and 38 gestational weeks and each weighing 2500–2800 g constituted the ideal outcome[53]. Thus, the recommendation of the IOM may require modification, with suggested total maternal weight gain in twin pregnancies ranging at least 40–45 lb (18–20 kg). Despite these differences,

**Table 51.4** Suggested weight gain (lb) per week of twin pregnancy, by pregravid body mass index (BMI) category. Adapted from reference 15

| *BMI* (kg/m$^2$) | *0–20 weeks* | *20–28 weeks* | *28 weeks–birth* |
|---|---|---|---|
| <19.8 | 1.25–1.75 | 1.5–1.75 | 1.25 |
| 19.8–26.0 | 1.0–1.5 | 1.25–1.75 | 1.0 |
| 26.1–29.0 | 1.0–1.25 | 1.0–1.5 | 1.0 |
| >29.0 | 0.75–1.0 | 0.75–1.25 | 0.75 |

**Table 51.5** Suggested weight gain (lb) goals per period of gestation of twin pregnancies, by pregravid body mass index (BMI) category. Adapted from reference 15

| *BMI* (kg/m$^2$) | *At 20 weeks* | *At 28 weeks* | *At 36–38 weeks* (term) |
|---|---|---|---|
| <19.8 | 25–35 | 37–49 | 50–62 |
| 19.8–26.0 | 20–30 | 30–44 | 40–54 |
| 26.1–29.0 | 20–25 | 28–37 | 38–47 |
| >29.0 | 15–20 | 21–30 | 29–38 |

acknowledging the importance of the pattern of weight gain, mothers should gain at least 24 pounds by 24 weeks' gestation[11,42,51–54].

Evidence from singleton pregnancies reveals that maternal weight gain in each trimester benefits fetal growth[11,55]. Similar results have also been shown in twin pregnancies[56]. The maternal weight gain pattern that enhances fetal growth involves weight gain in the first trimester, with greater weight gains in the second and third trimesters[2,56]. A rapid and linear weight gain pattern of twin pregnancies occurs as early as 8 weeks' gestation[52,57]. Luke and colleagues described a 'ripple effect' of early maternal weight gain on mid- and late gestational fetal growth leading to increased birth weight[56,58]. These investigators reported that fetal birth weight increased by 8.5 g, 10 g and 9 g per maternal pound gained up to 20 weeks, from 20 to 28 weeks and after 28 weeks, respectively[49]. The pattern of weight gain is an important contributor to fetal growth and birth weight, and is more clinically relevant than total weight gain during the course of antenatal care[11,58,59].

Early weight gain contributes to maternal nutritional and fat stores for fetal and maternal consumption as metabolic demand increases. Thus, patients with higher pregravid body mass indices may not require the same total weight gain since their fat stores are adequate prior to pregnancy[11]. However, overweight and obese patients with multifetal pregnancies must meet nutritional demands and should also gain a minimum of weight. Although one should advise against weight loss in the first trimester, current evidence does not specify the amount to gain. A weight gain of approximately 4–6 lb has been suggested for the first trimester in multifetal pregnancies[2].

Tables 51.4 and 51.5 show the rate and goals of maternal weight gain. Mid-gestational maternal weight gain may contribute the most to fetal birth weight[11,42,59,60]. Luke and colleagues[56] analyzed patterns of maternal weight gain, concluding that early and midgestational maternal weight gain was associated with an increase in midgestational fetal growth. In addition, midgestational maternal weight gain enhanced mid- and late gestational fetal growth and birth weight. Inadequate weight gain in the first and second trimesters, defined as <0.70 to <0.85 lb/week and <1.0 to 1.3 lb/week, respectively, contributes to individual twin birth weight <2500 g[2,59,60]. Low weight gain of <6 kg (13.2 lb) prior to 20 weeks has been associated with poor fetal growth and increased morbidity[42,49,56,60]. Fetal weight increases most in the third trimester, whereas maternal weight gains from the preceding trimesters are largely manifest in maternal plasma volume expansion, fat stores and uterine and mammary enlargement[11,50]. These components are critical for fetal growth. Micronutrient deficiencies may underlie the mechanism leading to inadequate plasma volume expansion[61]. Low plasma volume expansion may impair fetal growth through inadequate transfer of nutrients to the fetus[50]. Thus, available research supports adequate weight gain in multifetal pregnancies by 20–24 weeks with suggested weight gain of 24 lb by 24 weeks[42,49,56,60].

Maternal weight gain after 20–24 weeks also contributes to fetal growth and birth weight. To reach a total weight gain of 40–45 lb, Luke and colleagues[60] suggest a maternal weight gain of 1.25 lb/week after

**Table 51.6** Maternal weight gain for ideal outcomes by plurality. Adapted from reference 57

| | *Singletons* | *Twins* | *Triplets* | *Quadruplets* |
|---|---|---|---|---|
| Maternal weight gain (lb) | | | | |
| to 24 weeks | 12 | 24 | 36 | 50 |
| total | 25–35 | 40–45 | 50–60 | 65–80 |
| Gestational age (range, weeks) | 38–41 | 36–38 | 34–35 | 31–33 |
| Average birth weight (g) | 3700–4000 | 2500–2800 | 1900–2200 | 1500–1800 |

24 gestational weeks. Lantz and associates[59] suggest a maternal weight gain of 1.5 lb/week after 20 gestational weeks in women with a normal pregravid BMI. Poor late weight gain is also associated with poor fetal growth[42]. The latter half of the third trimester marks an important point in fetal growth, and women who are unable to continue to gain weight at this time may give birth to smaller babies[2,42,52].

Maternal pregravid BMI strongly influences the pattern of maternal weight gain that optimizes fetal birth weight in twin gestations. Fetal growth is promoted by adequate early weight gain, at least 1 lb/week until 20 weeks, in underweight women[49,59]. Underweight women who gained 1.13 lb/week versus those who gained 0.70 lb/week before 20 weeks gave birth to twins weighing > 2500 g each[59]. After 20 weeks, Lantz and associates[59] recommend that underweight and normal-weight gravidas gain at least 1.75 lb/week and 1.5 lb/week, respectively. Luke and colleagues[60] recommend 1.25 lb/week weight gain after 24 gestational weeks. Weight gain before 20 weeks contributed the most to birth weight in underweight women, whereas weight gain before 20 weeks and after 28 weeks equally contributed to twin birth weight in overweight women. In normal-weight women, early, late and midgestational (20–28 weeks) antenatal weight gain contributed equally to twin birth weight[49].

Antenatal weight gain in triplet and higher-order multiple gestations likely follows similar principles that govern weight gain in singleton and twin pregnancies, such as maternal pregravid BMI status and emphasis on weight gain of underweight women (Table 51.6). Studies of triplet gestations suggest that maternal weight gains of 48.5 lb (22 kg) or 45.1–50.6 lb (20.5–23 kg) in 31.8–33.8 weeks are required to achieve mean birth weights of 1666–1911 g[33,49,62–64]. Luke and colleagues[65] described maternal characteristics that promoted fetal growth and birth weight of triplets. Maternal weight gain was more influential in under- and normal-weight women than in overweight gravidas[65]. Multiparity, previous good pregnancy outcomes and maternal weight gain of 36 lb before 24 weeks yielded favorable outcomes. However, when applied to 1705 triplet pregnancies, only 32.8% met this weight gain recommendation. In addition, a reduced incidence of very-low-birthweight (VLBW) neonates but not an increase in total triplet birth weight (TTBW) was seen. This positive effect was evident in nulliparas in all pregravid BMI categories (Sharma and colleagues, unpublished data). In 1825 triplet pregnancies of women with a normal pregravid BMI, multiparous patients who gained greater than 1.1 lb/week (0.49 kg/week) achieved higher TTBW and lower frequency of VLBW than nulliparas[66]. Until further studies are performed, current antenatal management of triplet pregnancies may advise maternal weight gain of 36 pounds (16.4 kg) by 24 weeks followed by weight gain of 1.25 lb (0.57 kg).

Fewer studies exist in quadruplet gestations, with one series of five quadruplet pregnancies reporting a mean maternal weight gain of 68.2 pounds in 31 weeks[63] and another series of 71 pregnancies with an average of 45.8 pounds in 31 weeks (Sharma and colleagues, unpublished data). However, an association between neonatal outcomes and ideal weight gains cannot yet be determined[67].

## SUMMARY

Multifetal pregnancies place a high demand on maternal nutritional stores. As in singleton gestations, pregravid body mass index influences fetal growth and birth weight. Although proper nutritional support is essential in all pregnancies, it is particularly beneficial in underweight women. The IOM maternal weight gain guidelines are towards the lower range for twin gestations, compared with ranges investigated in recent retrospective studies. Further research is essential to establish more accurate recommendations regarding micronutrient and vitamin supplementation and ideal prospective antenatal nutritional management of multiple gestations.

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# Maternal Cardiovascular Adaptation

*J. Nizard and B. Arabin*

**52**



## INTRODUCTION

Profound changes take place in the maternal cardiovascular system during pregnancy, beginning after conception and continuing as gestation advances. Most changes are reversible within weeks to months after delivery. Maternal tolerance to twin pregnancies, however, is different from that of singleton pregnancies. The earlier onset of asthenia, the subjective difficulty in leading a normal, active life and the need for more rest all point to what extent the maternal cardiovascular system must adapt in multiple compared with singleton pregnancies. This chapter reviews the available data on why and to what extent the maternal cardiovascular system adapts to twin pregnancy.

## VENOUS VASCULAR BED AND VENOUS RETURN

Venous compliance increases progressively during pregnancy, probably due to the relaxing effect of progesterone or endothelium-derived relaxant factors, resulting in a decrease of flow velocity and subsequent stasis[1]. Consequently, pregnant women are more sensitive to autonomic blockade; this phenomenon results in decreased venous return and venous pooling of a large part of the plasmatic volume. Calf venous pressures are higher than those of the forearm, and this difference becomes more exaggerated as gestation advances, partly due to the increasing size of the uterus[2]. In twin pregnancies, these effects are therefore even more exaggerated.

Uterine volume in twin compared with singleton pregnancies is enlarged, and plasma volume in twin compared with singleton pregnancies is increased as early as 21 weeks of gestation[3]. This difference persists until the end of pregnancy. Moreover, whereas plasma volume reaches a plateau at around 32 weeks in singleton pregnancies, it continues to increase in twin pregnancies, as is shown in one cross-sectional study[3]. Here, total plasmatic volume increased from + 6% at 21–24 weeks to + 14% at 37–40 weeks in twin compared with singleton pregnancies, and from + 41 to +67% during the same interval in comparison with non-pregnant controls. Similarly, total red blood cell mass increases in twin gestation, but to a lesser extent. The total blood volume, indexed to the body surface, increases by +1 to + 5% at 21–28 weeks and by + 5 to + 15% in the third trimester in twin compared with singleton pregnancies. These data are summarized in Table 52.1.

It has been suggested that the benefits from hypervolemia with a dilution of the red blood cells is a relative reduction of the cardiac workload, considering the increase in cardiac output[5]. This suggestion holds true for twin pregnancies as well, considering the greater increase in plasma volume.

The relationship between the rise in plasma volume and plasma levels of atrial natriuretic peptide (ANP) and aldosterone is not clear. Comparing singleton and twin pregnancies longitudinally, a significantly increasing concentration of ANP was observed in singleton pregnancies at 20, 28 and 30 weeks[6,7]. In the same population, the aldosterone levels increased in both singleton and twin pregnancies, but increased to a significantly greater extent in twin pregnancies at 20, 28 and 32 weeks. These studies were not performed in early pregnancy, however[6,7].

**Table 52.1** Plasmatic, total red blood cell and total blood volume changes in singleton and twin pregnancies compared with non-pregnant controls[3,4]. Measurements were performed only after 20 weeks of gestation. All values were indexed to the body surface before analysis

| | *Plasma volume* | | *Red blood cell volume* | | *Blood volume* | |
|---|---|---|---|---|---|---|
| | *2nd trimester* | *3rd trimester* | *2nd trimester* | *3rd trimester* | *2nd trimester* | *3rd trimester* |
| Singleton pregnancies | +34 to +39% | +44 to +49% | +13 to +23% | +21 to +31% | +27 to +34% | +39 to +44% |
| Twin pregnancies | +41 to +49% | +55 to +67% | +1 to +22% | +30 to +40% | +28 to +40% | +51 to +59% |

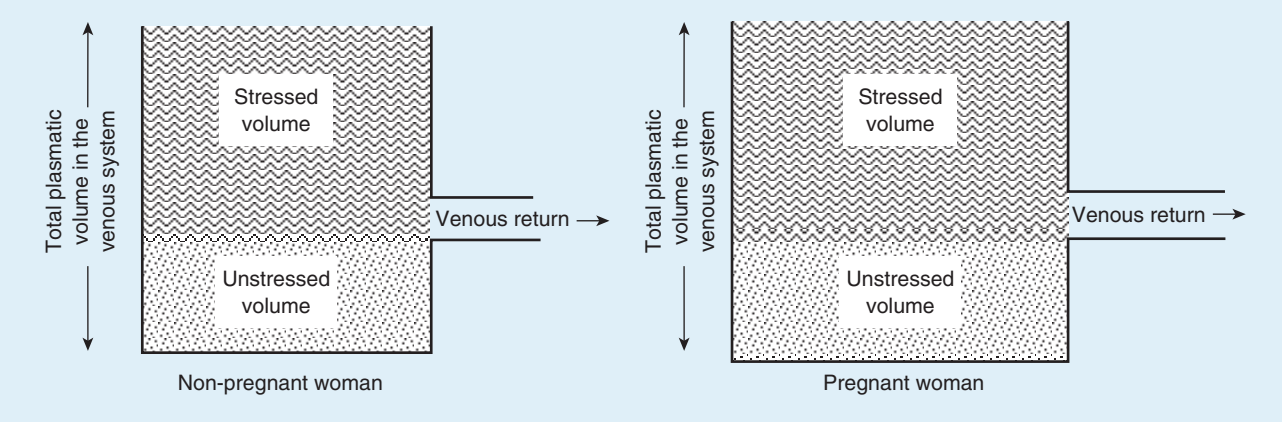



**Figure 52.1** Illustration of the relationship between stressed and unstressed volumes in the venous system. An increase of the stressed venous plasmatic volume contributes to an increase in plasmatic volume. This constrained volume does not increase the cardiac preload if the venous tone is not increased. Patients with a twin pregnancy probably have larger stressed and unstressed compartments due to greater compression of the venous return by the size of the uterus, and by the larger blood volume contained in the placenta

The venous return is not solely dependent on the plasma volume. The plasma volume of the venous system can be divided into 'stressed' and 'unstressed' portions (Figure 52.1). The unstressed volume is the portion that fills the venous system without contributing to venous distension. In contrast, the stressed volume (difference between total blood volume in the venous system and unstressed volume) distends the venous reservoir, and is responsible for a hydrostatic pressure gradient that drives the venous return back to the right atrium. This driving pressure is also characterized as the 'mean systemic pressure', and depends on venous vasoconstrictive tone and blood volume. An increase in the venous vasoconstrictive tone reduces the venous capacity and converts unstressed volume into stressed volume, thereby increasing venous return.

## ARTERIAL SYSTEM

Physiologic vascular adaptation starts early in pregnancy. Whether the first changes leading to peripheral vasodilatation are due to estradiol, progesterone, nitric oxide or prostaglandins alone or acting together is not yet clear. The primary decrease in systemic vascular resistance might be responsible, together with the increasing plasma volume, for an early increase in cardiac output. However, the early drop of arterial blood pressure, beginning as early as the 7th week, represents incomplete compensation for the increasing cardiac output[8]. Futhermore, systemic vascular resistance is also reduced by the low resistance in the placenta.

In a normal singleton pregnancy, the placenta represents a very-low-resistance vascular system in parallel with the rest of the maternal vascularization. As in electrical systems with several resistances in parallel, the total resistance of the circuit will be low if one of the resistances is low (Figure 52.2). In the case of twin pregnancies, total resistance therefore depends on the volume of the placenta, which is understandably larger compared with singleton pregnancies. This in effect means that the area of low-pressure shunt is larger in twin pregnancies due to the placental volume. During

**Table 52.2** Reference values of cardiovascular parameters of non-pregnant female controls[4,12]. Values are expressed as mean ± SD

| *Population* | *Technique* | *Heart rate* (beats/min) | *MAP* (mmHg) | *Stroke volume index* (ml/m²) | *Cardiac index* (ml/min/m²) |
|---|---|---|---|---|---|
| *n* = 6 | dilution technique | 81.0 ± 10.2 | 82.5 ± 6.4 | 43.6 ± 6.0 | 3460 ± 110 |

MAP, mean arterial blood pressure

**Table 52.3** Cardiovascular parameters in singleton (*s*) and twin (*t*) pregnancies (8–16 gestational weeks). Values are expressed as mean ± SD (when SD available)

| *Authors* | *Population* | *Technique* | *Gestational weeks* | *Heart rate* (beats/min) | *MAP* (mmHg) | *Stroke volume index* (ml/m²) | *Cardiac index* (ml/min/m²) |
|---|---|---|---|---|---|---|---|
| Capeless and Clapp[8] | *s* = 8 | echo Doppler | 8–16 | 70 | 65.5 | 81* | 5670* |
| Robson *et al.*[13] | *s* = 10 | echo Doppler | 8–16 | 82 | 78 | 82.5* | 6765* |
| Lees *et al.*[14] | *s* = 11 | dilution technique | 11–13 | 88 ± 10.2 | 82 ± 9.6 | 69 ± 10* | 5920 ± 630*† |
| Nizard *et al.* unpublished | *s* = 21 | echo Doppler | 11 + 5 | 80 ± 7.5 | 83.6 ± 6.0 | 46.1 ± 7.9 | 3778 ± 642 |
| Nizard *et al.* unpublished | *t* = 11 | echo Doppler | 11 + 6 | 77 ± 6.6 | 88.6 ± 9.7 | 49.2 ± 10.4 | 4300 ± 849 |

*Value not indexed to the body surface; †value given by the authors not recalculated; MAP, mean arterial blood pressure

the mid-trimester in twin pregnancies, mean arterial blood pressure and systemic vascular resistances decrease more than in singleton pregnancies[9,10], although this is not a consistent finding[11]. The differences in mean arterial blood pressure measured by various authors at different gestational ages are indicated in Tables 52.2–52.5.

The contradictory results tend to show that if there is a difference between the mean arterial blood pressure of women pregnant with either a singleton or twins, it is probably minute. The small reduction of mean arterial blood pressure results from the combination of the placental shunt (Figure 52.2) and increase of plasmatic volume. Interestingly, when singleton and twin pregnancies are stratified by maternal age and weight gain during pregnancy, the reduction in diastolic blood pressure seems to stay constant[9].

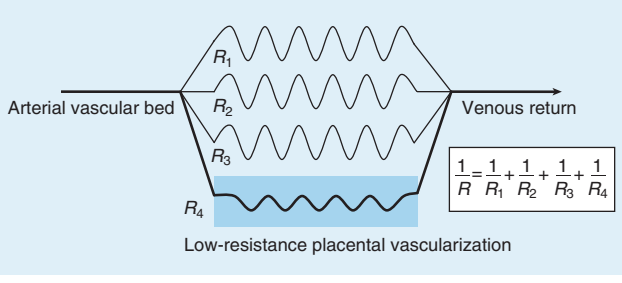



**Figure 52.2** In a system with resistances 'in parallel', such as in the vascular system, the total resistance of the system ($R$) depends on the branch with the lowest resistance, here the placental vascular bed ($R_4$). If $R_4$ is close to 0, $R$ will be low as well

## THE HEART

The heart of a healthy patient adapts to the increase in venous return, relative hemodilution and reduction of mean arterial blood pressure with an increase in cardiac output. Cardiac output is the product of heart rate and stroke volume, and is a measure of the functional capacity of the heart. However, the physiologic increase in cardiac output is reflected in selective regional distribution. Uterine blood flow, for example, increases ten-fold to 500–800 ml/min[15],

**Table 52.4** Cardiovascular parameters in singleton (*s*) and twin (*t*) pregnancies (20–28 gestational weeks). Values are expressed as mean ± SD (when SD available)

| *Authors* | *Population* | *Technique* | *Gestational weeks* | *Heart rate* (beats/min) | *MAP* (mmHg) | *Stroke volume index* (ml/m²) | *Cardiac index* (ml/min/m²) |
|---|---|---|---|---|---|---|---|
| Rovinsky and Jaffin[3,4,12] | *s* = 6 | dilution technique | 21–24 | 86.7 ± 8.9 | 84.2 ± 4.8 | 55.2 ± 6.3 | 4800 ± 140 |
| Thomsen *et al.*[6] | *s* = 40 | echo Doppler | 20 | 76 | 77 | 85* | 6480* |
| Thomsen *et al.*[7] | *t* = 10 | echo Doppler | 20 | 84 | 81 | 92* | 7560* |
| Veille *et al.*[11] | *s* = 16 | echo Doppler | second trimester | 75 ± 10 | 77 ± 8 | 76 ± 13* | 3700 ± 700 |
| Veille *et al.*[11] | *t* = 6 | echo Doppler | second trimester | 86 ± 11 | 81 ± 10 | 85 ± 15* | 4600 ± 600 |
| Rovinsky and Jaffin[3,4,12] | *t* = 2 | dilution technique | 21–24 | 84.0 ± 8.5 | 81.8 ± 0.2 | 60.0 ± 7.6 | 5020 ± 110 |
| Robson *et al.*[10] | *t* = 10 | echo Doppler | 20–24 | 89 | 80.2 | 89* | 7845* |
| Thomsen *et al.*[6] | *s* = 40 | echo Doppler | 28 | 82 | 81 | 92* | 7530* |
| Thomsen *et al.*[7] | *t* = 10 | echo Doppler | 28 | 96 | 83 | 89* | 8290* |
| Rovinsky and Jaffin[3,4,12] | *s* = 7 | dilution technique | 25–28 | 89.4 ± 6.5 | 80 ± 6.7 | 55.6 ± 3.4 | 4990 ± 170 |
| Rovinsky and Jaffin[3,4,12] | *t* = 2 | dilution technique | 25–28 | 85.5 ± 2.1 | 82.7 ± 0.9 | 60.2 ± 3.5 | 5140 ± 170 |

*Value not indexed to the body surface; MAP, mean arterial blood pressure

**Table 52.5** Cardiovascular parameters in singleton (*s*) and twin (*t*) pregnancies (≥ 28 gestational weeks). Values are expressed as mean ± SD (when SD available)

| *Authors* | *Population* | *Technique* | *Gestational weeks* | *Heart rate* (beats/min) | *MAP* (mmHg) | *Stroke volume index* (ml/m²) | *Cardiac index* (ml/min/m²) |
|---|---|---|---|---|---|---|---|
| Rovinsky and Jaffin[3,4,12] | *s* = 6 | dilution technique | 29–32 | 90.7 ± 4.9 | 80.8 ± 2.9 | 51.6 ± 3.1 | 4650 ± 90 |
| Robson *et al.*[13] | *s* = 10 | echo Doppler | 28–32 | 86.5 | 80.5 | 84.3* | 7292* |
| Rovinsky and Jaffin[3,4,12] | *t* = 2 | dilution technique | 29–32 | 90.0 ± 1.4 | 85.3 ± 12.3 | 56.1 ± 2.1 | 4990 ± 110 |
| Robson *et al.*[10] | *t* = 10 | echo Doppler | 28–32 | 92 | 83.2 | 86.5* | 8370* |
| Thomsen *et al.*[6] | *s* = 40 | echo Doppler | 32 | 82 | 81 | 90* | 7490* |
| Thomsen *et al.*[7] | *t* = 10 | echo Doppler | 32 | 96 | 84 | 88* | 8270* |
| Rovinsky and Jaffin[3,4,12] | *s* = 7 | dilution technique | 33–36 | 92.0 ± 9.9 | 81.7 ± 6.8 | 44.6 ± 4.9 | 4100 ± 120 |
| Robson *et al.*[13] | *s* = 10 | echo Doppler | 36–38 | 87.5 | 85.7 | 83.9* | 7341* |
| Lees *et al.*[14] | *s* = 14 | dilution technique | 34–37 | 88 ± 8.4 | 88 ± 8.7 | 67.5 ± 11.5* | 5930 ± 570*† |
| Veille *et al.*[11] | *s* = 17 | echo Doppler | third trimester | 74 ± 9 | 75 ± 6 | 71 ± 12* | 3300 ± 600 |
| Veille *et al.*[11] | *t* = 14 | echo Doppler | third trimester | 83 ± 10 | 78 ± 4 | 93 ± 16* | 4900 ± 700 |
| Rovinsky and Jaffin[3,4,12] | *t* = 7 | dilution technique | 33–36 | 93.9 ± 4.9 | 83.3 ± 9.9 | 48.1 ± 2.9 | 4500 ± 100 |
| Robson *et al.*[10] | *t* = 10 | echo Doppler | 36 | 88 | 88.7 | 89.0* | 9180* |
| Thomsen *et al.*[6] | *s* = 40 | echo Doppler | 38 | 84 | 87 | 89* | 7540* |
| Thomsen *et al.*[7] | *t* = 10 | echo Doppler | 38 | 99 | 86 | 88* | 8440* |

*Value not indexed to the body surface; †value given by the authors not recalculated; MAP, mean arterial blood pressure

representing a shift from 2% in a non-pregnant state to 17% at term in singleton pregnancies[16]. The increase in cardiac output is even greater in twin compared with singleton pregnancies.

For a better understanding of the results provided by different authors, various techniques used in cardiologic assessment and some appropriate technical details are summarized in Table 52.6.

## Heart rate and stroke volume

The increase in heart rate begins early in pregnancy and continues until term[10]. Stroke volume, on the other hand, increases maximally during the first half of gestation, but slightly decreases towards term[10]. It is essential that the heart rate of patients with twin pregnancies increases throughout gestation at least as much as in singleton pregnancies. Although cardiovascular changes occur early in pregnancy, no published data are available on the cardiovascular system of twin pregnancies during the *first trimester*.

The following is based on our own investigations. In our population of 11 twin and 21 singleton pregnancies evaluated between 9 and 15 weeks of gestation, the mean heart rate showed a trend of lower rates in twin compared with singleton pregnancies ($77 \pm 6.6$ versus $80 \pm 7.5$ beats/min, respectively).

Data for the maternal heart rate in the *second trimester* are inconsistent. Veille and colleagues found in their population of 16 singleton and six twin pregnancies in the second trimester that the heart rate was significantly higher in the twin pregnancy group ($75 \pm 10$ versus $86 \pm 11$ beats/min, respectively)[11]. This contrasts with an earlier publication by Rovinski and Jaffin reporting heart rates of $87 \pm 9$ beats/min in singleton versus $84 \pm 9$ beats/min in twin pregnancies at 21–24 weeks[12].

In a similar fashion, data for maternal heart rate in the *third trimester* are inconsistent with regard to differences between twin and singleton pregnancies. Mean values were $74 \pm 9$ beats/min for singleton and $83 \pm 10$ beats/min for twin pregnancies in one study[11], compared with $92 \pm 10$ beats/min versus $94 \pm 5$ beats/min in a second study[12]. A third group of authors found a minute difference in maternal heart rate only before 32 weeks, but not thereafter[10,20]. If technology is not the cause of these variations, perhaps maternal position may account for them. However, this information is not given in the method section of the studies summarized in Tables 52.2–52.5.

## Cardiac output

Heart rate and stroke volume both contribute largely to the increase in cardiac output in singleton and twin pregnancies. Cardiac output is a measure of the functional capacity of the heart and depends on the stroke volume and the heart rate. To be comparable in different populations, stroke volume and cardiac output are indexed to the body surface and expressed per square meter. Because this index is not provided in many studies, data comparison is often not possible. Comparisons are even more complicated because authors do not agree on the patient's weight to use in the body surface formula. Some use the patient's weight at the time of the cardiac examination, whereas others utilize pre-pregnant weight. The latter group of investigators argues that the increase in weight during pregnancy derives mostly from non-oxygen-consuming tissues and water. This point is arguable, however, because the fetus, the placenta and the fat tissue are vascularized and consume oxygen.

Limited data have been obtained from normal pregnant patients by means of invasive methods[22]. The increase in cardiac output in singleton and even more so in twin pregnancies, together with an increase in plasma volume detected by the Evans blue dye dilution technique, has been understood since the mid-1960s[3,4]. More recently, M-mode echocardiography and Doppler studies were used to determine cardiac output during pregnancy and correlate with thermodilution techniques in patients who are ill[23]. Using non-invasive technology, the increase in cardiac output was shown to occur during the *first trimester* in singleton pregnancies[8,10,24]. Our personal data from the first trimester in twin pregnancies demonstrate that the early increase in cardiac output in twin compared with singleton pregnancies is due to the increase in stroke volume rather than an increase in heart rate. As shown in Table 52.3, indexed cardiac output was $4300 \pm 849$ ml/min/m$^2$ in twin and $3778 \pm 642$ ml/min/m$^2$ in singleton pregnancies.

During the *second trimester*, cardiac output increases in singleton pregnancies examined using echo Doppler techniques[8,10,14,24]. It appears that the cardiac output increases more rapidly in twin compared with singleton pregnancies, however. In contrast to our data in the first trimester, this increase seems to be due to an increase in the maternal heart rate rather than the stroke volume[11].

Results of examinations of maternal cardiac output during the *third trimester* are contradictory; here again, maternal position during echocardiography might be responsible for differences between the study groups[19,25]. McLennan and colleagues observed a difference of approximately 5% in the estimated cardiac output when comparing the supine with the left lateral position by continuous-wave Doppler ultrasound directed at the aortic arch[19]. This difference was also observed in their non-pregnant patients. The increase of cardiac output in the

**Table 52.6** Techniques used to evaluate maternal hemodynamics

| *Name of technique* | *Invasiveness* | *Measured parameters* | *Details* |
|---|---|---|---|
| Dye-dilution technique[3,4,12] | invasive | total plasmatic volume and cardiac output | Uses the variation in concentrations of a dye. The technique is no longer used during pregnancy, but has provided basic reference data |
| Thermodilution technique | invasive | cardiac output | The technique is best known as the Swan–Ganz pulmonary artery thermodilution technique. By measuring the difference in temperature up- and downstream from the right ventricle, after an infusion of cold fluid, the cardiac output is deduced |
| Gas exchange measurements | invasive | cardiac output | Following the Fick principle, it determines an outflow if the inbound, outbound and added gas volumes and/or concentrations are known |
| Impedancemetry | non-invasive | cardiac output | Using electrical impedance changes in the thoracic cavity during a cardiac cycle, it calculates the stroke volume. The calculations assume that all other thoracic and hematologic parameters are constant. It is therefore regarded as not sufficiently accurate during pregnancy[17] |
| Isolated Doppler velocity measurements[9,18,19] | non-invasive | cardiac output | Using measurements of blood flow velocities in the ascending aorta by continuous-wave Doppler technique, it gives an indirect result of the cardiac output. However, the technique assumes that the aortic diameter remains constant throughout pregnancy and neglects the blood directed at the coronary arteries |
| M-mode estimation of stroke volume[8,11] | non-invasive | cardiac output | Measuring the left ventricle diameters in telesystole and telediastole in M-mode on a long-axis view, it deduces the telesystolic and telediastolic left ventricular volumes. When subtracting the telesystolic from the telediastolic volume, the stroke volume is deduced |
| Combined Doppler and cross-sectional echocardiographic measurements (Figure 52.3)[10,20,21] | non-invasive | cardiac output | By measuring flow with continuous-wave Doppler technique at a precise point in the heart (e.g. heart valve or the left ventricle outflow tract) and multiplying the integral under the curve by the area where the measurement was performed, the stroke volume and the cardiac output can be calculated. This technique is considered to be the most reliable |

third trimester seems to be a consequence of an increase of both heart rate and stroke volume[11]. It is possible that the decline in stroke volume by the end of pregnancy affects placental perfusion. Such a decline was observed in twin compared with singleton pregnancies (Kamatas N, personal communication, unpublished data). Indeed, a decline in cardiac output may explain the increased rate of perinatal mortality and morbidity of twins compared with singletons from 38 weeks onward[26].

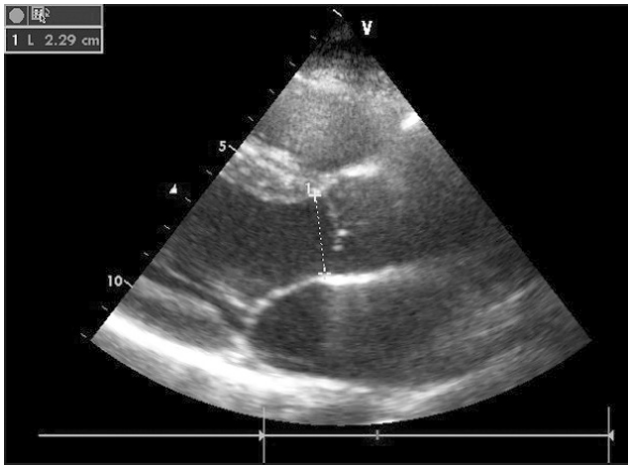
A schematic summary of cardiovascular changes during twin pregnancies is provided in Table 52.7.

## PATHOPHYSIOLOGY AND IMPLICATIONS

### The effect of β-mimetics on the maternal cardiovascular system

Twin pregnancies are characterized by a 6–8-fold higher rate of preterm labor than in singleton

pregnancies (see Chapter 1), and are thus more frequently treated with tocolytics. Of the available agents, $\beta_2$-mimetics have been used for many decades in both singleton and twin pregnancies, and their side-effects have been well studied and reported.



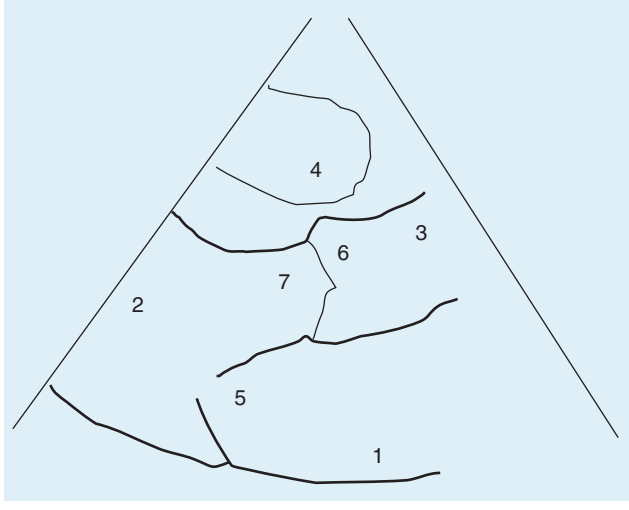




**Figure 52.3** Measurement of the left ventricular outflow tract (LVOT) on a long-axis two-dimensional ultrasound image (top) and its main structures: 1, left atrium; 2, left ventricle; 3, ascending aorta; 4, right ventricle; 5, mitral valve; 6, aortic valve; 7, LVOT

$\beta_2$-Mimetics have a preferential effect on the adrenergic receptors such as those found in uterine smooth muscle. β-Adrenergic stimulation leads to less specific ($\beta_1$ and $\beta_2$) cardiovascular side-effects due to their inotrope and chronotrope positive effects.

The well known and reported main severe side-effects with $\beta_2$-mimetic therapy are tachyarrythmia, myocardial ischemia and pulmonary edema. $\beta_2$-Mimetics are widely considered more dangerous in twin pregnancies because of the earlier and greater increase of both plasma volume and cardiac output[27,28]. In particular, multiple pregnancies are at high risk for pulmonary edema induced by β-mimetics[29–31]. Most present-day authors consider $\beta_2$-mimetics to be contraindicated in twin pregnancies, and suggest that other tocolytic agents should be applied in the case of threatening preterm labor[32,33].

### Corticosteroids

Corticosteroids are used to accelerate pulmonary maturation in the case of threatening preterm labor, thus frequently in twin pregnancies (see Chapter 49), and even in combination with $\beta_2$-mimetics. Corticosteroids increase the cardiovascular effect of β-mimetics, however, because they increase the circulating blood volume owing to their mineralocorticoid activity. Pulmonary edema is a known side-effect in patients receiving both corticosteroids and $\beta_2$-mimetics[34].

## CONCLUSIONS

Understanding the maternal cardiovascular physiology during twin pregnancies helps in understanding the adaptative mechanisms of patients with twin pregnancies. The increasing subjective difficulty of leading a normal, active life, especially during the third trimester, can be explained to a great extent by the modifications of the maternal cardiovascular system, as well as by the weight and volume of the abdomen by the end of pregnancy. Because early cardiovascular adaptation in twin pregnancies

**Table 52.7** Schematic summary of the cardiovascular changes during twin pregnancies. Column heads 1, 2 and 3 indicate trimesters

| | *Plasma volume* | | | *Heart rate* | | | *Mean arterial pressure* | | | *Stroke volume* | | | *Cardiac output* | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *1* | *2* | *3* | *1* | *2* | *3* | *1* | *2* | *3* | *1* | *2* | *3* | *1* | *2* | *3* |
| Twin compared with singleton pregnancies | ? | ↑ | ↑ | = | = or ↑ | = or ↑ | = or ↑ | ↓ or ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ |

with subsequent adverse outcome has not yet been studied, we do not know whether the physiologic adaptation mechanisms described in this chapter are prognostic factors for a favorable outcome. Unfortunately, the studies cited in this chapter derive from small cohorts. Large cohorts of patients with twin pregnancies would be needed to answer this question.

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# Hypertensive Disorders

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**53**



## INTRODUCTION

Hypertensive disorders occur in 12–22% of all pregnancies[1], making them one of the most common medical complications of pregnancy. Of equal and perhaps greater importance, hypertensive disorders are directly responsible for significant maternal and neonatal morbidity, and they have been implicated in approximately 20% of maternal deaths[1,2]. Recently, the definitions for gestational hypertension (elevated blood pressure without proteinuria after 20 weeks and returning to normal postpartum) and pre-eclampsia (gestational hypertension with proteinuria) superseded commonly used terminology such as pregnancy-induced hypertension (PIH), which is not only vague, but also had been used widely[1]. Although the precise pathophysiology for these conditions remains unclear, the common denominator for all patients is the placenta. Nulliparity, chronic hypertension or underlying cardiovascular disease, and extremes of maternal age remain risk factors for developing hypertensive complications. As patients with multiple gestations have increased placental mass and are increasingly likely to be nulliparous and older, it is not surprising that the incidence of gestational hypertension and pre-eclampsia (PEC) among these women is significantly increased, compared with that of women carrying a singleton[3–8].

## INCIDENCE IN TWINS

Few studies specifically record hypertension or PEC in multifetal pregnancies as a primary outcome. Most reports are retrospective, and utilize terminology that is not uniform or clearly defined. As early as the 1930s and 1940s, authors observed rates of 'toxemia' in twins to be 17–28%[6]. One of the earlier formal studies found that the rate of 'toxemia' defined by blood pressure criteria was 31.2% in a cohort of 234 twins[6]. Using more modern definitions of PEC, Long and Oats observed that 25.9% of twins developed PEC compared with 9.3% of a control group of singletons ($p < 0.001$)[7]. Coonrod and colleagues found lower overall incidences of PEC among their large groups of twins and singletons; however, the relative risk of developing PEC for their twin group was 3.5, irrespective of race and parity[4]. Santema and co-workers performed one of the few prospective, case–control studies looking at hypertensive disorders in twin pregnancies, again using strict definitions. Twenty-one per cent of the twins developed a hypertensive disorder, compared with 13% of the singletons ($p < 0.05$)[9]. This was mostly due to an increased rate of pregnancy-induced hypertension (PIH), rather than PEC among the twins. The most recent comprehensive study of hypertensive disorders in twins versus singleton gestations found gestational hypertension in 13% of twins compared with 6% of singletons (odds ratio (OR) adjusted for maternal age, mean arterial pressures, white race and smoking 1.76, 95% confidence interval (CI) 1.32–2.37))[3]. The same study found a 13% incidence of PEC in twins versus 5% in singletons (adjusted OR 2.48, 95% CI 1.82–3.38)[3]. Table 53.1 summarizes the incidence of hypertensive complications in studies of twins, including all patients labeled as having PIH, PEC or gestational hypertension. Although the average incidence is 16.7%, the reported ranges vary from 8.9 to 37%.

**Table 53.1** Summary of the incidence of pregnancy-induced hypertension/pre-eclampsia (PIH/PEC) in twins

| *Study* | *Year* | *Total twins (n)* | *With PIH/PEC (n)* | *Incidence (%)* |
|---|---|---|---|---|
| Bulfin and Lawler[6] | 1957 | 234 | 73 | 31.2 |
| McFarlane and Scott[8] | 1976 | 1045 | 193 | 18.4 |
| Long and Oats[7] | 1987 | 642 | 166 | 25.9 |
| Kovacs *et al.*[5] | 1989 | 939 | 218 | 23.2 |
| McMullan *et al.*[10] | 1989 | 54 | 20 | 37 |
| Spellacy *et al.*[11] | 1990 | 1253 | 162 | 12.9 |
| Seoud *et al.*[12] | 1992 | 115 | 20 | 17 |
| Macones *et al.*[13] | 1993 | 110 | 15 | 14 |
| Santema *et al.*[9] | 1995 | 187 | 36 | 19.2 |
| Coonrod *et al.*[4] | 1995 | 3221 | 298 | 9.25 |
| Groutz *et al.*[14] | 1996 | 70 | 13 | 18.6 |
| Lipitz *et al.*[15] | 1996 | 134 | 12 | 8.9 |
| Smith-Levitin *et al.*[16] | 1996 | 147 | 28 | 19.0 |
| Mastrobattista *et al.*[17] | 1997 | 53 | 12 | 22.6 |
| Fitzsimmons *et al.*[18] | 1998 | 164 | 29 | 17.7 |
| Sibai *et al.*[3] | 2000 | 684 | 182 | 26.6 |
| Maxwell *et al.*[19] | 2001 | 464 | 113 | 24 |
| Total | | 9516 | 1590 | 16.7 |

## INCIDENCE IN TRIPLETS

Women carrying triplets or more have even greater placental mass, and would therefore be expected to have even higher rates of hypertensive complications. In this regard, Seoud and colleagues demonstrated an increasing incidence of PIH with plurality (17% of 115 twins, 38.6% of 13 triplets and 50% of four quads)[12]. A study comparing the risks of multifetal pregnancy found PIH in 39% of triplets compared with 17% of twins[20]. Additionally, Mastrobattista and co-workers' study of 53 triplets matched for age, parity and race found a rate of PEC of 34% in triplets versus 23% in their group of twins, although this was not statistically significant[17]. Most studies comparing rates of hypertension in high-order multiple gestations with rates in twins are reports of multifetal pregnancy reduction (MFPR) that select incidence of hypertensive complications as one of the outcome variables. For example, Porreco and colleagues found PIH in 36% of 11 triplets compared with 7.7% of 13 reduced twins[21]. Macones and associates found PIH–PEC in 2/14 triplets (14.3%) compared with 5/47 reductions (10.9%) – a non-significant difference[13]. Boulot and co-workers also failed to find a higher incidence of PEC in 48 triplets (16.6%) compared with 32 twins resulting from MFPR (18.8%)[22]. Lipitz and co-workers' comparison was not statistically significant (13% in 84 triplets compared with 6.4% in 31 reduced twins)[23]. Sivan and colleagues found PEC in 13.5% of 103 triplet pregnancies compared with 10.6% in a group of 85 patients pregnant with twins after first-trimester multifetal pregnancy reduction ($p = 0.688$)[24]. In all fairness, these disparate results are likely due to small sample sizes and controls that are not matched for other risk factors for PEC. In one study where 38 IVF triplets were carefully matched for age, race and parity with 38 IVF triplets reduced to twins, PEC was found in 44.7% of the triplets compared with 15.8% of the twins ($p = 0.006$)[25]. These authors concluded that successful implantation alone is not associated with PEC in triplets, and that fetal number or placental mass may be a more important factor.

On average, it appears that the incidence of hypertensive disorders in triplets is approximately 24.6% (Table 53.2). Even in studies that look only at outcomes in triplets, there is a wide range in results extending from a low of 8.8% to a high of 67% in studies that vary considerably in size. For example, whereas Holcberg and colleagues found an incidence of PIH of 46% in 31 sets of triplets[26], Lipitz and associates found PIH in only 11.5% of their cohort of 78 patients carrying triplets[28]. Another study found PEC in 33.3% of 57 triplets[30]. Pons and co-workers note that 19% of their 91 triplets received Aldomet® to stabilize blood pressure, but they do not give an overall incidence of PIH or PEC[32]. Using standard definitions, Adams and colleagues found an incidence of PEC of 31.3% in a cohort of 32 mothers pregnant with triplets managed with out-patient bedrest[33]. Interestingly, their group found an incidence of only 8.8% in a historic cohort of 34 triplets managed with routine hospitalization in the third

**Table 53.2** Summary of the incidence of pregnancy-induced hypertension/pre-eclampsia (PIH/PEC) in studies of triplets. Adapted from Smith-Levitin M. Hypertensive disorders during triplet gestations. In Keith LG, Blickstein I, eds. *Triplet Pregnancies and their Consequences*. London: Parthenon Publishing, 2002:228

| *Study* | *Year* | *Total triplets (n)* | *With PIH/PEC (n)* | *Incidence (%)* |
|---|---|---|---|---|
| Holcberg *et al.*[26] | 1982 | 31 | 14 | 46 |
| Newman *et al.*[27] | 1989 | 198 | 28 | 14 |
| Lipitz *et al.*[28] | 1989 | 78 | 9 | 11.5 |
| Porreco *et al.*[21] | 1991 | 11 | 4 | 36 |
| Seoud *et al.*[12] | 1992 | 13 | 5 | 38.5 |
| Boulot *et al.*[22] | 1993 | 48 | 8 | 16.6 |
| Macones *et al.*[13] | 1993 | 14 | 2 | 14.3 |
| Clarke and Roman[29] | 1994 | 19 | 4 | 21 |
| Lipitz *et al.*[23] | 1994 | 84 | 11 | 13 |
| Albrecht *et al.*[30] | 1996 | 57 | 19 | 33.3 |
| Hardardottir *et al.*[31] | 1996 | 21 | 14 | 67 |
| Skupski *et al.*[25] | 1996 | 38 | 17 | 44.7 |
| Smith-Levitin *et al.*[16] | 1996 | 54 | 16 | 30 |
| Mastrobattista *et al.*[17] | 1997 | 53 | 18 | 33.96 |
| Adams *et al.*[33] | 1998 | 32 | 10 | 31.3 (out-patient) |
| | | 34 | 3 | 8.8 (in-patient) |
| Malone *et al.*[34] | 1998 | 55 | 15 | 27 |
| Devine *et al.*[35] | 2001 | 100 | 26 | 26 |
| Francois *et al.*[36] | 2001 | 110 | 24 | 21.8 |
| Sivan *et al.*[24] | 2002 | 103 | 14 | 13.5 |
| Al-Kouatly *et al.*[37] | 2003 | 126 | 53 | 42 |
| Total | | 1279 | 314 | 24.6 |

trimester ($p = 0.02$)[33]. In order to prove that this effect is true, the authors suggest that 64 mothers would need to be randomized to detect a 20% decrease in the incidence of PEC if PEC was the primary outcome in a prospective study of out-patient versus in-patient care[33]. Randomization of such therapy is not a realistic undertaking. A subsequent study retrospectively evaluated maternal and neonatal outcomes in 100 sets of triplets[35]. Twenty-six were complicated by PEC using criteria established by the American College of Obstetricians and Gynecologists (ACOG)[1,35].

Another theory that has been proposed as an etiology for PEC is an immunologic or an immunogenetic event early in pregnancy. Such an immunologic event could result, in part, from maternal recognition and subsequent rejection of the paternal contributions to the fetal syncytiotrophoblast composition. Based on this theory, PEC should be more frequent in dizygotic (DZ) than in monozygotic twins (MZ) due to a greater diversity of the antigens. There are a few studies that have investigated the association between zygosity and the risks of PEC. Campbell and associates showed no significant difference in the frequency of mild PEC (21.7% vs. 28.7%) and severe PEC (15.8% vs. 15.7%) between MZ and DZ twin gestations, respectively[38]. In a retrospective study of antenatal complications in a large series of twins delivered at a single institution over a period of 6 years, Kovac and colleagues compared the rate of PIH in 524 pairs of DZ twins with that in 189 pairs of MZ twins[5]. Although PIH occurred at a higher frequency in DZ twins (26.7% vs. 17.9%), it did not achieve statistical significance, and both groups had a similar incidence of severe PEC[5]. In a more recent study where placental pathology, gender and fetal ABO typing were used to determine zygosity, the incidence of PEC was 15% in MZ versus 20% in DZ twins ($p = 0.3$)[19]. The same study also performed a logistic regression analysis to control for maternal age, gestational age at delivery, assisted reproduction and male sex, and found that DZ twinning was associated with an OR of 1.4 (95% CI 0.5–3.9) for developing PEC in nulliparous women and 1.2 (95% CI 0.3–5.0) in multiparous women[19]. Although this study did not show a significant difference in the rate of PEC in MZ and DZ twin pairs, the number of patients was relatively small, and the power to detect a difference was limited.

It is important to understand that the reported incidence of hypertensive complications in multiple gestations is very likely to be an underestimate

because of the high rate of spontaneous preterm delivery among multiple gestations[3,7–9]. Simply stated, many twins and triplets deliver before hypertension is clinically manifest[3]. McFarlane and Scott found a three-fold increase in the incidence of PEC in a group of 1045 twins (18.4%) compared with a similar group of singletons over a 20-year span ($p < 0.001$)[8]. However, when all patients who delivered prior to 36 weeks' gestation were excluded, there was a four-fold increase in the incidence of PEC among the twins ($p < 0.001$)[8].

## DISEASE SEVERITY

The major maternal morbidity and mortality associated with hypertensive disorders occur in those patients with severe disease, a rare event in otherwise healthy patients carrying a singleton pregnancy[1]. It is also unusual that a singleton mother requires an iatrogenic preterm delivery with resultant neonatal morbidity and mortality for severe maternal hypertensive disease. In patients with a multiple gestation, however, it is not uncommon for PEC to present earlier, much more severely and with many more complications[2,3,7,19]. Early observations noted severe disease defined by blood pressure criteria in nearly half of twins presenting with PEC[6]. Hypertension was severe in 45.2% of twins with PEC compared with 20.9% of singletons with PEC in Long and Oats' study ($p < 0.001$)[7]. Furthermore, 68.7% of the twins presented with symptoms prior to 37 weeks' gestation compared with 24.4% of the singletons[7]. Lynch and colleagues found severe disease in 26% of their cohort of twins presenting with PEC at an average gestational age of 34 weeks[2]. PEC was an indication for induced delivery in 85% of the patients[7], and 75% of the twins presenting with 'PIH' in McMullan's cohort had severe disease[10]. Sibai and colleagues found severe PEC in 6.9% of the twins compared with 1.9% of the singletons, and severe gestational hypertension in 3.5% and 1.1%, respectively[3]. In contrast, Santema and associates found similar rates of severe PEC (4–5%) among twins and singletons matched for maternal age, parity and gestational age at delivery[9].

Triplet pregnancies are characterized by an even higher incidence of severe disease at gestational ages remote from term. Skupski and colleagues found severe PEC, using ACOG criteria[1], in 26.3% of the triplets compared with 7.9% of the matched twins ($p = 0.033$)[25]. In Devine's series of 100 triplets, 73% of the patients with PEC had severe disease at a mean gestational age of 32.8 weeks[35]. In a retrospective, but case–control study of 53 sets of triplets, severe PEC was found in 22.6% vs. 5.7% in a matched group of twins (OR 4.9, 95% CI 1.2–23.5)[17]. In another study evaluating causes of thrombocytopenia in triplet gestations, 42% of the 126 patients developed a hypertensive disorder, and 63% of these patients had severe disease[37].

## LIFE-THREATENING COMPLICATIONS

Life-threatening complications from hypertensive disorders in pregnancy are more common in women carrying multiple gestations. Eclampsia, the syndrome of hemolysis, elevated liver enzymes and low platelets (HELLP) and acute fatty liver of pregnancy (AFLP) occur more often among twins and triplets[3,7,12,30,39]. According to Blickstein, the risk of eclampsia in multiple pregnancies is 3–6 times higher than the risk of eclampsia in a singleton gestation[40]. In Long's study, 3.6% of the twin pregnancies with PEC seized compared with 0.7% of the singletons ($p < 0.01$)[7]. The same study reported a maternal death in a patient with twins who had two prior singleton pregnancies that were not complicated by hypertension. She presented with mild PEC at 36+ weeks' gestation but developed severe disease several days later. She seized *en route* to the delivery room, and died several days later from massive cerebral hemorrhage. Coonrod and colleagues reported eclampsia in 0.16% of their twin group and 0.04% of their singleton group[4]. Sibai and associates did not report the incidence of eclampsia separately, but found 'eclampsia or HELLP' in 1% of twins compared with 0.4% of singletons (crude OR 2.33, 95% CI 0.93–5.87)[3]. In contrast, other studies report no patients with eclampsia[6,9] and similar rates of HELLP syndrome among twins and singletons[6]. The scarce data available on the incidence of HELLP and eclampsia among twin pregnancies should not negate the impact of these devastating complications. Anecdotally, anyone who cares for large numbers of patients with multiple gestation is well aware of the frequency at which these complications occur.

There are few specific data on the incidence of eclampsia in triplets. The reported incidence of HELLP syndrome, however, is more striking among triplets and higher-order multiple gestations. Seoud and colleagues found HELLP syndrome in 7.7% of the triplets compared with 2.1% of the twins, although this was not statistically significant[12]. Albrecht and Tomich reported HELLP in 10.5% of the triplets[30]. In Devine's series, 9% had HELLP and 1% had eclampsia[35]. Boulot and co-workers do not provide the overall incidence of HELLP in their series of 48 triplets, but they reported one case of liver rupture, a rare complication, in a patient with severe PEC and HELLP at 34 weeks[22]. The criteria used to make a diagnosis of HELLP syndrome are not clearly defined in these studies. Some series that may have

used stricter criteria report a much lower incidence (1.6%) of HELLP syndrome in their triplet cohorts[37], or even none[25,33].

Thrombocytopenia occurs in approximately 6.6–11.6% of all pregnancies[37]. Although low platelets are a major feature of HELLP syndrome, gestational thrombocytopenia is the most common etiology for isolated thrombocytopenia in singleton gestations[37]. This is not true, however, in triplets. In a study of 126 sets of triplets in which 46 patients had some degree of thrombocytopenia (36.5%), 52% of the patients with low platelets had severe PEC and 4.3% had HELLP syndrome, using strict definitions[37]; 15.1% had counts of less than 100 000[37]. Therefore, an incidental finding of a low platelet count in a patient carrying more than one fetus warrants further investigation and close surveillance for signs of PEC.

Acute fatty liver of pregnancy (AFLP) occurs in only 1/13 000 deliveries or in 0.008% of pregnancies[39]. It is likely a variant of PEC and HELLP syndrome, as almost 50% of patients with it also show evidence of PEC, eclampsia or HELLP. Traditionally, it was associated with high maternal and fetal mortality (85%), but with prompt diagnosis, delivery and supportive care, mortality rates are currently less than 20%[39]. Although few of the studies reporting outcomes in twins mention AFLP, the entity is most often reported in women carrying more than one fetus. Many cases are likely labeled as HELLP syndrome or are not reported. In triplets, however, several series report a significant incidence of AFLP. The incidence varies from 1.8%[30] to 4%[35]. Most of the patients in these reports were diagnosed on the basis of a liver biopsy that showed classic pathology.

## CLINICAL PRESENTATIONS

The clinical presentation of PEC and its variants is often atypical in patients with twins and high-order multiple gestations. In the series reported by Lynch and co-workers, six of the 86 multiple gestations with PEC had gestational hypertension, no proteinuria and abnormal laboratory values or maternal symptoms[2]. Two had edema, proteinuria and abnormal liver function tests but normal blood pressure[2]. Some 3.8% of the triplets with a hypertensive disorder in Al-Kouatly's cohort were labeled as having 'atypical PEC'[37]. In another study, only half of the triplets with PEC had increased blood pressure prior to delivery, only three had proteinuria and only six had edema[31]. Of the eight patients with normal blood pressure, six were delivered for persistent clinical symptoms with deteriorating laboratory values and five developed HELLP syndrome after delivery[31]. In this study, it is possible that the routine hospitalization with bedrest at 20 weeks for all of the triplet pregnancies may have minimized blood pressure elevation and proteinuria[31]. The finding of a significantly lower rate of PEC among triplets managed with hospitalized bed-rest (8.8%) compared with out-patient bed-rest (31.3%) may support this concept[33].

## MANAGEMENT

Management of gestational hypertension, PEC and their complications in multiple gestations is particularly challenging. The necessity for iatrogenic preterm delivery arises more often with multiple gestations owing to the earlier onset of the disease; however, the implications are greater for multiple fetuses who are smaller for gestational age than singletons (see Chapter 60). Furthermore, the impact on parents having two or more preterm babies in a neonatal intensive-care unit is greater than having only one sick baby (see Chapter 95). Although there is a role for expectant management when patients present early in the third trimester in an attempt to achieve greater fetal maturity, the risk of life-threatening complications is higher in a mother of multiple fetuses than in a mother carrying only one fetus. In our opinion, there is no role for expectant management of PEC in a multiple gestation after 34 weeks.

In general, management protocols are similar to protocols for managing singletons with hypertensive disorders[1]. Magnesium sulfate can be used safely for seizure prophylaxis. Extra attention must be paid to fluid management, however, as patients with PEC and a multiple gestation are inherently more likely to develop pulmonary edema due to the decreased baseline colloid oncotic pressure, the increased baseline cardiovascular demands (see Chapter 52) and the increased incidence of severe disease in multiple gestations.

Most patients who present at less than 34 weeks can be safely observed for 48 hours to allow time for steroids to have their maximal effect on the fetuses. In each instance, however, the maternal status must be watched closely, with serial blood pressure monitoring, serial laboratory assessment and serial assessment of symptoms and physical examination findings. The status of the fetuses must be initially assessed with a complete sonographic evaluation of fetal growth, amniotic fluid, umbilical artery velocimetry and biophysical profiles. The fetal condition should then be evaluated with serial non-stress tests and biophysical profiles. The frequency of testing must be individually determined based on the initial assessment and the severity of the maternal disease.

According to Heller and Elliot, there may be a role for expectant management of HELLP syndrome in multiple gestations to avoid the devastating consequences of a significantly preterm delivery[41]. Others have advocated using high-dose steroids (dexamethasone 10 mg intravenously every 12 h) to treat HELLP in singletons[42], and a case series in which such a protocol was used in high-order multiple pregnancies complicated by HELLP has been published[41]. Two patients with triplets and two with quadruplets were able to gain significant time *in utero* with the protocol. One set of triplets presented at 28 weeks with mild PEC. One week later, she met criteria for HELLP and she was given a bolus of intravenous dexamethsone (4 mg) followed by decreasing doses over 5 days (2 mg every 4 h × 5, then 2 mg every 6 h × 48 h, then 2 mg every 8 h × 48 h) and then a maintenance dose (2 mg every 12 h). She improved until 32 weeks, when her platelets decreased again. She was bolused again with the dexamethasone (5 mg) and delivered at 33 weeks. The other set of triplets presented at 26+ weeks with low platelets (87 000) only. She was given the same protocol. One week later, she was noted to have increased transaminases, and she was bolused again. At 30 weeks, she was given another bolus due to dropping platelets and decreased urine output. Approximately 2 weeks later, she developed pulmonary edema and was delivered. One patient with quadruplets developed HELLP syndrome at 30 weeks. After receiving the dexamethasone protocol, she stabilized and was delivered at 34 weeks. The other set of quadruplets presented at 31 weeks with mild HELLP. Her laboratory values normalized after the steroids, but she developed pulmonary edema and central nervous system symptoms 1 week later and was delivered. All four patients and all 14 fetuses reportedly did well[41].

All patients pregnant with a multiple gestation should be counseled early in their pregnancies about the risks of hypertensive complications and the potential maternal and neonatal morbidities. Signs and symptoms should be reviewed with the patient and family. We recommend baseline uric acid, transaminases, serum creatinine and complete blood count with platelets early in pregnancy because of the high risk of HELLP syndrome and atypical presentations of PEC later in pregnancy. At a minimum, these laboratory tests should be repeated with the third-trimester blood work at 26–28 weeks. Patients with a multiple gestation should be evaluated by maternal weight, urine dipstick, blood pressure and assessment of edema at least every 2 weeks throughout the second trimester and early third trimester. After 32 weeks, evaluations should be weekly. The clinician must maintain a low threshold for obtaining repeat laboratory results or for hospitalizing the patient for closer observation. In order to avoid serious maternal and neonatal morbidity, the physician must assume that a patient with borderline blood pressures or a low platelet count and a multiple gestation truly has a potentially serious hypertensive complication.

## SUMMARY

In summary, women with multiple gestations are at increased risk of developing hypertensive disorders during pregnancy. The overall incidence and severity of hypertensive complications increases with increasing number of fetuses. The risk of hypertensive disorders remains greater for women who continue their pregnancies as a high-order multiple, compared with those who have a spontaneous or a multifetal pregnancy reduction to twins. Although there are various possible explanations for the increased rate of hypertensive complications among women with multiple gestations, further research is required to study and define the causes in spontaneous versus artificially conceived pregnancies. The clinical presentation of PEC and its variants is usually earlier in onset, more severe and often atypical in patients with twins and higher-order multiples. Management of multiple pregnancies with hypertensive disorders is challenging owing to increased risks of maternal complications and neonatal morbidities arising primarily from iatrogenic preterm delivery. All patients with multiple gestations should be counseled about these risks, monitored closely during the pregnancy and managed extremely carefully to prevent life-threatening complications of hypertensive disorders of pregnancy.

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# Diabetes

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**54**



## INTRODUCTION

Increased placental mass, or so-called hyperplacentosis, excessive maternal weight or weight gain and advanced maternal age are all commonly associated with gestational diabetes[1–3]. Coincidentally, all of these same pro-diabetic factors are increased during a typical multiple pregnancy. Hence, it could be anticipated that increased rates of gestational diabetes mellitus (GDM) are seen during multiple gestations. The fact is, however, that the association between GDM and multiple pregnancies is not so clear.

The importance of this putative association is accentuated by major and recent changes in the epidemiology of multiple gestations. First, the numbers of multiple gestations have reached epidemic dimensions in most developed countries[2,4], and second, more multiple pregnancies result from infertility treatment. As one example, recent data from the East Flanders Prospective Twin Survey suggest dramatic changes in the ratio of induced/spontaneous twins, from 1 : 46 in the 1970s to 1 : 2 in the late 1990s[3]. Because women who require infertility treatment are more likely to be older, the current, almost universal, trend of aging of the maternal cohort has special implications for triplet mothers (see Chapter 93)[3]. Despite significant recent changes in the typical mother of multiples, namely increased age and decreased rate of spontaneous conceptions, for which there is much documentation, scant information exists about the potential association between GDM and the epidemic of iatrogenic multiple pregnancies.

What is known about GDM is that it is one of the most common complications of human pregnancy, bearing a direct relationship to other complications such as preterm delivery, fetal macrosomia, birth trauma, unexplained antepartum fetal demise, pregnancy-induced hypertension and placental abruption. This chapter discusses the available evidence (some of which is 20 years old) related to GDM and multiple pregnancies as well as the potential impact of this disease in the era of epidemic numbers of iatrogenic multiples[1–3,5].

## EVIDENCE THAT SUPPORTS HIGHER RATE OF GESTATIONAL DIABETES MELLITUS IN MULTIPLES

In the past, hyperplacentosis in multiple pregnancies was presumed to increase hormone levels, which in turn created a pro-diabetic condition and an increased susceptibility to GDM. As early as 1978, Spellacy and colleagues[6] compared levels of the pro-diabetic hormone human placental lactogen (hPL) in singleton and twin pregnancies. These authors determined serum levels by radioimmunoassay in 75 singleton and 37 twin pregnancies and observed a significantly increased hPL level at 30 weeks (7.0 vs. 6.0 μg/ml) as well as at 36 weeks (9.2 vs. 7.4 μg/ml) in twins compared with singletons. Although the statistical significance of the difference is arguable by today's evidence-based standards, Spellacy and colleagues[6] concluded that the data support the hypothesis that twin pregnancies are associated with increased levels of the principal diabetogenic hormone.

Further support to the view that GDM is related to multiple pregnancies comes from an analysis of carbohydrate metabolism by the same authors[7]. In this

small case–control study, 24 twin pregnancies were compared with 24 singleton pregnancies matched for age, parity, weight and gestational age. A 25-g glucose tolerance test was performed in the second half of gestation, and blood glucose, hPL and plasma insulin levels were obtained. hPL levels were significantly higher, and the fasting as well as the 5- and 15-min insulin levels were significantly lower, in women with twins. The effect of the pro-diabetogenic hormone hPL on carbohydrate metabolism in twin pregnancies is not the only one. For example, the increase in hPL level may also be indirectly appreciated by the augmentation of erythropoietin action, as measured by the age distribution shift of erythrocytes in women with twin gestations[8].

More recently, it has been understood that the physiological reaction to eating and fasting may be different in twin gestations. Casele and her co-workers[9] conducted a 40-h metabolic study in non-diabetic gestations, and compared the metabolic response to eating a normal meal as well as the predisposition to starvation ketosis in ten twin and ten singleton pregnancies matched for age and pre-pregnancy weight. The values of glucose, the ketosis metabolite β-hydroxybutyrate and insulin excretion, in response to eating a meal, from 08.00 to 12.00 on day 1 were similar in twin and singleton pregnancies[9]. On day 2, when breakfast was delayed, a progressive but not significantly different decrease in glucose was observed in both twins and singletons. In contrast, a significantly greater ($p < 0.05$) progressive increase in β-hydroxybutyrate was observed in twins compared with singletons. These observations point to the propensity of twin gestations to undergo accelerated starvation of late pregnancy[9].

If hyperplacentosis is indeed the link between multiple gestation and GDM, one might expect that the frequency of GDM would correlate with the number of fetuses in a dose-dependent relationship. Marconi and her co-workers evaluated glucose clearance in 11 singletons, five twins and one triplet set[10]. Maternal fasting glucose concentration and the total fetal and placental weight significantly correlated with an increase in maternal glucose disposal rate, but glucose concentration and total pregnancy weight were interdependent variables[10].

The totality of the studies discussed above[6–10] supports the conclusion that the difference between multiples and singletons in terms of GDM may result from plurality-dependent larger metabolic demands of the multiple gestation. Accordingly, the association between GDM and plurality was examined by Sivan and colleagues[11] in terms of the effect of multifetal pregnancy reduction (MFPR) on the incidence of GDM. Their series of 188 consecutive triplet pregnancies born during the period 1994–98 included 103 pregnancies which continued as triplets, and 85 gestations that underwent MFPR to twins. If GDM and plurality indeed were independent events, the frequency of GDM would be similar in both groups. However, GDM was significantly higher in the triplet group than in the (reduced) twin group (22.3% vs. 5.8%, $p < 0.05$), a finding that rejects the null hypothesis and supports the conclusion that plurality influences the frequency of GDM. Critical reading of this study, however, shows that the authors did not control for two risk factors that were higher among the triplet pregnancies and could partially explain these results: family history of diabetes (44% vs. 25%, respectively) and body mass index at the end of gestation ($30.3 \pm 5$ vs. $27.6 \pm 3.95$ kg/m$^2$). Skupski and associates[12] used the same methodology to compare the risk for pre-eclampsia in triplet and in twin gestations (reduced from triplets). These authors found, as with GDM, that the triplet group had a significantly higher rate of severe pre-eclampsia than the twin group (26.3% vs. 7.9%). At the same time, other maternal complications of pregnancy were not different[12]. In these two studies, both cases and controls started as triplets and MFPR was performed during the early second trimester[11,12]. This methodological construct excludes an early effect of the trophoblastic mass and may indirectly point to a later effect, whereby fetal number, placental mass or factors unrelated to the success of implantation are more important to the development of pre-eclampsia and GDM than is successful implantation alone. Geva and colleagues[13] evaluated pregnancy outcomes of selective MFPR performed in the second ($19.7 \pm 3.3$ weeks, $n = 38$) versus the first ($11.7 \pm 0.7$ weeks, $n = 70$) trimester. No significant differences were found between the groups, but the rate of GDM was lower among second-trimester MFPR cases (0% vs. 6%).

Finally, Newman and Luke[14] complied data from 42 separate reports on the frequency of GDM in multiple pregnancies. This analysis clearly shows a plurality-dependent trend in the incidence of GDM (Figure 54.1). Admittedly, this compilation of data is derived from diverse populations and different time periods. As such, it may not represent the definite frequency of GDM according to plurality, but it unquestionably shows a clear trend.

## EVIDENCE SUPPORTING THE SAME RATE OF GESTATIONAL DIABETES MELLITUS IN MULTIPLES AS IN SINGLETONS

As implied by the heading of this section, not every published study supports a higher rate of GDM in multiple pregnancies. Naicker and colleagues[15] in 1983 performed an oral glucose tolerance test in 26 women carrying twins and in women carrying

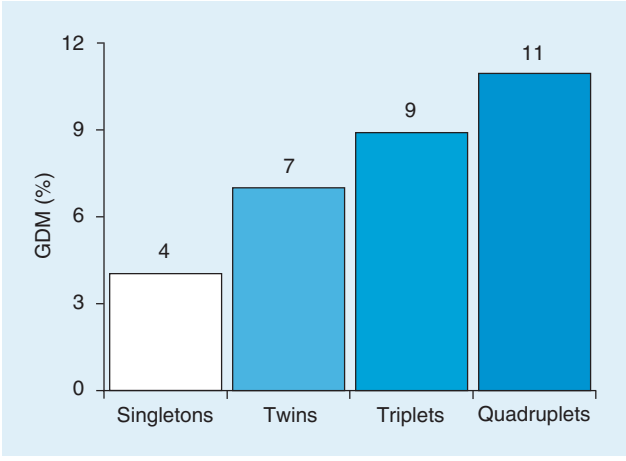


**Figure 54.1** Incidence (%) of gestational diabetes mellitus (GDM) according to plurality. Adapted from reference 14

singletons matched for age, parity and gestational age. Venous blood glucose levels and insulin responses were not significantly different between the two groups. This group of researchers subsequently reported 21 twin and 21 singleton pregnancies matched for age, weight, parity and gestational age[16]. All 42 patients received a 100-g glucose tolerance test. The only difference was lower plasma insulin levels at 60 min in the twin group. Again, no significant differences in venous plasma glucose levels and insulin responses were found between singleton and twin pregnancies. It was not stated, however, whether the patients in the two studies[15,16] were the same.

Naidoo and associates[17] in 1985 compared 20 twin and 20 singleton pregnancies matched for age, weight, parity and gestational age. Intravenous glucose tolerance tests (0.5 g/kg body weight) were performed in all women in the third trimester. No significant differences in mean venous insulin levels or glucose responses were found between singleton and twin pregnancies.

One of the most extensive studies, also performed in the 1980s, came from Spellacy and his colleagues, who assessed the risk of GDM by counting the frequency in a cohort of 101 506 pregnancies, including 1253 twins[18]. The twin group was compared with a 5% random sample of singletons ($n = 5119$). The data indicate that women in the twins group were slightly older, of higher parity, gained more weight during gestation and had a higher body weight at delivery. However, twin pregnancies were not at increased risk for GDM in this analysis.

More recently, Henderson and colleagues[19] used the 50-g, 1-h oral glucose challenge test to screen 9185 pregnancies, including 138 (1.5%) twin gestations. GDM was diagnosed when an abnormal screen was followed by two or more abnormal values on a 3-h, 100-g glucose tolerance test (National Diabetes Data Group criteria). The incidence of GDM was similar for singleton and twin gestations: 5.8% and 5.4%, respectively.

Blickstein and Weissman[20] in 1990 evaluated 56 twin pregnancies representing the tenth decile of the mean twin birth-weight distribution to investigate whether 'macrosomic' twins face the same increased perinatal risk as do macrosomic singletons. In both study and control groups, GDM was infrequent, and could not explain the increased birth weight among twins.

Even more recently, Mikola and co-workers[21] evaluated 99 pregnancies in women with polycystic ovarian syndrome (PCOS), compared with an unselected control population. The rate of twins was 9.9% vs. 1.1% ($p < 0.05$) in the PCOS group and the controls, respectively. GDM developed in 20% of the PCOS patients versus 8.9% of controls, and the average body mass index in PCOS patients was somewhat greater than in controls (25.6 vs. 23 kg/m$^2$). Intuitively, this study may suggest an association between PCOS-related insulin resistance, hyperinsulinemia and higher rates of GDM in twin gestations. At the same time, however, it is entirely possible that PCOS patients need ovulation induction more often, and hence their propensity to have twins. It follows that the higher rate of GDM is related to the PCOS itself and not to the multiple pregnancies.

## GESTATIONAL DIABETES MELLITUS IN MULTIPLE PREGNANCY

The question of whether twin pregnancies with GDM should be managed differently was evaluated by Schwartz and colleagues[22], who compared a number of variables including frequency, maternal age, weight, 1-h screen, glucose tolerance test results, post-treatment blood glucose values, insulin requirements and insulin dose in twin and singleton pregnancies associated with GDM and carbohydrate intolerance. These authors found that insulin requirements were not different in GDM in twins versus singleton gestations. This observation suggests a mild disturbance of carbohydrate tolerance in twins, which may be effectively managed by strategies similar to those used to control blood glucose abnormalities in singletons.

Ihara and associates[23] compared the effect of gestation on carbohydrate metabolism using a 75-g oral glucose tolerance test performed in 63 twin and 3791 singleton gestations during the third trimester. Plasma glucose concentrations were measured at fasting and at 30 min, 1 h and 2 h after a 75-g glucose oral load. Insulin concentration was measured at

fasting and at 30 min after the glucose oral load. Women with twin gestations had significantly lower plasma glucose concentrations at fasting and at 30 min after the glucose load, but no significant differences in plasma glucose levels at the other times. This observation suggests a lower tolerance to fasting but the same glucose tolerance and insulin levels in twin compared with singleton pregnancies.

Scant data exist concerning the effect of GDM on perinatal outcome in multiple pregnancies. Tchobroutsky and colleagues[24] reported a high frequency of fetal malformations in type I diabetic women with twin pregnancies; however, the small number of cases precluded the authors from reaching a final conclusion. Keller and associates[25] compared 13 twin pregnancies complicated by GDM with normal twin pregnancies matched for gestational age. There was a trend for greater likelihood of respiratory distress syndrome, hyperbilirubinemia and prolonged neonatal intensive-care nursery admission in the diabetic group. More recently, Zaw and Stone[26] reported a monozygotic (MZ) twin pregnancy delivered to a mother with pre-gestational insulin-dependent diabetes mellitus. Hemoglobin $A_{1c}$ was 8.2% during early pregnancy. One of the MZ (DNA proven) twins had caudal regression syndrome (Figure 54.2), a rare fetal complication that is 200 times more frequent among mothers with insulin-dependent diabetes, and often associated with long-term neurological, urological and orthopedic complications. Although the exact teratogenic mechanism is unknown, hyperglycemia is believed to play a crucial role in the genesis of this condition, and is one of the reasons that stringent control of diabetes is generally recommended. The importance of this unusual case, in which only one of the MZ twins was affected, casts some doubt on the generally accepted proposed teratogenic mechanism of diabetic embryopathy, and suggests that as yet unidentified factors other than hyperglycemia are included in its causation[26].

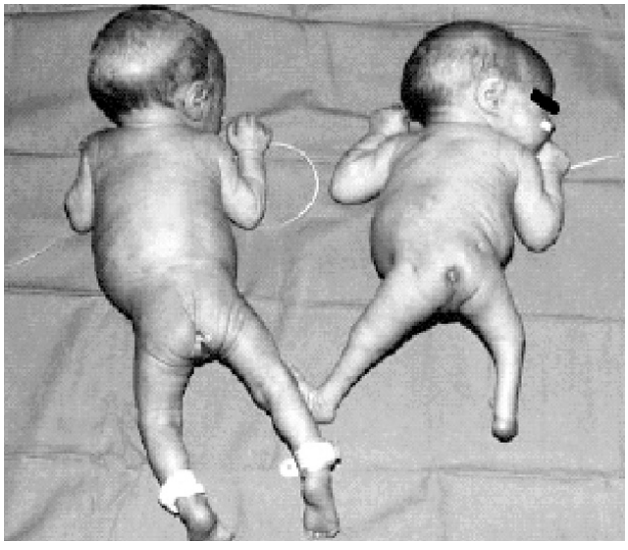

**Figure 54.2** Monozygotic twins born to a diabetic mother[26]. The baby on the right has caudal regression syndrome including muscle wasting below two knees (hypoplastic lower limbs), fusion of L2 and L3 vertebrae and absence of vertebrae below that level. Image courtesy of Win Zaw, Department of Child Health, University of Aberdeen, Scotland

## SUMMARY

The evidence presented in this chapter, despite the inherent logical expectations, does not support a clear-cut association between GDM and multiple pregnancy (Table 54.1). However, several reservations exist concerning the available data. First, many of the cited studies published long ago may reflect

**Table 54.1** Clinical data related to gestational diabetes mellitus (GDM) and multiple pregnancies[5]

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|---|
| *Evidence supporting higher GDM rate in multiples* |
| Hyperplacentosis and higher hPL levels |
| Exaggerated response to fasting and food |
| Higher age |
| Higher BMI and weight gain in twin gestations |
| Plurality-dependent frequency of GDM |
| *Non-supporting evidence concerning GDM and multiple pregnancies* |
| Similar prevalence of GDM in twin and singleton pregnancies |
| No difference in glucose challenge and tolerance tests between twins and singleton pregnancies |
| Management of twin gestations complicated by GDM is similar to that of singleton pregnancies |
| Similar insulin requirements in twin and singleton pregnancies complicated by GDM |
| Higher rate of PCOS in multiple pregnancies |

hPL, human placental lactogen; BMI, body mass index; PCOS, polycystic ovarian syndrome

different methods of ascertainment as well as assessment and clearly do not include the input of maternities resulting from the current epidemic of iatrogenic multiple pregnancies. Moreover, the remarkable difference between the ages of newly pregnant mothers before and after the epidemic of multiple pregnancies which began in the 1990s[1,2] casts serious doubt on whether the prevalence of GDM cited in older papers is still valid today. Second, most, if not all, information available in these studies derives from hospital-based data sets and lacks any population-based perspective. This means that the data available on maternal adaptation to carbohydrate metabolism during a multiple pregnancy are flawed because of small sample size and lack of sufficient statistical power. Third, time-lead bias, which overlooks changes in diagnosis, assessment and management over time, has not been considered. For example, it would be interesting to know how the rate of PCOS in multiple pregnancies influences the rates of insulin resistance and GDM, and how recommendations to prevent excessive weight gain during early stages of a multiple pregnancy[14] influence carbohydrate metabolism.

As a final point, there is a striking shortage of evidence related to high-order multiples, especially triplet pregnancies. If indeed, as Newman and Luke[14] suggest, GDM is plurality-dependent, post-epidemic population-based data will enforce this point.

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# Pregnancy Management: Assessment of Cervical Status

*B. Arabin, J. Nizard and J. van Eyck*

**55**



## INTRODUCTION

Lifestyle changes of women in developed countries during the second half of the 20th century mean that the age at which childbirth is desired has increased. Involuntary infertility and naturally reduced fecundity of advanced age have required new treatments[1]. As a result of higher maternal age and the use of poorly monitored ovulation induction and assisted reproductive technologies (ART), the incidence of twin and multiple births increased in the United States from 1971 to 1997 by epidemic proportions, with the immediate consequence of an increase in the numbers of infants born at < 33 weeks (1.7% of singletons, 13.9% of twins and 41.2% of triplets)[2]. Likewise, twin births have increased in most developed countries since the late 1970s[3]. Several studies indicate that twin infants originating after *in vitro* fertilization (IVF) have an even greater tendency to prematurity than naturally conceived twins[4].

The high rate of perinatal mortality and morbidity associated with twin pregnancy is mainly due to prematurity[5] (see Chapter 1). The numerous strategies suggested until now have failed to prevent spontaneous preterm birth (SPB). Despite this, infant mortality rate has fallen by nearly half over the past 15 years[6]. In contrast, the reduction in morbidity related to premature birth has been decidedly less pronounced, and preterm births remain responsible for 70% of neonatal deaths and 50% of neonatal neurological disabilities, including cerebral palsy[7].

This chapter reviews the recent literature and our own data regarding cervical assessment to improve early diagnosis of SPB at a stage when it might have an impact on preventive or therapeutic strategies.

## PATHOPHYSIOLOGY

The cervical structure and its mechanical properties depend on regulation of the connective tissue and its extracellular matrix. Physiological and preterm cervical ripening is characterized by high collagen solubility and collagenolytic activity, a decrease of total collagen content and an influx of inflammatory cells with increasing levels of cytokines and prostaglandins[8]. Premature cervical ripening may be the result of a congenital disposition of the connective tissue, prenatal exposure to diethylstilbestrol, traumatic damage to the structural integrity, uterine overdistension, vascular lesions in the placenta inducing membrane destabilization and, finally, local or ascending intrauterine infections. This last condition is now thought to lead to the activation of all components of the preterm labor syndrome, whereby functional loss of cervical integrity, inaccurately termed cervical incompetence, is the common terminal pathway[9]. Cervical shortening and opening of the internal os as pregnancy progresses may facilitate the ascension of micro-organisms, injuries to the decidua–chorioamnion interface and, finally, membrane activation and amnionitis. In one study of singleton, twin and triplet gestations, ultrasonographic findings of the cervix were compared with placental lesions. A greater frequency of acute inflammatory lesions was present in patients in whom cervical shortening developed during the second trimester[10]. Further, causal links with well-defined molecular pathways have been established between infection and preterm parturition. In singleton pregnancies with SPB, a positive microbial culture retrieved by amniocentesis was observed in 21.6% of cases[11]. If cervical dilatation of > 2 cm was present

between 14 and 24 weeks, 51% of patients had an amniotic fluid culture positive for micro-organisms[12]. In contrast, microbial invasion of the amniotic cavity occurred in only 11.9% of twin gestations presenting with SPB[13].

Accordingly, intra-amniotic infection does not seem to be responsible for the excessive rate of SPB observed in twin pregnancies. However, uterine overdistension, and the fact that the cervix is aligned centrally with higher pressure above it and no support below it except the non-resistant vagina, may be one of the leading pathogenic factors for preterm labor in twin gestations.

## HOW AND WHEN TO ASSESS THE CERVIX

Early diagnosis of twin pregnancy and the membrane status by ultrasound screening is mandatory, not only for appropriate planning of antenatal visits but also to provide information to the parents about potential outcomes. Twin pregnancies represent a risk for preterm parturition *per se*. This risk is even higher in monochorionic (MC) compared with dichorionic (DC) gestations, and in symptomatic compared with asymptomatic twin pregnancies. To date, no evidence-based guidelines have been published on how and when to assess the risk of SPB by means of cervical examination.

In one often quoted study, digital examination was performed in 86 twin gestations at weekly intervals, and a score was determined by subtracting the clinical cervical dilatation from the estimated cervical length. Intervals to delivery decreased significantly with lower scores, e.g. a short and/or dilated cervix[14]. Regardless, correct clinical experience suggests that cervical shortening and dilatation of the internal os can be better diagnosed by sonographic cervical examination. Moreover, images from successive examinations and taken by different examiners can be compared to document the progression of change. Also, three-dimensional multiplanar sonography of the cervix can improve our understanding of cervical morphology[15]. Currently, the two-dimensional transvaginal approach with probes of 5–8.5 MHz is regarded as the most feasible imaging modality for routine detection or exclusion of patients at risk for SPB based on cervical change, because it provides better resolution than that of the translabial or transabdominal route.

### Technique of transvaginal sonography

Before cervical examination, the woman empties her bladder. Recognition of the lowermost edge of the maternal urinary bladder is useful to detect the upper limit of the uterine cervix[16]. When the examiner introduces the probe into the anterior vaginal fornix, the sonographic image is checked in a sagittal view until the endocervical canal is visualized, after which the examiner retracts the probe to avoid compression of the cervix. The length of the closed portion of the endocervical canal should be visualized in a manner whereby the anterior and posterior cervix appear to be equally thick.

The distance between the internal and the external os is not always a straight line, and in around 50% of cases it is visualized as a curve[17]. The ratio of curved/straight cervix decreases with decreasing length, and therefore the disparity of a curved or a straight cervix does not have essential clinical implications. After serial measurements, the shortest result should be considered.

Cervical length (CL), width and form of the external or internal os, position of the cervix in relation to a horizontal line and, to some extent, thickness of the endocervical mucus can all be determined from ultrasound images. In patients with opening of the internal os, the shape of the dilatation (Y- or U-shaped), the width, the length and even the area of the internal opening can be described (Figure 55.1).

Most examiners perform their examinations with the woman in a supine position. Postural challenge has been advocated by only a few groups[18,19] in singleton pregnancies. In a pilot study of twin pregnancies, however, our group demonstrated that the closed endocervical length may shorten when the mother assumes the upright position, owing to increasing opening of the internal os as an indirect response to pressure from the uterine contents (Figure 55.1)[20]. Later, we characterized these changes as a risk factor for the occurrence of SPB[21]. More recently, the effect of maternal position on CL measurement was evaluated by a second research group among uncomplicated twin pregnancies[22]. In agreement with our results, these investigators found that the shorter is the cervix in the recumbent position, the greater is the difference in CL between the recumbent and upright positions.

To detect early signs of functional (as opposed to anatomic) cervical incompetence, we currently conduct nearly every examination in both the supine and the upright position, presuming, of course, that the membranes are intact. At the appropriate time, the patient places one foot on a footstool and guides the transvaginal transducer into the lower part of the vagina until it can be directed by the examiner (Figure 55.2). In patients with pre-existing cervical dilatation, not only may the width of the internal os increase in the upright position (Figure 55.1), but the membranes may even progressively dissociate, inducing additional risks for membrane activation

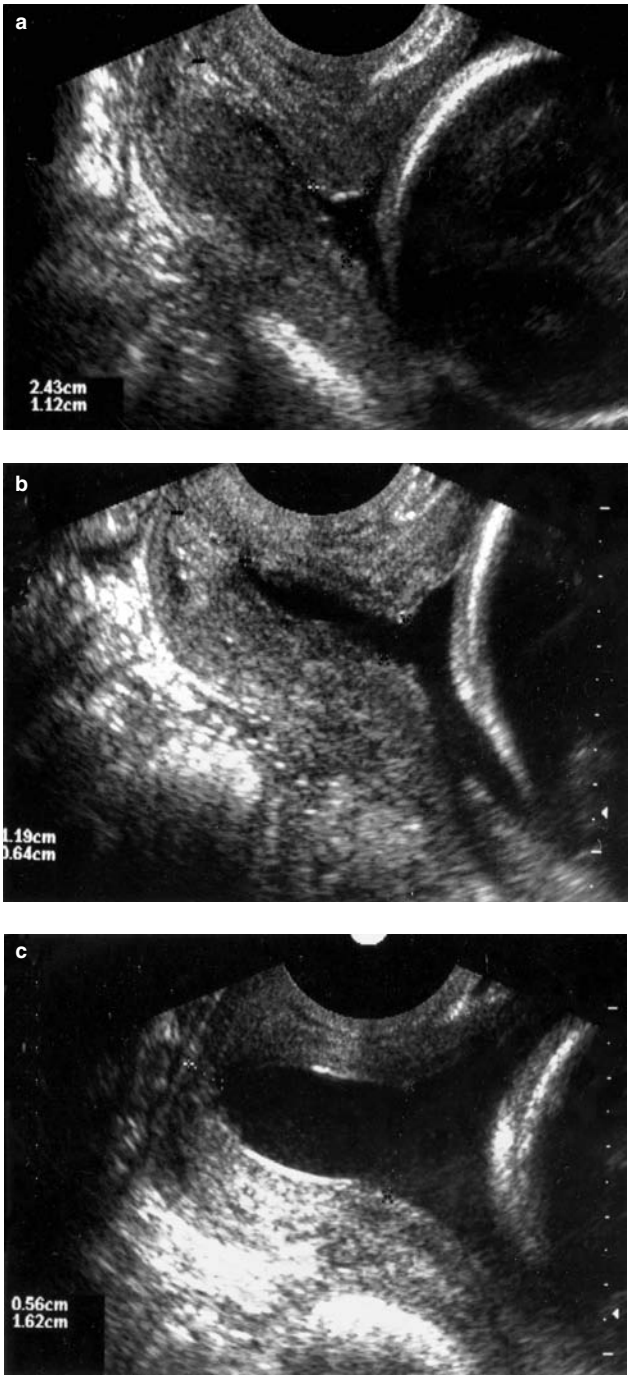


**Figure 55.1** Transvaginal sonogram of a cervix of a twin gestation (25 weeks) (a) in the supine position and (b) after 1 min and (c) after 2 min in an upright position, demonstrating increasing opening of the internal os and shortening of the functional endocervical length

and preterm premature rupture of the membranes (PROM). These examinations clarify the risk of postural stress for the patient, and may be particularly useful if maternal lifestyle changes are deemed appropriate. Conversely, insignificant changes may motivate the patient to lead a normal life or the physician to avoid unnecessary interventions.

## Timing of cervical assessment

In early pregnancy, the space between the cervix and the uterine cavity (the so-called 'virtual internal os') can be identified by high-resolution sonography, visualizing the cervical glands as a hypoechogenic area[23]. If this visualization is impaired, the location of the 'virtual' internal os can be determined using the urinary bladder as a reference point, as it is situated approximately 1.6 cm inwards from the vesicocervical fold[16]. The entire CL can be assessed as early as 12 weeks' gestation[24], but it is doubtful that cervical assessment in the first trimester has prognostic value to predict SPB. To date, no data have been collected in twin gestations.

Between 12 and 15 weeks, the distance between the gestational sac and the internal os remains nearly unchanged in singleton pregnancies[24]. In high-risk singleton pregnancies, on the other hand, the cervix can begin to shorten as early as 15 weeks of gestation, and the shortening is more rapid in pregnant women who deliver prematurely[25] or who have a history of SPB[26]. Most studies investigating the cervix in twin gestations have used the interval between 20 and 25 gestational weeks or thereafter for the prediction of SPB, employing either the length of the cervical canal or the width of the internal os as reference (Table 55.1).

## Normal values

Gradual cervical changes precede the onset of labor over several weeks. With regard to the shortening of the CL and the opening of the internal os, differences exist between singleton and twin pregnancies[21,41,44–46]. We collected data on the CL, width of the internal os and the anterior angle with a presumed horizontal line, reflecting the degree of curvature, for singleton, twin and triplet pregnancies in both the supine and upright positions. Only results from those pregnancies not treated by any interventions to prevent SPB, and which delivered at ≥ 36 weeks, were used to determine 'normal' values for twin pregnancies[21]. We found that the CL decreased significantly from 15 weeks to term in both positions ($p < 0.001$) (Figure 55.3a), and that the values between the two positions were significantly different from 20 weeks onwards ($p < 0.001$).

In normal twin pregnancies, a width of the internal os of more than 5 mm (funneling) was observed in an upright position at > 30 gestational weeks (Figure 55.3b), and differences in funneling between the positions were statistically significant from 25 weeks onwards ($p = 0.005$). These observations suggest a correlation with epidemiological data


**Figure 55.2** A mother pregnant with twins (a) introducing the transvaginal probe and (b) observing the result

demonstrating that workload and physical activity have an adverse effect on the cervix[47]. The anterior angle decreased in both positions ($p < 0.001$) (Figure 55.3c), but differences of the angle between both positions were not significant.

Most centers use defined cut-off values to select patients with a risk for SPB. However, not all patients with threatening premature labor are identified at a specific gestational age. Some who have a CL of > 2.5 cm in the supine position still demonstrate a shorter cervix or even funneling in the upright position.

The reference values for different positions in uncomplicated twin pregnancies can be integrated into daily practice. We recommend interventions such as a reduction of physical stress and workload in multiple gestation when values are outside the 50% 'box', e.g. below the 25th centile for CL. We also advise application of a pessary when the CL is less than the 10th centile and pregnancy is < 30 weeks of gestation, and tocolytic treatment in patients with significant contractions and CL below the 10th centile in either the supine or the upright position. However, the effect of interventions based on these parameters to date has only been evaluated using historical controls; in this analysis of two periods of 3 years, the rate of SPB < 36 weeks and < 32 weeks decreased in twin pregnancies from 35 to 16% and from 10 to 5%, respectively[21].

Apart from our longitudinal results, few others describe dynamic cervical changes with advancing twin gestation[46]. The normal CL values of this study are comparable to our data. In our study, values of CL decreased from 44 to 30 mm between 18 and 36 weeks. In the study of Bergelin and Valentin, values of CL decreased from 41 to 31 mm between 24 and 32 gestational weeks[46]. The same authors describe a higher shortening rate in women delivering preterm. In agreement with our results, two studies found that the cervix widened with advancing gestation[44,46]. In contrast to our results, this change was not consistent in one study, and there were slightly longer values for CL in multiparous compared with primiparous women[44], a finding not yet confirmed by other authors. In patients who had multifetal pregnancy reduction to twins, the CL was

**Table 55.1** Comparison of studies[17,27–43] dealing with the prediction of spontaneous preterm birth (SPB) in twin pregnancies by detection of cervical length (CL) by transvaginal sonography. 'Variables' include additional investigated parameters

| *Source* | *Population (n)* | *Gestational age at examination* (weeks) | *Cut-off CL* (mm) | *Outcome parameter/ threshold of SPB* (weeks at birth) | *Variables* | *Study design* |
|---|---|---|---|---|---|---|
| Shulman *et al.*, 2002[27] | 57 | 24/27 | 30 | interval to delivery | — | AS–PROS |
| Vayssiere *et al.*, 2002[28] | 251/215 | 22/27 | 25 | < 32/35 | FU, FU + TFP | AS–PROS |
| Soriano *et al.*, 2002[29] | 54 | 18–24 | 35 | > 34 | WG, BMI, SM, WO | AS–PROS |
| Skentou *et al.*, 2001[17] | 464 | 18–24 | 20/25/40/60 | < 33 | — | AS–PROS |
| Iams *et al.*, 2001[30] | 188 | 24–28 | 20 | < 32/35/37 | REL | AS–PROS |
| Shapiro *et al.*, 2000[31] | 66 | < 30 | 20/25/30 | < 28/35 | — | AS–RET |
| Venditelli *et al.*, 2001[32] | 26 | 18–36 | 30 | < 37 | FU | SY–PROS |
| Persutte *et al.*, 2000[33] | 105 | 20–32 | 25 | < 37 | — | SY–PROS |
| Guzman *et al.*, 2000[34] | 131 | 15–20/21–24/25–28 | 20 | < 28/30/32/34 | FU, CI | AS–PROS |
| Yang *et al.*, 2000[35] | 65 | 22–24 | 25/30/35 | < 35 | FU | AS–PROS |
| Weisz *et al.*, 2000[36] | 50 | 18–22 | 35 | < 34 | — | AS–PROS |
| Althusius and Dekker, 1998[37] | 101 | 16–32 | 30 | <34 | — | AS–RET |
| Granovski-Gisaru *et al.*, 1998[38] | 43 | 18–29 | 30 | <34 | — | AS–PROS |
| Souka *et al.*, 1999[39] | 215 | 22–24 | 15/25/35/45 | ≤ 28/30/32/34 | — | AS–PROS |
| Imseis *et al.*, 1997[40] | 85 | 24–26 | 35 | < 34 (± intervention) | — | AS–PROS |
| Crane *et al.*, 1997[41] | 26 | 23–33 | 30 | < 34/< 37 | D, FU | SY–PROS |
| Wennerholm *et al.*, 1997[42] | 121 | 24–34 (at intervals) | 33 | < 35/37 | BV, E, FI | AS–PROS |
| Goldenberg *et al.*, 1996[43] | 147 | 24–28 | 25 | < 32/35/37 | BV/FI | AS–PROS |

Variables: BMI, body mass index; BV, bacterial vaginosis; CI, cervical index; D, digital examination; E, endotoxin; FI, fibronectin; FU, funneling; REL, relaxin; SM, smoking; TFP, transfundal pressure; WG, weight gain; WO, working during pregnancy
Study design: AS, asymptomatic twin pregnancies; PROS, prospective; RET, retrospective; SY, symptomatic twin pregnancies

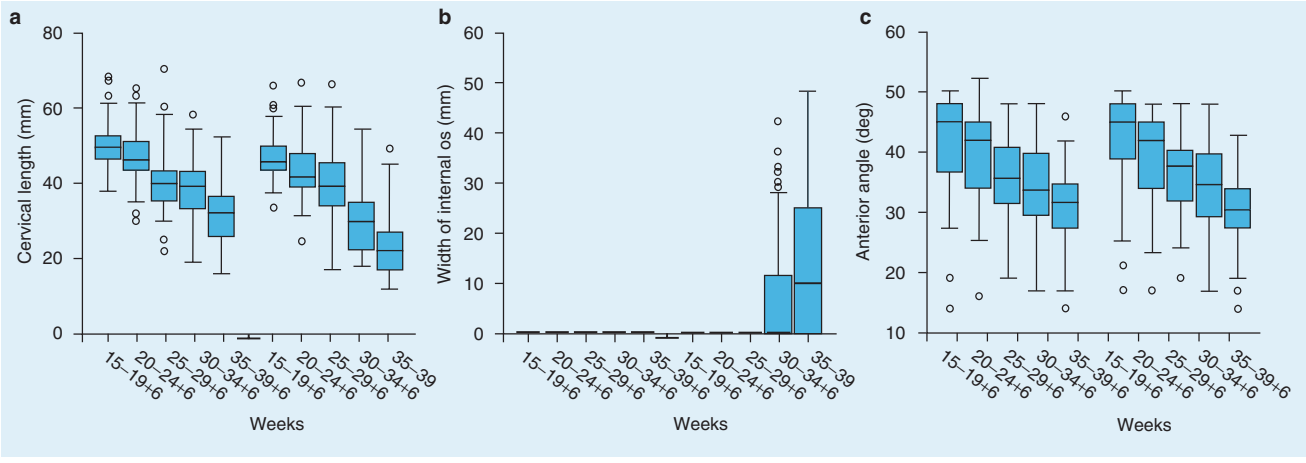


**Figure 55.3** Box–whisker plots of (a) cervical length, (b) width of the internal os and (c) presumed anterior angle with a horizontal line in normal twin pregnancies with delivery ≥ 36 weeks without any intervention to prevent preterm birth ($n$ = 71): all boxes on the left side of each diagram signify values in a suspine position, all boxes an the right signify values in an upright position. There are five intervals: 15–19 + 6 weeks, 20–24 + 6 weeks, 25–29 + 6 weeks, 30–34 + 6 weeks and 35–39 + 6 weeks. The 'box' includes 50% of the values between the 25th and 75th centiles and the median; the 'whisker' marks the 1½ time fold of the 25th and 75th centiles

compared from 14 to 32 weeks with that in a control group without pregnancy reduction. Despite the likelihood of inflammatory responses and bleeding, the CL across gestation was not significantly affected by multifetal pregnancy reduction[48].

## PREDICTION OF SPONTANEOUS PRETERM BIRTH BY CERVICAL ASSESSMENT

Most studies using transvaginal sonography to identify women at risk for SPB in singleton and multiple gestations have examined the possibility of using one or two cervical measurements. Wide variations exist among studies with respect to gestational age at testing, definition of abnormality thresholds and the outcome reference in twin pregnancies[17,27–43] (Table 55.1). A recent review identified published studies from different databases and manual searching of bibliographies. Data were stratified according to singleton or twin pregnancy, gestational age at testing, CL and funneling width thresholds or reference standards, and then pooled to produce summary estimates of likelihood ratios[49]. The given thresholds to predict the likelihood of SPB varied, even if symptomatic and asymptomatic patients were analyzed separately (Table 55.2). Both CL measurement and funneling, whether alone or in combination, appeared to be useful in predicting SPB in twin pregnancies. In another study, it was also demonstrated that CL and funneling both predicted very preterm birth of twins, whereas CL appeared to be the predictor of choice at 27 weeks of gestation. At 22 weeks, the diagnostic values of both parameters were comparable[28].

Previous studies have shown that once dilatation of the internal os has occurred, the interval to delivery is comparable in patients who subsequently go into either spontaneous term or preterm labor[50]. In our longitudinal data set of normal and pathological twin pregnancies, we observed that CL < 25 mm and funneling width > 10 mm between 20 and 28 weeks in both positions predicted a risk for SPB. In addition, disparities of CL and width of the internal os due to the maternal position increased with advanced gestational age and were more pronounced in twin pregnancies at risk for SPB compared with normal controls[21].

In practice, clinicians should be able to make informed and explicit decisions based on probabilities generated by cervical assessment and other tools with regard to the risk of SPB.

As reported in the first National Institute of Child Health and Human Development Maternal–Fetal Medicine Network preterm prediction study dealing with twin pregnancies, the most widely known risk factors for SPB were not significantly associated with SPB of twins. At 24 weeks, a CL ≤ 25 mm was the best predictor of SPB. Of all other risk factors evaluated at 28 weeks, fetal fibronectin was the only statistically significant predictor of SPB[43]. In our data set, we found that a combination of cervical assessment of either CL or funneling in both positions and fibronectin were significant predictors of SPB in twin pregnancies between 20 and 28 weeks[21].

**Table 55.2** Likelihood ratios (LRs, individual and pooled) for predicting spontaneous preterm birth for a range of thresholds for cervical length measurements among asymptomatic and symptomatic twin pregnancies. Adapted from reference 49

| *Subgroups testing gestational age 'thresholds'* | *Spontaneous preterm birth before 34–35 weeks* | |
|---|---|---|
| | *+LR (95% CI)* | *–LR (95% CI)* |
| *Asymptomatic* | | |
| < 20 weeks | | |
| 20 mm | 59.89 (3.46–103.48) | 0.71 (0.52–0.96) |
| 20–24 weeks | | |
| 15 mm | 7.60 (2.09–27.67) | 0.89 (0.81–0.97) |
| 20 mm | 4.54 (1.46–14.14) | 0.75 (0.64–0.90) |
| 25 mm | 5.02 (3.31–7.61) | 0.75 (0.54–1.06) |
| 30 mm | 2.31 (1.08–4.93) | 0.69 (0.91–1.17) |
| 35 mm | 1.47 (1.09–1.97) | 0.88 (0.69–1.12) |
| 45 mm | 1.12 (1.00–1.26) | 0.45 (0.15–1.40) |
| > 24 weeks | | |
| 20 mm | 3.44 (2.05–5.78) | 0.41 (0.21–0.80) |
| 25 mm | 1.82 (1.26–2.63) | 0.83 (0.72–0.95) |
| 30 mm | 2.11 (1.43–3.12) | 0.61 (0.42–0.87) |
| 35 mm | 1.84 (1.48–2.29) | 0.29 (0.08–1.09) |
| *Symptomatic* | | |
| 30 mm | 2.33 (1.42–3.82) | 0.15 (0.01–2.14) |

+LR, positive likelihood ratio; –LR, negative likelihood ratio; CI, confidence interval

**Table 55.3** Comparison of the diagnostic values of fibronectin, cervical length, Bishop score and premature contractions in twin pregnancies at risk for spontaneous preterm birth ($n$ = 180 with delivery ≥ 36 weeks, $n$ = 70 with delivery < 36 weeks), all parameters detected between 24 and 26 gestational weeks[21]

| *Parameter* | *Sensitivity (%)* | *Specificity (%)* | *PPV (%)* | *NPV (%)* | *+LR* | *95% CI* |
|---|---|---|---|---|---|---|
| Fibronectin | 48.5 | 90.2 | 64.3 | 90.2 | 3.2 | 2.1–4.2 |
| Cervical length | 64.9 | 81.5 | 52.1 | 81.5 | 2.6 | 1.5–3.8 |
| Bishop score | 65.2 | 80.0 | 54.8 | 80.0 | 2.5 | 1.8–3.2 |
| Premature contractions | 59.7 | 83.1 | 50.0 | 83.1 | 2.9 | 1.7–4.2 |

PPV, positive predictive value; NPV, negative predictive value; +LR, positive likelihood ratio; CI, confidence interval

In a recent study of asymptomatic twin pregnancies, a CL of ≤ 2.0 cm measured between 15 and 28 weeks' gestation appeared to be a reasonable parameter for predicting SPB in twin gestations[34]. The high specificities indicate that CL is better at predicting the absence than the presence of threatening SPB[34]. Both a CL ≤ 30 mm and cervical funneling in twin pregnancies under 26 weeks' gestation were independently and strongly associated with a risk for SPB[34]. Because a long cervix, > 35 mm, is associated with very low risk (4%) for preterm birth, pregnant women with these results can be reassured[35]. After 30 weeks, CL was shown to be not predictive of SPB[31]. A simple equation using the CL (mm)/3 can predict mid-gestation scan-to-delivery interval in twin gestation[27]. In symptomatic twin pregnancies transvaginal sonography can identify impending SPB before advanced cervical dilatation, and may therefore help to indicate maternal (*in utero*) transfer to a level III hospital, tocolytic treatment or the application of antenatal steroids (see below). We found that uterine contraction monitoring has a lower sensitivity for detecting women at risk of SPB compared with cervical assessment and fetal fibronectin in the vaginal fluid in twin pregnancies (Table 55.3)[21]. The high specificities underline that current use of CL and fetal fibronectin are of importance in situations where negative results can avoid unnecessary interventions[51]. However, obstetricians should be aware that there will always be a group of mothers of twins who deliver preterm unexpectedly.

**Table 55.4** Effect of interventions for the prevention and therapy of spontaneous preterm birth (SPB) and neonatal outcome based on randomized controlled trials, many of them not separately performed for twin pregnancies[52–60]

| *Interventions in pregnancies at risk for SPB* | *Proved advantage* | *Eventual advantage* | *Eventual disadvantage* |
|---|---|---|---|
| Bed-rest/hospitalization | | | ×† |
| Corticosteroids (single dose) | ×* | | |
| Corticosteroids (multiple dose) | | × | × |
| TRH in combination with corticosteroids | | | × |
| Antibiotics in patients with bacterial vaginosis and risk factors | | × | |
| Antibiotics in asymptomatic bacteriuria | ×* | | |
| Prophylactic antibiotics in PROM | | × | ×‡ |
| Prophylactic antibiotics with intact membranes | | | × |
| Ritodrine (β-mimetic) | | × | ×§ |
| Atosiban (oxytocin antagonist) | | ×* | × |
| Indomethacin (prostaglandin antagonist) | | ×* | × |
| Nifedipine (calcium antagonists) | | ×* | |
| Magnesium sulfate | | | × |
| Cerclage | | ×* | × |

*Only in singleton pregnancy; †specifically for twin pregnancy; ‡co-amoxiclav; §mainly in twin pregnancy; TRH, thyrotropin-releasing hormone; PROM, premature rupture of the membranes

## CERVICAL ASSESSMENT FOR MONITORING INTERVENTIONS AND EXPECTANT MANAGEMENT

Several therapies have been introduced to prevent SPB in twin pregnancies without defined indications and without evidence about under which circumstances these interventions would have any benefit. Some lack any evidence at all about whether they contribute to improved outcome or add unnecessary costs and risks for both mother and fetus (Table 55.4). Among all therapies used in pregnancies at risk for SPB, few distinguish interventions in singleton, twin or triplet pregnancy. In addition, few studies prove a positive effect for twin gestations, even in the presence of evident disadvantages. The lack of well-designed randomized controlled trials (RCTs) in twin pregnancies has led to a policy whereby management decisions are based on indirect conclusions from RCTs in singleton pregnancies, although results could be quite different in twin pregnancies. Cervical assessment and the described thresholds (Tables 55.1 and 55.2) have therefore been developed as an essential tool to exclude patients from unnecessary and possibly even harmful therapies (Table 55.4).

### Routine hospitalization and bed-rest

Routine hospitalization for bed-rest in the third trimester for mothers with multiple pregnancies is an intervention that was introduced in Europe in the 1960s and 1970s without adequate evaluation of its efficacy. It was hypothesized that it would be of importance to tide mothers over the dangerous period of risk of preterm birth and growth restriction by limiting activity and provision of a uniform diet. However, hospitalization was a stressful experience for twin mothers and their families, as well as costly for the health-care system[52]. Currently, no observational study describes cervical changes during hospitalization. The results from RCTs suggest that bed-rest may even be harmful for uncomplicated twin pregnancies in that the risk of very preterm birth is increased[52] (Table 55.4). Hospitalization for bed-rest did not reduce the rate of SPB or any outcome parameter even in pregnant twin mothers with cervical effacement and dilatation[52]. Nevertheless, based on the earlier studies of Papiernik and colleagues[47], a reduction of physical stress for women with multiple pregnancies in an out-patient setting is recommendable *per se*, and even more so when early signs of cervical shortening or widening of the internal os became evident. In the future, studies should control for the reduction of physical stress and its long-term effect on the cervix in twin pregnancies.

### Tocolytic treatment

Although tocolytics prolong pregnancy, as of yet they have not been shown to improve perinatal and neonatal outcomes. Moreover, they cause adverse

effects in women in preterm labor[53] (Table 55.4). Premature labor occurs frequently in twin gestations, but no RCTs have been designed for twin pregnancies. Intravenous magnesium sulfate and β-mimetics have commonly been prescribed, and have been compared in twin versus singleton pregnancies. For magnesium sulfate, frequencies of side-effects, durations of therapy, numbers of days until delivery and delays in delivery during the first 72 h were the same, and the therapy was deemed equally safe in both groups[53]. However, when β-mimetics were used, multiple pregnancies were associated with a marked increase in the duration of therapy, incidence of delivery before 37 weeks and incidence of maternal cardiovascular complications such as pulmonary edema. There was no effect on the neonatal outcome[61]. A further study confirmed that pulmonary capillary pressure, cardiac index and the ratio of pre-ejection period/left ventricular ejection time were significantly increased during the infusion period with β-mimetics in twin gestations[62]. These results stress the importance of cervical assessment before any tocolytic therapy in twin pregnancy, mainly to avoid unnecessary maternal complications in patients with a cervix indicating a low risk for later SPB.

Oxytocin antagonists and calcium channel blockers have been used, but no data in twin gestations are available. There is evidence that calcium channel blockers are preferable to any other tocolytic agents in patients with a cervical assessment indicating a high risk of SPB[54]. Prospective trials of the newer tocolytics for perinatal and maternal outcomes are needed. Although the lack of data prevents us from judging the efficacy of calcium channel blockers or oxytocin antagonists in twin gestations, it seems logical to use them as first-line drugs considering the increased risk of cardiovascular complications with β-mimetics (see Chapter 52).

## Corticosteroids

Antenatal treatment with corticosteroids is indicated for pregnant women at risk for preterm birth delivering more than 24 h and less than 7 days after start of treatment, as it results in a substantial decrease of neonatal mortality and morbidity, as well as in savings of health-care costs[55]. The use of repeated doses in women whose risk of preterm delivery persists for more than a week may reduce the incidence of respiratory distress syndrome, but may also cause harmful effects in mother and fetus[55] (Table 55.4). A recent study of 189 at-risk pregnancies highlights the difficulty in recognizing the 'right' time to give steroids based on clinical criteria[63]. Antenatal corticosteroid therapy appears to be less beneficial in multiple than in singleton pregnancies, with pharmacological studies suggesting that the current dose may be insufficient for multiple pregnancies. Reasons for this concern relate to the shorter half-life of betamethasone in mothers with twin pregnancies, which may cause subtherapeutic levels of betamethasone in terms of lung maturation in twins[64]. A recent study with the largest series of retrospectively evaluated non-randomized antenatal glucocorticoid responses in twins concluded that corticosteroids have no proven beneficial effect on the risk of respiratory distress syndrome in preterm twin babies, but expose a large number of infants to unnecessary treatment that might adversely affect growth[65]. Similarly, the Cochrane database states that, to date, studies show no clear benefit of antenatal standard doses of glucocorticoids in twin pregnancies[55], possibly because the causes of SPB in singletons are different from those in twins who are supposed to be relatively 'unstressed'.

All these data support the concept that cervical assessment is mandatory before the administration of glucocorticoids in twin gestations. The given thresholds and likelihood ratios (Tables 55.1 and 55.2) with a negative test result help the obstetrician in charge to avert corticosteroid therapy in patients who have a good chance of continuing for more than a week. At the same time, dynamic cervical assessment and the observation of increased shortening due to postural stress and within a short period of time might help to determine the appropriate timing of steroid therapy at an early gestational age. As the risks and benefits of repetitive application are still controversial in singleton pregnancies, multiple doses should not be encouraged in twin pregnancies in the absence of well-designed RCTs. As clinicians await results from studies comparing the efficacy of higher doses of corticosteroids in twin gestations, antenatal corticosteroid therapy should be used at the usual doses but with strict indications.

## Antibiotics

Antibiotics are recommended during pregnancy for the prevention of SPB in patients with recurrent symptomatic bacterial vaginosis and a history of SPB[56], as they reduce the incidence of pyelonephritis during pregnancy and possibly that of SPB[57]. There is no firm evidence that antibiotics improve the outcome in pregnancies with intact membranes and threatening SPB, but there is concern about increased neonatal morbidity[58]. Although no specific studies exist for twin pregnancies, it seems probable that the results from singleton pregnancies also hold true for twins. Antibiotic administration following PROM is associated with a delay of preterm birth

**Table 55.5** Study design and outcome of cervical cerclage/pessaries in twin pregnancies[69–74]

| Source | Twins (n) | Treatment | Study design | Outcome of treatment group |
|---|---|---|---|---|
| Arabin *et al.*, 2003[74] | 23 | pessary (therapeutic) | case–control | improved in treatment group |
| Newman *et al.*, 2002[69] | 21 | cerclage (therapeutic) at ≤ 25 mm CL | RC | no improvement by cerclage |
| Seki *et al.*, 2000[70] | 20 | cerclage (prophylactic) | HS | fewer patients hospitalized |
| Bognoni and Quartuccio, 1997[71] | 1 | cerclage (emergency) at ≤ 24 weeks | case report | delay of 11 weeks |
| Benifla *et al.*, 1997[72] | 3 | cerclage (emergency) at > 20 weeks | RET–OBS | 2/6 perinatal deaths |
| Maly and Deutinger, 1993[73] | 35/41 | cerclage (therapeutic/prophylactic) | RET–OBS | no improvement by prophylactic cerclage |

Study design: HS, historical control; OBS, observational; RC, retrospective cohort; RET, retrospective; CL, cervical length

and with an improvement of the major indicators of neonatal outcome[59]. In a study considering twin pregnancies after PROM it was shown that the latency period was significantly shorter in twins, and more twins were born within 48 h, compared with singletons[66]. The role of cervical assessment in pregnancies with PROM has been evaluated only in singleton pregnancies[67].

## Cerclage

Soon after the introduction of a cervical cerclage by McDonald and Shirodkar for anatomical cervical incompetence, 'prophylactic' cerclages in twin pregnancies were embraced with enthusiasm but questionable indications. In a prospectively conducted randomized trial of the Royal College of Obstetricians and Gynaecologists, no significant differences in perinatal or neonatal mortality were found in spite of a reduced rate of SPB at < 33 weeks in the study, compared with the control group[68]. Moreover, the risk of a long hospital stay, further interventions and maternal complications was increased in the study group. Even the most recent report of *The Cochrane Library* provides no evidence that prophylactic or therapeutic cerclage has a significant impact on the outcome of patients at risk for SPB[60] (Table 55.4). Additionally, no separate prospective studies exist for twin pregnancies, and management decisions are based on indirect conclusions from singleton data or the few retrospective studies in twins[69–73] (Table 55.5).

After the introduction of transvaginal sonography, the cervical structure could be followed before and after cerclage, and the distance of the suture, which appears as an echodense structure, to the internal and external os can be measured (Figure 55.4). In cases with 'unsuccessful' cerclage, the distance of the suture to both the internal and the external os as well as the total length of the cervical canal decrease. Indeed, after cerclage, the internal os can weaken

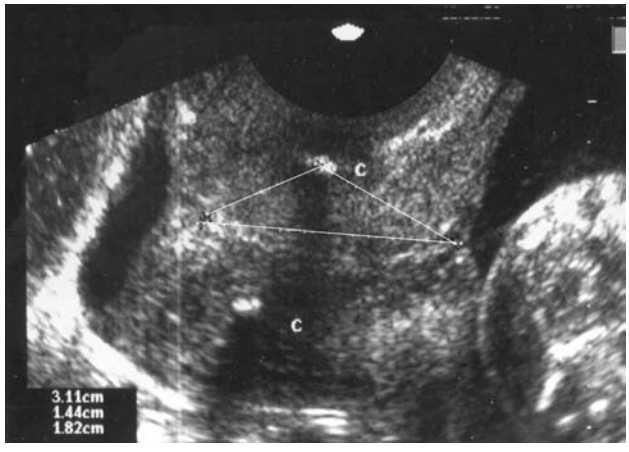


**Figure 55.4** Transvaginal sonogram of a cervix after performance of a Shirodkar cerclage demonstrating sufficient distances to the internal and the external os

and the membranes descend to the level of the cerclage suture. These findings were associated with earlier preterm delivery in a study group of 44 singleton, six twin and three triplet gestations with cervical cerclage, and all births occurred before 28 weeks[75]. Surprisingly, the residual CL after cerclage placement was not associated with gestational age at delivery.

Currently, results from studies in women with twin gestations who may benefit from a cerclage based on transvaginal sonography results are rare and conflicting (Table 55.5). In one observational study, cases with multiple pregnancy and 'prophylactic' cerclage were compared with cases with a cerclage based on sonography findings[73]; the duration of pregnancy did not differ between groups. In patients without prophylactic cerclage, the frequency of preterm contractions was lower. However, the frequency of PROM was higher, and it was concluded that prophylactic cerclage did not improve the outcome of twin pregnancies (Table 55.5). In a more recent prospective

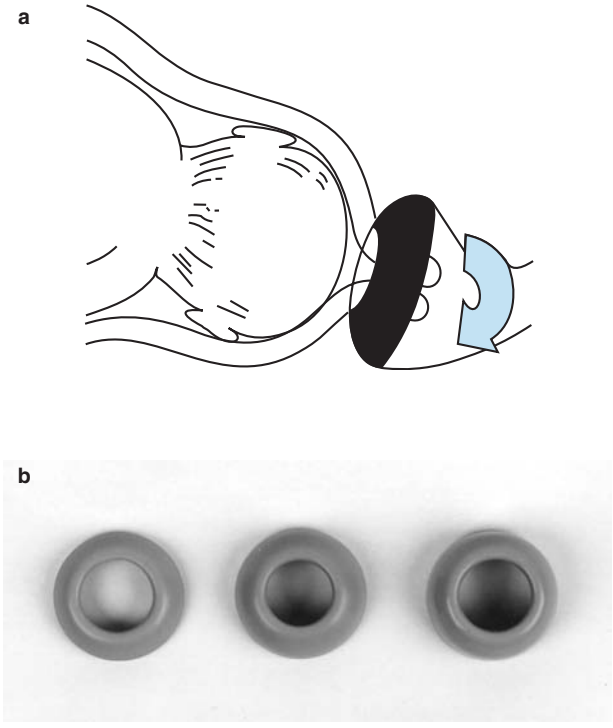


**Figure 55.5** Vaginal pessaries are designed to shift the cervix posteriorly and thus provide relief of pressure complaints. (a) Model showing the rotating effect, (b) variety of sizes with respect to diameter and height used in our study demonstrating the shorter diameter directed upwards towards the cervix and the larger diameter directed towards the pelvic diaphragm

(non- randomized) cohort study of 147 twin pregnancies with transvaginal sonography measurement between 18 and 26 weeks' gestation, cerclage was offered to 21 women with a CL ≤ 25 mm. The results were compared with data from 13 twin pregnancies with the same sonography results but no cerclage[69]. Decreasing CL was significantly associated with a shorter length of gestation, delivery at ≤ 34 weeks and PROM; however, none of these outcomes was altered by cerclage placement (Table 55.5).

Considering the results from all observational studies to date in twin gestations (Table 55.5) and large prospective multicenter studies in singleton pregnancies based on transvaginal sonography, it remains questionable whether cervical cerclage might have a place as routine policy in twin pregnancies with or without signs of cervical shortening. The observational trials of twin pregnancies do not motivate the design of further large RCTs of cerclage in twin gestations.

## Vaginal pessaries

Vaginal pessaries are generally used for pelvic organ prolapse. In multiple gestations, the functionally incompetent cervix is aligned centrally with no support except the non-resistant vagina. Vaginal pessaries have been used in pregnant women to direct the cervix more posteriorly, thus changing the inclination of the cervical canal so that the weight of the uterine contents is directed more towards the anterior lower segment (Figure 55.5a). It is postulated that such a maneuver might prevent further opening of the internal os or even premature rupture of the membranes based on pressure-related problems. The effect is better followed by clinical rather than by sonographic examination because the pessary itself absorbs ultrasound waves. Compared with operative cerclage, pessaries have the advantage of being cost-effective and operator-independent. Studies of indications for and outcomes of pessary therapy have been summarized elsewhere[76].

We performed a matched-control analysis of 23 pairs, i.e. 46 pregnant women with twin pregnancies and short CL[74]. All had a short cervix of less than the 10th centile before 28 weeks; 23 pregnant women were treated with vaginal pessaries which were developed by ourselves (Figure 55.5b) and 23 had expectant management. The interval from treatment to delivery was 85 (43–129) days in the treatment group and 67 (21–100) days in the control group ($p = 0.001$), and gestational age at delivery was 35 + 6 and 33 + 2 weeks, respectively ($p = 0.02$). Within the pessary group, there were 8/23 cases with SPB at < 36 weeks but none with SPB at < 32 weeks, compared with 12/23 cases with SPB at < 36 weeks and 7/23 with SPB at < 32 weeks in the control group ($p < 0.001$). Survival analysis of the pregnancy is demonstrated in Figure 55.6.

## Cervical surveillance in cases with progressive dilatation

Cervical assessment has not yet been integrated into the population-based routine surveillance of twin pregnancy. It is still common practice to wait until clinical symptoms such as uterine contractility, bulging membranes or PROM are 'unpredictably' present, although the condition might have been apparent earlier or even preventable. In all such instances, maternal transfer to perinatal centers must be encouraged in view of the benefits of in-born status compared with postnatal transfer for all twins before 32 gestational weeks. One of the most frequent indications for *in utero* transfer of a multifetal pregnancy to level III facilities is threatened preterm delivery with progressive dilatation when the first symptoms have been missed or unsuccessfully treated. In contradistinction to many centers where routine cesarean delivery is performed in all premature twin pregnancies with a

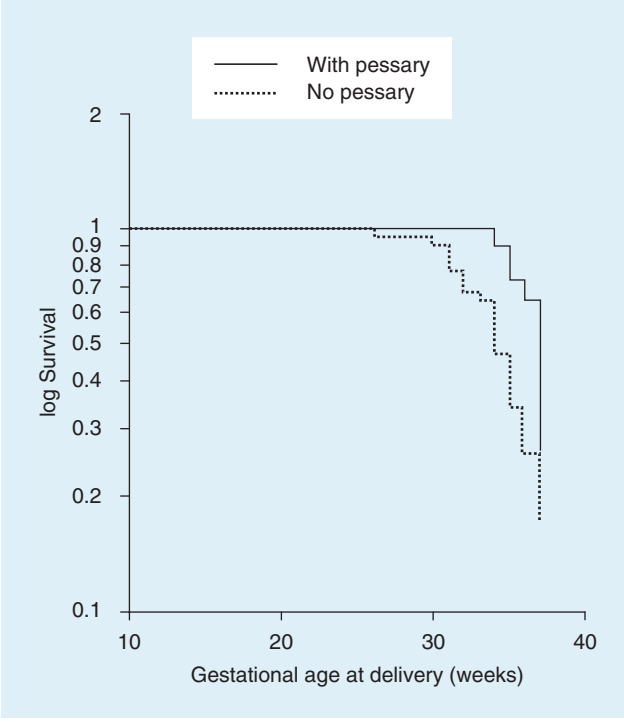


**Figure 55.6** Gestational age at delivery expressed as log rank survival with and without pessary treatment started between 20 and 28 weeks of gestation, in 46 twin pregnancies, matched pairs

cervical dilatation of > 4 cm, we postpone pregnancy even with dilatation below 32 gestational weeks using a prospective protocol. In these patients, transvaginal sonography is useful to detect the degree of protrusion ('ballooning'), the position of the first or even both twins (Figure 55.7), as well as the umbilical cord, and whether there is dissociation of the membranes. In our first 30 patients (20 pregnancies with twin gestations) with progressive dilatation and ballooning at < 28 weeks at admission, we could prolong the interval to delivery for 2 weeks (mean) and a maximum of up to 4 weeks. In these patients, longitudinal transvaginal sonography is a non-invasive procedure for surveillance of progression.

### Delayed-interval delivery

In delayed-interval delivery of twin pregnancies, transvaginal sonography is used for cervical assessment before and even more after the delivery of the first twin. In the past 10 years, we have performed delayed-interval delivery in more than 30 twin gestations. Cervical assessment helps to predict the success of the procedure. In the twin pregnancy with the longest interval between delivery of the first and of the second twin (106 days), we observed that

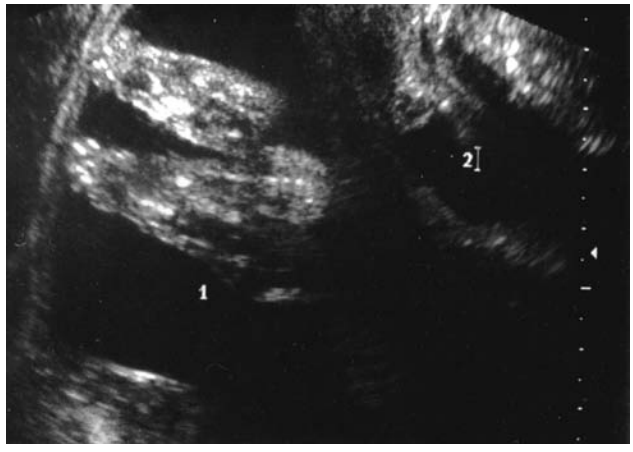


**Figure 55.7** Transvaginal sonogram of a twin pregnancy at 24 weeks' gestation, full dilatation, and preceding feet of the first (1) and the second (2) twin

the umbilical cord of the first twin had completely disappeared above the internal os and that the cervix became restored to a length of more than 3 cm (see Chapter 75). During the past few years, we tried to avoid the typical delayed-interval procedure by prolonging pregnancy with both twins at an early gestational age (< 28 weeks) for as long as possible, even if the first twin is present within the vagina (Figure 55.7). In exceptional cases, we perform peridural anesthesia for maternal pain relief. In all cases, transvaginal sonography is mandatory to diagnose the position of fetuses and umbilical cord, something that is frequently impossible by the abdominal approach.

## CONCLUSIONS

In the future, cervical assessment should be incorporated into the routine care of twin pregnancies by educating patients to recognize first symptoms of spontaneous preterm birth or to reduce physical stress, and by educating physicians to perform transvaginal sonography at regular intervals or even initiate interventions based on sonography results. Specially trained staff and twin clinics are desirable. Cervical assessment allows researchers to target randomization in at-risk patients when evaluating the effectiveness of interventions to prevent spontaneous preterm birth. Collaborative studies are needed with a definition of dynamic thresholds of cervical assessment and defined outcome parameters such as gestational age at delivery, morbidity, mortality, and long-term follow-up separate for mono- and dichorionic twins.

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# Fetal Fibronectin

*D. A. Netta and C. V. Ananth*

**56**



## INTRODUCTION

Preterm birth is one of the most challenging problems encountered in modern clinical obstetrics. Not only is it the leading cause of perinatal morbidity and mortality, but its cause and means of prevention are strikingly unclear[1]. Since 1981, the preterm birth rate has increased by 20%, and identifying patients who are truly at risk for delivering preterm poses a clinical dilemma[2]. Risk factor scoring predicts, at best, less than half of women destined to deliver preterm[3–5]. Twin pregnancies are at particular risk, with 56% delivering prior to 37 weeks of gestation, compared with 11.8% in singleton pregnancies[6]. In addition, although twins account for less than 3% of newborns in the United States, they represent approximately 12% of all premature births and 15% of neonatal mortality[6,7].

A number of methods have been introduced to predict the likelihood of preterm birth in twin pregnancies, including sonographic assessment of cervical length and dilatation (see Chapter 55), measurements of salivary estriol and fetal fibronectin testing in the cervical and vaginal secretions. As multiple gestations pose such a significant risk for preterm delivery, it is uncertain whether and how these newer clinical markers may be used to predict spontaneous preterm birth.

## WHAT IS FETAL FIBRONECTIN?

Fibronectins are a family of proteins found in the plasma and extracellular matrix. Fetal fibronectin can be distinguished from other fibronectins by the presence of a unique region known as the 3CS (connecting segment) domain, an area recognized by the monoclonal antibody FDC-6[7,8]. Immunohistochemical studies of the placenta show that fetal fibronectin is localized in the extracellular matrix of the decidua basalis adjacent to the intervillous space and syncytiotrophoblast of the chorionic membrane[9,10]. Fetal fibronectin has been described as the 'glue' between the fetal membranes and the underlying uterine decidua (Figure 56.1). It is normally found in cervical and vaginal secretions before 20 weeks' gestation, and again near the end of pregnancy[11,12]. However, it is uncommon for fetal fibronectin to be present in cervical and vaginal secretions between 22 and 37 weeks' gestation (Figure 56.2). Thus, the presence of fetal fibronectin, in amounts > 50 ng/ml, after 22 weeks' gestation, may be considered a marker of disruption of the interface between the decidua and the chorion.

Studies suggest that fetal fibronectin can be used as a biochemical marker for preterm delivery[9,13–15]. The United States Food and Drug Administration has approved use of the fetal fibronectin assay, including a rapid form, as an aid for the diagnosis of preterm labor in both symptomatic and asymptomatic women. However, its value in multiple gestations, especially in asymptomatic patients, remains unclear.

## TECHNIQUE FOR PERFORMING FETAL FIBRONECTIN TEST

Samples for fetal fibronectin are obtained from the posterior fornix of the vagina during a speculum

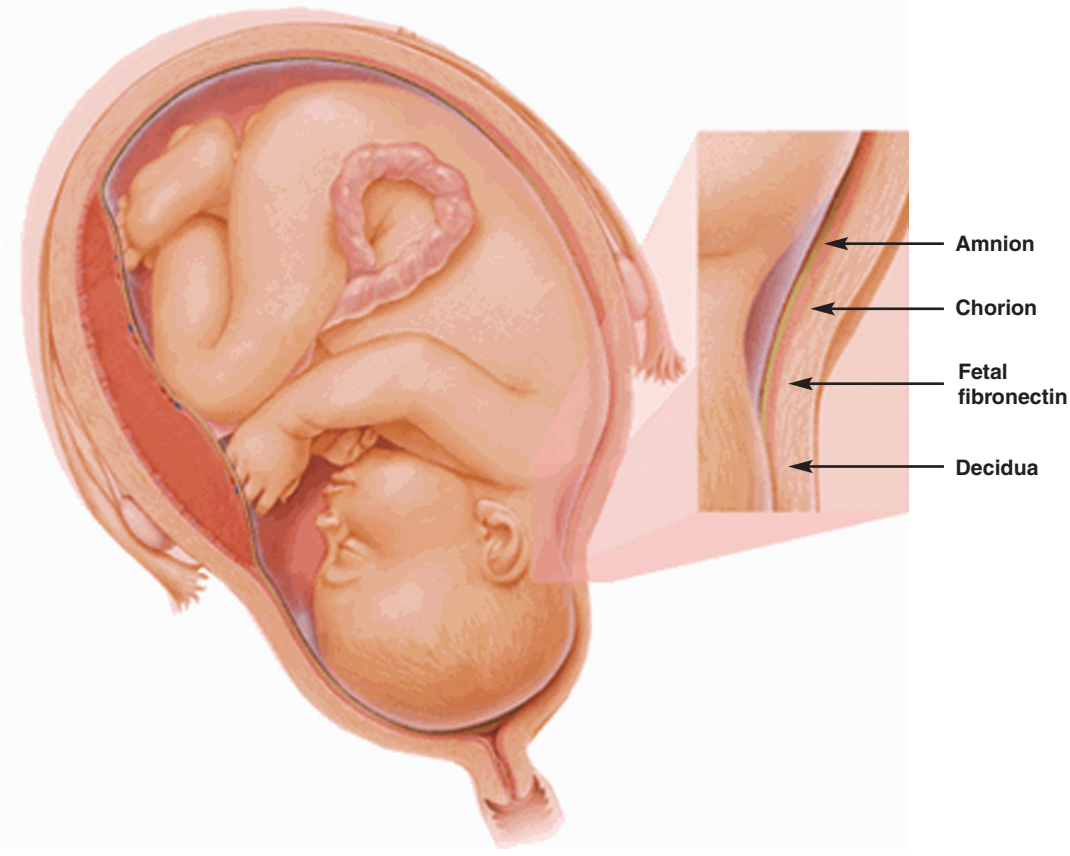


**Figure 56.1** Fetal fibronectin in relation to amnion, chorion and decidua. Modified and reproduced with permission from Adeza Biomedical Corporation, Sunnyvale, CA

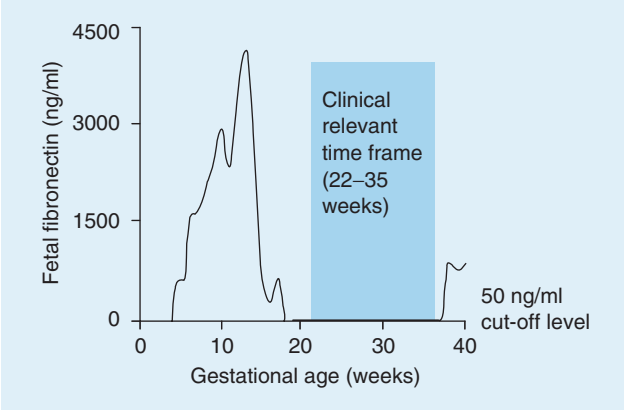


**Figure 56.2** Normal fetal fibronectin expression at each gestational age. Presence of ≥ 50 ng/ml fetal fibronectin in the cervicovaginal secretions of pregnant women between 22 and 35 weeks' gestation is associated with preterm delivery. Adapted with permission from Adeza Biomedical Corporation, Sunnyvale, CA

examination, prior to digital cervical evaluation. A non-lubricated Dacron™ polyester swab is inserted into the vagina and lightly rotated across the posterior fornix for approximately 10 seconds. Results must be readily available (within 2 hours) for the test to be clinically useful. The examination should not be performed if the patient has had a recent pelvic examination, vaginal ultrasound scan, significant vaginal bleeding or sexual intercourse. If the decision to perform a fetal fibronectin test is made after a cervical examination has been performed, it is recommended that the test be delayed for 6–8 hours. If intercourse has been recent, current recommendations are to delay testing for 24 hours. However, both these time limits have been arbitrarily set and need further evaluation.

## FIBRONECTIN AS A MARKER OF PRETERM DELIVERY

In 1991, Lockwood and co-workers first suggested that cervicovaginal fetal fibronectin could be an effective tool in identifying gestations at risk of preterm birth. These investigators identified the presence of cervicovaginal fetal fibronectin in the second and third trimesters of singleton pregnancies

at high risk for preterm delivery[9]. Of the 117 women presenting with preterm labor, all but ten delivered prior to 37 weeks when the fetal fibronectin test was positive. In contrast, when the fetal fibronectin test was negative, 81% (47 of 58 women) of the study patients delivered at term. Lockwood and co-workers proposed that the presence of cervicovaginal fetal fibronectin in women presenting with premature uterine contractions could distinguish between those who would and would not deliver preterm.

Since the first report by Lockwood and co-workers, additional studies have reached similar conclusions, the greatest benefit being seen in the high negative predictive value of the test, i.e. 95–99.7%, for delivery within the next 7–14 days[13–17]. In this respect, fetal fibronectin is similar to cardiac enzymes in the evaluation of chest pain. It is used as a test to avoid overdiagnosis and thus unnecessary and potentially harmful interventions[1,18]. At the same time, a positive result identifies patients at risk for preterm birth who may benefit from intervention such as parental tocolytics. Although tocolytics do not prolong pregnancy for inordinately long times, despite spectacular individual case histories, the early detection of preterm labor, and therapy with tocolytics, particularly in twins, provides time for transfer to a tertiary-care facility, administration of corticosteroids and group B streptococcus prophylaxis.

Most of the studies examining the value of fetal fibronectin in predicting preterm birth in symptomatic women have been in singleton gestations. Morrison and colleagues examined a population of symptomatic women that included ten with multiple gestations. In these latter instances, the sensitivity, specificity and positive and negative predictive values were similar to those found in women with singleton pregnancies[19]. A multicenter study by Peaceman and colleagues involved 763 patients, including 36 patients with twin gestations all of whom presented with threatened preterm labor[13]. These investigators found that 86% of patients with positive fetal fibronectin delivered within the following 7 days. More important, 99.5% of women with a negative test did not deliver within 7 days of testing. In the subgroup evaluation of patients with twin gestations, 100% of women with a negative value did not deliver within 7 days of testing. However, the positive predictive value was only 20%, with only 1/5 patients with a positive test delivering within a week.

Two large meta-analyses examined the role of fetal fibronectin in the prediction of preterm birth. Leitich and associates described 27 studies evaluating symptomatic (those presenting with threatened preterm labor) as well as asymptomatic patients for the presence of fetal fibronectin and the risk of delivering preterm[20]. Fetal fibronectin had a sensitivity and specificity of 61% and 83%, respectively, for predicting delivery prior to 34 weeks' gestation and 56% and 84% for predicting delivery prior to 37 weeks' gestation[20]. In this study, serial testing resulted in higher sensitivity (92% for delivery prior to 34 weeks and 71% for delivery prior to 37 weeks), but lower specificity (59% and 79%, respectively). The authors concluded that fetal fibronectin was one of the most effective markers for preterm delivery, particularly among patients with symptoms, who will give birth within 7 days of sampling. A second meta-analysis by Faron and colleagues showed that the presence of fetal fibronectin in cervicovaginal secretions was associated with delivery at < 34, < 35 or < 37 weeks in both high- and low-risk populations[21]. In low-risk women without symptoms of threatened preterm labor, 28% of women with a positive fetal fibronectin test delivered preterm. In high-risk women, a negative fetal fibronectin was associated with a reduced risk of preterm delivery. These associations were consistent with both single and multiple test strategies. The authors recommended randomized trials to assess both testing as well as interventional programs to determine whether fetal fibronectin screening can be used effectively to identify candidates for intervention to decrease the incidence of preterm delivery and its sequelae. Similar meta-analyses have not been performed for twin gestations.

## SUMMARY OF CURRENT TWIN STUDIES

Goldenberg and co-workers examined 147 twin gestations (Table 56.1)[22]. The primary outcome measured was spontaneous preterm birth after preterm premature rupture of membranes or spontaneous labor at <35 weeks. Additional outcomes examined were delivery at <32 weeks and at <37 weeks. Asymptomatic patients with twin gestations were identified between 22 and 24 weeks' gestation and underwent testing for fetal fibronectin every 2 weeks. The test was considered positive if ≥50 ng/l. Women with positive fetal fibronectin had a greater risk for spontaneous preterm birth when fetal fibronectin was positive at 28 weeks ($p=0.04$) and at 30 weeks ($p=0.002$). Additionally, the authors found the combined presence of fibronectin and a shortened cervix led to a very high rate of preterm birth, with 100% of patients delivering prior to 37 weeks, 75% delivering prior to 35 weeks and 50% delivering prior to 32 weeks' gestation[22].

In a similar study by Wennerholm and colleagues, asymptomatic twin gestations were examined for several different markers of preterm delivery[5]. One

**Table 56.1** Summary of fetal fibronectin as a marker for preterm birth in twin gestations: design study

| *Authors* | *Inclusion criteria* | *Exclusion criteria* | *Sampling interval* |
|---|---|---|---|
| Goldenberg *et al.*[22], 1996 | twin gestations identified at < 22–24 weeks | cervical cerclage, placenta previa, severe fetal anomaly | every 2 weeks from 24 to 30 weeks |
| Tolino *et al.*[24], 1996 | multiple gestations identified at ≥ 24 weeks | rupture of membranes, cervical dilatation at time of recruitment | weekly |
| Wennerholm *et al.*[5], 1997 | twin gestations identified before 20 weeks | induced preterm delivery for maternal or fetal indications | every 2 weeks from 24 to 30 weeks |
| Oliveira *et al.*[23], 1998 | twin gestations at 24–34 weeks | preterm birth for medical reasons | every 2 weeks from 24 to 34 weeks |
| McMahon *et al.*[25], 2002 | twin or triplet gestations identified at < 20 weeks | cervical cerclage, rupture of membranes at time of recruitment | 20 weeks and 24 weeks |

**Table 56.2** Summary of fetal fibronectin (fFN) as a marker for preterm birth in twin gestations: results

| | | | | *Test characteristics* | | | |
|---|---|---|---|---|---|---|---|
| *Authors* | *n* | *Timing of fFN* (weeks) | *GA at delivery* (weeks) | *Sensitivity* (%) | *Specificity* (%) | *PPV* (%) | *NPV* (%) |
| Goldenberg *et al.*[22], 1996 | 147 | 28 | <32 | 28.6 | 96.1 | NA | NA |
| | | 28 | <35 | 57.1 | 26.5 | NA | NA |
| | | 30 | <32 | 37.5 | 98.9 | NA | NA |
| | | 30 | <35 | 62.5 | 72.7 | NA | NA |
| Tolino *et al.*[24], 1996 | 68 | single + fFN | <37 | 90.9 | 68.5 | 73.1 | 88.8 |
| | | two consecutive + fFN | <37 | 86.6 | 78.9 | 76.4 | 88.2 |
| Wennerholm *et al.*[5], 1997 | 101 | 24 | <32 | 50.0 | 88.8 | 30.8 | 94.7 |
| | | 28 | <35 | 50.0 | 92.0 | 62.5 | 87.3 |
| Oliveira *et al.*[23], 1998 | 52 | 24–34 | <34 | 80.0 | 38.1 | 23.5 | 88.9 |
| | | | <37 | 89.3 | 50.0 | 67.6 | 80.0 |
| McMahon *et al.*[25], 2002 | 109 | 20 | <32 | 0.0 | 100.0 | 0.0 | 88.7 |
| | | 24 | <32 | 42.9 | 93.9 | 37.5 | 95.1 |

GA, gestational age; PPV, positive predictive value; NPV, negative predictive value; NA, value not available

hundred and twenty-one twin gestations were identified at < 20 weeks' gestation. Patients were screened for the presence of fetal fibronectin every 2 weeks, with ≥ 50 ng/l being considered as positive. Forty-six per cent of the patients delivered preterm. However, 20 patients were excluded secondary to maternal or fetal indications. Of the 101 remaining patients, 36% delivered prior to 37 weeks' gestation and 22% delivered prior to 35 weeks' gestation. A positive fetal fibronectin at 28 weeks predicted delivery before 35 weeks' gestation. A positive fetal fibronectin at this gestational age was also associated with increased neonatal morbidity (odds ratio 11.3, 95% confidence interval 2.7–46.9), with a significantly higher number of infants requiring intensive care for more than 7 days. Positive fetal fibronectin at 24 weeks predicted delivery at < 32 weeks' gestation and was accompanied by worse neonatal sequelae; 50% of these early preterm births were detected by a positive fetal fibronectin test with specificity of 89% and positive and negative predictive values of 31% and 95%, respectively (Table 56.2).

Additionally, Oliveira and associates showed in a study of 52 asymptomatic patients with twin gestations that a positive fetal fibronectin could identify 90% of twin pregnancies that would deliver prior to 37 weeks' gestation[23]. The presence of fetal fibronectin in the cervicovaginal secretions had a sensitivity of 89% for predicting delivery prior to 37 weeks' gestation and 80% for predicting delivery prior to 34 weeks' gestation. These investigators suggested that owing to its low specificity (38% for delivery prior to 34 weeks

and 50% for delivery prior to 37 weeks) fetal fibronectin should be evaluated in combination with cervical length to identify more easily twins likely to deliver preterm[23].

Further, Tolino and colleagues found that results differed when fetal fibronectin was positive on two consecutive samples versus when only a single sample was positive[24]. With a single positive test, the sensitivity was 91%, specificity 69%, positive predictive value 73% and negative predictive value 89% for delivery prior to 37 weeks' gestation. When results were positive from at least two consecutive samples, on the other hand, the sensitivity was 87%, specificity 79%, positive predictive value 76% and negative predictive value 88% for delivery prior to 37 weeks' gestation. The authors concluded that in pregnancies already at risk for preterm delivery, such as multiple gestations, the specificity of the test could be increased by requiring two positive tests for definitive diagnosis without markedly decreasing the sensitivity. They also postulated that by identifying patients at significant risk, early therapeutic approaches including bed-rest, the administration of tocolytic agents, patient education, perinatal monitoring and home nursing care might help to decrease the incidence of preterm delivery.

Finally, McMahon and co-workers undertook a study of 88 twin and 29 triplet gestations[25]. The mean gestational age at delivery was 35.9 weeks for twin gestations and 34.3 weeks for triplet gestations. A positive fetal fibronectin test at 24 weeks' gestation had a sensitivity, specificity, and positive and negative predictive value of 43%, 94%, 38% and 95%, respectively, for predicting delivery prior to 32 weeks' gestation. Interestingly, these investigators found that combining cervical length and fetal fibronectin failed to improve the accuracy of the test substantially. Negative fetal fibronectin at 24 weeks' gestation was similar to cervical length on ultrasound of ≥ 3.0 cm for predicting pregnancies likely to deliver beyond 32 weeks' gestation.

## RECOMMENDATIONS

Twin pregnancies are at significant risk for spontaneous premature birth. Current risk scoring methods are imprecise in predicting which twins will deliver prematurely. Cervicovaginal fetal fibronectin appears to be a promising marker for both preterm delivery and morbidity in twin gestations. However, its main role is in its excellent negative predictive value for delivery within 2 weeks of testing. Although most data on the use of fetal fibronectin for predicting preterm delivery in symptomatic patients are from singleton pregnancies, some data suggest that it can be used for the same purpose in twin pregnancies[13,19]. Unfortunately, it is still unclear how fetal fibronectin may be used in screening women with twin gestations who are asymptomatic. If patients at high risk for preterm delivery can indeed be identified, then interventions such as patient education, decreased activity, bedrest, home uterine monitoring, hospitalization, long-term tocolytics, prophylactic cerclage, corticosteroids administration, maternal transfer (if appropriate) and group B streptococcus prophylaxis may help either to prolong pregnancy or to decrease neonatal morbidity. As with many other tests, randomized controlled trials are needed to prove the clinical usefulness of these interventions.

## AUTHORS' ADDENDUM

The value of vaginal fetal fibronectin assay following multifetal pregnancy reduction showed that for delivery within 2 and 3 weeks of a single test, fetal fibronectin had a negative predictive value of 99.5% and 98.6%, respectively. The authors concluded that the fetal fibronectin test has similar validity to predict spontaneous preterm delivery in these high-risk pregnancies as in other cohorts.

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# Preterm Rupture of the Membranes

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## INTRODUCTION

Spontaneous rupture of the fetal membranes is a normal component of labor and delivery, and most often occurs during the active phase. In contrast, rupture of the membranes before the onset of labor at any stage of gestation is designated prelabor rupture of the membranes (PROM). If this occurs at a gestational age of less than 37 weeks, the event is characterized as preterm prelabor rupture of the membranes. Prelabor rupture of the membranes occurs in approximately 2.0–3.5% of all pregnancies and is associated with 30–40% of preterm deliveries[1]. As such, it is the leading identifiable cause of preterm delivery and its complications, including respiratory distress syndrome, neonatal infection and intraventricular hemorrhage[2]. Preterm PROM occurring very early in pregnancy carries a high risk of perinatal morbidity and mortality, primarily as a result of prematurity as well as acute complications such as infection, cord prolapse and abruption. According to the risk assessment study of Ross and co-workers, both multiple gestation and preterm premature rupture of the membranes are independently associated with at least a four-fold risk of neonatal intensive-care unit admission. Notably, triplet or greater gestation and preterm PROM carried the highest odds ratios (17 and 15, respectively)[3]. The risk of these complications increases with decreasing gestational age at membrane rupture. Mercer[4] suggested differentiating preterm pretern ROM into three broad categories according to clinical relevance: 'previable PROM', which occurs before the limit of viability (less than 23 weeks); 'preterm PROM remote from term' (from viability to about 32 weeks' gestation); and, finally, 'preterm PROM near term' (approximately 32–36 weeks' gestation).

Known risk factors for preterm rupture of the membranes include preceding preterm birth, intra-amniotic infection, multiple fetuses and placental abruption, as well as exogenous risk factors, including nutritional deficiencies, and smoking[1]. PROM occurs as a sudden, unpredictable event that is the culmination of many complicated and poorly understood biochemical and mechanical pathways.

Most studies report that more than 50% of twin gestations are delivered prior to 37 weeks[5]. Moreover, in triplets and other higher-order gestations, the mean gestational age at delivery is less than 34 weeks. According to the March of Dimes multicenter prematurity and prevention study[6], although preterm PROM occurred in 12% of all twin pregnancies versus 3% of all singleton pregnancies, PROM contributed significantly less to twin preterm births than to singleton preterm births (22% vs. 31%, $p = 0.004$). In a recent study by von Dadelszen and colleagues[7], the mean preterm PROM gestational age in twin pregnancies was 31.3 (± 3.8, standard deviation (SD)) weeks. The mean gestational age at PPROM in assisted reproductive technologies-associated twins versus spontaneous twins is not significantly different (31.4 ± 4.7 and 27.8 ± 8, not significant (NS), respectively), and the same is the case for triplets (25.4 ± 8.5 and 29.6 ± 3.7, NS, respectively)[8]. [Editors' note: Readers should be aware, however, that the absence of statistical difference is not the same as absence of clinical significance.] Santema and co-workers[9] compared triplet with twin pregnancy for perinatal complications. Triplets had half the incidence of PROM as compared with twins (12% vs. 24%).

Preterm PROM is one of the most difficult clinical problems confronted by obstetricians, especially if it occurs in multiple pregnancies. Despite the clinical significance of preterm ROM, our knowledge of the etiology and pathophysiology of this entity is limited. The literature about preterm PROM in singletons is extensive. In contrast, scant available data exist regarding preterm PROM in twin and higher-order multiple gestations. This chapter examines in detail the etiology, consequence and management of PROM in multiple pregnancies.

## PATHOPHYSIOLOGY

According to data based on singleton studies, premature rupture of the membranes is multifactorial in nature. Obstetricians traditionally attributed it to physical stresses that weaken the membranes, particularly those associated with labor. More recently, however, evidence suggests that membrane rupture is also related to biochemical processes, including disruption of collagen within the extracellular matrix of the amnion and the chorion and programmed death of cells in the fetal membranes[2]. In any given patient, one or more pathophysiological processes may be evident, including microbial invasion of the amniotic cavity, the latter having been found to play a major role in the pathogenesis of preterm labor and delivery in singleton pregnancy[10], whereby 33–40% of patients with preterm PROM have a positive amniotic fluid culture[11]. Whereas the traditional view is that microbial invasion of the amniotic cavity is the consequence of rupture of the membranes, a growing body of evidence suggests that PROM may be the result of subclinical infection and inflammation. Specifically, micro-organisms in the amniotic cavity or maternal compartment may reach the fetus and stimulate the biosynthesis of proinflammatory cytokines, which in turn stimulate enzymes capable of degrading the extracellular matrix of the chorioamniotic membranes. Thus, intra-amniotic infection is associated with a dramatic increase in amniotic fluid concentration of matrix metalloproteinases[12]. Maymon and associates[13] found that increased concentrations of neutrophil collagenase (matrix metalloproteinase-8) in amniotic fluid are associated with intra-amniotic infection, impending preterm delivery and adverse neonatal outcome in patients with preterm PROM. One explanation is that the amniotic fluid concentration of this enzyme is an index of the fetal inflammatory response syndrome. Such a phenomenon has survival value, and is initiated when the intrauterine environment is so hostile as to threaten the survival of the maternal–fetal pair[14]. This condition is frequently associated with microbial invasion of the amniotic cavity, but there are probably other pathological conditions yet to be elucidated that are potential causes of this state.

Mazor and colleagues[15] reported that the incidence of intra-amniotic infection in twin pregnancies and preterm labor is similar to that found in singleton pregnancies with preterm labor. One striking observation in this study was that the presenting sac was involved in 89% of patients with infection and, when both sacs were infected, the inoculum size of the micro-organisms was always higher in the lower sac than in the upper sac. Moreover, the micro-organisms isolated from the upper sac, when both sacs were involved, were always the same as in the lower sac.

Recently, Phung and colleagues[16] reported the association between chorionicity, discordant chorioamnionitis and funisitis in twin gestations. Although there was no significant difference between the frequencies of non-affected dichorionic and monochorionic pairs, the presenting twin was more frequently affected than the non-presenting twin. This latter observation was more marked among dichorionic compared with monochorionic pairs. Thus, dichorionic placentas confer significant protection against the spread of chorioamnionitis from the presenting to the non-presenting gestational sac. In the more advanced process that involved the umbilical cord, only the subset of separate dichorionic placentas confered this protective effect against the spread of inflammation[16].

## INCIDENCE

Although the reported range is variable, the incidence of PROM in twin gestations appears to be increased over and above that of singleton gestations. For example, Mercer and colleagues[17] found a two-fold increased risk for preterm PROM in twin gestations (99/1312 or 7.5%), compared with singleton pregnancies (3131/83 693 or 3.7%, $p < 0.0001$, relative risk (RR) 2.1). With regard to triplets, preterm PROM complicated two of 27 (7.4%) triplet pregnancies during this same time period, suggesting an increased risk of preterm preterm ROM with higher-order multifetal gestations, albeit based on small numbers. In contrast, other studies found significantly lower prevalence of PROM in twins (12.2% vs. 17.3%, $p < 0.006$)[18].

## PRESENTATION

Membrane rupture in twin pregnancy presents with one of several possible scenarios, including membrane rupture of the presenting or non-presenting sac, or even rupture of the intervening fetal membranes[19]. However, owing to the relative infrequency of twins, PROM in twin gestations is an

**Table 57.1** Clinical outcome of preterm premature rupture of membranes, twins vs. singletons

| | *von Dadelszen et al.[7] (2003)* | *Mercer et al.[17] (1993)* | | | *Bianco et al.[20] (1996)* | | | *Myeles et al.[21] (1997)* | | |
|---|---|---|---|---|---|---|---|---|---|---|
| *Outcome* | *Twins* ($n$ = 492) | *Singletons* ($n$ = 99) | *Twins* ($n$ = 99) | *p Value* | *Singletons* ($n$ = 116) | *Twins* ($n$ = 116) | *p Value* | *Singletons* ($n$ = 119 ) | *Twins* ($n$ = 28) | *p Value* |
| Chorioamnionitis (%) | 13.8 | 22.5 | 15.2 | NS | 14.6 | 16.4 | NS | 27.1 | 8.7 | NS |
| Latency period | 22.5 h | 97.8 h (± 203, SD) | 86.1 h (± 210, SD) | NS | 19.5 h (10.2–49.3, range) | 11.4 h (6.3–26.4, range) | < 0.05 | 8.6 days | 4.3 days | < 0.001 |
| GA at ROM (weeks, ± SD) | 31.3 (± 3.8) | | 30.1 (± 4.3) (19–36, range) | | 32.2 (± 3) | 32.4 (± 3) | NS | 30.0 | 29.5 | NS |
| GA of delivery (weeks, ± SD) | 32.0 (± 3.2) | 30.1 (± 4.3) | 30.6 (± 4.3) | NS | — | — | — | 31.2 | 30.1 | NS |
| Birth weight (g)* | 1758 | 1708 | 1483 | 0.02 | 2378 | 2030 | NS | 1698 | 1463 | < 0.03 |

*Birth weight for twins is average of those for two babies; GA, gestational age; ROM, rupture of membranes; NS, not significant

uncommon event. As a consequence, it is difficult to evaluate prospectively and analyze the outcomes of these pregnancy complications.

## CLINICAL COURSE

From the clinician's point of view, preterm PROM represents a clinical dilemma. A true danger of immediate preterm delivery is present, and with it an increased risk of maternal and fetal or neonatal infections. Data pertaining to the clinical characteristics and neonatal outcome of twin gestations complicated by PROM are scant. The study of Mercer and colleagues[17] reported the outcome of 99 twin pregnancies and 99 well-matched singleton pregnancies complicated by preterm PROM. Several interesting points were found. First, an early gestational age at preterm PROM in twins was associated with a longer latency period (median 1.5 day vs. 1 day, $p = 0.03$), whereas twin gestation itself did not confer an increased risk of rapid delivery over singleton gestation with preterm PROM. Second, there was no statistically significant difference in the rate of amnionitis between twins and singletons (15% vs. 23%, NS). Third, twin gestation had a significantly higher incidence of cesarean section (42% vs. 27%, $p = 0.02$). Fourth, twin pregnancy complicated by preterm PROM was associated with a lower mean birth weight than that of singletons (1483 g vs. 1708 g, $p = 0.02$). Finally, comparing the presenting and the non-presenting twin, an increased incidence of hyaline membrane disease was present in the non-presenting twin (20.9% vs. 7.1%, RR 2.9, $p = 0.01$), as well as a need for prolonged oxygen therapy (43.6% vs. 22.6%, $p = 0.003$), regardless of mode of delivery. Table 57.1 summarizes this study and others that compared the outcome of twin with singleton pregnancies complicated by PROM. Similar perinatal and neonatal outcomes were observed between 116 preterm twin gestations (< 36 weeks) complicated by preterm PROM and matched singleton gestations[20].

## PRETERM PRELABOR RUPTURE OF THE MEMBRANES OF THE NON-PRESENTING SAC

The incidence and clinical course of PPROM of the non-presenting sac are unknown. Borenstein and Shoham[22] reported a patient who was injected with Evans blue dye in the upper sac to confirm membrane rupture at 15 weeks' gestation. The patient was treated conservatively with antibiotics, and the leakage stopped spontaneously at 19 weeks. The patient delivered two healthy infants at 32 weeks' gestation after recurrent preterm PROM. How often this happens is unknown.

## RUPTURE OF THE INTERAMNIOTIC MEMBRANE

'Occult membrane rupture' between the sacs of diamniotic twins may lead to a catastrophic outcome. Gilbert and co-workers[23] reported eight cases of diamniotic twin gestation complicated by disruption of the dividing membrane. Seven out of eight (87.5%) were monochorionic (MC). Fourteen infants died (50%), including four stillbirths and three neonatal deaths. A thin dividing membrane was visualized before admission in four of seven gestations. One case followed iatrogenic amniorhexis at the time of laser ablation of anastomotic placental vessels. Another complicated a dichorionic (DC) gestation in which the dividing membrane was previously visualized by ultrasonography. In this case, one of the infants suffered entrapment of a foot and finger in an amniotic band. Here also, the frequency of this complication is unknown.

## EARLY SECOND-TRIMESTER RUPTURE OF THE AMNIOTIC MEMBRANE

Membrane rupture in multiple pregnancies during the second trimester has an ominous prognosis, as the majority of the fetuses die after preterm delivery. The practitioner caring for the patient with mid-trimester PROM must make management decisions that have immediate life and death implications. Issues that should be addressed early in the course of management include continuation of pregnancy, maternal and fetal evaluation, and referral to a tertiary-care center. Regardless of the ongoing management plan, intensive psychological support is essential to complement the comprehensive patient-care regimen. The ultimate goal of therapy must be safety of the mother, then consideration for optimum perinatal outcome. Active management of preterm PROM before 23 weeks' gestation is associated with neonatal death, whereas aggressive attempts to delay delivery may expose the mother to severe morbidity[24]. In addition, the potential benefit of improved neonatal outcome from delaying delivery must be balanced against the fetal risk of a potentially hostile and even life-threatening intrauterine environment. Mercer[4] reported that 33% of live-born and resuscitated infants delivered at 23 weeks survived to discharge from hospital. Of those who survive, however, serious perinatal morbidity may lead to long-term sequelae (i.e. cerebral palsy, blindness and deafness). The risk of infection includes chorioamnionitis, maternal wound infection and neonatal sepsis. The complications of prolonged oligohydramnios for the fetus include pulmonary hypoplasia, pneumothorax and skeletal deformities, especially if PROM occurs prior to 24 weeks' gestation.

**Table 57.2** Infant outcome of preterm premature rupture of membranes, twins vs. singletons

| Outcome | *von Dadelszen et al.[7] (2003)* | *Bianco et al.[20] (1996)* | | | *Myles et al.[21] (1997)* | | |
|---|---|---|---|---|---|---|---|
| | *Twins* ($n = 492$) | *Singletons* ($n = 112$) | *Twins* ($n = 116$*) | *p Value* | *Singletons* ($n = 119$) | *Twins* ($n = 28$) | *p Value* |
| Stillbirth (%) | 0 | 3 | 3 | NS | 1.6 | 3.5 | — |
| Neonatal death (%) | 4.5* | — | — | — | — | — | — |
| IVH (%) | 6.3* | 4.3 | 2.6 | NS | — | — | NS |
| Sepsis (%) | 9.4* | 0.8 | 0 | NS | — | — | NS |
| NEC (%) | — | 0.8 | 0 | NS | — | — | NS |
| RDS (%) | 40* | — | — | — | — | — | NS |

*Presenting twin; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; RDS, respiratory distress syndrome; NS, not significant

The natural history of second-trimester PROM in multifetal pregnancies is delivery of all the fetuses after a relatively short latency period. This occurs in most cases because the events leading to delivery of the first fetus continue and finish with delivery of the remaining fetuses. On those rare occasions when the uterus becomes quiescent after delivery of the first fetus, the risk of ascending infection and severe chorioamnionitis is significant, and most obstetricians opt for measures to accelerate delivery of the remaining fetuses. For those reasons, continuation of pregnancy after delivery of the first fetus in multiple pregnancies is a relatively rare event. Nevertheless, there are an increasing number of cases described in the recent literature in which efforts have been made for continuation of pregnancy (see Chapter 75).

## NEONATAL OUTCOME

Membrane rupture can involve the presenting or the non-presenting sac. In either instance, the fetus with intact membranes is also at risk, owing to brief latency or intrauterine infection after membrane rupture of its sibling. Kilpatrick and colleagues[25] reported the perinatal mortality in 790 twins born after 30 weeks of pregnancy and in matched singletons. Perinatal mortality in preterm singletons delivered for premature rupture of the membranes was significantly greater than for twins ($p = 0.03$). Table 57.2 summarizes other studies of infant outcome of twin pregnancies complicated by PROM. According to von Dadelszen and colleagues[7], the rate of adverse perinatal outcomes (perinatal mortality, sepsis, bronchopulmonary dysplasia, necrotizing enterocolitis and severe intraventricular hemorrhage) was less with more advanced gestational age at PROM (odds ratio (OR) 0.53, 95% confidence interval (CI) 0.40–0.72) and shorter latency period (OR 0.73, 95% CI 0.54–0.98).

Accelerated pulmonary maturation in the presenting fetus of a twin pregnancy is controversial. The findings of Arnold and co-workers[26] support the hypothesis of accelerated maturation in the presenting fetus, or reflect accelerated pulmonary maturation after preterm PROM in the presenting sac. In contrast, Leveno and co-authors[27] demonstrated that pulmonary maturity testing is synchronous in twins.

## TREATMENT

Several authors discuss the benefits of aggressive treatments following membrane rupture in a single sac of a multiple gestation. The presence of an intact sac with a normal amount of amniotic fluid and normal fetal development, albeit with risk for infection, provides the clinician with a series of clinical, sometimes ethical challenges.

If a presenting fetus in a multiple gestation is extruded following preterm rupture of its membranes at a previable gestational age, delayed-interval delivery may be an option to prolong the gestational time for the remaining fetuses (see Chapter 75). Until now, no systematic data have been available to assess delayed delivery in cases with early PROM. Obvious contraindications to delayed-interval delivery include profuse hemorrhage, hemodynamic instability or intra-amniotic infection. Whether a MC placenta is a contraindication too for delayed-interval delivery is controversial, and discussed by many authors[28]. Arias[29] reported the outcome of a small series of multifetal pregnancies with delivery of the first fetus after premature rupture of the membranes and extention of intrauterine life for the remaining fetuses. Clinical management included cervical cerclage, tocolysis and antibiotic therapy after vaginal

delivery of the presenting fetus. Aggressive treatment was associated with the survival of six of ten remaining fetuses after a mean latency of 49 days. There was an increase in mean birth weight of over 700 g for the fetuses whose delivery was delayed, compared with the initially delivered fetus. No significant maternal morbidity was noted in this study[29]. The study by Arias highlights the potential for improved latency with expectant management in this clinical setting. In addition, it also points to the potential for delayed delivery near the limit of viability in this extremely high-risk population. Analysis of possible reasons for the failure of the procedure suggests that gestational age at the time of first delivery is not an important factor. The main factors characterizing patients with failure were the presence and extension of intrauterine infection. Although the optimal management is not defined, intervention with tocolysis, antibiotics and cervical cerclage after delivery of the first fetus may be a reasonable option for some patients with multiple pregnancies and preterm PROM in the second trimester. However, the use of cervical cerclage for delayed-interval delivery remains controversial. On the one hand, a potential exists for an improved latency period with expectant management; on the other, delivery soon after viability may convert the pregnancy from one with infant losses to one resulting in delivery of a live-born infant with significant lifelong morbidity. In addition, in a multicenter study of 35 cases, Fayad and co-workers[24] failed to find any significant difference concerning cerclage, antibiotic therapy, tocolysis and hospitalization. In the data set of van Eyck and co-authors[30], delayed delivery in triplets was more problematic than in twin gestations. Out of three triplet gestations only two fetuses had a normal outcome. In two patients with early loss of the first triplet, the remaining triplets died in the perinatal period mainly due to amnion infection; in another case one triplet died postnatally due to neonatal sepsis.

Another treatment opportunity of early mid-trimester PROM is the use of selective termination of a twin with ruptured membranes. Selective feticide of the fetus with early mid-trimester PROM in the absence of maternal signs of infection may improve the former unfavorable pregnancy outcome. The use of second-trimester selective termination for fetal abnormalities is a well-established and relatively safe procedure. Dorfman and colleagues[31] reported the use of this procedure for the twin with membrane rupture and severe oligohydramnios at 18 weeks, and continuing pregnancy for the viable second twin who was delivered at term. There was rapid elimination of fluid leakage and continuation of good growth of the second twin. In a study by De Catte and co-workers[32] the overall preterm PROM delivery time interval was 21 weeks, and the baby take-home rate was 66% after selective feticide of the fetus with early mid-trimester PROM.

In summary, amniocentesis of both sacs should be offered for the diagnoses of intra-amniotic infection and fetal lung maturity. Antibiotics should be administered in all cases of multiple pregnancies with preterm PROM as is done in singleton gestations. In addition, corticosteroids should also be administered in cases with preterm PROM in multiple pregnancies, as is the rule in singleton gestations. It remains to be determined in future well-designed studies how long the latency period should be in cases with PROM with conservative treatment (glucocorticoids and/or antibiotics), and when induction of labor or cesarean section should be considered. There is an urgent need for randomized blinded trials to address the problem of PROM in multiple gestations. Until the results of such studies are available for clinical management, preterm PROM in multiple gestations should be managed as in singletons.

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# Psychological Adaptation

*E. Noble*

**58**



## INTRODUCTION

The adjustment to multiple pregnancy varies with each woman and depends on many factors, some changeable and some not, including her age, fertility history, the events surrounding her birth and upbringing and, finally, cultural influences. Her marital status may change during the twin pregnancy and her economic level almost invariably falls as a result of such an event. The amount and nature of the support provided by her partner and family, as well as her general state of health, can be improved, although there is always the threat of medical complications. The major challenge to her adaptation, however, is the so-called *nocebo* effect[1] – the 'evil twin' of the *placebo* effect. However well-intentioned, the suggestion that something is wrong or likely to go wrong with her body, when indeed no problem exists in truth, often compounds the negative image that many women develop in pregnancy.

Table 58.1 depicts two extremes of potential reactions. Because ambivalence is common in every pregnancy, many women fluctuate between positive and negative reactions, especially in cases of a multiple gestation. It is particularly important for health-care providers to recognize real or perceived negative reactions on the part of either parent, and to deal with them by providing acknowledgment, information, counseling and appropriate support. For the majority of mothers-to-be in these circumstances, networks, clubs and newsletters of the various multiple birth associations are often described as 'lifesavers' (see Chapter 106). The internet plays an important role in reducing isolation by providing medical information as well as social sharing through chat rooms and special interest groups. Furthermore, connecting with other parents of multiples is a great help with practical details such as supplies and arranging home help that increase the parents' sense of being able to cope.

Ultrasound provides the opportunity for earlier acceptance and adjustment to a multiple pregnancy. All the same, obstetric outcome was better before the use of ultrasound to diagnose multiple pregnancy, according to data from the US National Center for Health Statistics[2]. Although perinatal mortality has decreased in the past 30 years, the incidence of preterm births and low-birth-weight babies has continued to increase. *The Cochrane Review* concluded that fetal surveillance has not been effective, and certainly not cost-effective for ultrasound-detectable conditions such as placenta previa, twin–twin transfusion syndrome, etc.[3] Indeed, in some instances, the very intensity of the fetal surveillance may magnify the iatrogenic effect.

## ACCEPTANCE

Acceptance of the existence of multiple pregnancy is the first step in the process of psychological adaptation. To a large extent, acceptance depends on how, when and where the diagnosis is disclosed. Although many mothers suspect that they are carrying twins, confirmation often represents a major transition. Indeed, the news may be accompanied by feelings of excitement and wonder on the one hand, or powerlessness, regret, fear of the future – or even complete devastation – on the other. This is especially true for women whose conceptions resulted from assisted reproductive technologies (ART) or ovulation-inducing treatments and, despite knowing the risks

**Table 58.1** Reactions to pregnancy

| *Negative* | *Positive* |
|---|---|
| Suspected twin pregnancy disclosed with anxiety by technician or doctor (*nocebo* effect) | suspected twin pregnancy, confirmed with sensitivity and support |
| Diagnosis experienced as a shock | diagnosis received as a wonderful surprise or 'dream come true' |
| Unplanned pregnancy; unwilling to bear multiples | planned pregnancy/conscious conception, optimistic about outcome of fertility treatments |
| Perceives large abdomen as 'too fat' | enjoys blossoming of her body |
| Feels like a sow, like she's having a litter | grateful for abundance – 'two babies for the price of one' |
| Resents size, appearance, social comments | welcomes questions about large belly, due-date |
| Anxious about high-risk pregnancy and preterm birth | strongly motivated to learn how to achieve term pregnancy |
| Depressed by bodily changes and discomforts of pregnancy | views adaptation of body with sense of wonder and appreciation |
| Unaware of differences between babies; just feels disturbing kicking | begins prenatal bonding with babies as unit and individually identifies their movements |
| Fears labor, sees cesarean as an easy way out | looks forward to spontaneous labor, finds providers to facilitate natural birth |
| Rejects idea of breast-feeding | joyfully plans long-term breast-feeding |
| Feels overwhelmed by the thought of having and caring for two or more babies | sets up support systems for birth and postpartum well in advance |

of multiple pregnancy in these situations, had still hoped for one child.

Regardless, most families are poorly prepared for news of a multiple pregnancy, let alone the prenatal restrictions and monitoring that invariably follow. In this regard, the sudden swing from infertility to abundance can be an enormous shock. As aptly noted by Cheek and Le Cron[4], patients with idiopathic infertility often were neither biologically nor emotionally ready to conceive! This observation is of particular relevance today, when previously infertile women comprise a growing number of mothers of multiples, some of whom may be faced with the additional dilemma posed by the real or perceived need for selective reduction.

The diagnosis of multiple pregnancy should be disclosed by the midwife or doctor with the utmost sensitivity, in an open-ended session. To say the least, joking over the ultrasound machine is an inappropriate form of disclosure. *Immediate* contact with other parents of multiples should be arranged to avoid feelings of isolation or despondence. In addition, the newly informed woman (or couple) should leave the doctor's office with appropriate phone numbers (of mothers of multiples, the local or national Mothers of Twins Club) and, ideally, some literature or books about twins or reading and resource lists. Prepared health-care professionals have these documents at hand.

Adjustment is more complicated if there are other children in the family. The impending arrival of multiples stresses resources that already may be at their limits. Multipara often become pregnant 'to have an even number of children', or in the hope for a particular gender. When multiples are diagnosed such plans are upset, and health-care providers should not be surprised if the woman's reaction is less than enthusiastic at hearing the news.

Without doubt, two or more babies arriving at once represent a huge burden on space, time, income and lifestyle. The totality of these challenges and the changes that accompany them place families of multiples at increased risk of postpartum depression, drug and alcohol abuse, child abuse and divorce. Child abuse can be physical, verbal or emotional, or can simply result from neglect. Since the 1980s, we have learned that in half of the families studied by Groothuis[5], only the elder or younger sibling, not either of the twins, was abused, yet support for familes of twins has rarely increased.

Individuals who were abused as children tend to repeat this behavior, and therefore it is important to ask questions about past childhood abuse as part of the general prenatal historical survey. Anne Evans found that if a woman had experienced sexual abuse by a care-taker prior to the age of 18, she was twice as likely to deliver before 34 weeks of gestation, and two and a half times more likely to have a newborn with a medical problem, regardless of the number of previous pregnancies, education, race, use of alcohol or cigarettes, or history of additional physical abuse in childhood[6]. (Considering that sexual abuse is

currently estimated to occur in 60% of girls, this topic should be part of every prenatal interview, not only those of mothers of multiples[7].)

The reproductive history of the expectant mother and that of her own mother (which has a major influence during the expectant mother's formative years) is significant, as is the history and psychosocial experiences of twinning in the extended family. Positive or negative attitudes of other family members impact on family adjustment, whether they reflect feelings of pride or pity and determine whether the expectant mother is treated like a queen or an invalid.

Arranging a personal meeting between all newly informed patients and other mothers of multiples, both during pregnancy and well into the postpartum period, fosters the process of acceptance. Such encounters help to reassure apprehensive women that a huge belly is normal and that with exercise it will return to its former size in due time. Fatigue, plus the great increase in body size and weight, conspire against feelings of sensuality and sexuality for many women. A sense of humor helps the mother to accept the temporary nature of this often stressful transition.

## EDUCATION AND SUPPORTIVE MEASURES

A mother who is better informed feels empowered to cope with the many inevitable changes. Her personal health and well-being require optimal nutrition (see Chapter 51) and adequate rest. Both reduce fatigue and combat depression in addition to helping her carry her babies to term.

Ongoing financial assistance relieves some of the physical and social stresses of multiples but is commonly insufficient. Material needs must be accurately assessed and prioritized. A larger car, house and more income are often considered necessary, but acquiring them may be particularly difficult when the mother is asked to quit work. Housing and child-care subsidies, food supplements, extended leave from work, postpartum home-care and homemaker services for teens and single parents should all be sought as soon as possible so mothers feel that they will be able to cope. Becoming a mother is an endless growth process during which the woman confronts her limits and learns to stretch beyond them; twins serve to push those limits even more.

Frequently, financial burdens mean that the father has to seek extra work and has even less time to help at home, which may be required before the birth as well if the mother is confined to bed. In the nuclear family, the father's assistance is of primary importance to the mother's perception of being able to care for twins. Partners must be encouraged to attend as many prenatal visits as possible, as well as the birth.

Regardless of the partner's desire or ability to assist the mother, it is important that help be sought from family and neighbors for the postpartum months and organized well in advance. Invariably, families are reluctant to ask for help from outsiders and struggle to cope alone; such resistance can only increase their frustration and plummeting self-esteem. Contact with social workers may be invaluable as they know resources and are willing to be of assistance.

It is crucial that the woman has confidence in her obstetrician and that he/she has the requisite skills to handle multiples, particularly vaginal breech delivery. Couples expecting twins and higher-order multiples should visit a neonatal intensive-care nursery and take cesarean preparation classes. After such visits, they will not only be better-informed if a need for either arises but also highly motivated to prevent both. Many parents make extensive plans to deliver in a level III hospital so that a transfer will not be required should the newborns need intensive care.

Ideally, the need to 'be prepared for the worst' should not discourage, but rather encourage a pregnant woman to take the appropriate steps to minimize the likelihood of an adverse outcome. This she can clearly do by prioritizing nutrition, rest, appropriate exercise and self-education. A strong commitment to optimal health during pregnancy also means fewer problems later on. Full-time work can distract the mother from her enjoying her pregnancy, and may mean that little time exists for discovering who is living inside her womb. Expectant mothers of twins can benefit from disability leave, as explained below:

> *My doctor asked me how my days were going. I told him I was no longer able to meet the goals I had set for hydration, nutrition, exercise and rest while I was working. Without hesitation, he authorized short-term disability (at 29 weeks). I'm convinced that my ability to focus on those basic needs allowed me to carry my babies almost to 39 weeks. I was able to swim every day for 30 minutes, nap 2 hours every day and organize an excellent diet with lots of water.*

Almost half of the mothers of twins *do* reach 37 weeks or more, and thus all women should be encouraged to think positively about carrying this long. A *nocebo* effect operates when intense preoccupation about risks and complications is conveyed by the physician and others. In the case of multiples, the term 'special needs' is always preferable to 'high risk'. The feeling of being different, or treated as being different, is often reinforced with comments like 'Oh, twins, we have never had them in the group before', or 'I don't know how this would apply in your case'.

Health-care providers should acknowledge concerns they might view as 'trivial' as reflecting deeper issues that may lie beneath. Often, a patient is simply testing the environment to see if she feels safe and supported in order to discuss a deeper problem. Bland reassurance, however well-intentioned, can be interpreted as a put-down. Rather, health-care professionals should listen actively, and encourage the patient to elaborate verbally by exploring any accompanying bodily sensations and recalling prior similar experiences and outcomes. The ideal dialog is open-ended and allows the patient to use her inner resources for creative solutions.

Finally, informal networks (social and the internet) have great value. Expectant parents of multiples benefit greatly from sharing their fears, expectations and experiences with parents who have personally experienced multiple births. In addition to such prenatal and postpartum support groups, special classes for parents of multiples should be offered. As well, anxious mothers and fathers should have the opportunity to talk with an experienced psychologist or social worker who has counseled other expectant parents of multiples.

## PRENATAL BONDING

The increasingly routine use of prenatal screening provides most expectant parents with information about the sex, placentation and, in about half of cases, the zygosity of their infants, which can be used to enhance bonding with each twin as an individual, and with both babies as a dyad. The mother usually bonds with the baby she envisages at the time of pregnancy diagnosis. When she learns there is more than one, she has to bond twice, a process which can be compared to falling in love with two people simultaneously. Parents expect one baby and have to integrate the extra one. Some can; others have difficulty.

Piontelli[8] studied twins with ultrasound, and confirmed that they interact in myriad ways, expressing their separate identity and responding differently to their respective positions in the uterus. She pointed out that myths, legends and popular beliefs about twins attribute a 'much more lively and adult life' to them than to singletons, who continue to be seen to some extent as 'more passive, amorphous and little differentiated creatures, as if the fact of sharing the nine months of the pregnancy gave twins some kind of special attributes'. Recent additional studies by Arabin and co-workers[9] confirm this early work (see Chapter 40).

The importance of early attachment between parents and infants gained attention in the 1970s. Today, with high-resolution ultrasound, parents start observing their babies from as early as 6–8 weeks, often obtaining a clear perception of each, its individual position and its level of activity. Knowing its gender before birth makes naming easier. An individual's name lies at the foundation of his or her identity, and therefore names should be chosen carefully. Clearly, each twin is part of a pair and shares a specific social unit, but, regardless, their names should be clearly their own, and proper names rather than 'Baby A' and 'Baby B' facilitate bonding.

Psychological adaptation and prenatal bonding develop simultaneously. How easily this attachment flourishes after birth depends to a great extent on how well emotional connections were established during pregnancy. After the mother has adjusted to the diagnosis of multiple pregnancy, she must begin to accept her babies as unborn persons. In the beginning, it is often easier for mothers to bond with the unit. Only later does differentiation of specific members occur. Parents can indeed learn to love more than one child, but it is easier when they arrive separately and years apart!

In the case of twins, however, the risk of polarization is always present, in which one twin is viewed as active and the other passive, large or small, extrovert or introvert, etc. Such differences may either truly exist or result from the parental need to find distinguishing characteristics for each infant. Some mothers and fathers can 'visualize' their babies by remaining open to their dreams, images, hunches and other dimensions of human intuition. At the same time, actual images of the fetuses can be obtained with ultrasonography, either still or real-time (see Chapter 40).

Parents must realize that each unborn baby is aware and is sensitive to sound, touch and emotional states. Because the experience of twinship *in utero* is understandably one of a struggle for space, mothers need to present the notion of sharing to the twins prenatally. When one baby is felt kicking, she can reassure the other that s/he is safe. Kicking, as distinct from turning and stretching, may be a sign of distress or related to tense uterine walls. Many babies malpresent because the uterus is too small to change position. In multiple pregnancy, the natural desire to change position is complicated by the presence of one or more companions and the subsequently reduced space.

Uterine muscle tension is not under conscious control, but its muscle tone can be reduced through techniques of imagery, mediation and haptonomy. Haptonomy[10], which is well known in Europe (especially France and Germany), involves the use of touch to change the tension in the muscle spindles of the gamma nervous system. (This approach is of great value for obstetricians who perform external

version, because Veldman has developed manual techniques to encourage a baby to change position.)

It is important for the parents to encourage activity in the 'quieter' twin by touching, talking and singing. The mother can 'allow her uterus to soften' on exhalation to provide more room for the babies, envisaging a relaxed uterus that will allow each baby to stretch and turn comfortably. Parents can place their hands on the uterus as they console their babies that there is enough room, oxygen, and love and attention.

Concepts of up, down, right, left, back and front, and body parts can also be introduced to the babies when family members talk and use their hands to communicate with each, stating their names when they speak (the ear is fully developed by the fifth month[11]). A statement such as, 'This is your brother, Joe', links the touch, voice and family relationship.

The psychological adjustment of each baby and the parents is enhanced if the individuality of each twin is affirmed. To facilitate this, the midwife or doctor can draw each baby's position on the skin with a felt-tipped pen at every prenatal visit. Referring to each by name and gender (if known), also helps the babies with their sense of selves. As psychiatrists Bernabei and Levi[12] point out, 'more than other people, twins must in each moment live with the problem and the question of identity of the "I" and of the "you" and their continuing relation'. At no time is this situation more pronounced than during prenatal development, and the effects of this interaction last a lifetime.

Our understanding of prenatal existence and birth is hampered by the almost universal belief that we do not possess prenatal memories. Chamberlain[13] proposes that memory is innate rather than developmental, noting that after 80 years of intensive research, memory storage remains non-local. There is an impressive, growing body of evidence regarding memories of intrauterine experiences and the achievements in documenting this by the Association for Pre- and Perinatal Psychology and Health (www.birthpsychology.com) and the International Society of Pre- and Perinatal Psychology and Medicine (www.isppm.de). Anecdotes dealing with early twin experiences recalled during various regression therapies are described in my books *Having Twins – and More,* 3rd edition[2], and *Primal Connections*[14].

## JOURNAL WRITING

Encourage parents to keep a journal in which to express negative and positive feelings about the pregnancy, and to help bond with the twins as a unit and as individuals. It also creates a priceless record of the multiples' prenatal existence. These early writings have additional importance, because there is little time to maintain the journal after the delivery. As Leonardo da Vinci noted so aptly: 'the child grows daily more when in the body of its mother than when it is outside'.

## SETTING GOALS

Parents should turn anxieties into goals. Energy follows thoughts; for example, instead of worrying about the need for a repeat ultrasound scan, the mother can write the goal, 'The next scan shows that my babies are developing normally and all is well', to stay focused on a positive outcome. A list of goals like this for every worry, read aloud every day and reviewed frequently, is of great help to both partners.

## PSYCHOLOGICAL SUPPORT AT THE TIME OF COMPLICATIONS

Allopathic medical professionals often treat symptoms without exploring the cause. As a result, the psychological dimensions of specific complications may be overlooked. Every symptom has an underlying emotion that should be considered, especially in pregnancy. The late obstetrician David Cheek discovered that mothers of twins who develop contractions of preterm labor or high blood pressure can help resolve these complications if encouraged to talk frankly about what is going on in their lives. After 35 years of experience, he concluded that preterm labor is often caused by unconscious fears[15], and reduced the incidence in his practice to 1%. He explained how fears become reinforced by dreams of losing a baby/ies that lead to increased sensitivity to the normal Braxton-Hicks' contractions. As the contractions become more painful, the fear becomes conscious. Ideomotor questioning techniques under hypnosis can easily locate the fears and help the mother to resolve them. With his last 250 patients (expectant mothers of both twins and singletons), Cheek avoided preterm deliveries by encouraging women (who had presented with preterm labor contractions) to call him – even during the night (half of his patients would wake from their sleep with contractions) – so that he could conduct hypnosis over the telephone. In view of the benign nature of this therapy and the frequent failure of tocolytics, hypnosis is certainly worth a trial. The success of this low-risk alternative in the treatment of preterm labor and hypertension has been documented by Cheek and co-workers[4,15–17], Peterson[18] and Lewis Mehl[19].

## BED-REST LOW-RISK ALTERNATIVES

There is no accepted definition of bed-rest, but evidence exists that the reduction of physical workloads

in twin pregnancy improves outcome[20]. I advocate resting twice daily for at least a half-hour. However, total confinement in bed creates a paradoxical situation with its own 'diseases of recumbency'. Guilt may develop if the mother feels that she is neglecting her house, her other children and/or her job. The *Cochrane Review* concluded that evidence shows this practice to be worse than useless – it is harmful[3].

Whether and whenever a mother's activities are restricted, regular telephone or personal contact is essential. In Freeman's symposium on home monitoring of contractions, one group found that daily contact with the medical staff was very important, especially if the medical staff initiated it. A reduction in the incidence of preterm labor was observed even when the monitor strips were not interpreted and phone calls were the primary intervention[21].

Physical therapy to provide appropriate exercise improves the mother's confidence and well-being. Such activity relieves many physical problems as well as the mental depression that is often associated with prolonged confinement. Use of a pool helps relieve the anxiety, tension, excitement and insomnia that may result from the use of tocolytic drugs. Water facilitates movement as well as relaxation, and provides resistance for strengthening. Even if the mother requires transport by wheelchair, the benefits of immersion to reduce swelling, diminish uterine contractions and improve morale are certainly worth the effort. She can enjoy the support of the water, and also float and swim in the prone position.

## THE BIRTH AND AFTER

If events happen too fast or without the mother's full understanding, she may become less conscious of her actions and feelings, leading to 'missing pieces' in her recollection of important episodes.

### Vaginal delivery

Although almost all quadruplets, and most triplets, are routinely scheduled for cesarean section in the USA, it is ideal when the woman can give birth to twins vaginally with her pelvic joints free from compression (standing, kneeling or squatting). Natural childbirth, without medication/anesthesia, is important psychologically for the mother of twins to feel that her body has functioned normally. Although fewer and fewer mothers experience this for a variety of reasons, those who do feel empowered. The moment of birth and immediately after is a key period where hormonal surges and peak emotions facilitate attachment, as shown by Michel Odent[22]. The more directly the mother experiences each event of pregnancy and birth, the more secure she feels to trust her instincts to develop parenting skills.

### Cesarean delivery

Today, a large percentage of twins enters the world surgically for a variety of reasons. The proponents of vaginal delivery (unless contraindicated) are few indeed. Cesarean section is not in the best interests of all, given the need for postoperative recovery when the mother is challenged by rigorous demands related to the care of two babies. Furthermore, research suggests that childhood asthma is increased in the cesarean-born[23].

Even though time is often extremely short when an emergency cesarean is being set up, it is important that the parents explain to their babies what is happening and to reassure them that they will be delivered safely and lovingly, if not in the way nature intended. Staff can help the mother to feel comfortable expressing disappointment if she had truly hoped for a vaginal birth.

After cesarean delivery it is particularly important for the mother to breast-feed, in order to experience the special intimacy of nursing her infants and to increase her self-esteem. This bonding is especially important for mothers of twins, who often feel that they do not have time to give each baby 'enough' closeness.

Just as cesarean babies need additional attention, cesarean mothers need extra care, too. Physical rehabilitation restores normal muscle strength and helps prevent backache and injury. Rehabilitation should commence in the recovery room and continue for at least 6 weeks[24].

Unless the infants require special attention or admission to the intensive-care nursery, it is important that the mother holds them – together as well as singly – as soon as possible after delivery. In this manner, she can physically experience the reality of two or more babies. Hospital staff can help by assisting the mother with simultaneous breast-feeding and positioning for cuddling.

During the hospital stay, twins should share the same crib. Twins suffer double deprivation, from their mother as well as their co-twin. That co-bedding after birth is virtually unheard of indicates the poor appreciation of the emotional needs of newborn multiples both by society and by the medical profession. When the babies require intensive care, this argument is even more persuasive. Failure to thrive can occur from lack of touch and human contact in early life. By the same token, a sick multiple, separated both from his or her sibling, as well as from his or her mother, suffers even greater stress and anxiety.

### Breast-feeding

Doctors and nurses do little to help breast-feeding in the case of twins, and even less with triplets and higher-order multiples. *This is a grave disservice to parents as well as the babies*. The physiological and emotional advantages of nursing cannot be too strongly emphasized, and these benefits are even more valuable in cases of prematurity and illness (see Chapter 88). Moreover, the financial cost (up to $12 000 a year in the USA) and labor associated with bottle-feeding should be made clear, and parents should be informed that breast-fed babies develop a higher intelligence quotient (IQ)[25]. Mothers of twins need a lot of help to pump and store breast-milk if one or more twin is in the neonatal intensive-care unit (NICU). Breast-feeding is often a challenge for single, working or poor mothers, as well as mothers with other children, but bottle-feeding is *not* the solution. Instead, more financial support, home help and encouragement by maternity-care providers is required to ensure successful breast-feeding for *at least* 5–6 months.

### Circumcision

Mothers may blame themselves when a baby is fussy, unresponsive or nurses poorly, when in fact this has nothing to do with her maternal skills but is the logical result of this surgical procedure which significantly interferes with bonding and breast-feeding[26–32]. The infant (male, in the USA; females are protected by Federal law) is often in shock, withdrawn and, of course, in pain. During nursing, the boy's wounded penis is pressed against his mother's body[33]. Genital cutting is not recommended by any medical society. Performing medically unnecessary surgery is a violation of the United Nations Bill of Human Rights and the United Nations Charter of the Rights of the Child. Despite this evidence, the operation is widely practiced by parents with and without religious imperatives. Recent lawsuits and the growth of international organizations concerned with stopping circumcision and promoting foreskin restoration demonstrate that the victims are increasingly resentful of this sexual amputation. Extensive documentation on all aspects of circumcision, as well as the psychological trauma of losing 15 square inches of specialized tissue, can be found on dozens of web sites such as www.cirp.com and www.nocirc.com.

### Postpartum adjustment

Postpartum adjustment depends to a large extent on the quantity and quality of preparation and planning that the couple set up in the prenatal period. 'Twin shock' can overwhelm the best-prepared mother as she copes with marathon feedings, lack of sleep and crying babies, all of which are especially exhausting if she must soon return to work. There are also radical changes with regard to the parents' relationship that require new strategies. The new mother and her partner are now parents first, and spouses and lovers second.

Difficulty in distinguishing identical twins or preferring one over the other often leads to feelings of guilt, because new mothers have not as yet worked through a series of changing attachments. Monozygotic (MZ) twins not only look alike, but they behave very similarly. Sometimes parents themselves cannot distinguish their babies for months without the help of name bracelets, painted nails or other identifying marks. Different colored crib covers and clothes help, too. Zazzo[34] even found that 10% of mothers of MZ twins could not remember which one was given which name!

At all costs, the 'supermom' image should be tossed aside. Both parents can make the adjustment with twins easier, to ensure that they do not 'lose touch' with each other and at the same time feel that their twins are enjoying extra contact. With each parent, frequent physical contact is easily achieved by the family bath, by massaging the babies and by wearing baby carriers (one in front and one in back, or a baby per partner).

Much infant equipment, although a godsend in emergencies, is designed to separate babies from their mothers. Babies prefer *skin-to-skin* contact with each parent when they are carried, bathed, rocked and nursed. For prevention of crib death, parents should take care to protect their infants from toxic gases that arise from mattresses according to the protocols developed by New Zealand forensic scientist, Jim Sprott[35].

### Hospitalization of one or more multiples

It is a challenge for parents to bond with an infant in intensive care, as understandably they want to protect themselves emotionally in the event that the baby does not survive. Parents in such circumstances often refer to their baby as 'it'. Photographs of the baby or babies are essential when they are confined in the NICU. Make sure you obtain photos of both babies together. Today, with digital cameras and the internet, photos can be available in minutes for regularly monitoring their progress. This is an enormous help for parents who have children at home, and for whom hospital visits are difficult to organize. The parent–infant bond is a very important constant when the babies are exposed to multiple care-takers, and this is threatened as the number of people involved increases.

If a mother has a tendency to attach more to the first-born (some mothers experience the second baby as an 'extra'), she will bond strongly with the baby who comes home first. In recent years the emphasis has been on waiting until both twins can be discharged together. (Jane Spillman observed that 72% of mothers had a favorite twin, and for 84% of them it was the heavier of the pair[36].)

A mother looking after one baby attends to his or her needs without consideration. In contrast, a mother of twins must constantly choose which one is more upset, which one should be picked up first, which one is hungrier, etc., and this forces her to make distinctions. If only one baby was anticipated, and the diagnosis of twins did not sit well she may continue to view one as an 'extra' that she did not request. Meeting the needs of each twin will constantly vary, and twins, like all siblings, must learn to take turns, and from the very beginning.

## DEALING WITH OLDER SIBLING(S)

The older sibling(s) often represents a major source of stress. Regressive behavior such as bed wetting, nail biting and increased incidence of minor accidents is not uncommon with the arrival of any younger sibling. Of course twins are not just siblings, but represent celebrities, both within and outside the family. This possibility must be dealt with from the outset by making extra efforts to ensure that any older child(ren) feel affirmed of their worth and value to the family unit, and avoids hostility, indifference and, in some instances, aggressive feelings toward the twins. Ideally, each sibling should have supervised time with each twin separately. Sensitive friends and families will offer special gifts and invitations to the siblings in recognition of their individual place within the family.

Figure 58.1 shows the exponential complexity of interactions between all family members, especially when doubling of the lines of communication occurs simultaneously.

## INFANT HOSPITALIZATION

Any situation which separates the twins is taxing for both mother and co-twin. If one baby is struggling to survive, it is an enormous challenge for the mother to bond with the healthy baby while attempting to 'do enough' for the one who is ill. It is important that the healthy twin and sibling(s) – no matter how young – visit and have close contact with the baby who is ill. Otherwise, the healthy child(ren) will be disturbed by this absence, a circumstance which further increases maternal stress. Infant twins are highly distressed by separation, although they may be too premature or sick to show it. Placing them together in the same incubator can restore homeostasis. Indeed, the world was touched by the famous photo of a preterm twin placing her arm across her sick co-twin, which led to a rapid improvement once they rested together in the same incubator.

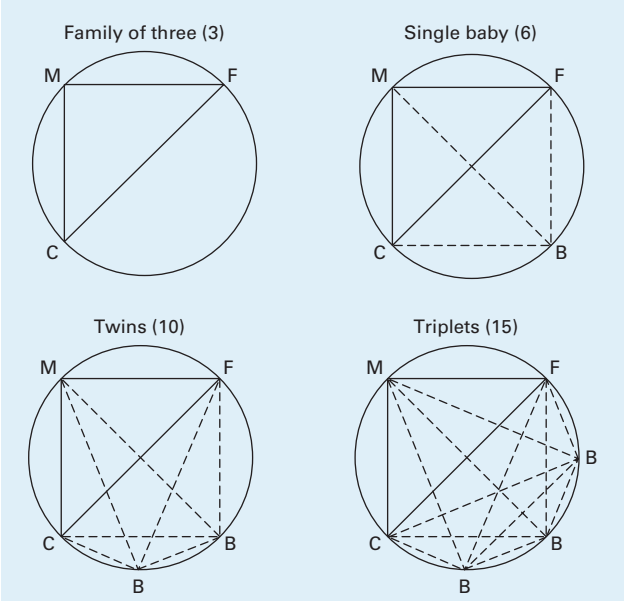


**Figure 58.1** Relationships become more complex with each child. M, mother; F, father; C, child; B, baby. Courtesy of the Multiple Birth Foundation

## COPING WITH FETAL LOSS

Many more twins exist in the shadowy world of early prenatal ultrasound (some estimates are as high as 70%) than are born (see Chapters 103 and 104). Although spontaneous fetal reduction (also called 'vanishing twin syndrome') is a benign medical event, it may be a turbulent emotional experience.

At any stage of the pregnancy, parents need to grieve after their loss, *particularly in the case of twins where the couple must continue to bond with the surviving baby*. Every possible memento should be saved: scans, autopsy report, lock of hair and, if possible, photographs of the twins together, and in each parent's arms, in any condition. The parents should hold the dead baby as often and for as long as they wish, without pressure from the staff to look after the living baby.

*The mother should never be told that she is lucky to have another living baby, or that God did not mean for her to handle an extra baby or that it is just as well because something was wrong*. As Elizabeth Bryan emphasizes, a loss is a loss and should be treated as such[37]. Because loss among multiples occurs more frequently than with singletons, maternity-care providers need to

develop bereavement skills (see Chapter 103). Encouraging the parents to grieve fully after a loss actually facilitates the processes of letting go and bonding with the survivor. Memories of traumatic events, which later become unconscious, may adversely affect the health and development of any surviving multiple(s) if the death is not openly discussed during the formative years.

It is important to remember that mothers always think of their offspring in the original number. As for the survivor, he/she is still a twin regardless of what society says. Respecting this reality is essential for family dynamics as well as for the survivors themselves, so that each one knows if s/he was once a twin. Unfortunately, society accentuates the loss by statements such as 'What a cute baby', not recognizing that the baby (and later adult) once had a twin.

In summary, multiple pregnancy has the potential to be an exciting and fulfilling time, or an anxious struggle beset with complications. Sensitive disclosure, in-depth interviews, education and counseling, assistance with physical and financial needs, and utilization of support networks facilitate optimal psychological adaptation.

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# Maternal Mortality

*I. Blickstein*

**59**



## INTRODUCTION

Almost 1 million women die annually from complications of pregnancy and childbirth[1]. The World Health Organization and United Nations International Children's Emergency Fund estimate that less than 1% of maternal deaths occur in developed countries, in contrast to the vast majority which occur in Asia and sub-Saharan Africa (almost 90%) and other developing countries (10%)[1]. This disproportion is exemplified by the estimated lifetime risk of maternal mortality (probability of maternal death faced by an average woman over her entire reproductive lifespan) of 1 in 48 in developing countries compared with 1 in 1800 in developed regions[1]. The single most important intervention to prevent these deaths is appropriate perinatal care[1].

All too often, serious morbidity precedes mortality, but morbidity registration is not calculated on local, national or continental bases; it would be next to impossible to relate it to the scant data on mortality. However, as almost all maternal complications occur more frequently during multiple compared with singleton pregnancy, contemporary authorities tend to assume that multiple gestations predispose to maternal mortality[2,3]. Unfortunately, the literature fails to support or refute this assumption for the following reasons:

(1) Because the recent 'epidemic' of multiple births mainly affects developed societies, multiple pregnancies are less frequent in countries where the maternal mortality ratio (number of maternal deaths per 100 000 live births) is high, and more frequent in countries where mortality ratios are low. The net effect is the rare occurrence of maternal mortality in multiples. By combining the probability of twin delivery (1 in 50 live births – which is often the case in countries where assisted reproduction is routine) with the probability of maternal mortality (1 in 10 000 live births), a rough estimation of the incidence can be made. In such circumstances, the co-occurrence of these events, given that they are stochastically independent, is extremely low (1/500 000 deliveries). The same calculation would yield 1/900 000 deliveries in a country where twinning is rare (1 in 90 deliveries). In countries where natural conceptions are the rule, this figure may decline in Asia, or increase in Africa, based on naturally different racial propensities to twins.

(2) Maternal death as a result of a multiple gestation or birth is not generally recorded, because the International Classification of Diseases-9 list of causes of maternal death does not include plurality[2]. For example, death from eclampsia will be recorded as such, but not as a hypertensive disorder affecting a triplet pregnancy. Similarly, death from severe postpartum bleeding may be recorded as a hemorrhagic process, but will not include information about the preceding twin gestation.

(3) In developed countries, 97% of pregnant women receive antenatal care, whereas fewer than 65% of pregnancies receive care in developing countries[1]. Also, the quality of antenatal care is less optimal in resource-poor societies. It follows that multiple pregnancies, duly considered at high risk in developed as well as

**Table 59.1** Prevention of maternal mortality

| *Prevention* | |
|---|---|
| Primary | improving women's health during their reproductive years<br>pre-conception identification of women in whom pregnancy might prove deleterious<br>reduction of the number of iatrogenic multiples |
| Secondary | antenatal care to distinguish low-risk from high-risk patients<br>to identify those who are at excess risk within the group of high-risk patients |
| Tertiary | to intervene in a deteriorating situation to avoid mortality |

in resource-poor societies, may receive better perinatal care in the former, thus further reducing potential mortalities.

Avoiding maternal mortality is closely associated with implementing preventive measures (Table 59.1). The primary prevention is amelioration of the general health of women during their reproductive years. Primary prevention also refers to pre-conception screening procedures to identify women in whom pregnancy might prove deleterious. It goes without saying that healthy mothers better endure potentially dangerous situations. For example, an anemic patient with depleted iron stores is less capable of withstanding postpartum hemorrhage. In the context of multiple pregnancies, primary prevention may refer to the urgent need to reduce the number of iatrogenic multiples in developed countries.

Secondary prevention refers to antenatal care and its ability to distinguish low-risk from high-risk patients. Although many women can carry multiples without difficulty, there is general agreement that all pregnant women carrying multiples are at risk for serious perinatal complications, and it is important to identify those who are at excess risk.

Tertiary prevention refers to the possibility to intervene in deteriorating situations to avoid mortality. Under optimal circumstances, these patients may be characterized as 'near-fatal cases' (discussed below), in contrast to other situations where maternal death is inevitable.

This chapter discusses the documented risk of maternal mortality in multiple pregnancies in general, and the risk assessment of mortality by specific conditions which are known to be more frequent among multiple pregnancies and births.

## THE NEAR-FATAL CASES

One of the most significant advances of modern obstetrics is the potential to intervene and, frequently, to save the life of a critically ill patient. This fact, however, is never discussed in relation to maternal mortality in general or multiple pregnancy in particular. The following paragraph describes the concept of near-fatal cases.

A simple, and subjective, definition of a near-fatal case is one that in other circumstances would have resulted in maternal mortality. 'Other circumstances' refer to the time and setting in which life is saved because of a timely intervention. The situation is quite similar to the distinction between near-collision and collision, whereby both the number of collisions plus the number of near-collisions defines the limits of safe transportation. In contrast, 'safe motherhood' is usually quantified solely by mortality ratios, whereas the frequency of near-fatal obstetric cases is not documented. It is obvious that what constitutes a near-fatal case in one setting may be a fatal case in another. Hence, lower mortality among mothers in developed countries may partly result from the rapid availability of the technology necessary to deal with life-threatening conditions, a possibility that may not exist under the same circumstances in developing countries.

The lessons to be learnt from an honest audit of near-fatal obstetric cases involving multiples would be particularly important to understand the sequence of events leading to the emergency situation and to avoid similar mistakes in the future. Maternal mortality audits were common in the mid-20th century, at least in the United States. No data exist on how often these audits are practiced at present. It is unknown if 'near-fatality' audits are utilized at all in modern obstetrics.

## THE ASSOCIATION OF MULTIPLE PREGNANCIES AND MATERNAL MORTALITY

Table 59.2 shows the occurrence of global causes of maternal mortality during multiple pregnancy and birth. Although the cause of death may vary considerably between developing and developed countries, the general idea is that all major causes of maternal mortality are more likely to occur during a multiple gestation. For example, Waterstone and colleagues[4]

assessed predictors of severe obstetric morbidity in 588 such cases from England, and found that multiple pregnancy had an adjusted odds ratio of 2.2 for all severe morbidities, and, in particular, 3.3 for severe pre-eclamptic toxemia (PET) and 2.3 for severe sepsis. The results of a population-based survey conducted in West Africa were not much different, in the sense that multiple pregnancies ranked among the most significant predictors of severe maternal morbidity[5]. Data obtained from the National Center for Health Statistics for the year 1989 showed that all morbidities with a potential for maternal death were more frequent among mothers of twins[3].

An important variable that must be included in estimates of maternal mortality in multiple pregnancy is maternal age[6]. There is substantial evidence to suggest that the age of the maternal cohort is increasing worldwide, and this is especially true for mothers of multiples. Figure 59.1 is an adaptation of data from the US National Vital Statistics report for the period 1980–98 to indicate the frequency of mothers aged ≥ 40 years by plurality[7]. Compared with the gradual increase in mothers of singletons, from 0.7 to 2.1%, no change was noted during the 1980s for mothers of twins, but a gradual four-fold increase from 0.8 to 3.5% was noticed between 1990 and 1998. The frequencies of older mothers of high-order multiples did not practically change until 1995, but then increased 11-fold, from 0.5 to 5.8%.

The older the mother, the higher the likelihood that she has accumulated chronic diseases before attempting pregnancy. Many of these conditions, such as hypertension and/or diabetes, may directly affect complications during pregnancy. Fortunately, the combined unfavorable effect of older mothers of multiples who may be prone to pregnancy complications is somewhat attenuated by the higher odds that pregnancy at these ages is achieved by one of the costly assisted reproductive technologies (ART). It is quite plausible that older mothers are of a different socioeconomic background, have more intense medical care and may more frequently and adequately comply with medical recommendations[6].

Finally, it should be acknowledged that a selection bias could be introduced in interpreting these data because mothers of multiples may receive more medical attention and may undergo more screening procedures to detect underlying diseases. Regardless, the association between a multiple pregnancy and severe morbidity cannot be dismissed.

**Table 59.2** Occurrence of global causes of maternal death during multiple pregnancy and birth. Adapted from reference 1

| *Condition* | *Overall frequency (%)* | *Occurrence in multiple pregnancy* |
|---|---|---|
| Severe bleeding | 25 | increased |
| Indirect causes* | 20 | increased |
| Infection | 15 | increased |
| Unsafe abortion | 13 | similar |
| Eclampsia | 12 | increased |
| Obstructed labor | 8 | increased |
| Direct causes† | 8 | increased |

*Anemia; †embolism, anesthesia-related

## MATERNAL DEATH IN MULTIPLE COMPARED WITH SINGLETON PREGNANCIES

Few studies compare mortality rates between mothers of multiples and mothers of singletons.

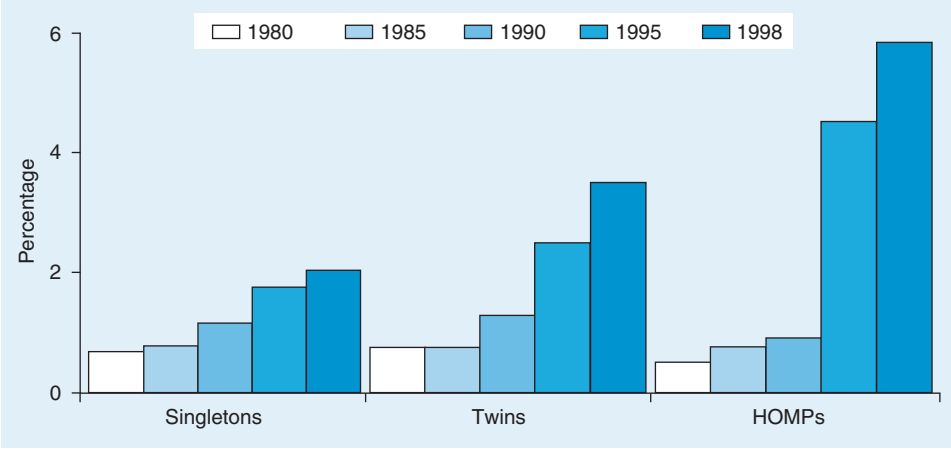


**Figure 59.1** Percentage of mothers aged ≥ 40 years according to plurality and year. HOMP, high-order multiple. Data adapted from reference 7

One recently reviewed historical account from a rural German community during the 18th and 19th centuries showed that maternal mortality during the first 42 days postpartum was not significantly different among mothers of twins compared with mothers of singletons[8]. On the other hand, mothers of twins who delivered twins a second time were almost four times more likely to die, compared with mothers of twins who later delivered singletons. This latter observation was also true for mortalities occuring during the first year postpartum, as also shown by Haukioja and colleagues[9].

More recently, a population-based study from Malawi during the period 1987–90 found a sevenfold risk for maternal mortality in multiple gestation, compared with singleton births[10]. The authors estimated that multiple pregnancies contributed 11.5% of the maternal deaths in this sub-Saharan population.

Another, albeit far more comprehensive estimate of the association between multiple gestation and frequency of adverse maternal outcomes derives from the database of the Latin American Center for Perinatology and Human Development[11]. Among parous women, multiple gestation was associated with a two-fold increase in risk of death compared with singleton gestations. Moreover, the adjusted relative risks for PET, eclampsia, anemia, postpartum hemorrhage and endometritis were 2.2, 3.0, 1.8, 2 and 1.8, respectively[11].

Only one study from developed countries directly addresses the association between multiple pregnancy and maternal death[12]. In France, maternal mortality was 10.2 vs. 4.4 per 100 000 live births in multiples versus singletons. According to Senat and colleagues, the corresponding figures were 14.9 vs. 5.2 for all of Europe[12].

## SPECIFIC MATERNAL CONDITIONS LEADING TO MATERNAL DEATH IN MULTIPLE PREGNANCIES

As noted above, maternal morbidity during a multiple pregnancy may lead to life-threatening circumstances that precede mortality. As early as the 4th century BC, Hippocrates provided a description of what today would also be characterized as a maternal death after twin delivery[13]:

> 'Case IV. In Cyzicus, a woman who had brought forth twin daughters, after a difficult labor, and in whom the lochial discharge was insufficient, … On the fourteenth, frequent convulsions; extremities cold; not in anywise collected; suppression of urine. On the sixteenth loss of speech. On the seventeenth, she died. Phrenitis. Explanation of the characters. It is probable that death was caused, on the seventeenth day, by the affection of the brain consequent upon her accouchement.'

### PET and eclampsia

Hypertensive disorders are among the most serious complications, affecting as many as one in three or as few as one in ten multiple pregnancies (see Chapter 53). In either case, these numbers are significant. After many centuries of study, and despite the fact that none of the currently existing theories to explain why pre-eclampsia is more frequent among twins is convincing, the association between PET and multiple gestation is clinically apparent.

PET in multiples is characterized by the following observations:

(1) PET is more frequent than in singletons. Case–control studies show a 2.5–3.5-fold increased incidence[14–19];

(2) The increased risk of PET seems to be more pronounced in nulliparas[14,17,20];

(3) PET occurs earlier during multiple pregnancy[19,20];

(4) PET is more severe[19,20];

(5) PET is plurality-dependent, i.e. frequency increases with the number of fetuses and decreases following multifetal pregnancy reduction[21];

(6) Women who conceive multiple gestations through ART have a 2.1-fold higher risk of PET than those who conceive spontaneously[22].

The life-threatening complication of PET is eclampsia, occurring in 1.7–2.3% of PET cases in multiples[14,17,20]. Comparison with singleton cohorts indicates that eclampsia is significantly more frequent among twins[14,17]. A UK national eclampsia survey[23] found a relative risk of 6.0 for eclampsia in a multiple pregnancy, compared with eclampsia in singleton gestations. In this survey, nearly 1 in 50 women (1.8%) died. Lopez-Llera and colleagues[24] analyzed 37 cases of eclampsia in twins and found a three times higher incidence compared with the general population. Maternal mortality was slightly higher in mothers of twins, and lower in cases delivered by cesarean section.

Two series reported a 1 : 6 rate of death in cases of eclampsia in mothers of twins[14,24]. Both were small, and the largest included only six cases[24]. Notwithstanding, a probationary clinical profile can be constructed: half of the patients were nulliparas, all mortalities occurred near term (> 37 weeks' gestation), two-thirds had vaginal birth, five of the 12 fetuses died, five of the six patients had like-sexed

male pairs, half of the eclampsia cases occurred before birth and two-thirds of cases were complicated by brain hemorrhage. In the Czech Republic, five of ten PET cases presenting with convulsions leading to coma and death were multiple pregnancies[25].

In sub-Saharan Africa, the risk described above is accentuated. In a report from Mali, where the maternal mortality ratio was 327 per 100 000 live births, there were 64 twin deliveries[26]. Hypertensive disorders were the main underlying cause of death (four of 13), of which one case of eclampsia occurred in a mother of twins[26].

The HELLP syndrome (hemolysis, elevated liver enzymes and low platelets) is considered a variant of severe PET. As a subtype of PET, the occurrence of HELLP syndrome is expected to be higher in pregnancies that are more likely to develop severe PET. Hence, the increased association with a multiple pregnancy is logical, particularly in high-order multiples[27–29].

Maternal death in a twin pregnancy complicated by HELLP has been reported[30]; however, it must be emphasized that mortality cases may be registered as a hypertensive disorder rather than HELLP syndrome. In addition, diagnosis of the syndrome requires laboratory corroboration, which might be unavailable in resource-poor countries[31]. Together, it seems that HELLP-related deaths are under-reported.

Regrettably, no biochemical marker accurately predicts PET. Elevated serum uric acid levels, attributed to decreased renal urate excretion, frequently precede the onset of PET (73% sensitivity, 74% specificity at 30–31 weeks)[32]. A positive correlation is found, irrespective of maternal size, between the concentration of serum uric acid and the number of fetuses, suggesting that, for clinical purposes, the cut-off level might have been adjusted to plurality[33].

## Tocolysis

Preterm birth is the most serious perinatal complication affecting multiple gestations, and is a direct consequence of the inability of the human female to gestate efficiently more than one fetus at a time. The result is an inverse relationship between gestational age at birth and plurality. By singleton standards, a significant proportion of twins and almost all higher-order multiples are delivered preterm. In one often quoted analysis of the US population of multiples, 14% of twins and 41.3% of triplets were born at less than 33 weeks' gestation[34] (see Chapter 1 for updated information). The need for tocolysis is frequently encountered in multiple pregnancies (see Chapter 72). However, traditional tocolytic agents often lead to a significant increase in cardiac output. Figure 59.2 shows how each component of a multiple pregnancy in preterm labor contributes to the increase of cardiac output[35]. In such circumstances, it is quite obvious that the risk of cardiac failure is significant. Intravascular overload, incipient infection and, to a lesser extent, enhancement of lung maturation by steroids further complicate tocolysis with β-mimetics. At least three cases of maternal mortality in twin pregnancy have been associated with β-mimetic treatment[36–38].

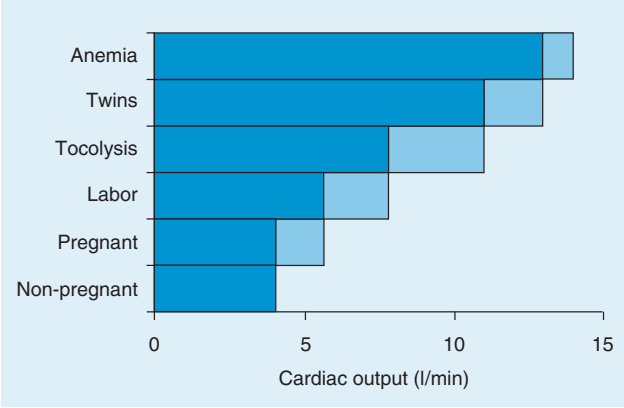


**Figure 59.2** Components of preterm labor in twins and their contribution to cardiac output (l/min). Adapted from reference 35

The need for careful and prudent use of tocolytic agents in patients with multiple pregnancies is generally acknowledged. Currently, tocolysis is most often given with the primary intention to postpone birth for at least 48 h, in order to enhance lung maturity by administering corticosteroids. Prolonged, and perhaps more aggressive, tocolysis may be also considered in unique situations and under special obstetric intensive care. In addition, our current understanding of the cardiovascular effects of the available medications, and the laborious quest for new and better tocolytic agents, will minimize the risk of maternal death from tocolysis.

## Acute fatty liver of pregnancy

Acute fatty liver of pregnancy is a serious condition of liver failure that may prove fatal for both mother and fetus (see Chapter 53). The reported frequency in triplet gestations – 7% – is much, much higher than that in the general population (1 in 10 000 pregnancies)[27]. It has been suggested that triplet gestations may contribute to the onset of acute fatty liver by further stressing the fatty acid oxidation capabilities of susceptible women[39]. The same authors describe three cases in which the presenting features were vague abdominal complaints with elevated hepatic aminotransferase levels. Clinical resolution followed prompt cesarean delivery performed

immediately after the diagnosis of acute fatty liver was confirmed by liver biopsy[39]. The initial subtle clinical picture calls for close monitoring for the early signs of acute fatty liver. The need for postpartum orthotopic liver transplantation following fulminant hepatic failure from acute fatty liver in a triplet gestation has been described[40].

## Placental abruption

Placental abruption is more frequent in multiple gestations. This may be simply a result of more placentas per pregnancy, a result of increased likelihood of sudden decompression of an overdistended uterus or because of the frequent association of abruption with PET, which is much more common in multiple pregnancies. In a typical case, premature separation of the placenta may occur after rupturing the membranes for twin B following the decompression after delivery of twin A. Abruption is a potential complication of amniodrainage therapy in twin–twin transfusion.

In a population-based comparison between twins and singletons, Ananth and colleagues[41] found that abruption is twice as likely to occur in twins (12.2 vs. 5.9 per 1000 births) (see Chapter 84). These authors also found a differing risk factor profile in mothers of twins, suggesting a different pathophysiological process[41]. Abruption was the direct cause of 2.1% pregnancy-related maternal deaths in the United States[42]. One of the six mortalities associated with eclampsia among mothers of twins had a 45% abruption[24].

## Delivery-related mortality

In most developed countries, the incidence of cesarean births for twins and high-order multiples is about 60% and almost 100%, respectively[43]. However, the rate of cesarean deliveries is much lower in developing countries. At the time of birth, and irrespective of the mode of birth, maternal anemia is 2.4 times higher in twin gestations compared with singletons[3,16,44], adding to the complications associated with delivery of multiples. Indeed, hemorrhage (see Chapter 83) is a significant cause of maternal mortality, because the accentuated tendency to greater blood loss may be more risky in multiple gestations[26].

Some idea about delivery-related maternal deaths in twin gestations may be obtained from observations recorded in developing countries. Most specific causes for pregnancy-related mortalities[42], such as bleeding, embolism, infection and anesthesia-related fatalities, occur more often during abdominal delivery. Unuigbe and colleagues[45] examined the outcome of cesarean section in twin pregnancy in a teaching hospital in Nigeria, and found that the maternal mortality ratio for cesarean section for twin delivery (20/1000) was considerably higher than that for all cesarean sections (7/1000) and the overall maternal mortality ratio within their maternity unit (4/1000). In Mali, three of the 13 reported mortalities were due to sepsis after cesarean section[26]. In Gabon, the most frequent maternal complications in multiple pregnancy were hypertensive disorders and anemia. Here, the maternal mortality was three times higher than in singleton deliveries, and was related to postpartum hemorrhage[46]. In Guinea-Bissau, where the maternal mortality ratio is around 800 per 100 000, only twin birth was found to be significant in the adjusted model of maternal mortality factors[47].

A significant and unique predisposing factor for maternal complications is the delivery of a retained second twin. In developing countries, the first-born twin may be delivered outside the hospital and the second twin, sometimes after many hours and often dead, is delivered when the parturient is eventually transported to the hospital. By that time the parturient may be septic and bled out[26]. In the Nigerian study, as many as 26.8% of cesareans in twins were for a retained second twin[45]. Moreover, 85% of all retained second twins occurred following birth of the first twin under the supervision of a traditional birth attendant[48]. Lassey and Ghosh[49] found one case of maternal death among 33 cesareans performed for the delivery of twin B.

It is clear that cesarean section carries different risks in developed and in developing countries. The differences may result from the preoperative condition of the patient as well as the indication for surgery itself. Regardless, cesarean delivery of twins seems to carry a significantly higher risk of maternal puerperal infectious morbidity. Suonio and Huttunen[50] compared maternal infectious complications of abdominal deliveries of twins and singletons. They found a nearly three-fold increased risk for endometritis and a nearly two-fold increased risk for abdominal wound infection among twin gestations.

One conclusion from these studies might be that, irrespective of antenatal course and early labor progress, twins in developing countries should be delivered where facilities for cesarean section are available[48]. In this way, the need for intervention when complications occur is more aptly met. This potential solution is not realistic, as any reader of the literature on maternal mortality in singletons can attest. Indeed, a distance of over 25 km from a regional hospital is associated with a seven-fold risk of maternal death[47]. Other authors had previously proposed similar cautions, but many countries are simply unable to ensure effectively such safety measures.

## SUMMARY

Complications, which are increased in multiple gestations because of unique physiological changes in combination with specific perinatal pathologies, create a true potential for maternal mortality. It is not surprising that reports of maternal deaths associated with multiple gestations come mainly from resource-poor countries, where lack of efficient perinatal care is the rule rather than the exception. Quite often, the lack of national resources acts in concert with local traditional ways for perinatal management to increase the risk for both mother and fetus(es).

As the prevalence of multiples is escalating in most developed nations, it is reasonable to surmise that the risks associated with multiples are also increasing. Although the lesson learnt from developing countries may not be fully applicable to other populations, the inherent risk for maternal mortality associated with multiple pregnancies cannot be underestimated.

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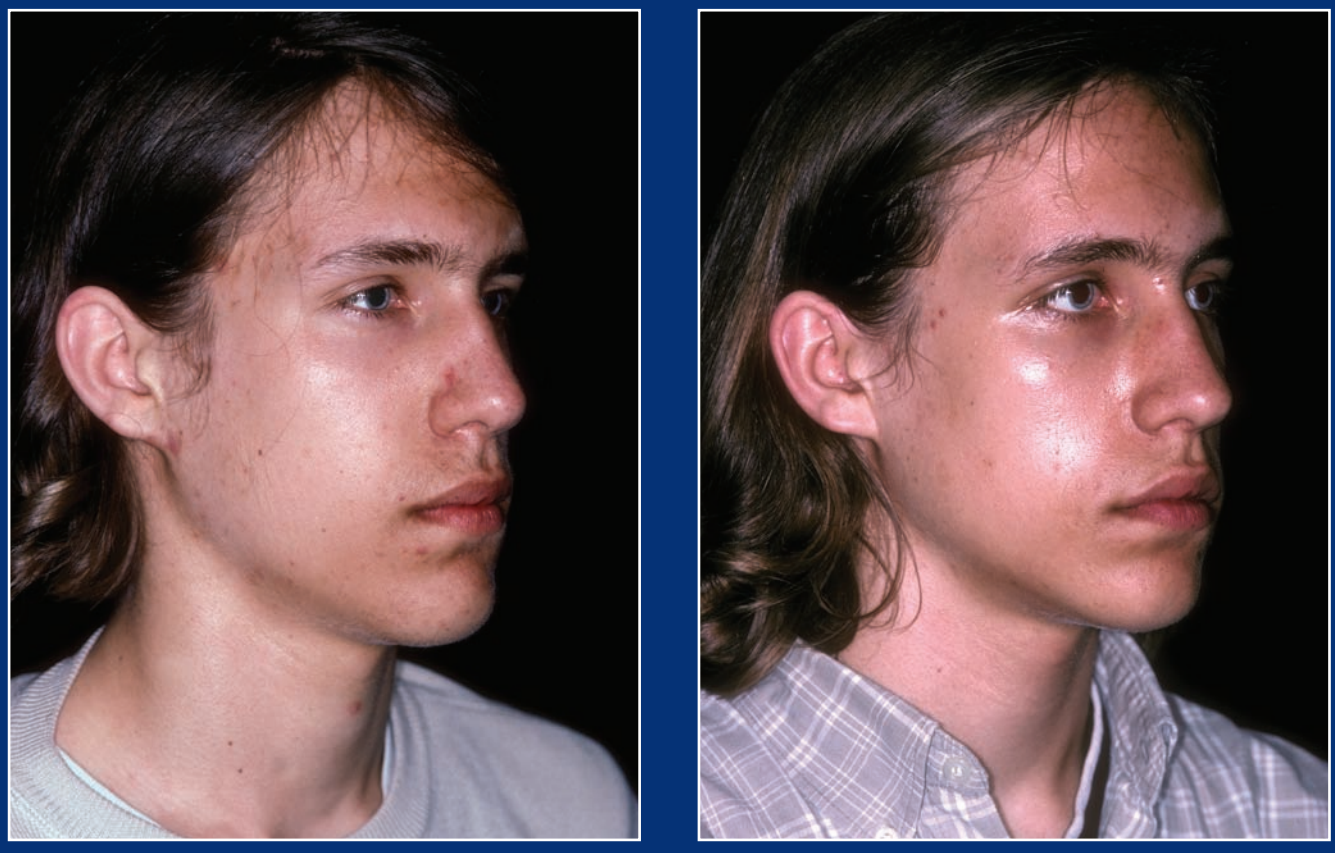
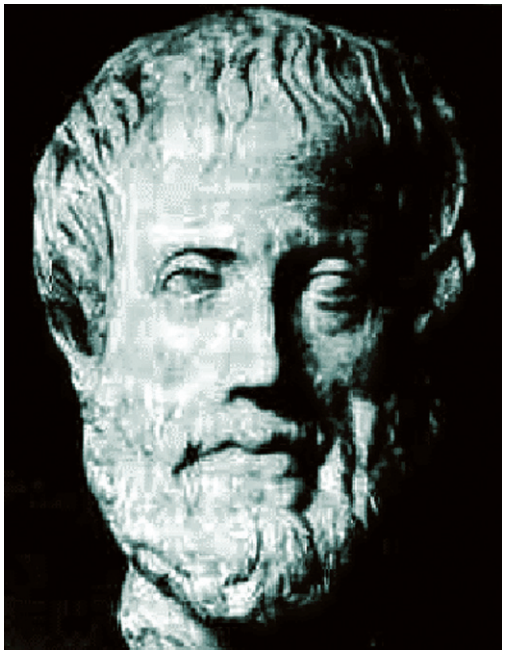
# SECTION V

# PREGNANCY MANAGEMENT: FETAL GROWTH AND WELL-BEING



**16-year-old male monozygotic, monochorionic, mirror twins, Belgium, 2004.**

Participants since birth in the East Flanders Prospective Twin Study. Twin A left, Twin B right.



Aristotle (384–322 BC)

The earliest documented scholastic approach to twinning is probably found in Aristotle's Historia Animalium. In simple terms, the Aristotelian concept about twinning is summarized in two Latin statements: '*praeter ut il pluribus*' (outside that which occurs frequently) and '*praeter naturam*' (outside Nature's common course).

He commented as follows (Book VII, Chapter 4): '*…some animals produce one and some produce many at a birth, but the human species does sometimes the one and sometimes the other. As a general rule and among most nations the women bear one child at birth…*' The Aristotelian view is, in many ways, still valid. The human female is not expected (by Nature) to carry a multiple pregnancy. As a result, fetal development in a multiple pregnancy is not the same as in singleton gestations, a fact that is reiterated throughout this book.

Although multiples are prone to many specific and non-specific complications, the majority of cases, especially twins, enjoy an uneventful course. Under these circumstances, the clinician should concentrate on two interrelated issues: are the fetuses appropriately grown and do they exhibit signs of distress? These questions are dealt with in this section.

*I.B. and L.G.K.*

# Contents of Section V

# Intrauterine Growth

*I. Blickstein*

60



## INTRODUCTION

Spontaneous twins and higher-order multiples are rare, constituting only about 1% of human births. This observation alone suggests that the reproductive system of the human female is not programed by nature to carry more than one fetus at a time. The fact that almost 99% of human gestations are monotocous may further suggest that the uterine milieu is indeed inadequate to nurture more than a singleton fetus.

In terms of intrauterine growth, a positive relationship usually exists in singleton pregnancies between gestational age and birth weight, whereby fetal size increases as gestational age increases. If this were the case in a multiple pregnancy, multiples would weigh the same as singletons throughout gestation. However, careful examination of the so-called twin and triplet 'growth curves' (birth weight by gestational age) adapted from US data clearly implies that the uterus is able to nurture each of the multiples almost to the same extent as in singleton gestations only until about the 28th week (Figure 60.1)[1].

Thereafter, and in all probability as a result of the restricted capability of the uterine environment to nurture more then one fetus at a time, the positive relationship between gestational age and fetal size seen in singletons cannot be maintained in multiple pregnancies. These antepartum observations are based on sonography-derived curves that plot various fetal indices as well as the estimated birth weight by gestational age. Ultrasound assessments of these growth parameters demonstrate a pattern of deceleration that occurs sometime between 30 and 33 weeks' gestation[2,3]. Moreover, this pattern is observed earlier in triplets[3] than in twins[2] and in twins earlier than in singletons.

A closer look at the growth curves shown in Figure 60.1 suggests two points of deviation: deviation of the multiples' curves from that of singletons (at about 28 weeks) and deviation of the triplets' curve from that of twins (at about 35 weeks). These dates coincide with changes in other growth trends, two 'milestones' in the growth of multiples that are discussed below.

This chapter discusses the evidence that demonstrates the limits of the uterine ability to nurture twins and triplets and the inevitable manifestations of uterine and fetal adaptations to the multiple pregnancy.

## LOW-BIRTH-WEIGHT AND SMALL-FOR-GESTATIONAL-AGE MULTIPLES

That twins and triplets are smaller than singletons is well known. Alexander and colleagues[1] showed that the frequency of birth weight < 2500 g (i.e. low birth weight, LBW) was 6.1, 52.2 and 91.5% for singletons, twins and triplets, respectively. When a lower cut-off value was selected, the frequency of birth weight < 1500 g (i.e. very LBW, VLBW) was 1.1, 10.1 and 31.9% for singletons, twins and triplets, respectively. The likelihood of delivering one or two VLBW twins was studied from a database comprising 12 567 live-born twin pairs delivered between 1993 and 1998 in Israel[4]. The frequency of at least one VLBW twin was significantly higher among nulliparas than multiparas (odds ratio (OR) 2.3, 95% confidence interval (CI) 2.1–2.6). Overall, the risk of having at least one VLBW infant was 1 : 5 among nulliparas and 1 : 12

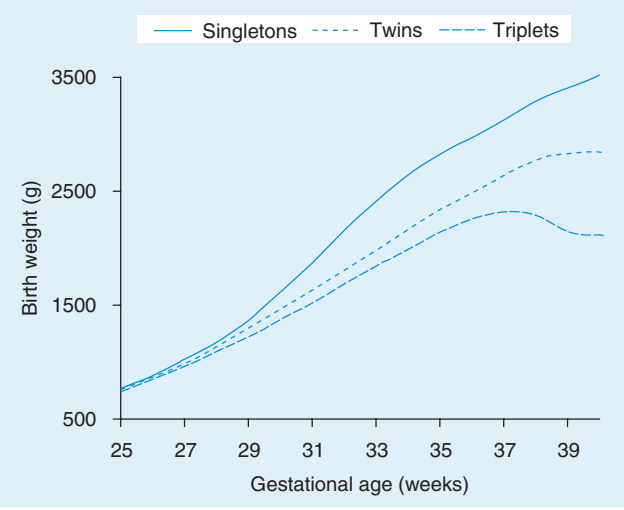



**Figure 60.1** The 50th birth-weight centile by gestational age curves for singletons, twins and triplets. Deviations from singleton standards appear after 28 weeks. Adapted from reference 1

among multiparas. These data also showed that the risk of having two VLBW twins among nulliparas (1 : 11) was double that of multiparas (1 : 22)[4].

In a similar manner, the likelihood of delivering one, two or three extremely LBW (< 1000 g, ELBW) triplet infants was studied in a nationwide perinatal database of 3288 triplets collected by Matria Healthcare, Inc. (Marietta, GA)[5]. The odds of an individual triplet pregnancy terminating with at least one ELBW infant were significantly higher among nulliparas (1 : 8) than among multiparas (1 : 14) (OR 1.9, 95% CI 1.9–2.5). The odds of having two or more ELBW triplet sibs in nulliparas (1 : 16) were twice higher than in multiparas (1 : 31) (OR 2.0, 95% CI 1.3–2.9). However, for an as yet undetermined reason, nulliparas and multiparas had similar odds of delivering three ELBW triplet infants (1 : 29 versus 1 : 40; OR 1.3, 95% CI 0.9–2.1)[5].

The indisputable fact that LBW is more frequent among multiples compared with singletons does not imply that growth of multiples is basically pathologic. Because multiples were quite uncommon until the past two decades, population-based growth curves for twin and triplets were not available until recently, and studies relied on singleton values. With the publication of plurality-specific curves, it became a matter of debate whether singleton standards should be used in assessing growth of multiples. This controversy is not only based on practical arguments, but also stems from accepting or rejecting the far more basic concept that intrauterine growth patterns of multiples differ from that of singletons.

One argument against using plurality-specific curves is that being growth restricted, rather than being small for gestational age (SGA), is of far greater clinical importance. To establish true intrauterine growth restriction (IUGR), one must follow fetal growth longitudinally[6], in order to detect that point in time when the growth pattern manifests 'crossing of centiles' (i.e. the growth of an individual fetus decelerates and does not continue along its initial growth curve). Indeed, only those fetuses that do not maintain their initial growth potential as pregnancy advances should be considered as exhibiting IUGR, and any growth curve – plurality-specific or singleton-based – may be suitable for this assessment. Regrettably, longitudinal assessment of fetal growth in multiples is frequently unavailable, and the clinician may be asked to decide whether, at a given point of time, one or more of the multiples is growth restricted. In this circumstance, the best way is to determine whether the individual fetus is SGA, because the likelihood of IUGR is higher among SGA fetuses. Furthermore, this likelihood increases when a stricter cut-off value for SGA is used (i.e. 3rd or 5th centile instead of 10th centile). It follows that using the 3rd centile of singleton standards or the 10th centile of plurality-specific standards may serve the same clinical purpose of depicting an SGA twin or triplet, as long as longitudinal evaluations are performed. Conversely, if a large singleton cut-off value is used in point observations, it is logical to assume that the greater is the gestational age the less accurate is the prediction of SGA[7].

Because there is no reason to suggest that defining multiples as SGA should be different from defining SGA singletons, it is interesting to see whether multiples are more frequently SGA by singleton standards. Figure 60.2 (using the US *Matched Multiple Birth File*[8]) shows the median birth-weight curves of twins and triplets compared with the 10th centile curve of singletons. The figure indicates that the median birth weight of twins is less than the 10th birth-weight centile of singletons (i.e. SGA by singleton standards) only after 38 weeks. For triplets, the median birth weight is less than the 10th birth-weight centile of singletons only after 35 weeks[9,10].

Based on these observations, one can conclude that twins or triplets are not multiple singletons that, fortunately or unfortunately, share the same uterine environment. Moreover, it follows that growth aberrations of twins and triplets should also not be defined as for singletons.

## GROWTH OF MULTIPLES COMPARED WITH GROWTH OF SINGLETONS

The observation that multiples are smaller than singletons (Figure 60.1) supports the assumption that he uterine milieu efficiently provides for fetal growth

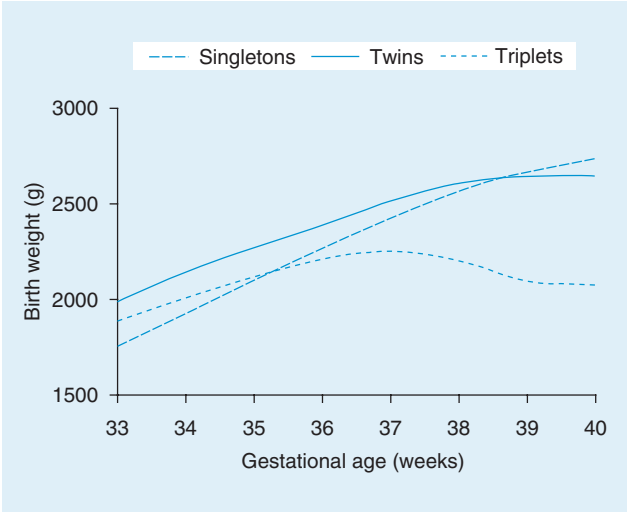



**Figure 60.2** The 50th birth-weight centile for twins and triplets compared with the 10th birth-weight centile for singletons (broken line). Both average twin and average triplet neonates weigh below the 10th birth-weight centile for singletons only after 38 and 35 weeks, respectively. US *Matched Multiple Birth File*[8]

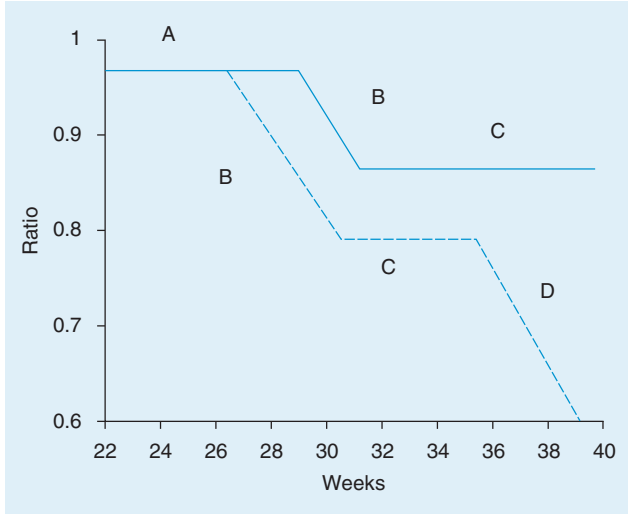



**Figure 60.3** Schematic presentation of trendlines describing the ratio between the median birth weight of twin/singleton and triplet/singleton. Broken line, triplets; solid line, twins. The four phases (A–D) are discussed in the text. Adapted from reference 9

until a certain gestational age is reached. Thereafter, a pattern of growth restriction for twins and triplets relative to singletons is seen. Even so, the individual growth of a given member of a twin or a triplet set exhibits a predictable pattern compared with singletons[9,10]. This pattern can be elaborated by reassessing the data presented by Alexander and colleagues[1] and by comparing the ratio between median birth weights of twin/singleton and triplet/singleton. Four phases (A–D) are schematically shown in Figure 60.3[9,10].

In phase A, a very similar birth weight to that of singletons is maintained (ratio of 0.9–1.0) until 28 and 30 weeks' gestation in triplets and twins, suggesting that the uterine environment is fully capable of providing growth of the individual multiple fetus to the same extent as for a singleton. Multiples delivered at this phase are not likely to demonstrate growth restriction, albeit they have very low birth weight.

Phase B starts at around 30 weeks in twins and earlier in triplets. During this phase there is a steady decrease in birth weight of the individual multiple relative to singletons, suggesting that the uterine milieu is insufficient to provide fully growth of the individual twin or triplet fetus whose birth weight is smaller relative to that of a singleton by as much as 15–20%.

During phase C, the ratio does not change significantly over time, implying that birth weights of multiples during this phase are maintained at about 15% and 20% less than that of singletons.

Phase D, seen only in triplets, represents an inability of the overwhelmed uterine milieu to adapt, leading to a marked decrease in triplet birth weight relative to singletons after 35 weeks.

Although the growth patterns of multiples shown in Figure 60.3 are based on cross-sectional observations, two different conditions are apparent. The first promotes age and maintains size (phases A and C), whereas the second promotes age and restricts size (phases B and D). From an individual fetal perspective, it appears that nature favors advanced gestational age (i.e. maturity) at the expense of size[9,10].

From the physiologic point of view, little doubt exists that the higher is the plurality, the greater is the challenge to the uterine environment. Jones and co-workers[11] showed that the linear growth of triplets lacks the accelerated growth pattern seen in singletons, and suggested that the lack of such acceleration results from suboptimal transfer of nutrients by the uteroplacental unit. More recently, the relationship between gestational age and both total and individual triplet birth weight was studied in a large data set[12]. The study used a 1988–2000 prospective cohort of 3238 live-born triplets in the United States. Mean individual (heaviest, middle and lightest) and total triplet birth weights were correlated with gestational age. Although it could be expected that each member of a triplet set would have a different growth pattern, neither the type (linear or nonlinear) nor the slope was predictable. It was also unknown whether all sibs had the same type of growth curve and whether the regression lines were parallel or diverging. The data indicated that the respective regression lines for each of the individual

triplets showed a significant linear correlation but were diverging in nature, suggesting a different growth velocity of the heaviest, the middle and the lightest triplet. These data also support a model of two distinct growth periods for triplets: an age- and growth-promoting period until 33 weeks and an age-promoting, growth-restricting period thereafter, in support of the trend shown in Figure 60.3[12].

Another way of looking at the growth of triplets is by evaluation of their ponderal indices. The ponderal index – a measure of size rather than weight – is a useful tool to differentiate growth-restricted from normally growing SGA infants. A recent study[13] examined the association between a low neonatal ponderal index (birth weight/(length)$^3$) defined as less than 1 standard deviation (SD) below the mean (2.0) and SGA (defined as birth weight below the 10th centile by triplet standards). In a sample of 2181 triplet sets, it was found that those delivered at ≤ 33 weeks had a lower mean ponderal index compared with those delivered at > 33 weeks. About 70% of SGA triplets do not have a low ponderal index, whereas 79.2% of infants with a low ponderal index are not SGA by triplet standards. Both the frequency of a low ponderal index and the frequency of infants with a low ponderal index who are not SGA decrease with increasing gestational age. The authors of this study concluded that the majority of triplets with a low ponderal index might not be considered growth restricted, supporting the concept that reduced fetal weight of triplets is more likely a physiologic rather than a pathologic phenomenon[13].

## THE MOTHER OF MULTIPLES AND FETAL GROWTH

Pregnancy is a demanding physiologic process, which produces remarkable changes in the expectant mother (see Chapter 49). One of the purposes of these changes is to supply sufficient nutrition for the growing fetus. Clearly, in a multiple pregnancy, there is a need to provide for the excess in fetal mass. Specifically, the median birth weight of 3289 g for a singleton at 40 weeks' gestation is achieved by a pair of twins as early as 31 weeks when the median total fetal birth weight (both twins) is 3358 g[9,10]. In triplets, the median singleton birth weight at 40 weeks is attained by the three combined fetuses even earlier, at 28 weeks[2,3]. Stated differently, if a mother were to provide the median singleton birth weight at 38 weeks for the entire twin or triplet pregnancy, each of her twins or triplets would weigh, on average, only 1650 and 1100 g, respectively. Fortunately, the average individual birth weight of twins and triplets at that gestational age far exceeds these values. It follows from the maternal perspective, therefore, that although each individual fetus in a multiple pregnancy might be smaller than a singleton, the entire multiple pregnancy is, nonetheless, *growth promoted* [9,10].

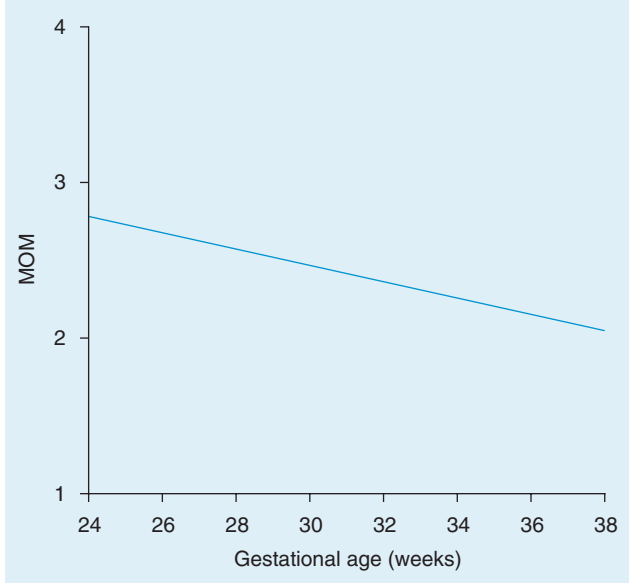



**Figure 60.4** Triplets' birth weights presented as multiples of the median (MOM) birth weight of singletons at the same gestational age (trend line). US *Matched Multiple Birth File*[8]

A novel approach to appreciate the excess fetal weight in a multiple pregnancy was considered recently, whereby total fetal weight in triplets was defined as multiples of the median (MOM) singleton birth weight for the same gestational age (Blickstein and colleagues, unpublished data). The average MOM values derived for 6466 triplet sets decreased as a highly significant, inversely linear, function of gestational age ($R^2 = 0.95$, Figure 60.4). Figure 60.4 also shows that sets with total birth weight approaching 3 MOM (i.e. thrice the singleton's median birth weight) were born mainly before 28 weeks, whereas sets with total birth weight approaching 2 MOM (i.e. twice the singleton's median birth weight) were born mainly after 32 weeks. Further, sets with average MOMs were always between two and three times the median birth weight of a singleton at the same gestational age. Importantly, sets with MOM < 1 SD, MOM ± 1 SD and MOM > 1 SD had significantly different neonatal death rates, suggesting that the uterine efficacy to nurture triplets is clearly associated with perinatal outcomes (data not shown).

Another way to evaluate the uterine efficiency was to count the frequencies of triplet sets delivered at less than 30, 30–32 or more than 32 weeks, which attained a total triplet birth weight exceeding the 90th centile for singletons at 36, 38 and 40 weeks' gestation[9]. The data indicate that for > 99% of triplet

sets delivered at > 32 weeks, the total triplet birth weight was heavier than a large-for-gestational-age singleton at 36 weeks or more. This finding implies that by 32 weeks' gestation, the uterine milieu for triplets is *definitely* performing to its full capacity.

Finally, it has been shown that the uteroplacental unit is still efficient even in cases of birth-weight-discordant twins[14]. The total birth weight of discordant pairs delivered before 28 weeks was >75% higher, compared with singletons. The excess mass gradually decreased to around 50%, a value that remained relatively unchanged with advanced pregnancy until approximately 37 weeks when it declined again[14]. These data suggest that even when severe discordance is present in twin pregnancies, the uteroplacental unit still supplies 50–75% more than for the average singleton gestation.

Because mass and energy are closely related, the requirement for mass represents a demand for more energy, and, in the case of multiple gestations, this involves greater nutritional requirements than for singleton gestations. Indeed, Luke and colleagues reported that maternal weight gain early during pregnancy might improve outcomes of twins[15] as well as triplets[16,17]. When maternal weight gain during pregnancy was adequate, improved outcomes were observed in terms of prolonging length of gestation and in larger birth weights[15–17]. Moreover, because multiple gestations have a shorter duration, the need for significantly earlier weight gain was emphasized[15–17]. It was recently confirmed that above-average weight gain during the first 24 weeks of triplet gestations improved neonatal outcomes in terms of greater total triplet birth weights and fewer VLBW neonates in both nulliparas and multiparas (G. Sharma and colleagues, unpublished data). However, the recommended weight gain[18], in relation to the influence of confounders such as parity and pre-pregnancy body mass index, requires further study in large series.

## RELATIVE GROWTH RESTRICTION: BIRTH-WEIGHT DISCORDANCE

Every set of fetuses is obliged to accommodate within a given uterine environment, as the potential to increase uterine volume and nutritional capacity is decidedly limited because of the physical constraints of the maternal abdominal cavity. In the worst-case scenario, the uterine milieu limits adequate growth for all fetuses. On the other hand, in less severe cases, growth is impaired for some of the fetuses, giving rise to the well-known phenomenon of birth-weight discordance, whereby disparity in birth weights occurs between the larger and the smaller infant of a multiple pregnancy set.

These circumstances underlie the fact that in any large series of multiples one seldom finds all members of a set with the same birth weight. On the contrary, some inter-sib variation is expected, and therefore the magnitude of the difference – the degree of discordance – has to be incorporated in the definition of discordance. Regrettably, none of the available definitions is perfect[19]. Nevertheless, of the several that have been proposed, the so-called '*per cent*' definition is by far the most common in practice, even today[19]. In this definition, birth-weight disparity is calculated as a percentage of the weight of the larger infant. A major deficiency of this definition, however, is that it does not refer to the actual size of the sibs. Thus, the per cent definition may assign the same degree of discordance (i.e. 20%) to a twin pair weighing 1500/1200 g and to a pair weighing 3000/2400 g. Using the per cent definition, about 75% of twins exhibit < 15% discordance, an additional 20% are 15–25% discordant and about 5% are more than 25% discordant[14] (Figure 60.5). Such differences are referred to as concordant, mildly discordant and severely discordant, respectively[20,21]. Observations in triplets suggest both a higher frequency and greater severity of birth-weight discordance, namely, discordance of 25–35% and > 35% in 19.4% and 9.5% of the 2804 triplets analyzed, respectively[22].

The definition of birth-weight discordance is even more complex in triplets. Authors usually use the '*per cent*' definition of twins and describe the difference between the largest and smallest triplet of each set. However, this definition ignores the middle sibling and, as a result, the true inter-triplet relationship. Recently, a new description of discordance in triplets was proposed, in which the relative birth weight of the middle triplet was defined[22]. In the first step of the analysis, the per cent definition was used to define concordance and discordance (> 25%). Then, the triplet set was defined as *symmetric* when the birth weight of the middle triplet was within ± 25% of the average birth weight between the larger and smaller triplet, as *low-skew* when the set comprised one large and two small triplets and as *high-skew* if the set comprised two large and one small triplets. Such designations more precisely denote different severities of triplet discordance. Interestingly, the frequencies of different types of triplet discordance remained unchanged with gestational age, suggesting three distinct, gestational-age-independent, types of discordant growth in triplets (average values: symmetric 57%, high-skew 30% and low-skew 13%)[22].

Of equal importance, these data further indicate that symmetrically discordant sets are probably the standard arrangement favored by the uterine

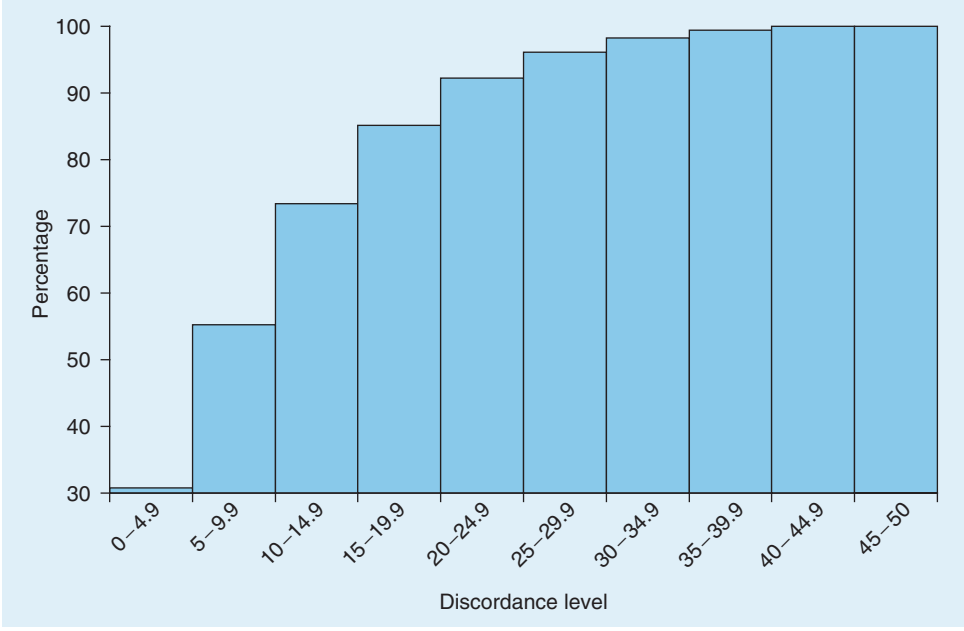



**Figure 60.5** Cumulative frequencies of twins by discordance level. US *Matched Multiple Birth File*[8]

environment and that, among discordant sets, one rather than two members of the set is more often smaller. In a similar fashion, and using the 1995–97 Centers for Disease Control and Prevention's *Matched Multiple Birth File*, Jacobs and colleagues[23] used the largest triplet's weight as a reference to calculate percentage birth-weight discordance for the middle-weight triplet. In this analysis, increasing birth-weight discordance was associated with increased risk of fetal death and being SGA. These authors considered birth-weight discordance ≥ 30% as the appropriate threshold differentiating between normal and abnormal cases[23].

## ETIOLOGY OF BIRTH-WEIGHT DISCORDANCE

Over the years, and following numerous studies, it became clear that the magnitude of variation between sibs, in terms of discordant birth weight, might have different etiologies[24]. At the lowest levels (probably at < 25%), discordance seems to be a normal variation resulting from the natural dissimilarities between sibs. Conversely, at the highest level (probably > 35%), discordance seems to be related to the exhausted uterine environment and reflects true growth restriction[14,25].

It has been hypothesized that birth-weight discordance might be an adaptive measure to promote maturity (i.e. advanced gestational age)[21,25]. In simple terms, this hypothesis suggests that within a limited uterine environment, the combination of one larger and one smaller twin may reduce uterine overdistention and increase gestational age. This hypothesis is indirectly supported by the observation that discordant twins are indeed delivered at a more advanced gestational age than concordant twins of the same total twin birth weight[26]. In a study of the US *Matched Multiple Birth File*, the mean gestational age was compared between concordant and discordant pairs at 250-g total birth-weight intervals. The mean gestational age of discordant pairs was significantly higher almost across the entire range of total birth-weight intervals. The effect of discordance on gestational age was modified by parity, with significant differences between concordant and discordant pairs among primiparas mainly at the lower birth-weight strata[26]. This methodology was recently repeated using the Swedish twin database, yielding the same results (Hirsh and Blickstein, unpublished data).

If some cases of moderate (i.e. < 35%) birth-weight discordance indeed represent an adaptive measure to promote maturity, it is logical to assume that outcome is not the same for all discordant pairs. Blickstein and Keith attempted to distinguish the discordant pairs that are at greater risk of adverse outcome by classifying pairs according to the birth weight of the smaller twin, using the US *Matched Multiple Birth* data set[27]. Here, the study group comprised 10 683 discordant pairs > 25%, classified by the birth weight of the smaller twin being < 10th, 10–50th or > 50th centile. The respective proportions of the three groups were 62.4%, 32.9% and 4.7%, suggesting that the smaller twin was not SGA in as many as 40% of twins with birth-weight differences as large as > 25%. Of importance, the neonatal mortality rate was significantly higher among pairs

**Table 60.1** Potential causes of birth-weight discordance

| |
|---|
| *Uterine characteristics* |
| Effect of parity |
| Effect of maternal height |
| *Placental characteristics* |
| Pathological lesions |
| Size |
| Structure |
| Production of growth factors |
| Chorionicity |
| *Inter-twin relationship* |
| Gender differences |
| Malformations |
| Presentation |

in which the smaller twin was SGA (29 vs. 11.1 and 11 per 1000; OR 2.7, 95% CI 1.3–5.7). This difference results from the higher mortality rates among the smaller but not the larger twins. The clinical message of this study is that even among severely discordant twins there is a substantial group in which there is no genuine growth restriction. As a result, identification of the discordant pairs with an SGA twin is imperative in order to avoid unnecessary interventions in the management of birth-weight discordance[27].

## FACTORS ASSOCIATED WITH BIRTH-WEIGHT DISCORDANCE

Table 60.1 gives a list of factors associated with birth-weight discordance. A short discussion of these factors follows.

### Parity and height

Multiparity is associated with fewer discordant twin pairs[21,25,26]. In triplets, the parity effect is similar, and primiparas have significantly fewer concordant sets[22]. The mechanism(s) whereby uterine changes following the first pregnancy (i.e. in primiparas) improve outcome in subsequent pregnancies (i.e. in parous women) are unknown. A possible explanation is that the parous uterus may develop a larger volume that enables better growth of multiples. This notion is supported by data from a large cohort of United States live-born triplets, showing a significant positive correlation between the mean total triplet birth weight and maternal height[28].

The association between maternal height and fetal growth was further analyzed in 774 triplet sets[29]. The analysis revealed that taller mothers deliver longer infants, irrespective of parity, whereas the effect of maternal height on the ponderal index (i.e. the interrelationship between length and weight) is parity-dependent[29].

### Placental causes

The numerous attempts to evaluate the placental origin of discordance mainly correlate placental structure (i.e. velamentous cord insertion), chorionicity (unequal placental sharing), size and pathologic lesions. Bleker and colleagues[30] in 1988 observed that the placental index (placental weights related to birth weights) was smaller in multiples delivered after 24 weeks, and coined the term 'placental crowding' to denote poor early-placental development preceding growth restriction in multiples. More recently, Victoria and associates[31] noted that the placenta of the smaller fetus in dichorionic twins with separate placentas, as well as the entire placenta in monochorionic twins, was significantly lighter in severely discordant twin pairs than in concordant or mildly discordant controls. In contrast, Eberle and co-workers[32] found that birth-weight discordance > 20% was not attributable to differences in placental weight, but to a significantly greater number of lesions in the placenta of the lighter twin compared with the heavier twin.

Recent data indicate that growth discordance of twins exposed to the same maternal environment may be due to variations in placental function, depending on factors such as insulin-like growth factor-I (IGF-I), IGF-II and insulin-like growth factor binding protein-1[33]. These views regarding the placental origin of birth-weight discordance cannot be settled, because it is impossible to determine whether the diminished rate of placental growth lags behind, parallels or exceeds the rate of diminished fetal growth.

### Chorionicity

Compared with the recognized adverse outcomes of monochorionic twins (see Chapter 28), the relation between chorionicity and growth aberrations is less distinct. Most authors agree that monochorionic twins are more likely to exhibit absolute growth restriction and low birth weight. However, the question whether monochorionic twins also exhibit discordant growth remains controversial, with some reports showing a more than twice likelihood of severe discordance among monochorionic twins[31,34,35], and, on the other hand, additional reports that find similar discordance frequencies in the two placental types[36–39]. Recently, a retrospective three-tier chorionicity analysis of 1155 twin placentas, performed under the auspices of the Center for Study of

Multiple Birth in Chicago, evaluated the birth weight characteristics of twins with different placental types (Blickstein and colleagues, unpublished data). Twins with dichorionic-separate, but not dichorionic-fused, placentas were heavier than monochorionic–diamniotic and monoamniotic twins. One or two SGA twins were less frequent among dichorionic twins. Importantly, twins of all placental types had similar discordance values.

### Fetal gender

Genotypic and phenotypic gender differences explain the fact that male infants weigh more than female infants. It follows that if differences in birth weights between males and females were merely 'structural', one should expect the mean birth weight of unlike-sex pairs to be similar to the average between female–female and male–male pairs, but not skewed towards either[40]. However, it has been repeatedly shown that the presence of a male fetus improves the uterine growth environment, and females in unlike-sex pairs tend to have higher birth weights compared with females in like-sexed dizygotic pairs[41]. In discordant pairs, the frequency of females among smaller twins is significantly higher than that of males, implying that males do better in the uterine environment of a twin gestation[42,43]. Blumrosen and colleagues[40] showed significantly higher birth weights of females in unlike-sex pairs, a trend existing irrespective of discordance level. The importance of the gender effect is more complex than it would appear at first glance, because if female fetuses indeed develop in an androgenic–anabolic environment caused by their male co-twins, they may possibly exhibit some form of hormone-mediated manifestation during adulthood, although this association at present is speculative.

## MANAGEMENT OF ABNORMAL GROWTH AMONG MULTIPLES

Abnormal growth is a risk factor for perinatal adverse outcome irrespective of plurality. The higher frequency of growth problems among multiples should be considered in the context of three conclusions: first, it is normal for multiples to be smaller than singletons; second, being smaller than singletons does not necessarily signify the existence of pathology; and finally, it is unfair to consider twins and triplets by singleton standards because they have different growth patterns (see above).

At the same time, it should be stressed that not all small multiples are a result of adaptive physiologic mechanisms. In fact, the adaptation process often fails when the uterine milieu of a multiple gestation is exhausted, and this exhaustion sets the stage for the onset of pathologic events such as placental insufficiency. Indeed, Demissie and co-workers[44] have shown that increased twin birth-weight discordance is associated with increased risk of intrauterine death and malformation-related neonatal deaths, and Branum and Schoendorf[45] demonstrated that twin pairs affected by severe birth-weight discordance (≥ 25%) are at disproportionate risk for neonatal mortality compared with concordant smaller or larger twins.

The first and foremost difficulty in the management of growth aberrations in multiples results from the limited accuracy in diagnosing birth-weight discordance[46,47]. Although the weight of an individual fetus can be estimated quite accurately, the diagnosis of discordance is relatively inaccurate because of the '±' factor that is inherent to sonographic measurements. Consider, for example, the situation in twins with the same actual birth weight (2000/2000 g). Accurate sonography (within ±10% of the actual weight) may overestimate one twin (+10%, 2200 g) and underestimate the other (–10%, 1800 g). Thus, despite the accurate individual sonographic estimation, the paired estimation will yield a discordance value of 18% (400/2200 g). One way to avoid such a difficulty is to follow twins biweekly from 28 weeks in order to identify changing growth patterns. This can be accomplished using singleton or twin growth curves. However, when growth restriction is suspected from the observed patterns, reference should be made to the absolute value shown in various recently constructed charts for twins and triplets. Figures 60.6 and 60.7 depict the three most useful centiles for twins and triplets (data derived from the *Matched Multiple Birth* data set by the National Center for Health Statistics, including 265 820 twins and 14 031 triplets). The key in many clinical situations lies in the ability to recognize rapidly the transition from physiologic adaptation to the pathologic process of growth restriction. This can only be achieved with frequent and repeated ultrasounds, with appropriate attention to individual patterns of growth.

It is recommended that SGA fetuses in a multiple pregnancy should be treated as any other SGA fetus. A work-up to exclude twin–twin transfusion, malformations and infections should be carried out. This algorithm would probably reduce many unnecessary preterm multiple births[48,49]. At times, especially at gestational ages remote from term, inter-twin conflicts may arise. For example, consider the case that may exist where one of the twins ceases to grow at 20 weeks' gestation and the other continues growing perfectly. The question arises: what to do if the smaller twin shows signs of fetal distress? Should this twin be sacrificed in order to allow further maturation of the appropriately growing twin, or

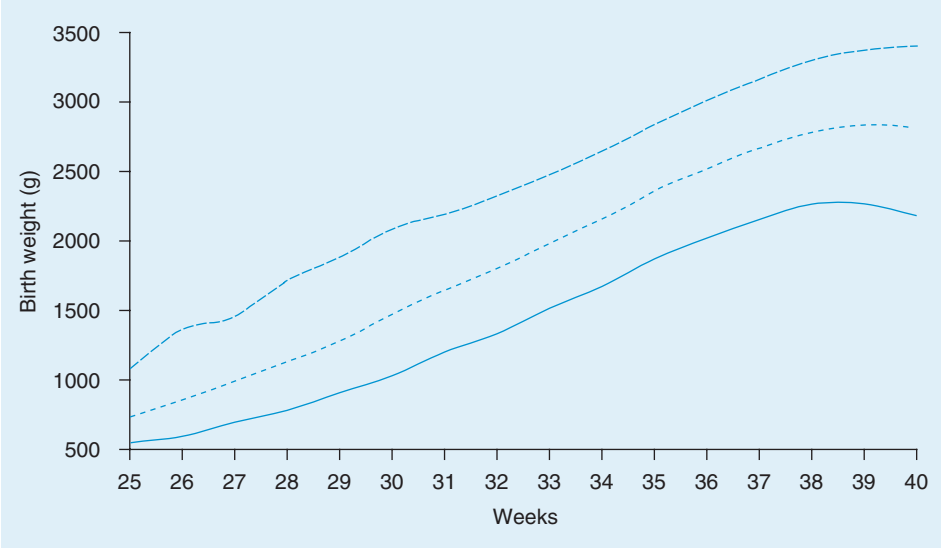



**Figure 60.6** Birth weight by gestational age curve for twins. Data derived from 265 820 live-born individual twins[8]. Data not corrected for anomalies and fetal gender. The 10th, 50th (median) and 90th centiles are shown

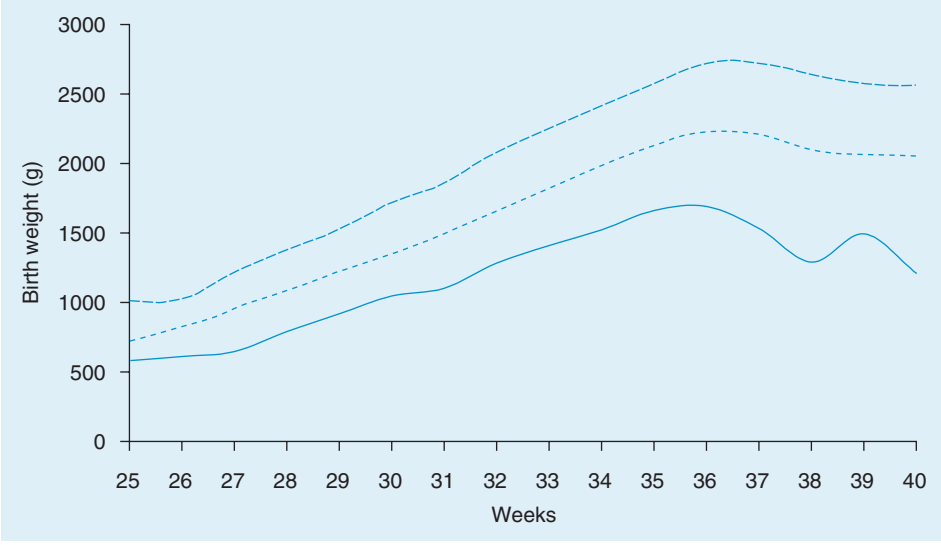



**Figure 60.7** Birth weight by gestational age curve for triplets. Data derived from 14 031 live-born individual triplets[8]. Data not corrected for anomalies and fetal gender. The 10th, 50th (median) and 90th centiles are shown

should the smaller twin be salvaged by delivering both twins despite the danger of extreme prematurity for the co-twin? Luckily enough, in the case described above (also discussed in Chapter 16), pregnancy continued until 32 weeks without signs of fetal distress, except the remarkable discordant growth. At birth, twin A weighed 450 g and the co-twin 1540 g (Figure 60.8a). Despite being severely growth restricted, neonatal interventions were unnecessary, and the small twin survived on room air and feeding. Figure 60.8b shows the twins at the age of 30 months, albeit still exhibiting a remarkable size difference.

## SUMMARY

This chapter discusses fetal growth in multiple pregnancies from various perspectives. Growth of multiples is an exceptional metabolic challenge for the expectant mother, who must do much more than a mother of a singleton in terms of achieving a much higher fetal mass. It is possible that, at the same time that the entire 'fetal mass' of twins or triplets far exceeds the birth weight of a singleton of the same gestational age, the individual fetus might well exhibit growth patterns compatible with adaptation

**Figure 60.8** (a) 24-hour-old twins of a 1450/450 g pair. Twin A did not grow after 22 weeks' gestation. Spontaneous labor ensued at 32 weeks. Neither needed any special neonatal intensive-care unit (NICU) treatment. (b) Considerable size discrepancy persists until today, at the age of 30 months, but both are neurologically intact

to a limited uterine environment. It follows that it is quite normal for multiples to be smaller than singletons, and that being smaller than singletons does not necessarily mean pathology, mainly because the uterine environment is too small for more than one fetus.

Adaptation may take the form of relative growth restriction (i.e. discordance), but when this form of adaptation fails, fetal growth may become genuinely restricted. Because twins and triplets have different growth patterns, their growth should not be assessed by singleton standards, as twins are not two singletons that just happen to meet at the same time and in the same place. Even in cases with significant discordance, about 40% of the smaller twins are not SGA. The key in these circumstances is the ability to recognize the transition from physiologic adaptation to the pathologic process of growth restriction. Thus, when an SGA fetus is observed in a multiple pregnancy, and when inter-fetal conflicts are resolved, the small fetus should receive the same attention and be managed as an SGA singleton.

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# Ultrasound Assessment of Growth

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61



## INTRODUCTION

Much has been written about ultrasound assessment of fetal growth in this volume (see Chapter 60). This chapter addresses the following specific aspects of growth in the twin fetus:

(1) The importance of correlating ultrasound measurements of the head circumference (HC), abdominal circumference (AC) and femur length to those derived from twin rather than singleton pregnancies;

(2) The distinction between estimates of birth weight in twins with dichorionic versus monochorionic placentation;

(3) Use of the best formula for estimating the *in utero* weight of the twin fetus and subsequently assigning the appropriate weight centile;

(4) The interpretation of antenatal findings in the normal twin relative to the discordant co-twin;

(5) Distinguishing the small-for-gestational-age (SGA) from the intrauterine growth-restricted (IUGR) fetus;

(6) Raising the index of suspicion regarding the possibility of the occurrence of twin–twin transfusion syndrome (TTTS) in any pregnancy with monochorionic placentation.

## GROWTH CURVES

In the past, it was thought that intrauterine growth in twin pregnancies began to fall below that of singletons at approximately the 30th week[1]. However, more recent observations indicate that twin ACs fall below singleton ACs as early as 15 weeks' gestation (Table 61.1) (unpublished data). Of importance is the observation that, as pregnancy advances, the differences in ACs between twin and singleton fetuses widen from approximately 1.0 cm to 2.0 cm at 31 and 38 weeks, respectively[2]. Likewise, the differences between the actual birth weights of single and twin fetuses increase with advancing gestation from approximately 150 g to 610 g at 31 and 40 weeks, respectively[1].

Of particular interest is that the 50th weight centile of twin fetuses crosses the 10th weight centile of singleton fetuses at approximately the 37th pregnancy week, and subsequently falls below the 10th centile of singletons (Figure 61.1). Differences in birth weights at varying gestational ages are present in monochorionic versus dichorionic twin pregnancies[3]. In a study of 1302 twin gestations, the mean birth weights (one standard deviation, 1 SD) of monochorionic twins (21% of total twin pregnancies) were significantly smaller than those with dichorionic placentation ($p < 0.05$)[3].

The differences in growth curves between twins and singletons, as well as between twins with monochorionic versus dichorionic placentation, underscore the importance of evaluating antenatal ultrasound measurements in relation to charts derived from twin pregnancies. The specific use of twin growth charts allows for:

(1) More accurate determination of the extent of discordance between twin fetuses;

(2) Better identification of the SGA as well as the IUGR fetus;

(3) Correction of the artifactual increase in the proportion of diagnosed SGA twins, solely because they are compared with the normally larger singleton fetus (see below).

**Table 61.1** Comparison of abdominal circumference (AC) measurements of single and twin fetuses at the 10th centile rank in pregnancies from 14 to 39 weeks' gestation (Sabbagha and colleagues, unpublished data)

| | *AC centiles in singletons* | | | *AC centiles in twin fetuses* | | |
|---|---|---|---|---|---|---|
| *GA* (weeks) | *5th* | *50th* | *90th* | *5th* | *50th* | *90th* |
| 14 | 6.6 | 9.0 | 10.8 | 6.7 | 9.1 | 11.0 |
| 15 | 7.7 | 10.1 | 11.4 | 7.3 | 9.6 | 11.0 |
| 16 | 8.8 | 11.1 | 12.7 | 8.6 | 10.9 | 13.0 |
| 17 | 9.8 | 12.2 | 13.7 | 9.6 | 12.0 | 14.0 |
| 18 | 11.5 | 13.8 | 14.7 | 10.6 | 12.9 | 15.0 |
| 19 | 12.5 | 14.8 | 16.6 | 12.5 | 14.9 | 17.0 |
| 20 | 13.6 | 15.9 | 17.4 | 13.3 | 15.6 | 17.0 |
| 21 | 14.5 | 16.8 | 18.4 | 14.3 | 16.6 | 18.0 |
| 22 | 15.6 | 17.9 | 19.5 | 15.4 | 17.7 | 19.0 |
| 23 | 16.6 | 18.9 | 20.8 | 16.7 | 19.0 | 21.0 |
| 24 | 17.7 | 20.1 | 21.5 | 17.4 | 19.7 | 21.0 |
| 25 | 18.8 | 21.1 | 23.2 | 19.1 | 21.4 | 23.0 |
| 26 | 20.0 | 22.3 | 24.2 | 20.1 | 22.4 | 24.0 |
| 27 | 20.9 | 23.2 | 25.0 | 20.9 | 23.2 | 25.0 |
| 28 | 22.4 | 24.7 | 26.3 | 22.2 | 24.5 | 26.0 |
| 29 | 23.4 | 25.7 | 27.2 | 23.1 | 25.4 | 27.0 |
| 30 | 24.4 | 26.7 | 28.6 | 24.5 | 26.8 | 29.0 |
| 31 | 25.4 | 27.7 | 28.61 | 24.51 | 27.82 | 29.0 |
| 32 | 26.7 | 29.0 | 30.1 | 26.0 | 28.3 | 30.0 |
| 33 | 27.6 | 29.9 | 30.8 | 26.7 | 29.0 | 31.0 |
| 34 | 28.5 | 30.9 | 31.5 | 27.4 | 29.7 | 32.0 |
| 35 | 29.7 | 32.0 | 32.5 | 28.4 | 30.8 | 33.0 |
| 36 | 30.9 | 33.2 | 33.7 | 29.6 | 31.9 | 34.0 |
| 37 | 31.5 | 33.8 | 34.5 | 30.4 | 32.7 | 34.0 |
| 38 | 32.2 | 34.5 | 35.3 | 31.2 | 33.6 | 35.0 |
| 39 | 33.0 | 35.3 | 36.5 | 32.4 | 34.7 | 36.0 |

GA, gestational age

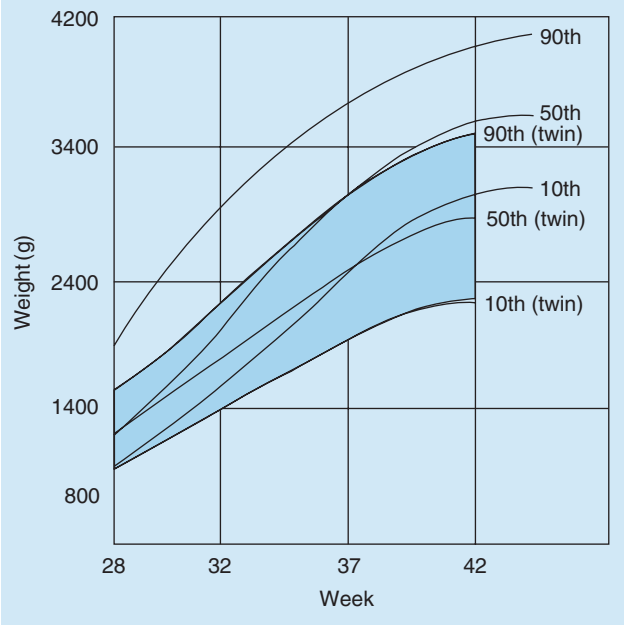


**Figure 61.1** Intrauterine growth chart for singleton and twin fetuses. Adapted from reference 1

## DISCORDANCE IN TWINS

Discordance in the estimated weights of twins is an important contributor to fetal death[4]. It is generally defined as at least a 15% difference in the estimated twin weights, calculated according to the larger twin. A 15% discordance is observed in up to 25% of twin pregnancies[4]. Severe discordance (30% or more) is noted in approximately 5% of twin pregnancies[4] (see Chapter 60). Divergence in the estimated twin weights of 25% is associated with a 6.5-fold increase in fetal death risk[5], whereas a divergence of 31–40% carries an odds ratio of 5.6 for fetal death[6].

In contrast, the association between birth-weight discordance and neonatal mortality is not as clear. Some reports show no significant increase in neonatal mortality[7], whereas others point to a significant elevation in neonatal mortality among twins with > 30% discordance[8].

Regardless of such issues, factors other than mere discordance come into play when assessing divergent intertwin growth. For example, approximately two-thirds of highly discordant twins, that is, those

differing in estimated weight by 30% or more, are in fact growth-restricted, weighing at or below the 5th centile for gestational age[9]. As a result, the presence of intrauterine growth restriction may be a greater contributor to neonatal mortality than is discordance *per se*[7,10]. Other factors contributing to outcome include, but are not limited to, observations regarding size of the abdominal circumference, evolution in biometric measurements over time, level of amniotic fluid, biophysical profile, non-stress test, umbilical Doppler systolic/diastolic ratio, presence of diastolic velocity flow and occurrence of twin–twin transfusion.

## THE SMALL-FOR-GESTATIONAL-AGE VERSUS THE INTRAUTERINE GROWTH-RESTRICTED FETUS

An SGA fetus is defined as a genetically small fetus but one that is not growth-restricted. Its weight generally falls at or close to the 10th centile rank. It is also not associated with markers of growth restriction such as low amniotic fluid level, poor interval growth and abnormal umbilical Doppler findings – all of which are observed in the IUGR twin (see Chapter 41).

In the twin fetus, the estimated weight, including the centile rank, will be incorrectly low if the comparison is made with charts derived from singleton pregnancies. As a result, the proportion of SGA and IUGR fetuses will be higher, and poor perinatal outcome will be inappropriately predicted.

### Estimating fetal weight

The best estimates of fetal weight by ultrasound are derived from mathematic formulae incorporating measurement of the HC, AC and femur length (FL). In a large study, Hadlock and colleagues obtained the following formula for estimation of fetal weight[11]:

$$\log_{10}(\text{weight}) = 1.326 - 0.00326(\text{AC} \times \text{FL}) + 0.0107\text{HC} + 0.0438\text{AC} + 0.158\text{FL}$$

In that study, the authors showed that the accuracy of estimates of birth weight varied by 14.8% (2SD). However, they also showed that the accuracy of the formula deteriorated to 19.4% (2SD) in smaller fetuses with a birth weight < 1500 g. Further, the formula by Hadlock does not take into account the specific growth curves of the three recognized fetal populations, namely: the small-, appropriate- or large-for-gestational age groups. Formulae targeted to the specific population in question have a smaller cumulative 2SD variation (see below)[12].

### Targeted weight formulae

In a particular fetus, the estimation of birth weight is more accurate if the formula used is derived from data applicable to the specific fetal population in question. Such formulae are known as targeted formulae and incorporate gestational age (weeks) + HC + 2AC + FL[12]. In targeted formulae, gestational age (in weeks) is included because the HC/AC ratio varies at different intervals in pregnancy[13]. The difference in the HC/AC ratio is noted regardless of whether fetal growth is normal or altered (Table 61.2). Further, the gestational age used should be based on either dates according to the last menstrual period (LMP) that are confirmed by ultrasound, or ultrasound results obtained by 26 weeks' gestation, because the 2SD variation in weeks increases beginning at the 27th pregnancy week. Moreover, targeted formulae doubly weight the AC, a measurement that best correlates with fetal weight[14]. Thus, the AC can be used to determine the specific growth curve of the fetus. When the AC is small (i.e. 5th centile, Table 61.1), the estimated fetal weight is best derived from a formula targeted to the SGA or IUGR fetus (Table 61.3)[12]. Likewise, when the AC falls in an average centile rank (AC > 5th and < 90th percentiles, Table 61.1), the estimated fetal weight is best derived from a formula targeted to the appropriate-for-gestational-age fetus (Table 61.3)[12]. Finally, when the AC is at the 90th centile the estimated fetal weight is best derived from a formula targeted to the large-for-gestational-age (LGA) fetus. However, since twins are rarely considered large for gestational age, the estimated fetal weight in the twin with an AC at the 90th centile can be appropriately derived from the formula targeted to the fetus with an average AC. Compared with the formula by Hadlock and colleagues, formulae targeted to gestational age and fetal AC centile ranks reduce the cumulative absolute 2SD variation by 21.7%, from 15.6 to 12%[12].

**Table 61.2** Dynamic changes in head circumference (HC) and abdominal circumference (AC) measurements in pregnancies with normal and altered fetal growth. Adapted from reference 13

| |
|---|
| HC/AC ratio is > 1.0 prior to 36 pregnancy weeks |
| HC/AC ratio is < 1.0 after 36 pregnancy weeks |
| HC/AC ratio is < 1.0 in the macrosomic fetus |
| HC/AC ratio is not altered in the LGA fetus |
| HC/AC ratio is not altered in symmetric IUGR |
| HC/AC ratio is > 1.0 in asymmetric IUGR |

IUGR, intrauterine growth restriction; LGA, large for gestational age

### Assigning *in utero* weight centile

Once the fetal weight is estimated, it should be assigned a centile rank. Recently, Ananth and associates published birth-weight centiles for both monochorionic and dichorionic twins (Tables 61.4 and 61.5)[3]. Interestingly, these investigators found that stratifying the data further relative to parity and gender yielded almost identical curves. The latter finding implies that parity and gender are not significant contributors to differences in the two twin birth-weight curves – an important finding, since both parity and gender have been implicated as factors influencing birth weight in singleton pregnancies.

A distinct advantage of the birth-weight centiles published by Ananth and associates[3] is that the data shown begin at the 23rd pregnancy week and not at the 28th or 32nd pregnancy week, as presented in other reports[15]. Additionally, the data of Ananth and associates are based on accurate estimation of gestational age. Specifically, ultrasound was used either to confirm dates assigned by the LMP or to establish pregnancy dates by early ultrasound. However, it is essential to note that there are differences between the twin birth-weight centiles published by Ananth and associates and Alexander and co-workers[3,16]. Although such differences are small at the 50th centile level they are marked at the 90th and 10th centile ranks. Specifically, the twin birth weights of Alexander and co-workers are larger at the 90th rank but smaller at the 10th centile rank (Table 61.6). The differences noted by Alexander and co-workers can be explained, in part, by the following factors:

**Table 61.3** Targeted formulae used in the prediction of fetal weight. Adaped from reference 12

| *Group* | *Formula* |
|---|---|
| Appropriate for gestational age | $-55.3-(16.35\times SUM)+(0.25838\times SUM^2)$ ($r=0.97$, $r^2=0.94$) |
| Small for gestational age | $1849.4-(47.13\times SUM)+(0.37721\times SUM^2)$ ($r=0.96$, $r^2=0.92$) SUM = GA (weeks) + 2AC (cm) + HC (cm) + FL (cm) |

GA, gestational age; AC, abdominal circumference; HC, head circumference; FL, femur length

**Table 61.4** Smoothed birth-weight centiles for twins with monochorionic placentation. Adapted from reference 3

| *GA* (weeks) | *No. of pregnancies* | *Smoothed birth-weight centiles* | | | | |
|---|---|---|---|---|---|---|
| | | *5th* | *10th* | *50th* | *90th* | *95th* |
| 23 | 3 | 392 | 431 | 533 | 648 | 683 |
| 24 | 8 | 456 | 501 | 620 | 753 | 794 |
| 25 | 4 | 530 | 582 | 720 | 875 | 922 |
| 26 | 2 | 615 | 676 | 836 | 1017 | 1072 |
| 27 | 7 | 713 | 784 | 970 | 1178 | 1242 |
| 28 | 8 | 823 | 904 | 1119 | 1360 | 1433 |
| 29 | 6 | 944 | 1037 | 1282 | 1559 | 1643 |
| 30 | 8 | 1072 | 1178 | 1457 | 1771 | 1867 |
| 31 | 6 | 1204 | 1323 | 1637 | 1990 | 2097 |
| 32 | 15 | 1335 | 1467 | 1814 | 2205 | 2325 |
| 33 | 22 | 1457 | 1601 | 1980 | 2407 | 2537 |
| 34 | 27 | 1562 | 1716 | 2123 | 2580 | 2720 |
| 35 | 30 | 1646 | 1808 | 2237 | 2719 | 2866 |
| 36 | 47 | 1728 | 1899 | 2349 | 2855 | 3009 |
| 37 | 26 | 1831 | 2012 | 2489 | 3025 | 3189 |
| 38 | 27 | 1957 | 2150 | 2660 | 3233 | 3408 |
| 39 | 24 | 2100 | 2307 | 2854 | 3469 | 3657 |
| 40 | 2 | 2255 | 2478 | 3065 | 3726 | 3927 |
| 41 | 2 | 2422 | 2661 | 3292 | 4001 | 4217 |

GA, gestational age

**Table 61.5** Smoothed birth-weight centiles for twins with dichorionic placentation. Adapted from reference 3

| GA (weeks) | No. of pregnancies | Smoothed birth-weight centiles | | | | |
|---|---|---|---|---|---|---|
| | | 5th | 10th | 50th | 90th | 95th |
| 23 | 4 | 477 | 513 | 632 | 757 | 801 |
| 24 | 7 | 538 | 578 | 712 | 853 | 903 |
| 25 | 13 | 606 | 652 | 803 | 962 | 1018 |
| 26 | 10 | 684 | 735 | 906 | 1085 | 1148 |
| 27 | 10 | 771 | 829 | 1021 | 1223 | 1294 |
| 28 | 18 | 870 | 935 | 1152 | 1379 | 1459 |
| 29 | 16 | 980 | 1054 | 1298 | 1554 | 1645 |
| 30 | 27 | 1102 | 1186 | 1460 | 1748 | 1850 |
| 31 | 39 | 1235 | 1328 | 1635 | 1958 | 2072 |
| 32 | 41 | 1374 | 1477 | 1819 | 2179 | 2306 |
| 33 | 47 | 1515 | 1630 | 2007 | 2403 | 2543 |
| 34 | 86 | 1653 | 1778 | 2190 | 2622 | 2775 |
| 35 | 84 | 1781 | 1916 | 2359 | 2825 | 2989 |
| 36 | 210 | 1892 | 2035 | 2506 | 3001 | 3176 |
| 37 | 139 | 1989 | 2139 | 2634 | 3155 | 3339 |
| 38 | 146 | 2079 | 2236 | 2753 | 3297 | 3489 |
| 39 | 85 | 2167 | 2331 | 2870 | 3437 | 3637 |
| 40 | 46 | 2258 | 2428 | 2990 | 3581 | 3790 |
| 41 | 3 | 2352 | 2530 | 3115 | 3731 | 3948 |

GA, gestational age

**Table 61.6** Comparison of the 10th birth-weight centiles of twin pregnancies. Adapted from references 3 and 16

| Pregnancy week | Placentation | | | |
|---|---|---|---|---|
| | Dichorionic and monochorionic (Alexander *et al.*) | Dichorionic (Ananth *et al.*) | Monochorionic (Ananth *et al.*) | Average of three charts |
| 23 | 413 | 513 | 431 | 452 |
| 24 | 454 | 578 | 501 | 511 |
| 25 | 539 | 652 | 582 | 591 |
| 26 | 595 | 735 | 676 | 668 |
| 27 | 680 | 829 | 784 | 764 |
| 28 | 765 | 935 | 904 | 868 |
| 29 | 910 | 1054 | 1037 | 1000 |
| 30 | 1021 | 1186 | 1178 | 1128 |
| 31 | 1183 | 1328 | 1323 | 1278 |
| 32 | 1135 | 1477 | 1467 | 1359 |
| 33 | 1530 | 1630 | 1601 | 1587 |
| 34 | 1695 | 1778 | 1716 | 1729 |
| 35 | 1862 | 1916 | 1808 | 1862 |
| 36 | 2013 | 2035 | 1899 | 1982 |
| 37 | 2155 | 2139 | 2012 | 2102 |
| 38 | 2245 | 2236 | 2150 | 2210 |
| 39 | 2260 | 2331 | 2307 | 2299 |

(1) Twin birth weights represent population studies drawn from the 1991–95 Natality Data Files (from the National Center for Health Statistics), and include white and African-American racial groups;

(2) Gestational age in completed weeks is based on the interval between the recorded date of the last menses and the date of birth, but otherwise is not corroborated by ultrasound dating;

(3) Twin birth weights are not stratified by chorionic placentation, that is, they include both dichorionic and monochorionic twins.

It is important to realize, however, that only the differences observed at the 10th centile rank have significant clinical implications. For example, a particular co-twin can be classified as normal if evaluated by the Alexander and co-workers chart, but growth-restricted when compared with the data of Ananth and associates (Table 61.6). The best practical solution to this issue, at present, is to use the 10th centile data derived from the average of the three twin curves (Table 61.6), otherwise each center would have to obtain the 10th birth-weight centile applicable to its own population. Nonetheless, the twin birth-weight data of Ananth and associates can be used if the twins in question have similar population characteristics (Table 61.6).

Currently, placental chorionicity can be readily determined antenatally with an accuracy of 94% and 88% in dichorionic and monochorionic placentation, respectively[17] (see Chapter 39). Thus, the ultrasonographer is now capable of utilizing the appropriate birth-weight centile chart for the twin fetus in question.

## Interpretation of results

Having assigned the estimated birth weight and its centile rank, one is now able to compare the growth status of the twins. The following three examples illustrate the thought process in the interpretation of findings in some twin fetuses.

*Example 1*

| *Set A twins* | *Weeks' estimated gestation* | *Weight (g)* | *Centile rank for dichorionic pregnancy* | *Interpretation* |
|---|---|---|---|---|
| Co-twin 1 | 28 | 1000 | 15–20 | SGA twin* |
| Co-twin 2 | 28 | 1200 | 75 | |

**Interpretation* The twins are discordant in weight (at the 20% level) but twin 1 is not below the 5th or the 10th centile in weight and, thus, is not considered growth-restricted – although it is smaller in size than twin 2. One has to determine whether it has always been small or whether there has been a recent adverse occurrence. If the decline in weight is not of recent onset, it would be likely that the fetus is SGA rather than growth-restricted. The SGA diagnosis can be further corroborated by:

(1) The finding of normal amniotic fluid (subjectively and by presence of a vertical pocket of amniotic fluid > 2 cm);

(2) Normal umbilical Doppler study (systolic/diastolic (S/D) ratio falling within 2SD of normal);

(3) The presence of diastolic velocity flow.

Nonetheless, in such cases, close follow-up is still mandatory.

*Example 2*

| *Set B twins* | *Weeks' estimated gestation* | *Weight (g)* | *Centile rank for dichorionic pregnancy* | *Interpretation* |
|---|---|---|---|---|
| Co-twin 1 | 32 | 1390 | 5–10 | IUGR twin* |
| Co-twin 2 | 32 | 2000 | 75 | |

**Interpretation* The twins are discordant in weight (at approximately the 30% level). The weight of twin 1 is between the 5th and 10th centile ranks and by definition it is considered an IUGR fetus. As such, its risk of fetal death is increased 5–7-fold over the normally grown fetus[5,6]. Careful evaluation of amniotic fluid level and umbilical Doppler is recommended. Depending on these results, as well as on the attainment of fetal pulmonary maturity, preterm delivery may be indicated. In such cases the administration of steroids to the mother to enhance the development of pulmonary maturity may be a consideration, but details are beyond the scope of this chapter (see Chapter 60).

*Example 3*

| *Set C twins* | *Weeks' estimated gestation* | *Weight (g)* | *Centile rank for dichorionic pregnancy* | *Interpretation* |
|---|---|---|---|---|
| Co-twin 1 | 34 | 2000 | 25 | Normal twin* |
| Co-twin 2 | 34 | 2600 | 75–90 | |

**Interpretation* The twins are discordant in weight (at approximately the 23% level). However,

the centile rank of the smaller twin is considered normal. The likelihood is that twin 1 is smaller but otherwise normal. The diagnosis should also be corroborated by the finding of normal fetal anatomy, amniotic fluid level, umbilical Doppler study, biophysical profile and non-stress test.

## TWIN–TWIN TRANSFUSION SYNDROME

The interpretation of the findings in all three above examples (co-twins A, B and C) would carry another suggestion of caution if each of these pregnancies had monochorionic rather than dichorionic placentation – the former being associated with interplacental connecting vessels in up to 85% of cases[18] (see Chapter 27). Of note is that in such pregnancies approximately 10% of twins develop the twin–twin transfusion syndrome (TTTS)[17]. This syndrome may present in one of two ways.

The first is the 'stuck twin' phenomenon in which one fetus is growth-restricted and literally stuck to its membrane due to severe oligohydramnios (see Chapters 39 and 44). In comparison, the other twin or recipient shows marked hydropic changes in association with severe polyhydramnios. The pathophysiologic changes occur over time, but manifest in the early to mid-second trimester of pregnancy. The etiology of the pathophysiologic changes is unclear, but is theorized to be secondary to placental insufficiency involving the donor fetus, a condition which subsequently leads to an increase in its total peripheral resistance. This increase results in the shunting of blood to the recipient via the interconnecting placental vessels (see Chapter 65).

On the other hand, TTTS may occur in a more acute and emergent manner. The process begins when the IUGR twin dies and its blood pressure suddenly falls, resulting in the immediate shunting of blood from the 'healthy' co-twin. In this circumstance, the donor develops acute hypovolemia, anemia and hypoxia, insults that lead to subsequent severe renal and neurologic sequelae, including but not limited to periventricular leukomalacia[19,20]. Senat and co-workers have shown that transfusion of the surviving anemic fetus within a 24-h period may be a useful intervention for preventing the neurologic complications in some pregnancies[19]. However, only careful daily monitoring including possible blood sampling may lead to the diagnosis of TTTS.

In conclusion, the optimal care for twin pregnancies can only be provided when chorionicity is established early in gestation and co-twin growth monitored in relation to charts derived from twin rather than from singleton pregnancies.

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# Techniques of Biophysical Assessment

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## INTRODUCTION

Many biophysical techniques are used to assess fetal well-being in multiple pregnancy, including ultrasonography, Doppler velocimetry and cardiotocography. Considering the specific characteristics of multiple pregnancies in terms of higher rate of preterm delivery, higher incidence of fetal growth restriction and higher rates of obstetric complications as compared with singleton gestation, as well as specific problems related to chorionicity and to the number of fetuses, it is difficult to summarize generally the usefulness and role of each technique, or to provide a general standard of management. Rather, it is advisable to assess and manage each case individually on the basis of the presence of recognized risk factors, making use of each technique or of a combination of different techniques according to the specific information desired. These complexities also demand that the information obtained should be interpreted on the basis of a thorough understanding of the pathophysiology involved.

In twin pregnancy, the development of chronic and acute hypoxemia is a main contributor to morbidity and mortality. The criteria for diagnosis and management of specific conditions of twin pregnancy linked to alterations in fetal oxygen supply, such as discordant fetal growth, twin-to-twin transfusion syndrome and alterations in placentation, are addressed in other chapters of this book.

The aim of this chapter is to provide an overview of the pathophysiologic basis of chronic and acute fetal hypoxemia, and to summarize the current evidence related to the role of fetal Doppler velocimetry, biophysical profile and cardiotocographic evaluation in the diagnosis of fetal oxygen deficiency, focusing also on a description of the role of modern techniques for intrapartum fetal monitoring as represented by analysis of the fetal electrocardiogram.

## FETAL ASPHYXIA: DEFINITIONS

Fetal asphyxia can be defined as a combination of oxygen deficiency, metabolic acidosis and impaired organ function. It is important to remember that asphyxia occurs as a result of a cascade of events that happen over time[1]. The first step is represented by *hypoxemia*, that is, a reduction of oxygen carried in the blood as a result of a decreased oxygen partial pressure and decreased oxygen content. When defense mechanisms fail to compensate for the decrease in blood oxygen content, *hypoxia* develops, that is, the lack of oxygen now affects the tissues. The fetus, at this stage, can still supplement energy production with anaerobic metabolism and maintain organ function; however, anaerobic metabolism only produces one-fifth of the adenosine triphosphate (ATP) produced aerobically, and also leads to production of lactate that tends to accumulate, giving rise to metabolic acidosis. When energy production can no longer be maintained in this way, *asphyxia* develops and the risk of organ failure and tissue damage increases[1].

The diagnosis of asphyxia at birth requires the assessment of blood gas acid–base values and demonstration of hypoxia-related morbidity of the newborn in the neonatal period. Cord metabolic acidemia with a pH < 7.00 and a base deficit ≥ 12 mmol/l is

regarded as a marker of significant fetal metabolic adjustments to intrapartum hypoxia, and a level above which moderate or severe complications may occur[2]. In order to avoid the impact of respiratory acidosis on base deficit calculations, buffer changes should be calculated in the extracellular fluid[3].

## PATHOPHYSIOLOGY OF ANTEPARTUM FETAL RESPONSE TO CHRONIC HYPOXEMIA

Fetal hypoxemia may be the result of various fetomaternal pathophysiologic processes which can produce completely different fetal hemodynamic modifications, not only in relation to the quality, but particularly in relation to the chronology, of hemodynamic events. However, fetal antepartum oxygen deficiency is mostly due to placental vascular insufficiency, and it is important to point out that fetal hypoxemia–acidemia is part of the terminal pathway starting from placental functional and structural alterations through fetal intrauterine growth restriction (IUGR) that potentially lead to fetal damage or intrauterine fetal death. Sonography, in particular, Doppler ultrasound technologies can help in evaluation of antepartum fetal well-being, and especially in evaluating fetal hemodynamic adaptations to different maternal and fetal pathophysiologic conditions leading to fetal hypoxemia.

Several mechanisms are involved at the beginning of the processes that lead to the hemodynamic changes in the fetus from adaptation to decompensation during hypoxemia. These include fetomaternal immunologic tolerance alterations, failure of endothelial vasodilator tone control (possibly alterations of the nitric oxide (NO) system), reduction of maternal plasmatic expansion, increased maternal blood viscosity at a low shear rate, inappropriate trophoblastic invasions with histologic, morphologic and functional placental alterations, and others. All these processes are involved in uterine and umbilical arteries' hemodynamic alterations that characterize IUGR fetuses [4–10]. When structural and functional placental alterations appear and/or increase, the fetus adapts to this situation with decreased growth, alterations in behavior (i.e. decrease of episodes of body movements) and hemodynamic changes, in order to maintain the supply of oxygen and substrates for tissues with an active metabolism such as the brain, heart and adrenals[11].

Only when the obstruction of placental vessels is over 60% is there a detectable and clear alteration in the umbilical artery velocity waveform profile[10]. Thus, when a particular level of $pO_2$ is reached, the fetal blood flow redistributes. These hemodynamic modifications, known as the 'brain-sparing effect', produce a 'fetal hemodynamic centralization' and are thought to be protective against hypoxic insult. They consist of vasodilatation with an increase of blood flow in the fetal structures most sensitive to hypoxemia (such as the brain, adrenals and coronary arteries), and a decrease of blood supply in the peripheral vascular regions such as pulmonary, intestinal, cutaneous, renal and skeletal vessels[11–19].

These changes in arterial perfusion are mediated by neuronal stimulation, either directly through stimulation of the vagal center or through chemoreceptors in the aorta and in the carotid arteries. If the uteroplacental vascular bed alterations persist, this produces a further increase of impedance to flow in the umbilical artery and in the fetal aorta and, mainly as a result of the hypoxemia, in the renal artery. Moreover, these factors cause a further increase of the hypoxemic fetal status balanced by a more pronounced fetal blood flow redistribution with lowest impedance to flow values in the cerebral vessels. The 'centralization of blood flow' influences cardiac hemodynamics with a decrease in left ventricle afterload due to cerebral vasodilatation, and an increase in right ventricle afterload due to systemic vasoconstriction. This phase is characterized by the extreme response of the fetus to hypoxemia which leads, after a certain time, to the decompensation phase.

This last phase is characterized by impairment of fetal cardiac function, which is unable to balance all the factors mentioned above. Because of the persistent severe hypoxemia and the consequent polycythemia and increased blood viscosity, impairment of fetal cardiac contractility becomes the most important factor leading to the terminal decompensatory phase. Impairment of cardiac function causes a decrease of the cardiac afterload and an increase of the cardiac preload, leading to an increase in the atrioventricular gradient, and abnormal ventricular filling with an increase of venous pressure beyond the inferior vena cava, hepatic and ductus venosus circulation throughout the umbilical vein blood flow. Moreover, during this stage of reduced cardiac output and high blood viscosity, a reduction in cerebral perfusion leads to disappearance of the so-called 'brain sparing'. The disappearance of this latter effect may also be induced by a mechanical mechanism secondary to the edema produced by the brain damage of the hypoxic insult[14].

## PATHOPHYSIOLOGY OF FETAL RESPONSE TO ACUTE HYPOXEMIA DURING LABOR

Numerous events of labor can expose the fetus to episodes of reduction of placental blood flow and, thus, reduction of oxygen delivery. For example, cord compression impairs oxygen delivery to the

fetus by altering the fetal myocardial preload and afterload. Uterine contractions can also be responsible for intermittent reduction or interruption of fetomaternal gas exchange. The rise in intramyometrial pressure during uterine contractions can affect fetal perfusion by compression of the spiral arteries supplying the intervillous space of the placenta. Several maternal factors can additionally impair appropriate intrapartum fetal oxygenation, including maternal hypotension, maternal respiratory depression, anesthetic agents and drugs administered for a variety of maternal conditions. Other more rare acute events associated with labor that can affect oxygen delivery are placental abruption and cord prolapse[20].

The fetal ability to adapt to hypoxemia involves multiple defense mechanisms (for a more comprehensive review see reference 1). The fetus can compensate for hypoxemia by increasing blood flow to the most important organs – the brain, the heart and the adrenals – thereby counteracting the decreasing oxygen content. Hypoxemia causes a decrease in fetal heart rate and an increase in blood pressure, secondary to an intense vasoconstriction at the level of the skin, muscles and gut. This allows a greater proportion of cardiac output to be distributed to high-priority organs, so oxygen delivery to central organs can be maintained despite hypoxemia[21]. Aerobic metabolism can be maintained in this situation until the oxygen content of arterial blood is decreased by 70%[22].

A second line of defense is represented by the metabolic compensatory mechanisms. When cardiovascular mechanisms can no longer compensate for the hypoxemia, aerobic metabolism can be supplemented by anerobic metabolism of the glucose stores accumulated as glycogen. The importance of anaerobic metabolism in maintaining organ functions during hypoxia is well known, and depends on the pre-hypoxial content of glycogen of the heart and liver[23]. Anaerobic glycolysis, however, leads to the production of lactate that tends to accumulate in the tissues, giving rise to increasing metabolic acidemia. It is only when these compensatory mechanisms are insufficient or exhausted that asphyxia will develop, and along with it the possibility of central nervous system damage and handicap.

## TECHNIQUES OF ANTEPARTUM FETAL SURVEILLANCE

### Doppler evaluation of fetal hemodynamic adaptation and its chronology

#### *Doppler silent stage*

Considering the processes which lead to manifestation of uteroplacental vascular insufficiency, the fetal hemodynamic profile may remain 'normal' for a long period of time. In such circumstances the umbilical artery velocity waveform would show a positive blood-flow pattern throughout the whole cardiac cycle, and the impedance to flow values expressed as pulsatility index (PI) would be normal with a non-significant increase. Doppler velocimetry of the remaining main fetal vessels and regions (particularly aorta, renal artery, femoral artery, cerebral vessels, etc.) would also be in the range of normality with non-significant alterations. Under these so-called 'normal' conditions, the mean PI of the middle cerebral artery (MCA) would be higher than that of either the internal carotid (ICA) or the anterior cerebral artery (ACA), whereas that of the posterior cerebral artery (PCA) would be lower than that of the MCA and ACA and higher than that of the umbilical artery (UA).

The MCA, because of its size and the simplicity of its sampling, has been one of the most investigated cerebral vessels and appears to be one of the most sensitive to initial hypoxemia[12]; particularly in that its subcortical segment (M2) responds earlier than the proximal part of the vessel (M1). In addition, the ratio between the flow indices of the two parts of the vessel (M2/M1) becomes lower than two standard deviations in the presence of an initial fetal hypoxemic status[13]. Thus, in this initial stage, the alteration in the uteroplacental vascular bed and alterations in the placental metabolites and gas exchange produce only slight and not significant fetal hemodynamic modifications (slight increase of impedance to flow in the umbilical artery and the fetal peripheral vessels and a slight decrease in the cerebral vessels). The main hemodynamic change which is possible to detect with Doppler technology is the decrease in impedance to flow values characterizing the subcortical segment of the middle cerebral artery (MCA-M2), but the clinical usefulness of this hemodynamic event is still unclear.

#### *Early stage of fetal blood flow redistribution*

Fetal Doppler velocimetry shows an increase in impedance to flow values as expressed by an increase of pulsatility index of the umbilical artery, but also of the aorta and renal artery. The increase of vascular resistance of the aorta is probably related to different factors, including an increase in vascular impedance in the umbilicoplacental vessels and arterial vasoconstriction of peripheral vessels due to progressive hypoxemia.

During this phase, it is possible to observe some hemodynamic modifications that involve the whole fetal organism. These are related to substantial redistribution of the cardiac output towards the direction

of the tissues which are important for fetal survival. The inversion of the cerebroplacental ratio, called 'brain sparing', is the most evident hemodynamic effect. In this stage a statistically significant increase of blood flow and a decrease of resistance in all the cerebral vessels examined can be documented. At the same time, due to the hemodynamic redistribution, a decrease of peripheral flow in the umbilical artery, abdominal aorta, renal artery, femoral artery and other vessels, along with high impedance to flow values, can be observed[11–18].

The ratio between the PI of the middle cerebral artery and the PI of the umbilical artery, the so-called 'cerebroplacental ratio' (C/P), is the Doppler-flow expression of the 'brain-sparing effect'. The decrease of this ratio below two standard deviations is a sign of incipient severe hypoxemia. In its presence, it is possible to observe anomalies of the fetal biophysical profile, reduction of fetal heart rate variability and reduction of amniotic fluid volume[16].

During this stage, the pulsatility index of the umbilical artery and of the fetal aorta is elevated, but Doppler velocimetry frequency values continue to be positive throughout the whole cardiac cycle, even in the end-diastolic phase. On the other hand, it is possible to find high-velocity frequencies during diastole in all cerebral vessels, suggesting an increase of fetal cerebral blood flow.

### *Advanced stage of fetal hemodynamic redistribution*

This phase is essentially characterized by a further increase in impedance to flow in the umbilical artery, the fetal aorta and the renal artery. Looking at the umbilical artery flow velocity profile, a decrease of diastolic frequencies is observed, progressing towards the absence of diastolic flow. End-diastolic frequency disappears first, but subsequently the lack of blood flow is evident in the whole diastolic phase. Usually this occurs when 80% of villi arterioles are occluded[10]. Aortic velocity waveforms exhibit a similar pattern with absence of diastolic frequencies, usually preceding those observed in the umbilical artery. At the same time, impedance to flow values in the cerebral vessels shows a further decrease, leading to the lowest pulsatility index values in this region as a result of concurrent maximal vasodilatation of cerebral vessels[14]. Moreover, during this phase, it is possible to find a relative decrease in right cardiac output and an increased left cardiac output, characterized by an increased time to peak velocity in the aorta and by a decrease of the same parameter in the pulmonary arteries, both suggesting a preferential shift of cardiac output in favor of the left ventricle, leading to improved perfusion to the brain.

### *Decompensatory phase*

During this phase, cardiac output and peak velocity of the main arterial trunks gradually decline and, as a consequence, cardiac filling is impaired, suggesting a progressive deterioration of cardiac function. Therefore, these factors cause changes that induce hemodynamic alterations in all cardiovascular regions (intracardiac, arterial and venous). The incipient heart failure produces a decrease in cardiac output which causes a decrease in peak velocity of the outflow tracts, leading to reverse flow in the aorta, in the umbilical artery and, finally, as a terminal sign, in many other arterial vessels such as the cerebral vessels[19]. During this phase, the increased viscosity of the fetal blood, decrease in cardiac output and, probably, cerebral edema all tend to produce a decrease of brain perfusion, as shown by a decrease of blood velocity especially during diastole, and, thus, disappearance of the 'brain-sparing effect'[14–19].

At the same time, impairment of cardiac contractility causes an increased atrioventricular gradient, that is, abnormal ventricular filling underlined by a decrease of the E/A ratio (E: peak due to ventricular diastole; A: peak due to atrial systole) of the atrioventricular blood flow velocity waveforms. During atrial contractions the increased pressure gradient in the right atrium leads to evidence of reverse flow in the ductus venosus, and a high percentage of abnormal reverse flow in the inferior vena cava. The next step is extension of the abnormal reverse blood flow from the inferior vena cava beyond the ductus venosus and the hepatic circulation into the umbilical vein, causing typical end-diastolic pulsations in this vessel. This hemodynamic pattern is associated with the onset of severe fetal heart rate anomalies and with severe acidemia at birth[16].

## THE BIOPHYSICAL PROFILE IN MULTIPLE PREGNANCY

Reports on the usefulness of the fetal biophysical profile in multiple pregnancy are few. One of the first regarding twin gestation was published in 1986 by Lodeiro and associates[24]. These authors used the Vintzileos scoring system in 49 twin gestations as a means of follow-up of a non-reactive non-stress test (NST). Sixty-four fetuses had a reactive NST, and in all of them the biophysical profile score was 8. Of these, only two died of prematurity. Of the 34 fetuses with a non-reactive NST, about 82% had a biophysical profile score of 8 and all had a favorable outcome, whereas 18% had a biophysical profile score of < 8 and all were compromised at birth. In a prospective study of the biophysical profile in twins, Medina and associates[25] demonstrated that the use of

Manning's sonographic criteria to predict stillbirth had a sensitivity of 66.7%, a specificity of 98.8%, a positive predictive value of 50% and a negative predictive value of 99.4%.

The biophysical profile has been recommended in high-order multiple gestations when cardiotocography is technically difficult to perform. However, the biophysical profile can be difficult too, because of difficult assessment of the amniotic fluid volume. The presence of synchronous patterns of fetal activity might also interfere in interpretation, because gross body movements, breathing movements and accelerations of the fetal heart independent of chorionicity may be synchronous in 25, 50 and 50–60%, respectively[26].

Elliot and Finberg[27] reported the use of the biophysical profile in 18 sets of triplets and six sets of quadruplets. The biophysical profile was used as the primary method of fetal surveillance and was performed twice weekly starting from 28 weeks' gestation. Scoring was based on Manning's recommendations. Six pregnancies (25%, nine fetuses of five triplet sets and two fetuses of one quadruplet set) with 2/8 scores were delivered because of the biophysical scores and clinical situation, with good outcome. There was no morbidity or mortality in the 19 babies delivered because of an abnormal biophysical profile. Four pregnancies had poor outcome despite a normal (8/8) biophysical score. Despite this, these authors concluded that the biophysical profile appeared to be a reliable antepartum test of fetal well-being in triplets and quadruplets.

One of the more difficult variables to assess in multiple pregnancies is the amniotic fluid volume, because abnormalities occur more frequently than in singletons secondary to placental insufficiency, placental vascular anastomoses and maternal hemodynamic alterations. No agreement exists on the optimal sonographic method of evaluating amniotic fluid volume in multiple pregnancies, and no method has been validated for predicting perinatal outcome in multiple gestation. Chau and colleagues found that the amniotic fluid index (AFI), the vertical depths and the two diameter pockets measured at 2-week intervals were not significantly different between dichorionic and monochorionic pregnancies[28]. Furthermore, intraobserver variation in evaluating the amniotic fluid volume in diamniotic twin pregnancy was about 2–3%, approximately the figure cited for singleton pregnancies. The accuracy of the $2 \times 2$-cm pocket as a cut-off value for low amniotic fluid volume in twin pregnancies was studied by Magann and associates[29]. The sensitivity was 6.1%, the specificity 98.8%, the positive predictive value 66.6% and the negative predictive value 73.5%.

## TECHNIQUES OF INTRAPARTUM FETAL SURVEILLANCE

### Cardiotocography

It is outside the aim of this chapter to discuss in detail the interpretation of cardiotocographic patterns. Nonetheless, it is important to underline some of the problems linked with the clinical use of this technique. Most of these are common for both singleton and multiple pregnancy, while some are more specifically related to the latter.

Continuous fetal heart rate and uterine contraction recording (cardiotocography or CTG) is widely used to assess fetal well-being during labor[30]. This method has, however, certain limitations. A normal CTG trace reflects optimal fetal oxygenation and is of reassurance regarding fetal condition. In contrast, the significance of fetal heart rate changes is often unclear and therefore difficult to interpret. In the clinical scenario, this can result in unnecessary interventions for suspected fetal hypoxia or inappropriate delay in action with potentially disastrous consequences for the fetus[31]. Some of these difficulties can be overcome by better training of the medical and midwifery staff. Evidence also suggests that the use of expert systems for decision-making would provide a valuable contribution toward improving the detection and clinical management of cases with abnormal CTG patterns[32]. However, it is also evident that there are situations in which the CTG changes are not specific enough for the presence of fetal hypoxia, and additional information is necessary for appropriate decision-making.

Thus, the limitations of cardiotocography in the term fetus are mainly linked to the difficulty of interpretation of abnormal fetal heart rate patterns and to the poor specificity of the technique in identifying threatening hypoxia. Furthermore, twin pregnancy is often complicated by prematurity. Assessment of fetal well-being in the preterm fetus by analysis of the fetal heart rate presents, in addition to the limitations described, further and specific difficulties. The antepartum non-stress test, of recognized value in term fetuses, is of less well-defined value in the preterm fetus, owing to greater uncertainty in the relationship between baseline heart rate, reactivity and fetal conditions.

During preterm labor, the incidence of abnormal findings from intrapartum monitoring is higher, compared with term labor, when the same set of criteria for interpretation are used for both groups. The fetal heart rate is regulated through changes in the autonomic nervous system. Due to the immaturity of the fetal autonomic nervous system, the usual diagnostic and interpretative criteria for fetal heart rate analysis used for term fetuses are not entirely appropriate. In


**Figure 62.1** (a) Dual cardiotocography (CTG) in a twin pregnancy using two monitors. Note the two transducers for fetal heart rate and two transducers to record contractions. The output comprises two different strips, one for each fetus. (b) Dual CTG in a twin pregnancy using one monitor. Modern CTG monitors have the ability to differentiate between signals of twins. Note the two transducers for fetal heart rate and one transducer to record contractions. The output comprises one strip, with both fetal heart tracings. Images courtesy of I. Blickstein

particular, in the preterm fetus, the maturational process in the patterns of fetal heart rate results in a progressive decrease in basal fetal heart rate, in a progressive increase in the amplitude of fetal heart rate accelerations and in a progressive increase in long-term fetal heart rate variability with advancing gestation.

The interpretation of fetal heart rate patterns of the preterm fetus is also complicated by the impact of specific drugs more frequently used in women with threatened or actual preterm labor. It is well known, for example, that the administration of steroids or magnesium sulfate exerts a negative effect on fetal heart rate variability, and that administration of β-receptor agonists affects both fetal heart rate variability and baseline heart rate. The assessment of fetal well-being in the preterm fetus by electronic fetal monitoring therefore requires further study to develop interpretative criteria considering the specific physiologic aspects of the maturing fetus.

Another problem related to cardiotocographic fetal monitoring in twin pregnancy is that associated with the difficulty of obtaining a reliable dual tracing (Figure 62.1a and b). This difficulty can give rise to errors linked to double recording of the same heart rate, or inadvertent recording of the maternal heart rate that can be erroneously interpreted as fetal (Figure 62.2). Some examples of normal and abnormal antepartum tracings are shown in Figures 62.3–62.5. During labor and after membrane rupture, it is advisable to record the heart rate of the first twin by means of a scalp clip (Figure 62.6).

## ST waveform analysis of the fetal electrocardiogram

ST analysis has emerged not as an alternative to cardiotocography but as a support tool to allow more accurate interpretation of intrapartum events. The fetal electrocardiogram (ECG) is readily obtainable during labor from the same scalp electrode as used to obtain the fetal heart rate[33–37], utilizing a dedicated CTG plus fetal ECG monitor (STAN® S 21; Neoventa Medical AB, Gothenburg, Sweden).

Numerous experimental animal studies have clarified the pathophysiology of ST waveform changes of the fetal ECG during hypoxia[34,35]. The ST segment and T wave relate to the repolarization of myocardial cells in preparation for the next contraction. This repolarization process is energy-consuming. An increase in T-wave height, quantified by the ratio between T and QRS amplitudes, occurs when the energy balance within the myocardial cells threatens to become negative. A negative energy balance implies a situation when the amount of oxygen supplied to the cells no longer covers the energy required for metabolic activity. During hypoxia, this balance becomes negative and the cells produce energy by the β-adrenoceptor-mediated anaerobic breakdown of glycogen reserves. The ability of cells to produce energy in this manner and thereby maintain myocardial function is a vital compensatory defense mechanism. This process produces not only lactic acid but also potassium ions ($K^+$) that affect myocardial cell membrane potential and cause a rise of the ST waveform.

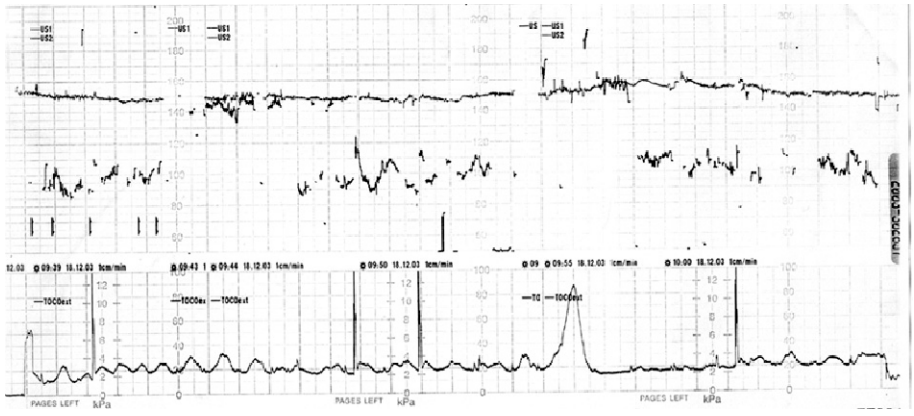

**Figure 62.2** Difficult antepartum tracing may be encountered in some cases. In this tracing, one twin was surrounded by polyhydramnios and was constantly moving, and hence its fetal heart rate tracing (lower part) is not interpretable. The other twin shows a 'silent' pattern, with reduced long-term variability. Image courtesy of I. Blickstein

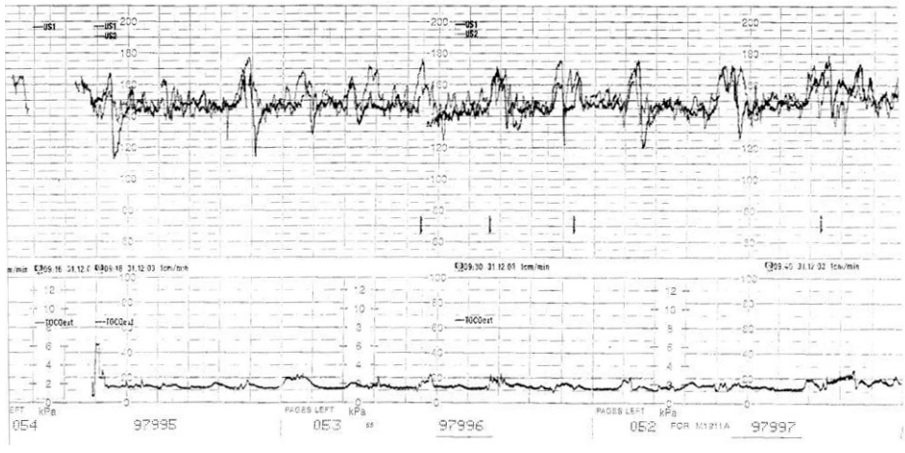

**Figure 62.3** Reassuring antepartum tracing of both twins. Image courtesy of I. Blickstein

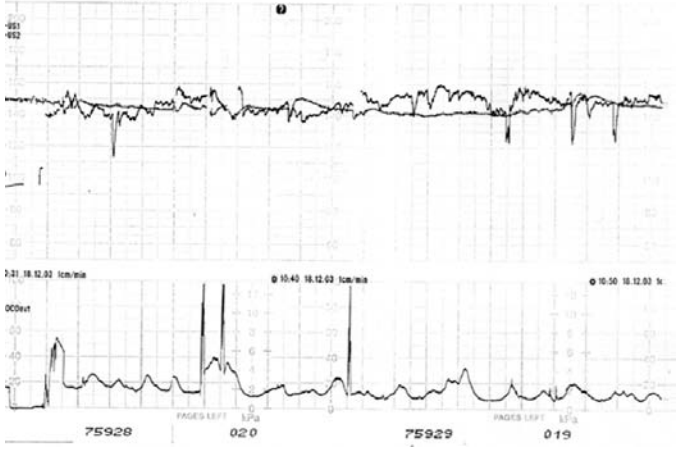

**Figure 62.4** Non-reassuring antepartum tracing in monoamniotic twins. There is loss of variability in one twin, whereas the other twin shows short variable decelerations. This case was complicated by cord entanglement. Image courtesy of I. Blickstein

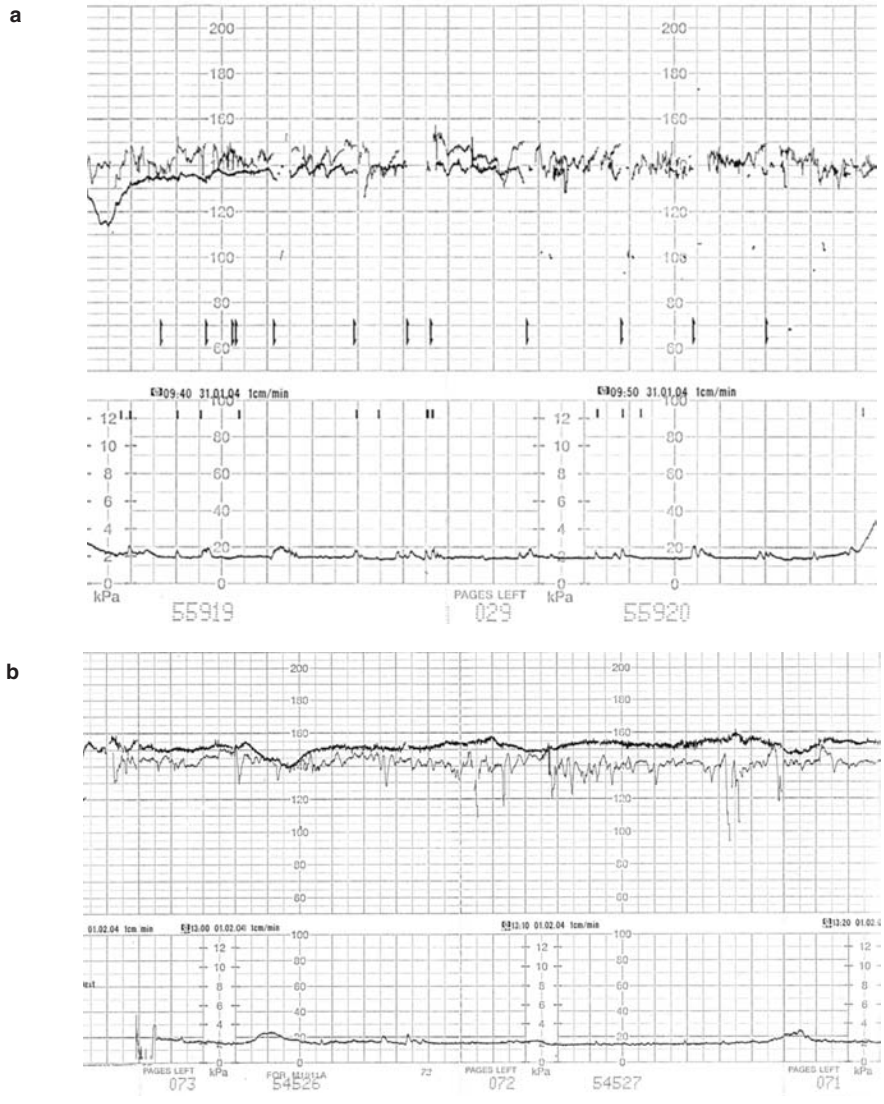


**Figure 62.5** (a) Dual antepartum tracing at 28 weeks in a case of twin–twin transfusion. The tracings are reassuring. (b) Dual antepartum tracing at 30 weeks of the same twins as in (a). Cardiotocography of one twin shows almost absent variability. Images courtesy of I. Blickstein

ST depression with negative T waves has been observed during hypoxia experiments in experimentally growth-retarded guinea-pigs[36]. Clinically, these changes have emerged as a specific sign of myocardial hypoxic stress. They reflect a myocardium that is not able or has not had the time to mobilize its defense to hypoxemia. The result is a decrease in myocardial activity and a risk of cardiovascular failure.

The evidence from experimental work indicates that ST waveform elevation reflects compensated myocardial stress and a switch to anaerobic myocardial metabolism. A progressive rise in T/QRS ratio represents continuing anaerobic metabolism, with a risk of eventual decompensation due to depletion of myocardial glycogen stores and progressive metabolic acidosis. Persistently biphasic and negative waveform changes indicate myocardial decompensation as a result of direct myocardial ischemic hypoxia. Clinical analysis of ST waveform changes is assisted by a specifically developed computerized ST log function that provides direct statements on specific significant ST events, giving additional user support[37]. This pathophysiologic model of interpretation has led to the development of specific clinical action guidelines that have been tested in several observational and randomized control studies[38–42]. These studies demonstrate the high sensitivity of CTG + ST to predict fetal acidosis, associated with a significant increase in positive predictive values as compared with CTG only.

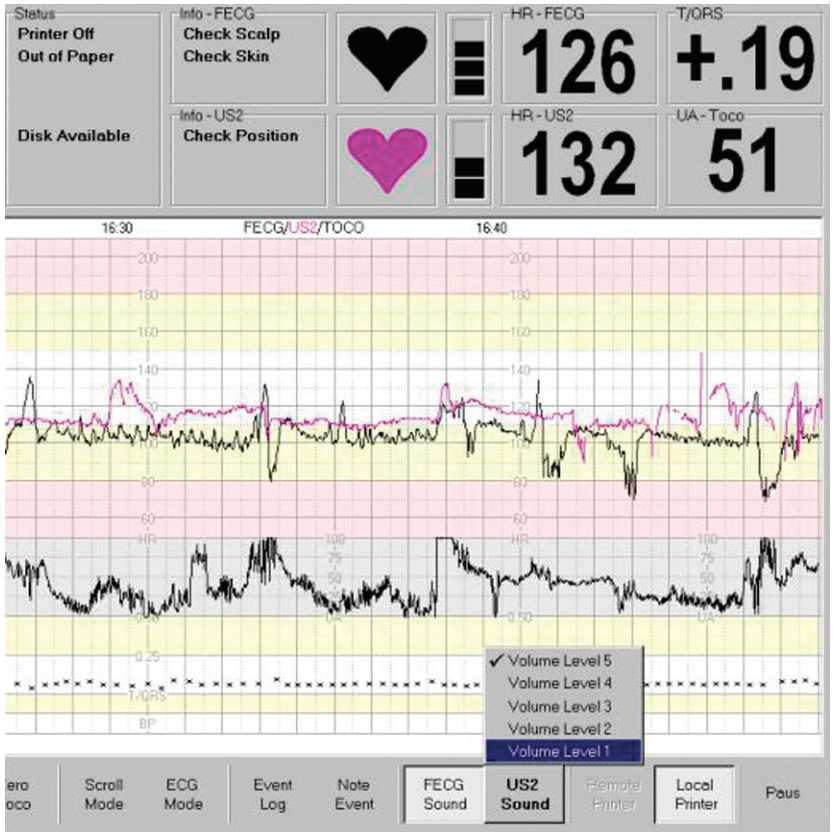


**Figure 62.6** Example of intrapartum cardiotocography (CTG) tracing in a twin pregnancy in labor. Twin 1 CTG fetal heart rate is recorded by a scalp clip (black trace) while the fetal heart rate of twin 2 is recorded externally (pink trace)

The first randomized trial comparing CTG only with CTG plus ST analysis in 2400 cases[41] showed in the CTG + ST arm of the trial a 46% reduction in operative interventions for fetal distress. The results from the recent Swedish randomized trial on CTG alone versus CTG + ST analysis (4495 cases)[42] showed in the CTG + ST arm of the trial a 60% reduction in the number of cases with metabolic acidosis (cord artery pH < 7.05 and base deficit > 12 mmol/l) accompanied by a 25% reduction in operative interventions for fetal distress as compared with the CTG-only arm, with no increase in operative deliveries for other reasons. The trial protocol allowed for an interim analysis after 1600 cases. This analysis showed frequent breaches of protocol, as clinical management in the CTG + ST arm was conducted according to the 'old' CTG information. The result of this lack of compliance was not only more operative interventions, but also babies being exposed to unnecessary intrauterine hypoxia with two babies requiring neonatal intensive care.

After retraining and enhanced experience with ST analysis that allowed a more rigorous application of the CTG + ST clinical action protocol, it was possible to obtain in the second half of the trial an even more pronounced reduction in metabolic acidosis (–75%), with no babies admitted to the neonatal intensive-care unit and a decrease of operative delivery rate for fetal distress of 44%. These results confirm the capacity of ST waveform analysis to provide diagnostic information on developing hypoxia during labor that can lead to a significant improvement in fetal outcome.

## CONCLUSIONS

The challenge of obstetric surveillance is to identify those fetuses whose physiologic defense mechanisms are compromised, so that the obstetrician is able to act before decompensation occurs. During the antenatal period, the evaluation of fetal hemodynamic adaptation to hypoxemia and the assessment of its chronologic evolution by Doppler technology is crucial. This assists in planning appropriate obstetric management and in reducing the risks of fetal damage. In addition to the conventional Doppler evaluation of fetal arterial regions, which is important for the diagnosis of fetal hemodynamic adaptation to hypoxemia, it is important also to consider the

intracardiac and venous hemodynamics. Evaluation of the output tracts, atrioventricular flow and vessels such as the ductus venosus, inferior vena cava and umbilical vein provides more detailed information on the incipient failure of the compensatory mechanism of the fetus, because this heralds development of right heart failure due to myocardial hypoxia.

Inadequate data exist to establish the value of the biophysical profile in multiple gestations. It appears that the biophysical score cannot differentiate between distressed and non-distressed fetuses in the same pregnancy. Therefore, an equivocal biophysical profile has limited value in predicting fetal distress in multiple pregnancies despite a high negative predictive value. Accordingly, serial assessment of fetal well-being should include all methods available: the non-stress test, the biophysical profile and Doppler velocimetry.

During the intrapartum period, the relative inaccessibility of the fetus and the complexity of the pathophysiology of fetal oxygenation make it difficult to obtain and interpret information on fetal response to the stress of labor. Due to the limitations of cardiotocography, additional information is required for appropriate decision-making during labor. The results of clinical randomized studies show the capacity of modern technology applied to fetal surveillance, and in particular analysis of the fetal electrocardiogram in term fetuses, to provide useful additional information that can improve our ability to interpret fetal reactions to labor events. A significant improvement in fetal surveillance, particularly in multiple pregnancies, is related not only to the availability of more specific information but also to the capacity of making better use of the information available. This requires clinical skill, knowledge of fetal physiology and understanding of the technical basis and limitations of the methodologies of monitoring used.

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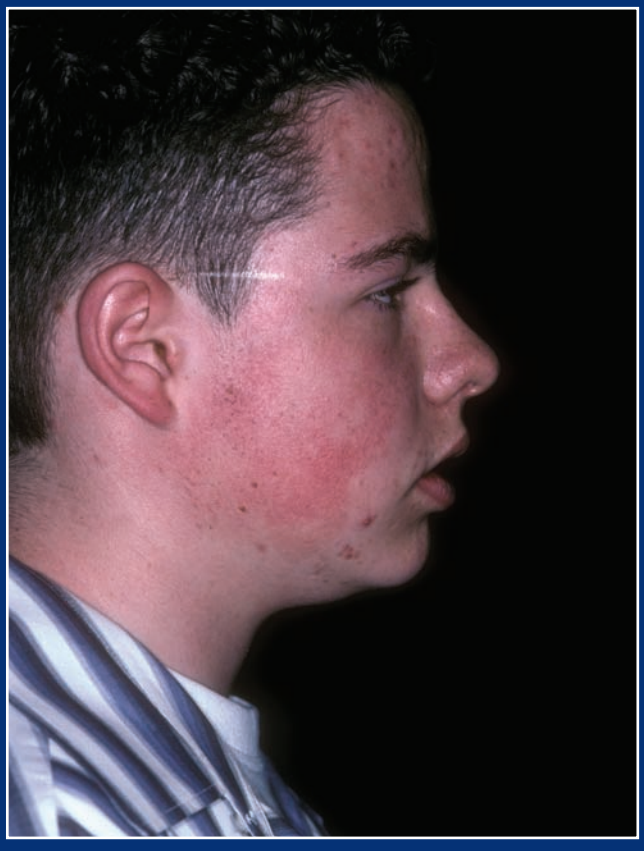
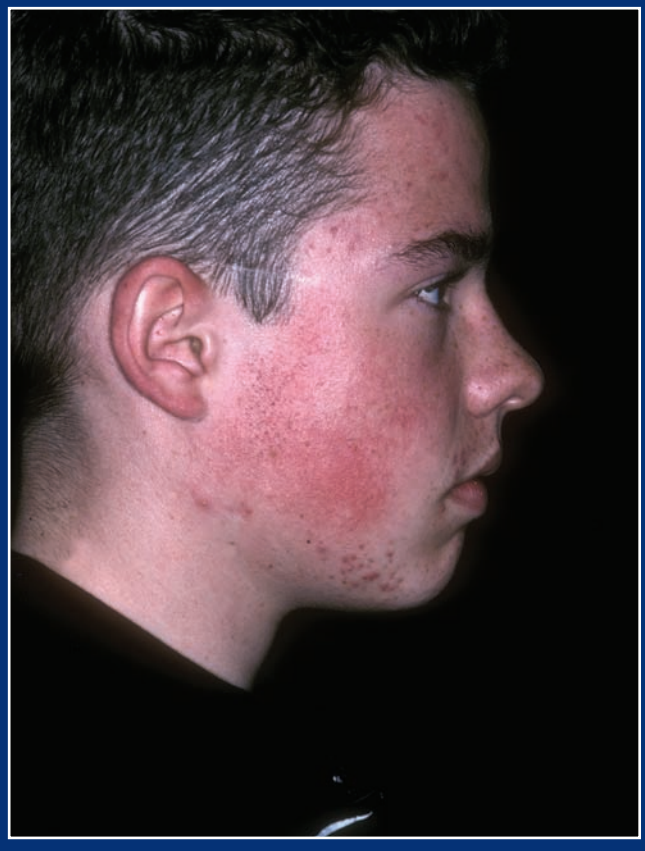
## SECTION VI

# PREGNANCY MANAGEMENT: INTERVENTIONS





**14-year-old male monozygotic, dichorionic, mirror twins, Belgium, 2004.**

Participants since birth in the East Flanders Prospective Twin Study. Twin A left, Twin B right.

Arteries (red and yellow) connect with veins (blue and green), to form the so-called Hyrtl anastomosis. Image of injection study of a monochorionic placenta (see Chapter 65 by Taylor and Fisk)

In recent years, much of the scientific attention has been directed to the most intriguing, albeit uncommon, complications related to monozygosity. In a nutshell, most of these complications can be traced to the arteriovenous anastomoses (Figure), first described by the German obstetrician Friedrich Schatz in 1875 and later confirmed by the Viennese anatomist Joseph Hyrtl. The presence of such anastomoses as the underlying etiology for the syndrome of twin-to-twin transfusion set the stage for developing the most sophisticated fetal therapies in the past decade.

As fascinating as it may be, monozygosity-related complications undoubtedly contribute far less to perinatal morbidity and mortality in multiple pregnancies than is the case with preterm birth. It should be acknowledged, however, that despite efforts and interest that far exceeds those devoted to the monozygosity-related complications, clinicians are still unable to decrease rates of preterm delivery effectively. Having said this, enormous attention is devoted to reducing the incidence of 'dangerously' premature births.

This section describes the reduction procedures, interventions used in monozygosity-related complications and the various efforts used to reduce the preterm delivery rates in multiple pregnancies.

*I.B. and L.G.K.*

# Contents of Section VI

# Multifetal Pregnancy Reduction

*M. I. Evans, D. Ciorica, D.W. Britt and J. C. Fletcher**

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## INTRODUCTION

More than 1 000 000 *in vitro* fertilization (IVF) babies have been born since Louise Brown's birth in 1978. Several million more have resulted from less aggressive fertility treatments. These positive numbers are not without their price, however. The recent epidemic of multifetal pregnancies, more specifically the twin pregnancy rate, commonly described for decades as 1 in 90, has now doubled to more than 1 in 45. Even in the past decade, twin pregnancies continued to rise by 20%, and triplets or more by nearly 200% (Table 63.1)[1]. The ratio of observed to naturally expected multifetal pregnancies shows that twins are at more than double the expected rate, and quintuplets occur at almost 1000-fold over expected numbers without infertility therapies (Table 63.2). More than 70% of all twins and 99% of higher-order multiples derive from infertility treatments.

The inherent risks of multifetal pregnancies are not always understood[2,3]. The major criteria for the extent of appreciated pregnancy losses relate to the gestational age at which one begins counting. Some reports by perinatologists are overly optimistic because these physicians do not start counting until they begin to see patients at nearly 20 weeks, at which time most losses have already occurred[4]. We previously estimated losses before viability from attempting to carry twins at 10%, triplets 18%, quadruplets 25% + and quintuplets 50%[3]. Serious morbidity rates also correlate with starting numbers.

In the 1980s, pregnancies were initiated with ovulation-induction agents such as Pergonal® in about 75% of multifetal pregnancy patients seeking reduction[5]. However, even with the first month of the lowest dose of Clomid®, quintuplets can occur. Over the years, cases induced by assisted reproductive technologies (ART) such as IVF have become increasingly common. Currently, about 70% of all cases are generated by ART (Table 63.3)[2,3].

Despite the increased utilization of ART[6], the proportion of cases significantly hyperstimulated and resulting in quintuplets or more has dramatically decreased to less than 10% of all cases relevant to us. Regardless, the 2000 report of the Society of Assisted Reproductive Technologies (SART) suggested that, of all pregnancies achieved by ART in the United States, 58.5% are singletons, 28% twins, 7.5% triplets or higher and 5.9% unknown[2,7]. In our experience with referred cases of ovulation stimulation, particularly those using follicle stimulating hormone (FSH) analogs, the proportion of cases that are quintuplets or more has fallen but not as dramatically. Such data continue to emphasize the significant role of vigilance in the monitoring of infertility therapies. The vast majority of multifetal pregnancies are associated with physicians who have the best of equipment and the best of intentions but who have an unfortunate and reasonably unpredictable or unpreventable maloccurrence rate. Despite this, some cases clearly might have been prevented if increased vigilance had been used.

Media hype associated with multifetal pregnancies extends back to the 1930s with the birth of the Dionne quintuplets in Ontario, Canada[8]. In the 1980s, quintuplets would attract national attention, but the bar keeps getting placed higher and higher for lay-press

*Deceased.

**Table 63.1** Multiple births (*n*) in the United States. Data from reference 1

| *Year* | *Twins* | *Triplets* | *Quadruplets* | *Quintuplets and higher multiples* |
|---|---|---|---|---|
| 2002 | 125 134 | 6898 | 434 | 69 |
| 2001 | 121 246 | 6885 | 501 | 85 |
| 2000 | 118 916 | 6742 | 506 | 77 |
| 1999 | 114 307 | 6742 | 512 | 67 |
| 1998 | 110 670 | 6919 | 627 | 79 |
| 1997 | 104 137 | 6148 | 510 | 79 |
| 1996 | 100 750 | 5298 | 560 | 81 |
| 1995 | 96 736 | 4551 | 365 | 57 |
| 1994 | 97 064 | 4233 | 315 | 46 |
| 1993 | 96 445 | 3834 | 277 | 57 |
| 1992 | 95 372 | 3547 | 310 | 26 |
| 1991 | 94 779 | 3121 | 203 | 22 |
| 1990 | 93 865 | 2830 | 185 | 13 |
| 1989 | 90 118 | 2529 | 229 | 40 |
| Change from 1989 to 2002 | 38.9% | 172.8% | 89.6% | 72.5% |

**Table 63.2** Ratio of observed to expected multiples. Total births in 2002: 4 021 726

| *Births* | *Observed (n)* | *Expected (n)* | *Ratio* |
|---|---|---|---|
| Twins | 125 134 | 44 686 | 2.80 : 1 |
| Triplets | 6 898 | 496 | 13.9 : 1 |
| Quadruplets | 434 | 6 | 72.3 : 1 |
| Quintuplets and higher multiples | 69 | 0.07 | 985.7 : 1 |

**Table 63.3** Changes in etiology of multifetal pregnancies

| *Ovulation* | *Induction* | *Assisted reproductive technologies* |
|---|---|---|
| 1980s | 75% | 25% |
| 1990s | 50% | 50% |
| 2000s | 70% | 30% |

interest. In the early 1990s, sextuplets, such as the Dilly family in Indiana, drew intense media attention. This family received help from diaper, formula and crib companies, and tremendous support of neighbors in their small town. The ultimate media circus surrounded the Iowa MacCaughy septuplets, where virtually the entire town was marshaled to help the family deal with the rigors of so many children at once. The state of Iowa bought them a house. The family was given a van by a local automotive dealer. Some commentators remarked at the time that there were already thousands of children in Iowa without adequate housing and why were these children less deserving? Miraculously, that pregnancy lasted until about 31 weeks, and the national media reported that all was doing well. Closer inspection revealed that the presenting fetus was a transverse lie which, rather than acting as the usual wedge to cause dilatation, actually blocked the cervix from opening. What the media now glosses over is that two of the children, now 6 years old, have been diagnosed with cerebral palsy, and a third is said to have epilepsy. Three required feeding tubes for their first several years. The Houston octuplets in 1998 received much less attention. Whether the media disinterest was because of saturation of the concept of multifetal pregnancies, or (more likely) due to the African origin of the couple, is open for speculation. One of these fetuses died very shortly after birth, and the other seven are said to be doing reasonably well.

## PROCEDURES

Multifetal pregnancy reduction (MFPR) is a clinical procedure that began in the 1980s when a small number of centers in both the United States and Europe attempted to ameliorate the usual and tremendously adverse sequelae of multifetal pregnancies by selectively terminating or reducing the number of fetuses to a more manageable number. The first European report by Dumez and Ourgy[9], and

the first American report by Evans and colleagues[10], followed by further reports from Berkowitz and colleagues[11] and later Wapner and associates[12], described a surgical approach to improve the outcome in such cases.

Even these early reports recognized the ethical conundrum faced by couples and physicians under such difficult circumstances[10]. In the mid 1980s, despite relatively mediocre ultrasound visualization, needles were inserted transabdominally and maneuvered into the thorax for the injection of KCl or mechanical disruption of the fetus by air embolization. Transcervical aspirations were also tried, without much success. Some centers used transvaginal mechanical disruption, but recent data suggest a significantly higher loss rate than with the transabdominal route[13].

Today, virtually all experienced operators perform the procedure by inserting needles transabdominally under ultrasound guidance. We find it best to line up the needle with the thorax first in the longitudinal plane. Under transverse visualization, the needle is carefully inserted into the thorax and a syringe attached to the needle. KCl is then injected slowly so as not to dislodge the needle tip. A pleural effusion should be seen, as well as cardiac asystole (Figure 63.1).

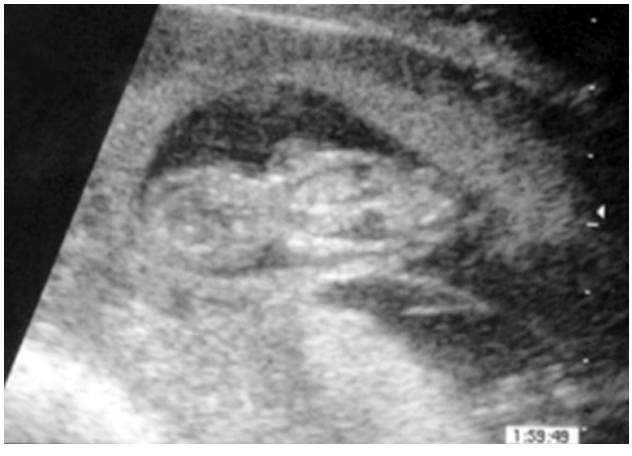

**Figure 63.1** Pleural effusion following KCl injection

## OUTCOMES

Several centers with the world's largest experience began collaborating to give leverage to the power of their data. In 1993 the first collaborative report showed a 16% pregnancy loss rate through 24 completed weeks[4]. This was a major improvement compared with the expectations of higher-order multiple pregnancies, particularly quadruplets and above. Further collaborative efforts were published in 1994, 1996 and 2001, and showed continued dramatic improvements in the overall outcomes of such pregnancies (Table 63.4)[14–16]. The 2001 collaborative data demonstrate that in terms of outcome, triplets reduced to twins, and quadruplets reduced to twins, now perform essentially as if they started as twins (Figure 63.2). Even with the tremendous advances in neonatal care for premature babies, the 95% take-home-baby rate for triplets and the 92% take-home-baby rate for quadruplets clearly represent dramatic improvements over natural statistics. Not only has the pregnancy loss rate been substantially lowered, but so has the rate of very dangerous early prematurity. Both continue to be correlated with the starting number. Data from the past few years show that the improvements are, not surprisingly, greatest for the higher starting numbers (Figure 63.3).

Finishing number data also show lowest pregnancy loss rates for those cases reduced to twins, with increasing losses for singletons followed by triplets. However, the rate of early premature delivery is, not unexpectedly, highest with triplets followed by twins and lowest with singletons. Mean gestational age at delivery is also lower for higher-order cases.

Birth weights following MFPR decrease with starting and finishing numbers, reflecting increasing prematurity. However, analysis of birth-weight centiles, particularly for singletons, reflects falling centiles with starting number, from 51.75 for two to one, to 31.26 for four to one. Furthermore, in remaining twins, the rate of birth-weight centile discordancy among twins increases from 0.57% for starting triplets to 4.86% for starting 5+. For remaining triplets, the centile differences are even greater[16]. Analysis of the data also shows that the improvements

**Table 63.4** Multifetal pregnancy reduction: losses by years. Data from reference 16

| | | *Losses (%)* | | *Deliveries (%)* | | | |
|---|---|---|---|---|---|---|---|
| | *Total (n)* | *< 24 weeks* | *> 24 weeks* | *25–28 weeks* | *29–32 weeks* | *33–36 weeks* | *37 + weeks* |
| 1986–90 | 508 | 13.2 | 4.5 | 10.0 | 21.1 | 15.7 | 35.4 |
| 1991–94 | 724 | 9.4 | 0.3 | 2.8 | 5.4 | 21.1 | 61.0 |
| 1995–98 | 1356 | 6.4 | 0.2 | 4.3 | 10.2 | 31.5 | 47.4 |

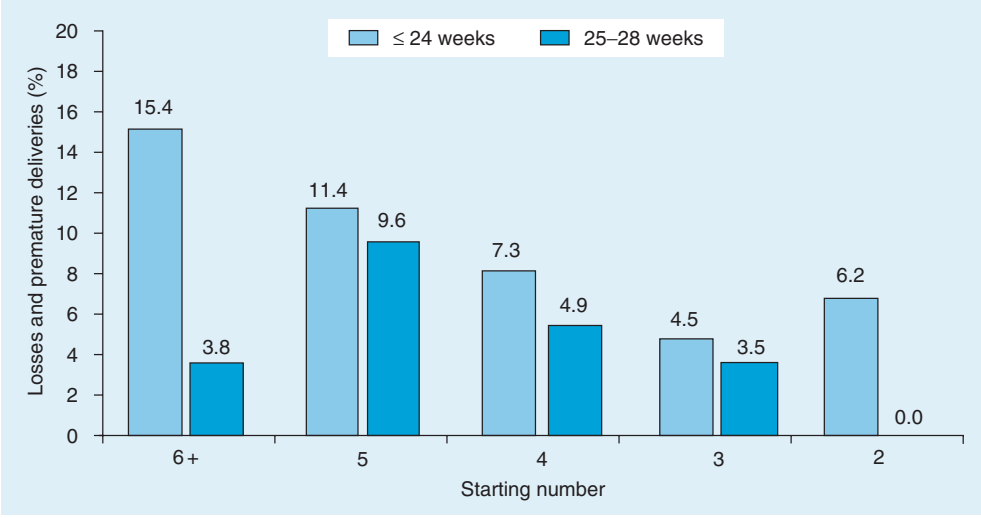


**Figure 63.2** Multifetal pregnancy reduction: losses (≤ 24 weeks) and very premature (25–28 weeks) by starting number. Adapted from reference 16

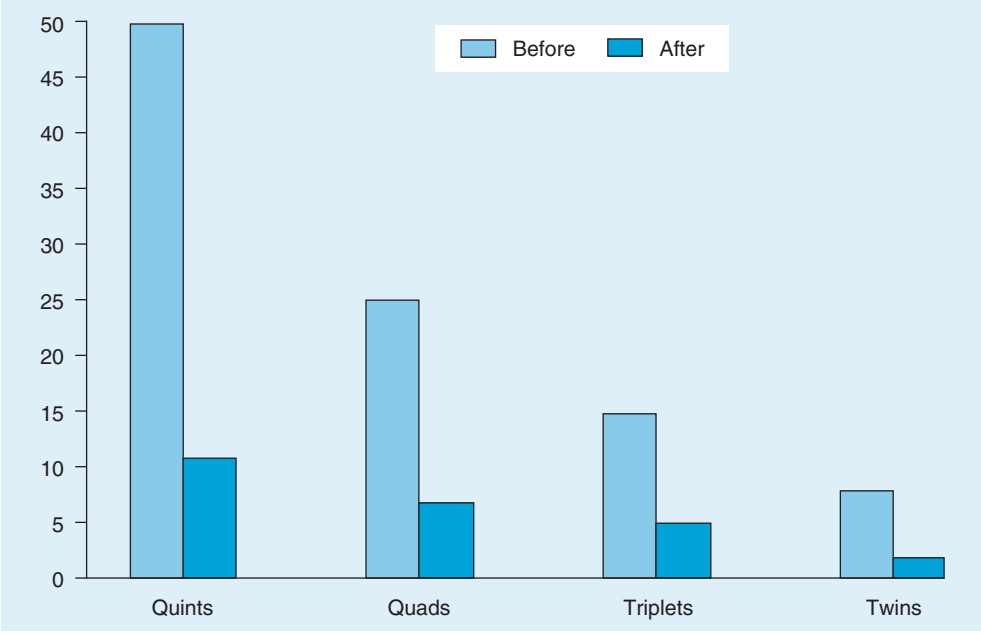


**Figure 63.3** Risk reduction as a function of starting number

in multifetal pregnancy reduction outcomes are a function of extensive operator experience combined with improved ultrasound.

Historically, except for those completely opposed to intervention on religious grounds, most observers have accepted MFPR with quadruplets or more and seen no need to use it for twins[17]. The debate has been over triplets. Whereas data in the literature are conflicting, our experiences suggest that triplets reduced to twins do much better in terms of loss and prematurity than unreduced triplets. We believe that if a patient's primary goal is to maximize the chances of healthy children, reduction of triplets to twins achieves the best live-born results.

To address the political and ethical questions about triplets, several previous papers have argued whether triplets have better outcomes 'reduced' or not. Yaron and colleagues[18] compared data for triplets reduced to twins with those for unreduced triplets and two large cohorts of twins. The data showed substantial

**Table 63.5** Reduced vs. 'unreduced' triplets comparison. Data for multifetal pregnancy reduction (MFPR) cases from reference 24

| Year/study | Losses < 24 weeks (%) | Deliveries (%) 24–28 weeks | 29–32 weeks | 33–36 weeks | 37+ weeks | Mean GA (weeks) | PMR/1000 |
|---|---|---|---|---|---|---|---|
| *MFPR cases* | | | | | | | |
| 1980s | 6.7 | 6.1 | 9.1 | 36.9 | 47.9 | 35.5 | 10.0 |
| 1990–94 | 5.7 | 5.2 | 9.9 | 39.2 | 45.2 | | |
| 1995–98 | 4.5 | 3.2 | 6.9 | 28.3 | 55.1 | | |
| 1998–2002 | 5.1 | 4.6 | 10.8 | 41.8 | 37.6 | | |
| 1998–2002 (three to one) | 8.0 | 4.0 | 12.0 | 4.0 | 72.0 | 39.5 | 0 |
| *Non-reduced triplets* | | | | | | | |
| Leondires *et al.*[20], 1999 | 9.9 | — | — | — | — | 33.3 | 55 |
| Angel *et al.*[22], 1999 | 8.0 | — | — | — | — | 32.3 | 29 |
| Lipitz *et al.*[21], 2001 | 25.0 | — | — | — | — | 33.5 | 109 |
| Francois *et al.*[23], 2001 | 8.3 | — | — | — | — | 31.0 | 57.6 |

GA, gestational age; PMR, perinatal mortality rate

improvement of outcome for reduced twins, compared with triplets. The data from the most recent collaborative series suggest that pregnancy outcomes for cases starting at triplets or even quadruplets reduced to twins are fundamentally as good as for those starting as twins. These data therefore support some cautious aggressiveness in infertility treatments to achieve pregnancy in difficult clinical situations. However, when higher numbers occur, good outcomes clearly diminish. A 2001 paper suggested that reduced triplets fared worse than continuing ones. However, analysis of that series showed a loss rate following MFPR of twice that seen in our collaborative series[19], and poorer outcomes in every other category for remaining triplets. Several other recent papers have likewise shown higher risks for 'unreduced' triplets than for reduced cases[20–23]. It is clear that one must use extreme caution in choosing comparison groups (Table 63.5).

Pregnancy loss is not the only poor outcome. Very early preterm delivery correlates with the starting number. It is not well appreciated that about 20% of babies born at weights less than 750 g develop cerebral palsy[25]. In Western Australia, Petterson and colleagues showed that the rate of cerebral palsy was 4.6 times higher for twins than for singletons per live birth, but 8.3 times higher when calculated per pregnancy[26]. Pharoah and Cooke calculated cerebral palsy rates per 1000 first-year survivors at 2.3 for singletons, 12.6 for twins and 44.8 for triplets[27]. The data on diminishing birth-weight centile in singletons from high starting numbers and discordancy in twins are of concern, and are consistent with a belief that there is perhaps a fundamental 'imprinting' of the uterus early in pregnancy that is not completely undone by MFPR[16].

In the 2001 collaborative report, the subset of patients who reduced from two to one (not for fetal anomalies) included 154 patients. The data suggested a loss rate comparable to that for three to two, but, in about one-third of the two-to-one cases, there was a medical indication for the procedure, e.g. maternal cardiac disease or prior twin pregnancy with severe prematurity, or uterine abnormality[16]. In recent years, however, the demographics are changing, and the vast majority of such cases are women in their 40s, or even 50s, some of whom are using donor eggs and who, more for social than for medical reasons, want a singleton pregnancy[28]. New data suggest that twins reduced to a singleton do better than those remaining as twins[29]. Consistent with the above, more women are desiring to reduce to a singleton. In a recent series of triplets, we found the average age of out-patients reducing to twins to be 37 years, and to a singleton, 41 years[24]. While the reduction in pregnancy loss risk for three to one is not as much as for three to two (15–7% and 15–5%, respectively), the gestational age at delivery for the resulting singleton is higher, and the incidence of birth weight < 1500 g is ten times higher for twins than for singletons[24]. These data have made counseling of such patients far more complex than previously (Figure 63.4). Not surprisingly, there are often differences between members of the couple as to the desirability of twins

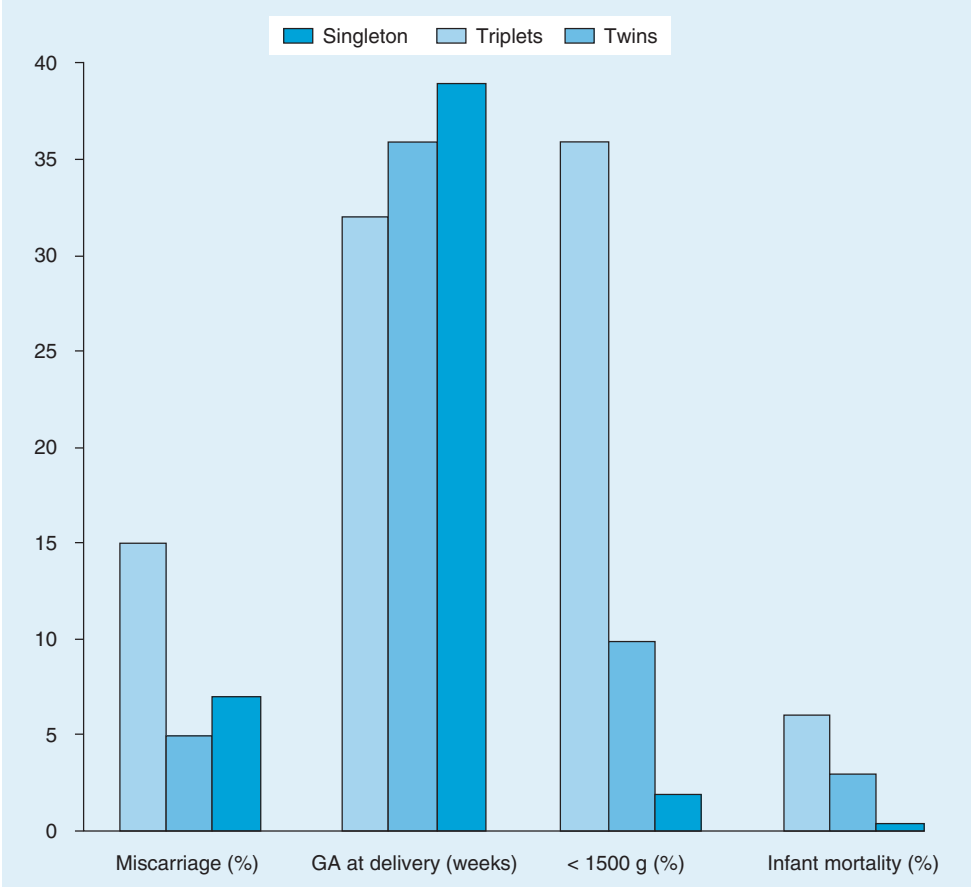


**Figure 63.4** Risks starting with triplets. GA, gestational age

or a singleton[30]. Profound public-health implications also attend these decisions, as recent United States data show that, of $10.2 billion spent per year on initial newborn care, 57% of the money is spent on the 9% of babies born at < 37 weeks[31].

## PATIENT ISSUES

The demographics of patients seeking multifetal pregnancy reduction have evolved over the past decade[19]. With the availability of donor eggs, the number of 'older women' seeking MFPR has increased dramatically. Over 10% of all patients seeking MFPR are over 40 years of age in several programs, and most are using donor eggs. As a consequence of the shift to older patients, many of whom already have previous relationships and children, there is an increased desire for these patients to have only one further child. The number of experienced centers willing to do two to one reductions is still very limited, but we believe it can be justified in the appropriate circumstances.

For patients who are older and using their own eggs, the issue of genetic diagnosis comes into play. By

**Table 63.6** Maternal age and assisted reproductive technologies, Society of Assisted Reproductive Technologies (SART) data, 2001. From reference 32

| | |
|---|---|
| All cases (*n*) | 81 915 |
| Fresh non-donor (*n*) | 60 780 |
| < 35 years (*n*) | 28 778 |
| 35–37 years (*n*) | 14 416 |
| 38–40 years (*n*) | 11 301 |
| 41–42 years (*n*) | 4 365 |
| 42+ years (*n*) | 2 190 |

2001, more than 50% of patients in the United States having ART cycles were aged over 35 (Table 63.6)[1,7]. In the 1980s and early 1990s, the most common approach was to offer amniocentesis at 16–17 weeks on the remaining twins. A 1995 paper suggested an 11% loss rate in these cases, which caused considerable concern[33]. However, a much larger collaborative series in 1998 settled the issue by showing that loss rates were no higher than comparable controls of MFPR patients who did not have amniocentesis[34]. The collaborative data showed a loss rate of 5%, which was

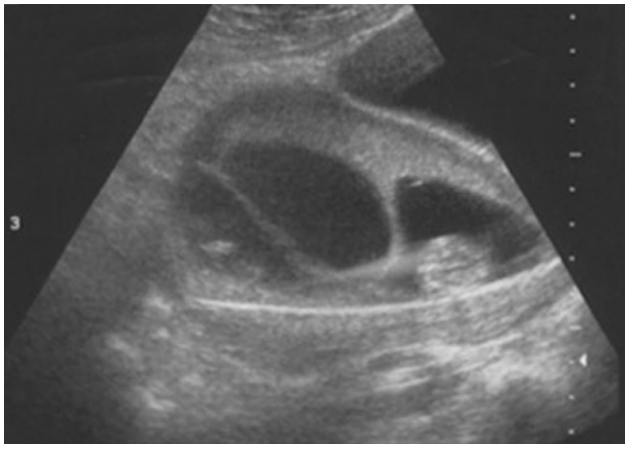

**Figure 63.5** Chorionic villus sampling for triplets prior to fetal reduction

certainly no higher than for the group of patients post-MFPR who did not have genetic studies.

Since the centers with the most MFPR experience also happened to be the ones who have similar experiences with chorionic villus sampling (CVS), combinations of the procedures are very logical. There are two schools of thought as to the best approach to first-trimester genetic diagnosis, i.e. should it be before or after the performance of MFPR? Published data in the early 1990s for CVS first followed by reduction suggested a 1–2% error rate as to which fetus was which, particularly if the entire karyotype was obtained before going on to reduction[35]. Therefore, for the first 10–15 years, the approach we used was generally to do the reduction first at approximately 10.5 weeks in patients reducing to twins or triplets, followed by CVS approximately 1 week later. However, in patients going to a singleton pregnancy, essentially putting 'all of their eggs in one basket', we believed that the best approach was to know what was in 'the basket' before reducing the other embryos[16,28]. In these cases we performed a CVS on usually all the fetuses, or one more than the intended stopping number, and carried out fluorescence *in situ* hybridization (FISH) analysis with probes for chromosomes 13, 18, 21, X and Y. Whereas about 30% of anomalies seen on karyotype would not be detectable by FISH with these probes[36], there is always residual risk[37]. The absolute risk given both a normal FISH and a normal ultrasound examination including nuchal translucency[38] is only about 1/500. We believe that the risk is lower than the increased risk from the 2-week wait necessary to get the full karyotype. We now commonly extend this approach to all patients who are appropriate candidates for prenatal diagnosis, regardless of the fetal number. Over the past few years, more than half of our patients have combined CVS and MFPR procedures (Figure 63.5).

The other approach, used by another group, was to perform the CVS and complete karyotype first and have the patient come back for the reduction. Although 'mistakes' were common 10 years ago, the chance of error has been considerably reduced, and they believe the benefits of the full karyotype justify the wait. The issue as to which is the better of these two approaches is currently unsettled.

## SOCIETAL ISSUES

MFPR continues to be controversial. Opinions on MFPR, in our experience, have never followed the classic 'pro-choice/pro-life' dichotomy. Rather, as far back as the mid- to late 1980s they were highly varied[17,39–41]. MFPR improves the outcome of triplets: it clearly does. We believe that the real debate over the next 5–10 years will not be whether MFPR should be performed with triplets or more. A serious debate will emerge over whether or not it will be appropriate to offer MFPR routinely for twins, even natural ones for whom the outcome has commonly been considered 'good enough'. Our data suggest that reduction of twins to a singleton actually improves the outcome of the remaining fetus[29]. No consensus on the appropriateness of routine two-to-one reductions, however, is ever likely to emerge.

The ethical issues surrounding MFPR will also always be controversial. Over the years, much has been written on the subject. Opinions will always vary substantially from outraged condemnation to complete acceptance. No short paragraph could do justice to the subject other than to state that most proponents do not believe this is a frivolous procedure, but see it in terms of the principle of proportionality, i.e. therapy to achieve the most good for the least harm[10,39–41].

How patients 'hear' and internalize data has been fascinating to us over the years. We have developed the concept of 'framing', i.e. through what lens do patients view the data[42–44]? In our experience, patients' backgrounds and education are paramount. Patients who come from a scientific or medical background need to see numbers and look at a hard analysis of the data. Those who come from a devout religious background frame the data through the lens of minimizing damage to their tenet of avoiding termination at all possible costs. Conflicts between partners and for patients who also worry about the impact of multiples – particularly those that may be compromised – are very troubling to patients[30]. Not surprisingly, we have found differing patterns of reactions to the diagnosis of fetal anomalies. For most patients with a wanted, singleton pregnancy,

the diagnosis brings devastation to them. For those with a multiple pregnancy considering selective reduction, the diagnosis of an abnormality in one fetus actually brings profound relief – making the decision to reduce easier for them.

## SUMMARY

Over the past 15 years, MFPR has become a well-established and integral part of infertility therapy and attempts to deal with the sequelae of aggressive infertility management. In the mid-1980s, the risks and benefits of the procedure could only be guessed[10–12]. We now have very clear and precise data on the risks and benefits as well as an understanding that the risks increase substantially with the starting and finishing number of fetuses in multifetal pregnancies. The collaborative loss rate numbers, i.e. 4.5% for triplets, 8% for quadruplets, 11% for quintuplets and 15% for sextuplets or more, seem reasonable ones to present to patients for the procedure performed by an experienced operator. Our own experience and anecdotal reports from other groups suggest that less experienced operators have worse outcomes.

Pregnancy loss is not the only poor outcome. The other main issue with which to be concerned is very early preterm delivery and the profound consequences to such infants. Here again there is an increasing rate of poor outcomes correlated with the starting number. The finishing numbers are also critical, with twins having the best viable pregnancy outcomes for cases starting with three or more. Triplets and singletons do not do as well. However, an emerging appreciation that singletons have prematurity rates less than those of twins is making the counseling far more complex. We continue to hope, however, that MFPR will become obsolete, as better control of ovulation agents and assisted reproductive technologies makes multifetal pregnancies uncommon.

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# Selective Termination of the Anomalous Fetus

*R. Peltz and S. Lipitz*

64



## INTRODUCTION

The incidence of fetal malformations is higher in multifetal pregnancies than in singletons[1,2]. In dizygotic twin gestation the risk per pregnancy of a fetal malformation is slightly more than double (independent probabilities per fetus). In a monozygotic twin gestation there is an increased risk of structural malformation. Table 64.1 lists the structural malformations in twins[3]. The presence of a fetus with a major anomaly in a twin gestation increases the risk of preterm delivery[4].

The application of modern techniques for clinical prenatal diagnosis, such as chorionic villus sampling, amniocentesis, ultrasonography, fetal blood sampling and fetoscopy, along with appropriate laboratory techniques including cytogenetic, biochemical and molecular genetic evaluations, makes it possible to detect an increasing number of fetal abnormalities in the antepartum period[5].

The diagnosis of twin pregnancy discordant for chromosomal, mendelian or structural anomaly compels the parents to choose between three options: first, continuation of the pregnancy, giving birth to the abnormal twin for the sake of securing the normal one; second, termination of the pregnancy, despite the presence of the normal twin; and finally, selective termination of the abnormal twin. The parents' decision depends upon the following considerations: the implications of the abnormality on the longevity and quality of the life of the affected twin; the risks and benefits of the procedure offered for selective termination; and, in the case of a lethal anomaly such as anencephaly, which alternative serves best the health and survival of the normal twin.

**Table 64.1** Categories of structural defects in twins. Adapted from reference 3

| *Category* | *Defect* |
|---|---|
| Malformations more common in twins than in singletons | neural tube defects<br>hydrocephaly<br>congenital heart disease<br>esophageal and anorectal atresias<br>intersex<br>genitourinary tract anomalies |
| Malformations unique to monozygotic twins | amniotic band syndrome<br>twin-reversed arterial perfusion sequence<br>conjoined twins<br>twin embolization syndrome |
| Placental malformations | single umbilical artery<br>twin–twin transfusion syndrome<br>velamentous cord insertion |
| Deformations due to intrauterine crowding | skeletal malformations |

The different procedures employed for selective termination in dichorionic versus monochorionic twin pregnancy make it crucial for chorionicity to be accurately determined. Attempts should be made to

assign chorionicity sonographically, using parameters such as number of placentas, fetal sex, septum thickness and 'twin peak' signs[6,7] (see Chapter 39). If ultrasonography is insufficient to determine chorionicity, amniocentesis and DNA fingerprinting for zygosity determination must be considered[8].

## THE PROCEDURE

In dichorionic pregnancies, selective termination procedures are initiated by using ultrasonic guidance to insert a needle into the heart of the abnormal fetus. In cases with chromosomal aberrations, fetal blood is taken for rapid karyotyping to confirm that the abnormal twin is indeed the one being selected. Feticide of the affected twin is performed by intracardiac injection of 2–3 ml of 15% potassium chloride (KCl) under direct visual guidance. This relatively small volume of KCl is harmless to the mother, and is similar to the volumes injected in multifetal pregnancy reduction of two or three fetuses in the first trimester. Currently, cardiac puncture, air embolization, exsanguination and cardiac tamponade are infrequently used alternatives.

Using intracardiac KCl is not suitable in pregnancies suspected of being monochorionic. Owing to the presence of vascular communications between the fetuses, such a procedure would create a significant risk to the healthy fetus. Moreover, in cases where chorionicity is uncertain, careful ultrasonographic determination must be carried out before advising the parents that the procedure is relatively harmless to the healthy fetus.

Techniques for selective feticide in monochorionic twins must include a method which completely and permanently arrests blood flow in the cord of the target fetus[9]. Surgical removal of the anomalous twin, occlusion of its umbilical cord or selective removal of an acardiac fetus by hysterotomy[10,11] have been reported in selected monochorionic pregnancies. Techniques of umbilical cord occlusion include embolization of the umbilical vessels, endoscopic cord ligation, endoscopic or ultrasound-guided laser coagulation and bipolar coagulation[12–14]. Figures 64.1 and 64.2 illustrate the laser procedure, and Figure 64.3 shows the findings at birth following fetoscopic cord coagulation (see Chapter 39).

Extreme care should be taken in correct identification of the fetus to be terminated. When the indication for termination is a structural or chromosomal abnormality in a gender-discordant pair, there is no difficulty in identifying the abnormal fetus immediately prior to the procedure. However, in cases of chromosomal abnormalities in a same-sex pair, cordocentesis or fluorescence *in situ* hybridization analysis of amniotic fluid should be undertaken to confirm diagnosis according to different fetal positions. Termination is carried out only after the genetic results (approximately 24–48 h) have been evaluated.

In one of the cases reported by Evans and colleagues[15], the healthy fetus was erroneously terminated after prenatal diagnosis of Down's

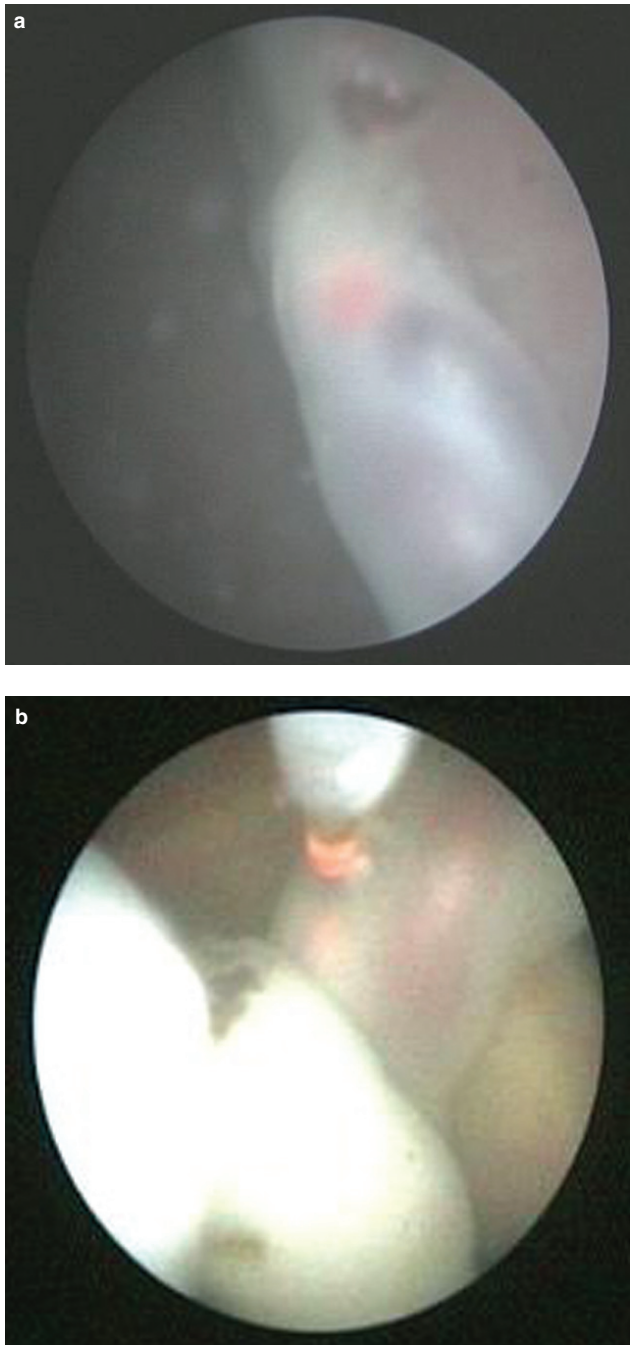


**Figure 64.1** Fetoscopic images of (a) umbilical cord coagulation by laser and (b) laser cord transsection. For selective feticide in monoamniotic twins, the cord is first coagulated and then transsected to avoid later cord entanglement. Images courtesy of Drs Liesbeth Lewi and Jan Deprest, Leuven, Belgium

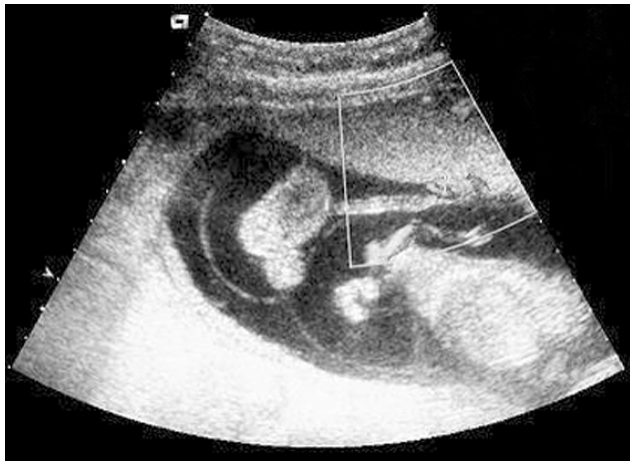

**Figure 64.2** Ultrasound image of Doppler examination to confirm arrest of flow after umbilical cord coagulation by fetoscopic laser in a case of twin-reversed arterial perfusion at 17 weeks' gestation. Image courtesy of Drs Liesbeth Lewi and Jan Deprest, Leuven, Belgium

syndrome in the other twin by amniocentesis. This dramatic accident stressed the absolute need for precise identification of each twin during fetal tissue sampling procedures, as well as the risk of misleading reports of fetal positions at the time of amniocentesis, especially if 2–3 weeks elapse until the results become available. Documentation of which fetus has the anomaly at the time of prenatal diagnostic procedures is critical, and must include an *in utero* mapping of both fetal and placental topography.

Post-reduction follow-up includes ultrasonographic examinations once every 2 weeks, and frequent evaluation of fetal well-being with the use of the non-stress test and biophysical profile. Evans and colleagues[15] reported that there were no instances of clinically evident or laboratory-appreciated coagulopathies detected in the mothers. Assessment of the risk of preterm labor may be accomplished by one of several means, such as uterine contraction monitoring, determination of cervicovaginal fibronectin levels[16] or ultrasonographic measurements of cervical length (see Chapters 55 and 56). Tocolytic agents are not used routinely, and are added only if uterine activity is recorded in association with cervical change. Glucocorticoids are administered when necessary.

## OUTCOMES OF SELECTIVE TERMINATION

### Dichorionic pregnancies

In the late 1970s, Alberg and associates[17] reported the first successful selective birth from a twin

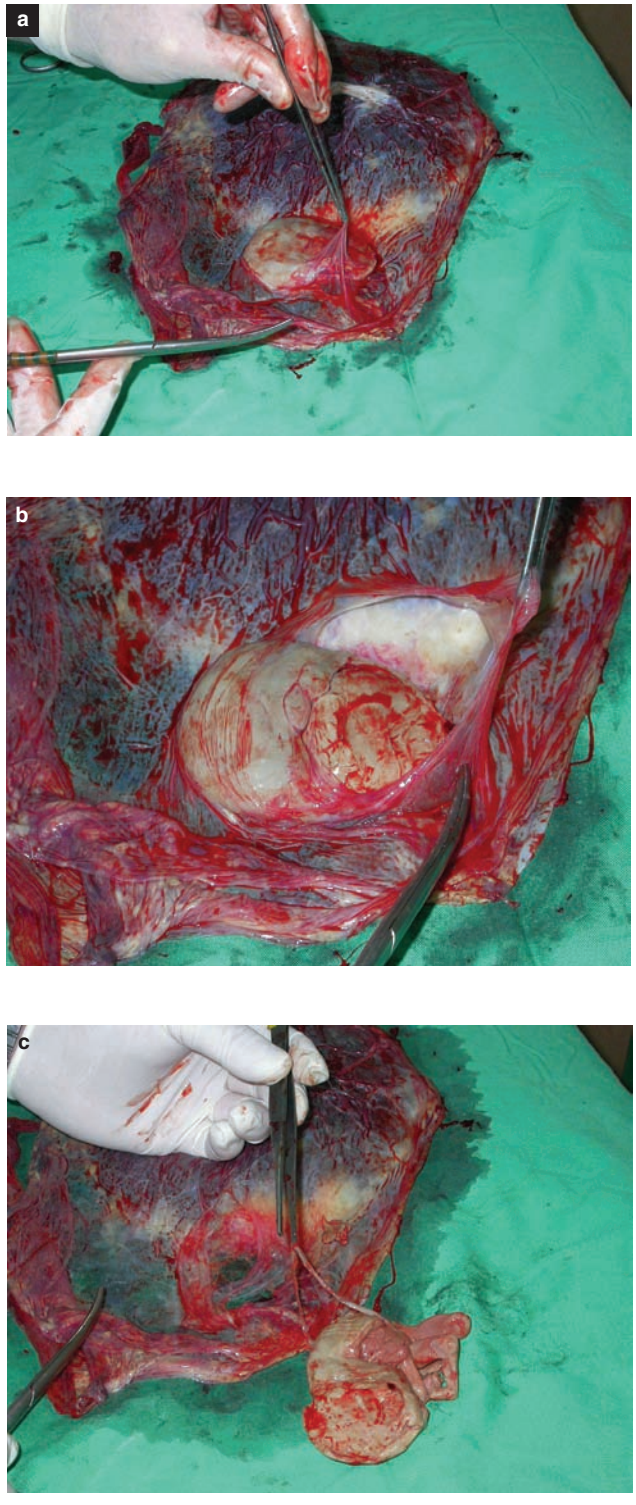


**Figure 64.3** Findings following selective feticide by fetoscopic cord occlusion in monochorionic twins. The procedure was performed on a hydrocephalic twin at 19 weeks, in a pregnancy complicated with twin-to-twin transfusion. (Images courtesy of Isaac Blickstein, MD). (a) Forceps holding intertwin membrane covering the macerated twin. (b) Trimmed membranes uncovering the macerated twin. (c) Macerated twin removed from its niche in the placenta. Forceps pointing to the severed umbilical cord

pregnancy discordant for Hurler's syndrome. In 1978, Kerenyi and Chitkara[18] reported selective birth in a twin pregnancy discordant for Down's syndrome. Throughout the 1980s, several reports of second-trimester selective termination appeared in the literature, most of which recorded very high loss rates and morbidity, and none of which had sufficient data to reach reasonable conclusions concerning the safety and efficiency of the procedure[19–21].

In 1994, Evans and colleagues[22] reported a multicenter experience with 183 such procedures. Selective termination was technically successful in 100% of cases. No coagulopathy or ischemic damage was observed in survivors of dichorionic pregnancies, and no maternal morbidity was noted. In experienced hands, selective termination of a dizygotic, abnormal twin was found to be safe and effective when performed with KCl. A total of 83.8% of viable deliveries occurred after 33 weeks, and only 4.3% between 25 and 28 weeks. Gestational age at the time of the procedure correlated positively with loss rate, and inversely with gestational age at delivery. However, this study included only five cases in which termination was performed at > 24 weeks' gestation. Consequently, at that stage, the appropriateness of selective termination was not established for those patients seeking treatment after the pregnancy reached viability.

This latter issue was addressed by a multicenter study conducted in Israel[23]. Israeli law permits late termination in singleton as well as in multifetal pregnancies under special restrictions and regulations, thus providing an excellent opportunity to analyze the perinatal outcome of twin pregnancies after late selective termination of one malformed fetus. In the cited series, a total of 36 dichorionic twin pregnancies underwent selective fetal termination after 24 complete gestational weeks. Only five women (13.8%) delivered before completing 34 weeks. Death of the normal twin occurred in one case (2.8%) as a result of termination of the malformed fetus. This report disputes the earlier international collaborative study of second-trimester selective terminations for fetal abnormalities in twin pregnancies[22] which reported a significantly higher miscarriage rate when the procedure was performed later in pregnancy (14.5% >16 weeks) compared with earlier procedures (9% < 16 weeks), as well as a negative correlation between gestational age at the time of selective termination and gestational age at delivery. In that series, the rate of preterm delivery, namely < 32 weeks, was 14.2%. Therefore, a higher rate of preterm labor and prematurity for late terminations (> 24 weeks) may have been expected. However, the rate of prematurity in the Israeli series was relatively low (14.3% before 34 weeks), and the median gestational age at delivery in the study group (37 weeks) was similar to that of uninterrupted twin gestations in one American series[24]. Consequently, there were no cases of significant morbidity associated with prematurity among the live-born infants.

The outcome of performing selective termination in the third trimester was addressed by Shalev and co-workers[25] who performed intracardiac injection of KCl in 23 cases at 28–32 weeks of gestation, after betamethasone treatment for enhancing lung maturity. All 23 twin pregnancies had an uneventful course after the termination procedure performed at 28–32 weeks. All birth weights were > 2000 g.

Evans and colleagues[15] later reported the outcomes of 402 selective terminations performed with intracardiac KCl injection from eight centers in four countries. All cases were believed to be dizygotic. There were 345 twins, 39 triplets and 18 quadruplets. Selective termination resulted in delivery of a viable infant in > 90% of cases. Miscarriage occurred before 24 weeks in 30 of the 402 patients (7.5%). When only twins were counted, the loss rate up to 24 weeks was 7.0%. Breakdown of the data by gestational age at procedure showed a loss rate at 9–12 weeks of 5.4%; 13–18 weeks of 8.7%; 19–24 weeks of 6.8%; and > 25 weeks of 9.1%. The correlation between loss or prematurity and gestational age at the time of the procedure noted in the previous report[22] did not hold with the larger data set, except that first-trimester cases showed a trend towards lower loss rates, with 78% of all viable deliveries occurring after 33 weeks and only 6% at 25–28 weeks.

A much lower pregnancy loss rate was reported by Eddelman and associates[26], who summarized the outcome of 200 selective termination procedures performed at a single center. The procedure was performed on 164 sets of twins, 32 triplets and four quadruplets. Median gestational age at the time of procedure was 19.6 weeks. The overall unintended pregnancy loss rate was 4%. The loss rate was 11.1% in patients carrying three or more fetuses but only 2.4% in twins. The only factors associated with a higher risk of pregnancy loss in this series were the starting number of fetuses (three or more) and having more than one fetus selectively terminated. There was no correlation between gestational age at the time of termination and pregnancy loss or preterm delivery.

## Monochorionic pregnancies

Selective termination in monochorionic twins is less frequently indicated, and therefore the data are

insufficient to conclude which method is optimal. One of the first techniques described for interruption of umbilical blood flow was embolization of cord vessels. However, Denbow and colleagues[27] discouraged further use of this technique owing to frequent damage to the co-twin.

Neodymium : yttrium–aluminum–garnet (Nd : YAG) laser photocoagulation is reported as being capable of obliterating vessels[14,28–31], albeit with a high failure rate beyond 20–22 weeks' gestational age. The successful use of laser cord coagulation has been reported in 9/10 cases at < 21 weeks' gestation. It failed in 7/9 cases at gestational age > 21 weeks. Along with premature rupture of the membranes (PROM), the risk of this procedure theoretically includes vessel perforation[32] (Figures 64.1–64.3).

Fetoscopic cord ligation is not limited by the cord's size[33,34]. The main problem with this technique is the high risk of PROM related to the increased number of ports and longer operating time. The survival rate with this procedure approaches 70%[31].

Bipolar cord coagulation is an ultrasound-guided procedure. Deprest and colleagues[35] reported 20% (2/10) pregnancy loss following the procedure (Figure 64.4). Nicolini and associates[36] reported experience with ultrasound-guided bipolar cord coagulation in 17 complicated monochorionic pregnancies (nine cases of twin-to-twin transfusion syndrome, two with twin-reversed arterial perfusion, six with discordancy for fetal abnormality). Cord occlusion was accomplished in all cases between 18 and 27 weeks' gestation. There were two deaths of a co-twin within 12 h, and one neonatal death after delivery at 27 weeks. All other co-twins were alive and well, although two pregnancies were complicated by preterm delivery and PROM before 30 weeks' gestation.

Based on practical and technical considerations, Challis and co-workers[31] suggest the following algorithm. Prior to 21 weeks, coagulation of the cord with Nd : YAG laser should be attempted. If unsuccessful, or if the gestational age is > 21 weeks, bipolar coagulation should be the method of choice.

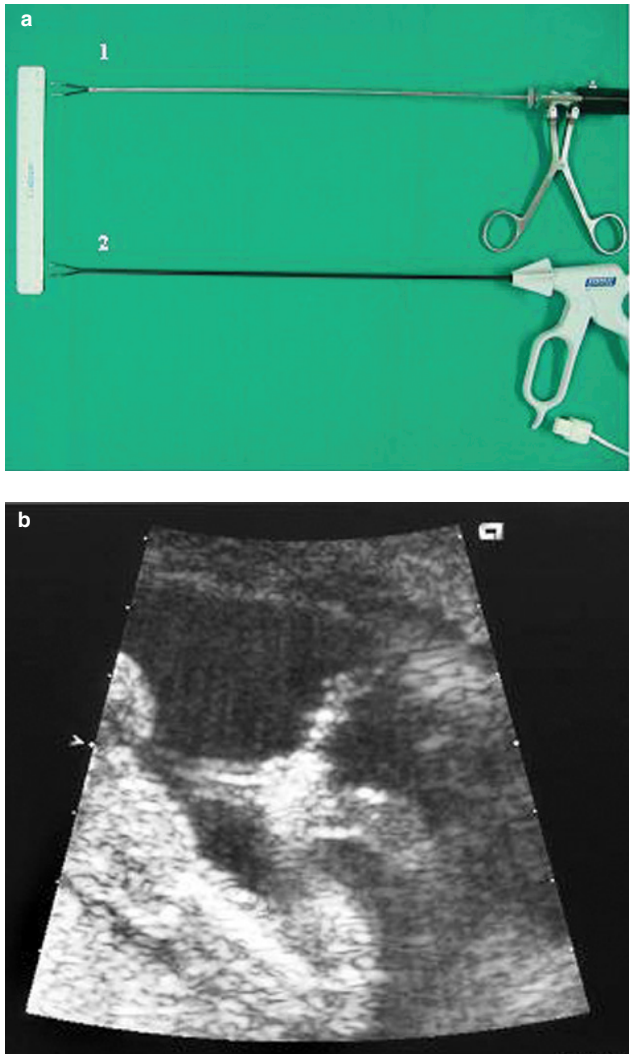


**Figure 64.4** (a) Bipolar forceps: 1, reusable 2.4-mm bipolar forceps (Storz Company); 2, disposable 3-mm Everest bipolar forceps (Gyrus Medical Company). (b) Ultrasound image of bipolar cord coagulation. Image courtesy of Drs Liesbeth Lewi and Jan Deprest, Leuven, Belgium

## TIMING OF THE PROCEDURE

Theoretically, and if the law permits, when discordance for fetal anomaly is diagnosed late in pregnancy and selective termination is requested and approved, three options exist regarding the timing of the procedure:

(1) As soon as possible, with the potential risks of pregnancy loss and premature delivery associated with the procedure;

(2) Following lung maturity enhancement and verification at about 30–32 weeks;

(3) When labor starts (or after 36 weeks) to avoid possible prematurity of the unaffected fetus.

The two later options may prevent potential procedure-related risks to the healthy fetus. However, in postponing the termination, live delivery of the malformed fetus may occur. Since current data indicate that selective termination is a safe procedure with a low pregnancy loss rate when performed by experienced operators, we tend to offer an immediate procedure when the anomaly is diagnosed before

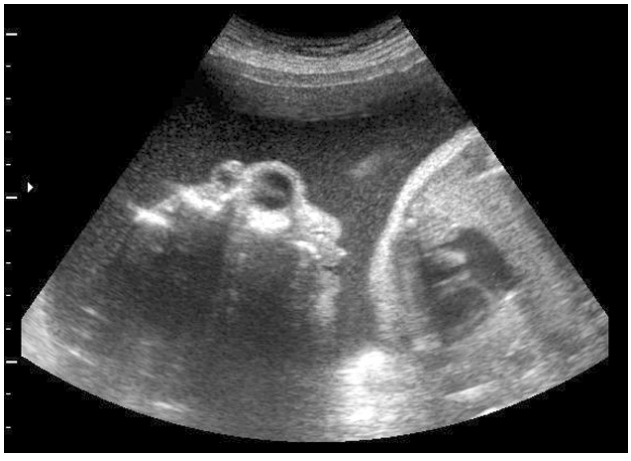

**Figure 64.5** Monochorionic twins discordant for anencephaly. This case was diagnosed at 21 weeks. Despite the risk of twin-to-twin transfusion syndrome and the difficulty in diagnosing the transfusion (both twins had polyhydramnios), pregnancy was carried to the third trimester. (Image courtesy of B. Caspi, MD). The anencephalic twin (left) faces the normal twin (right) scanned at the level of the heart

viability (< 20–21 weeks). We consider postponing the procedure when one of the following occurs: the anomaly is diagnosed at or shortly after viability (~ 24 weeks or after) to avoid severe prematurity; the risk of preterm delivery inherent to the anomaly is low; identifying the anomalous fetus is easy, and invasive diagnostic procedures prior to termination are not necessary; the anomaly is more likely to be lethal. A mandatory feature of postponing the procedure is that the couple understand and accept the risk of live birth of the malformed fetus if the procedure is postponed.

Another unsettled issue is the appropriateness of selective termination for a lethal anomaly such as anencephaly. In such cases, one has to balance two risks: on the one hand, conservative management of the pregnancy might result in polyhydramnios, which will in turn increase the risk of preterm labor of the healthy fetus; on the other hand, performing the procedure may subject the healthy fetus to procedure-related complications (pregnancy loss, PROM and preterm delivery). Currently there are insufficient data to settle this point[15]. If such an anomaly were diagnosed long before viability, the risk of selective termination is probably lower than the risk of polyhydramnios associated with the anomaly. If, on the other hand, the lethal anomaly is diagnosed at a later stage close to viability, we usually follow conservatively and intervene when polyhydramnios develops (Figure 64.5).

The dilemma of conservative management versus invasive intervention also exists in cases of acardiac malformation. A thorough review of this issue has recently been published[37] (see Chapter 45).

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## COMMENT

### ANOMALOUS TWIN REDUCTION

Trisomy 21 was diagnosed by chorionic villus sampling (CVS) in a dichorionic twin pregnancy in a 37-year-old patient (clomiphene citrate-induced pregnancy). Following counseling, the mother decided to reduce the anomalous twin (see Figure).

(a) The twin to be reduced is on the right of the sonographic image (transverse section). *In utero* 'mapping' of the fetal location is a crucial step before attempting reduction.

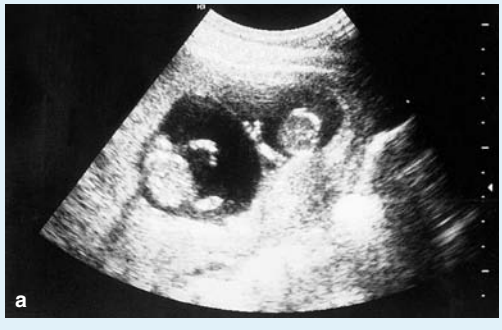
(b) The needle is introduced into the gestational sac of the anomalous twin. The needle is seen as a bright line at 2 o'clock. Some clinicians may remove some amniotic fluid for cytogenetic confirmation (*post hoc*) that the anomalous twin was reduced.

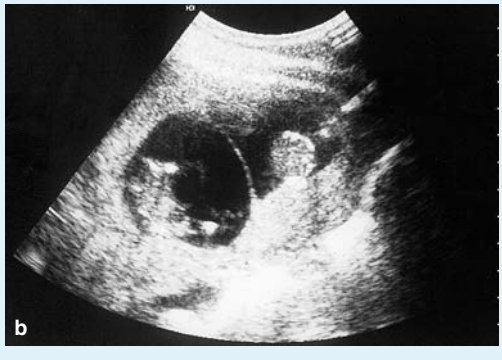
(c) The needle is inserted into the fetal heart. If amniocentesis was not performed in the previous step, some clinicians remove some fetal blood for cytogenetic confirmation that reduction was performed on the anomalous twin.

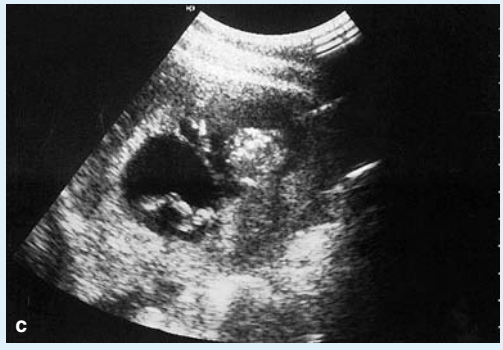
(d) Feticide: in this step, KCl is injected into the fetal heart.

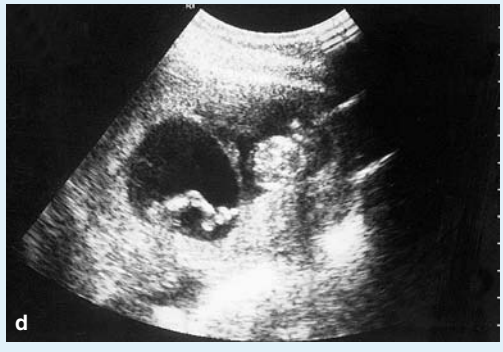
(e) The needle is withdrawn.

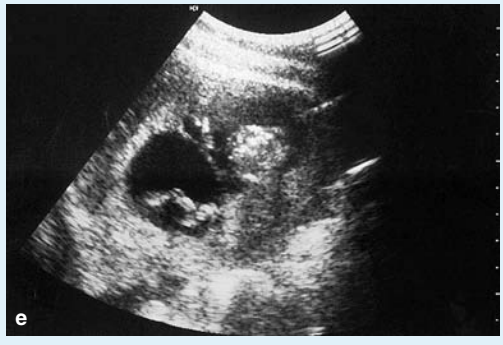
(f) Confirmation of feticide: cardiac arrest is established in this sagittal view of the reduced twin.

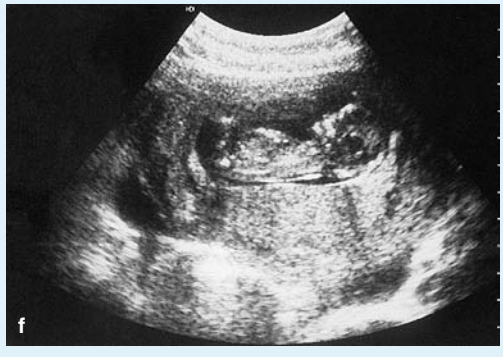



Images courtesy of B. Caspi and Z. Appelman, Kaplan Medical Center, Israel. From: Blickstein I, Keith LG, eds. *Iatrogenic Multiple Pregnancy: Clinical Implications*. Carnforth, UK: Parthenon Publishing, 2001

# Management of Twin–Twin Transfusion Syndrome

*M. J. O. Taylor and N. M. Fisk*

**65**



## INTRODUCTION

Although the diagnosis and treatment of twin–twin transfusion syndrome (TTTS) has improved greatly in recent decades, this condition represents one of the greatest challenges in modern fetal medicine. First, two fetuses are involved. Second, the natural history of fetal loss or damage is extremely high compared with other fetal pathologies. Third, because the defect originates in the placenta, these fetuses are structurally normal, and thus potentially completely salvageable. Finally, it is relatively common, occurring in 10–15% of monochorionic (MC) twins, affecting about 1 : 3200 pregnancies or 1 : 1600 fetuses[1]. Significant barriers to developing rational treatments have been the lack of understanding of the underlying vascular pathophysiology as well as the lack of an appropriate animal model.

## CLINICAL FEATURES

One of the earliest allusions to TTTS is found in Genesis where Esau, son of Isaac and Rebekah, came forth red all over 'like a hairy mantle', suggesting that he was a recipient, in contrast to his twin brother Jacob who was pale. Indeed, for many years the clinical diagnosis of TTTS was based on neonatal discordance in hemoglobin of ≥ 5 g/dl, which was often accompanied by marked differences in skin color. Such neonatal criteria, however, are now regarded as obsolete. Instead the diagnosis is made antenatally by the simple criterion of discordance in amniotic fluid volume in MC twins usually between 15 and 28 weeks' gestation in the presence of the oligo-polyhydramnios sequence, the deepest vertical pool in the donor being ≤ 2 cm and in the recipient ≥ 8 cm (as outlined in Chapter 44)[2]. Other features in the donor are small or non-visible bladder, abnormal umbilical artery Doppler waveforms (absent or reverse end-diastolic frequencies) (AEDF/REDF) and growth restriction[3,4] (Figure 65.1). Anhydramnios in the donor often leads to the appearance of a 'stuck' twin. Recently, Quintero and Chmait described the slung appearance in 16% of cases where a non-'stuck' donor is cocooned in amniotic membrane similar to a chrysalis[5]. In contrast, the recipient shows signs of hypervolemia including atrial natriuretic peptide (ANP)-mediated polyuria, polyhydramnios, visceromegaly, abnormal venous Dopplers[6–8], cardiac enlargement/failure and, in extreme cases, hydrops. The differential diagnosis includes discordant intrauterine growth restriction which complicates up to 40% of MC twins[9]. This is distinguished by the absence of recipient phenotypic features in the co-twin, along with the absence of polyhydramnios. Controversy surrounds whether TTTS can occur in monoamniotic (MA) twins, presumably because MA twins are themselves rare (1 : 10–30 000 pregnancies) and because the absence of an intervening membrane in MA twins would be expected to disguise some of the characteristics of TTTS. In our clinical material, we have only very rarely observed mild TTTS features in MA twins, and thus conclude that monoamnionicity is largely protective against TTTS.

## PATHOPHYSIOLOGY OF TWIN–TWIN TRANSFUSION SYNDROME

The lack of a suitable animal model for monozygous twinning – other than the armadillo[10] – restricts

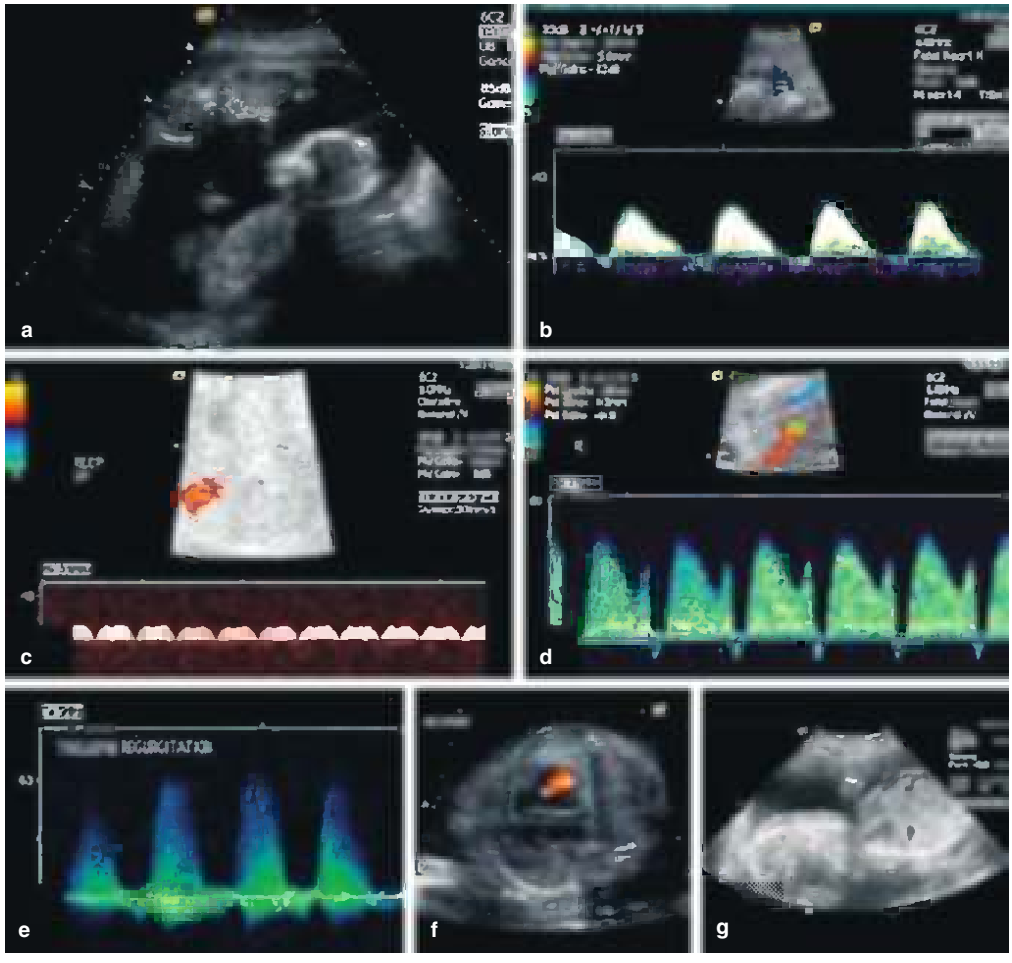



**Figure 65.1** Ultrasound and Doppler findings in twin–twin transfusion syndrome (TTTS). Features of stage II TTTS include oligohydramnios–polyhydramnios sequence with growth discordance and non-visualization of donor bladder (a). Manifestations of hemodynamic compromise in stage III TTTS include reversed end-diastolic frequencies (REDF) in umbilical artery of donor twin (b), and pulsatile flow in umbilical vein (c), reversed flow in ductus venosus (d) and marked tricuspid regurgitation (e,f) in recipient. Worsening cardiovascular dynamics in recipient result in fetal hydrops, i.e. stage IV (g)

investigators to the use of clinical and computer models[11,12]. A clinical model has self-imposed limitations, as all invasive procedures chosen as investigative tools present risks to the pregnancy and, unless there are clinical indications, are avoided for obvious ethical reasons. On the other hand, computer modeling, while risk-free and able to yield reproducible results, relies on numerous assumptions about key physiologic variables, and is thus prone to substantial error. These obstacles have hampered our understanding of the underlying pathophysiology of TTTS.

*Ex vivo* placental injection studies have shown that almost all MC placentas contain vascular anastomoses (Figures 65.2 and 65.3)[13,14]. Thus, intertwin transfusion syndrome must be considered a normal event in MC twins. This concept is supported by injection studies in which the passage of a marker substance injected into one twin is detected in the other[15]. If intertwin transfusion is a normal event in MC twins, it must be relatively balanced to avoid clinical manifestations. It follows that TTTS is a consequence of unbalanced intertwin transfusion, as suggested more than a century ago by Schatz[16] and more recently supported by both computer modeling[11] and *ex vivo* and *in vivo* studies of anastomotic configurations in TTTS[17,18].

Three types of interplacental anastomoses are identifiable on the chorionic surface or plate: arterioarterial (AA), venovenous (VV) and arteriovenous (AV). AA and VV anastomoses are superficial and permit bidirectional flow. In contrast, deep AV anastomoses comprise a cotyledon supplied by a chorionic

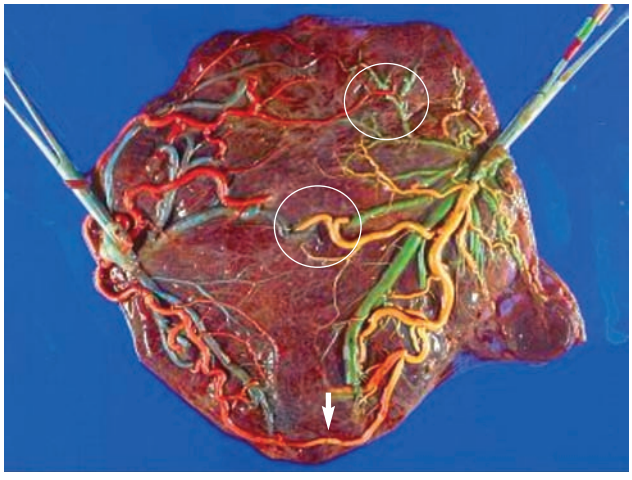


**Figure 65.2** An injection study of a monochorionic placenta. Arteries from the left and right twins' placental cord insertions are shown in red and yellow with veins in blue and green, respectively. An arterioarterial anastomosis is seen (arrow) along with multiple arteriovenous anastomoses (circles). Reproduced with permission from *American Journal of Obstetrics & Gynecology*

artery from one twin, and drained by a chorionic vein of the co-twin. Strictly speaking, an AV anastomosis is not an anastomosis, as it does not bypass the normal capillary circulation, and instead represents a shared cotyledon. Whereas AA and AV anastomoses are found in the majority of MC placentas, VV anastomoses are present in fewer than 25%[14,17,19].

We recently hypothesized that anastomoses arise in the embryologic stage of connection of embryonic and extraembryonic circulations[20], and that, during placental growth, there is random loss of these anastomoses. TTTS develops when this results in asymmetric flow resistance to net intraplacental transfusion. Initial *ex vivo* injection studies confirmed that TTTS placentas have more deep than superficial anastomoses compared with MC controls[13,19]. The largest study to date of placental angioarchitecture in TTTS compared 21 TTTS with 49 non-TTTS MC placentas and demonstrated that only the frequency of AA anastomoses was different, in contrast to the AV or VV anastomoses[17]. Not only were those affected by TTTS less likely to have AA anastomoses, present in only 24% compared with 84% of MC controls, but at least one AV anastomosis was always present in TTTS placentas in contrast to none in 16% of MC controls. Seventy-eight per cent of twins connected to a placenta with ≥ 1 AV and no AA anastomoses developed TTTS.

Under these circumstances, it thus appears that AA anastomoses have a potential for compensating any hemodynamic imbalance set up by unidirectional AV anastomoses by virtue of their high pressure differential. Indeed, the protective role of AA anastomoses in MC twin pregnancies has been validated by imaging studies[18,21]. AA anastomoses can be identified antenatally by color Doppler from as early as 11 weeks' gestation (Figure 65.4), and *in vivo* studies have validated the absence of AA anastomoses as being associated with an increased risk of TTTS (61% vs. 15%, odds ratio 8.6)[18]. Furthermore, computer modeling studies confirm that AA anastomoses confer greater protection against TTTS than oppositely directed AV anastomoses[22].

Abnormal placental development such as eccentric or velamentous cord insertions are also implicated in the development of TTTS[23,24]. For instance, in one study of 38 MC twins, Fries and colleagues found abnormal cord insertions in 64% of TTTS (7/11) cases compared with 19% (5/27) without TTTS[23]. However, a larger study of 90 MC placentas showed a similar incidence of velamentous cord insertion in TTTS placentas (60%, 18/30 vs. 70%, 42/60)[25]. Discordant placentation in MC twins as a contributor to the pathogenesis of growth discordance and/or TTTS is suggested by the higher incidence of resistance to blood flow and diminished placental microvasculature associated with oligohydramniotic fetuses compared with polyhydramniotic recipients[24]. Stated another way, there are fewer small muscular arteries (< 90 μm external diameter) in the placental territory of donor compared with recipient fetuses.

## CARDIOVASCULAR PATHOPHYSIOLOGY

Unbalanced net intertwin transfusion accounts for much of the hemodynamic change present in TTTS. Doppler studies of recipients show venous waveform patterns consistent with raised central venous pressure. Typically, donor fetuses show little abnormality in cardiac function, whereas recipient fetuses frequently develop cardiomegaly, tricuspid regurgitation and ventricular hypertrophy. Decreased glomerular filtration and renal perfusion in the donor may be responsible for a renal defect which may be more primary developmental rather than secondary to ischemia. Degenerative changes and decreased mass of renal tubules in the donor kidney may progress to renal tubular dysgenesis, with apoptosis-mediated loss of proximal and medullary tubules a marker of more diffuse renal tubular atrophy.

In the recipient, phenotypic features have largely been attributed to hypervolemia. High atrial natriuretic peptide (ANP), secreted in response to fluid

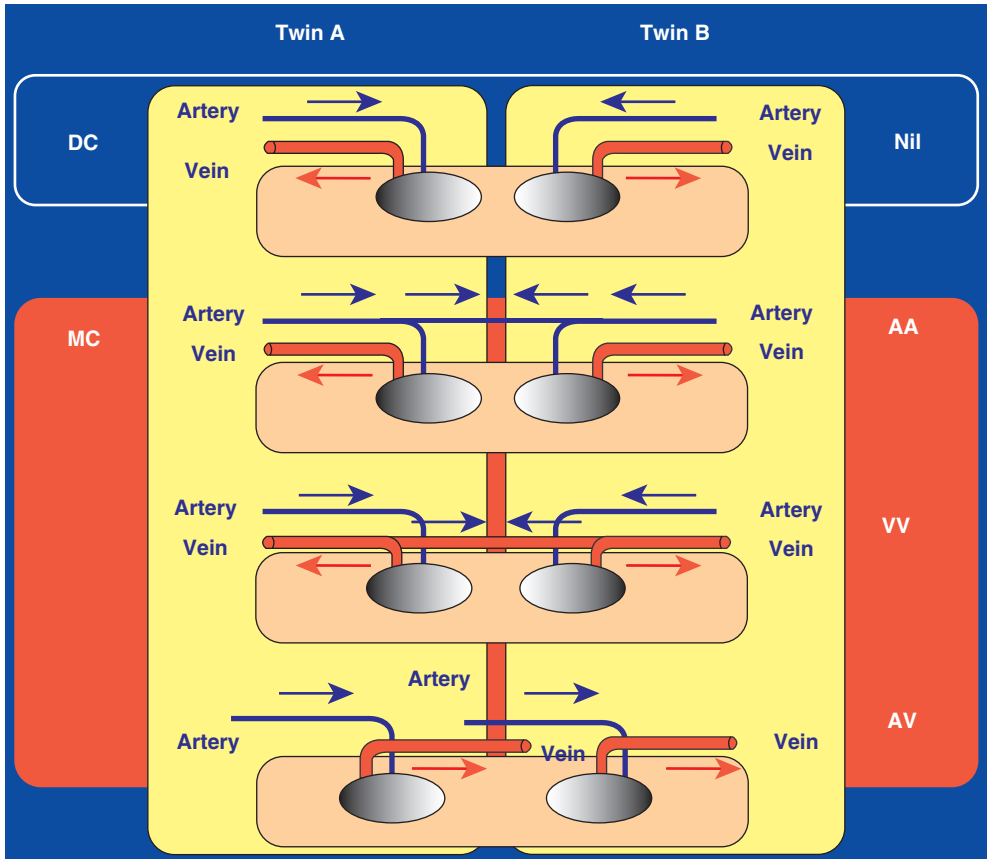



**Figure 65.3** The three types of anastomoses in monochorionic placentas, the superficial arterioarterial (AA) and venovenous (VV) and the deeper arteriovenous (AV) anastomoses. DC, dichorionic; MC, monochorionic. Reproduced with permission from RCOG Press

overload, along with concomitant suppression of antidiuretic hormone (ADH), mediates the associated polyuria and polyhydramnios[26]. Hypervolemia also elevates cardiac preload. Findings of hypertension in the recipient[27] indicate that elevated afterload may also contribute to cardiovascular dysfunction. Implicated in this is endothelin, levels of which are raised in the recipient compared with the donor[28]. Cardiac hypertrophy secondary to raised afterload sometimes results in functional right-ventricular outflow obstruction, of sufficient severity to warrant valvotomy in infancy[29,30]. Recipient kidneys are enlarged, congested and show hemorrhagic infarction, with glomerular and arterial changes resembling those found in polycythemia and hypertension[31].

Several features of TTTS are not explained by fluid volume disturbances. In the recipient, these include systemic hypertension[27] and hypertrophic outflow tract obstruction[29,30]. In the donor these include increased placental vascular resistance *in utero* and reduced arterial compliance in infancy[32]. Further, little correlation exists between hemoglobin discordance and disease severity[33]. Discordant long-term vascular programming in genetically identical survivors, which appears preventable with timely intrauterine therapy, implicates deranged fetoplacental vascular function *in utero*[34].

Disturbances of the renin–angiotensin–aldosterone system (RAS) have been described in the donor as well as the recipient[35,36]. There is up-regulation of renin expression in donor kidneys, presumably as a result of chronic hypoperfusion. Mahieu-Caputo and colleagues hypothesized that increased renin and/or angiotensin in the blood passing through placental anastomoses may, by an endocrine action, suppress renin synthesis in the recipient kidney, thereby increasing renal blood flow and contributing to polyuria and polyhydramnios. In the donor, the associated increase in angiotensin II, although possibly beneficial for adaptation to hypovolemia, may worsen the donor's fetoplacental vasoconstriction, thereby decreasing renal and placental blood flow, promoting growth restriction and worsening oliguria and oligohydramnios. This could be further aggravated by increased aldosterone production. Transfer of

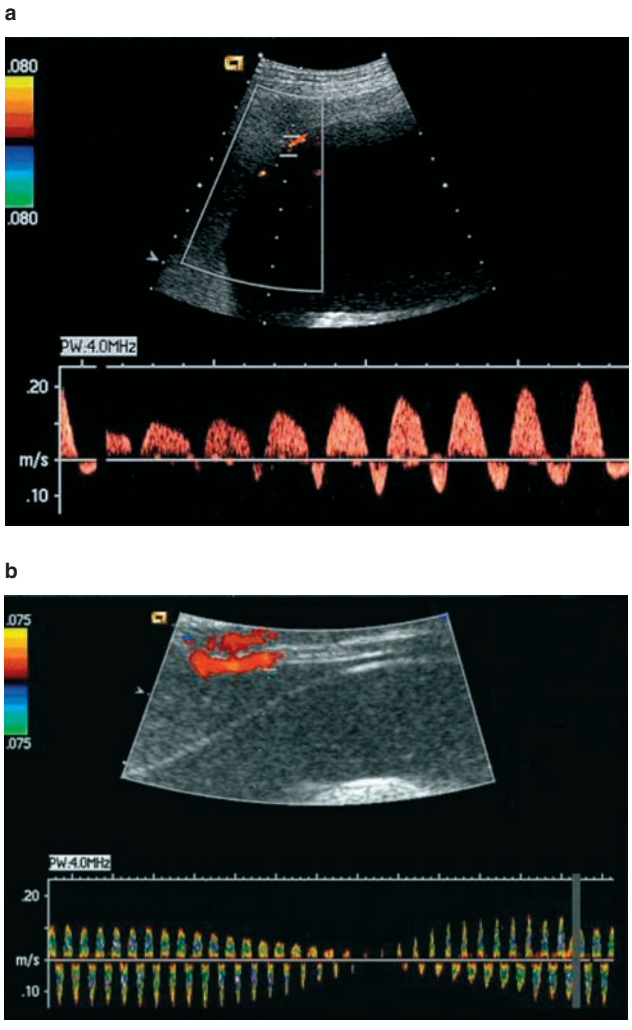



**Figure 65.4** The characteristic interference pattern (a) seen with pulsed-wave Doppler insonation of an arterioarterial anastomosis. Superimposition of two umbilical artery waveforms results in the three characteristics: a bidirectional waveform, a speckled appearance when viewed by spectral Doppler and a periodicity dependent upon the difference in twin heart rates. Reproduced with permission from *Human Reproduction*. The periodicity of the Doppler waveform is highlighted by using a slower sweep (b) (25 mm/s vs. 50 mm/s)

donor renin and/or angiotensin II to the recipient, along with raised recipient levels of endothelin, might explain the relative hypertension observed in recipient twins antenatally and neonatally[27,37]. However, we believe that Mahieu-Caputo's proposed mechanism of anastomotic transfusion of RAS effectors from donor to recipient is unlikely for the following reasons[35]. First, the half-life of angiotensin II is short (< 2 min). Second, the proportion of donor blood transfused into the recipient per minute is likely to be only a tiny fraction of the recipient blood volume. And third, low volume transfusion is inconsistent with recipient angiotensin II levels being the same if not higher than donor levels.

## CLINICAL COURSE

The median gestational age at diagnosis of TTTS is around 21 weeks, and 29 weeks at delivery[38,39]. The natural history of TTTS shows a high perinatal loss rate (>80%), and long-term morbidity in survivors, especially neurologic sequelae[1,40]. Neonatal deaths outnumber fetal deaths by 2 : 1, although the latter may be attributed to late gestational age at presentation in older series[41–43]. Where arterial Doppler abnormalities are present, i.e. AEDF/REDF in the donor umbilical artery or venous abnormalities in the recipient, perinatal death of one or both babies occurs in two-thirds of cases[44]. Whereas the donor is prone to hypoxia and intrauterine death, the recipient suffers from circulatory complications as a result of hypertrophic cardiomyopathy and polycythemia, and both are at risk of polyhydramnios-mediated prematurity.

Death of one twin *in utero* complicates approximately 30% of affected pregnancies[38,45–47]. This adverse event may result in improvement in the condition of the surviving co-twin with resolution of TTTS due to cessation of the intertwin transfusion. However, substantial risks fall to the surviving twin, including a 25% risk of ischemic brain injury or renal lesions and a comparable risk of immediate co-twin fetal death[48,49]. Fetal blood sampling and cerebral Doppler studies support the theory that the increased risk of death or neurologic injury in the surviving MC co-twin is due to exsanguinatory intertwin transfusion from the surviving into the dead twin's vascular compartment[47,50]. The outcome for the survivor is poorer in the presence of an AA anastomosis, presumably because of more rapid mediation of agonal intertwin transfusion[51]. Notwithstanding, AA anastomoses are less frequent in advanced-stage disease, and are usually associated with double survival[52].

Discordant hemodynamics may result in long-term cardiac sequelae. In a prospective study of the fetal cardiovascular system in 136 MC–diamniotic (DA) twins, a seven-fold increase in structural abnormalities was present in MC twins compared with singletons[30], presumably mediated as part of the monozygous twinning process. TTTS further increased the likelihood of structural cardiac defects to 12-fold that of the background population, with right-ventricular outflow tract (RVOT) obstruction largely accounting for the increased prevalence in recipients. The cause of RVOT obstruction in recipients is yet to be determined, but the association with

**Table 65.1** TTTS Staging according to Quintero *et al*. Adapted from reference 57

| *Stage* | *TOPS* (P > 8 cm, O < 2 cm) | *Absent bladder visualization* | *Critical arterial Doppler (absent/reversed end diastolic flow)* | *Hydrops* | *Demise* |
|---|---|---|---|---|---|
| I | + | – | – | – | – |
| II | + | + | – | – | – |
| III | + | + | + | – | – |
| IV | + | + | + | + | – |
| V | + | + | + | + | + |

TOPS, twin oligo-polyhydramnios sequence (values refer to amniotic fluid pocket); O, oligohydramnios; P, polyhydramnios

right-ventricular hypertrophy and pulmonary stenosis suggests that a vascular response to the hyperdynamic circulation is responsible. However, Sebire and colleagues' observation that the prevalence of nuchal translucency (NT) thickness above the 95th centile and discordant intertwin NT are both higher in MC twins with TTTS than in non-TTTS twins raises the possibility that discordant cardiac function and/or defects may have a primary role in the etiology of TTTS-mediated cardiac lesions rather than as a secondary response[53].

Discordant NT measurements observed in 28% (12/43) of pregnancies that subsequently developed TTTS compared with 10% (25/244) of non-TTTS pregnancies[54] suggest a limited role of NT to predict TTTS with a likelihood ratio of 3.5 (95% confidence interval (CI) 1.9–6.2). Other potential predictors of TTTS include folding of the intertwin membrane[54] and the absence of AA anastomoses[18]. Membrane folding, observed at 15–17 weeks, was seen in 32% of MC pregnancies, 43% of which subsequently developed TTTS (likelihood ratio 4.2, 95% CI 3.0–6.0). The utility of this subjective finding in predicting TTTS remains debatable, however. AA anastomoses can be detected after 18 weeks using spectral Doppler with 85% sensitivity and 97% specificity, although detection as early as 11 weeks is possible. Typically, the presence of an AA anastomosis is diagnosed by a directional speckled pattern on color or power Doppler. In a series of 105 patients with MC pregnancies, 68 (65%) had an AA anastomosis confirmed by *ex vivo* injection studies, 58 (sensitivity 85%) of which were correctly identified *in vivo* by Doppler. Doppler findings of AA anastomoses have been validated in several ways: by computer modeling, by observation of an AA anastomosis following single intrauterine death and by comparison with postnatal injection studies[55]. Computer modeling supports bidirectional flow in the AA anastomosis[11], the periodicity of which is a function of the difference in twin heart rates. This bidirectional pattern transfers to unidirectional flow in the event of intrauterine demise of one twin[55]. Interestingly, cyclic changes are seen in the umbilical artery Doppler waveform in growth-restricted MC twins (in the absence of TTTS). These are secondary to retrograde transmission from a large AA anastomosis[56]. Factors that facilitate detection of AA anastomoses are anterior placenta, larger-diameter AA anastomoses, gestational age 20–30 weeks and serial scanning. Absence of an AA anastomosis is a good predictor of development of TTTS, or more significantly, of severe TTTS associated with poor prognosis. Therefore, attempts should be made to identify AA anastomoses on ultrasound between 14 and 28 weeks, not only to predict prognosis, but also to select the appropriate management[52]. The main clinical issue with this test is distinguishing a true negative result from a false negative due to early gestation.

## STAGING

Quintero and colleagues developed an intuitive staging system to categorize disease severity[57] (Table 65.1). Stage I characterizes the oligo-polyhydramnios sequence, with stage II commencing when additionally the bladder is no longer visible in the donor. Stage III heralds the onset of abnormal Doppler flow (AEDF or REDF in the donor umbilical artery Doppler, and/or in the recipient, reverse flow in the ductus venosus or pulsatile flow in the umbilical vein). Stage IV indicates the presence of hydrops and, finally, stage V is present with the demise of one or both twins. This staging system for TTTS was designed to assist with prognostication and to standardize comparison of treatment results[57,58]. However, attempts to validate staging by outcome can be distorted by the treatment paradox, i.e. improving

outcomes in the presence of worsening disease. Our group attempted to validate the staging system in a population of 52 consecutive cases of TTTS treated with non-laser methods[59,60], with stage ≥ III being found in 63% at presentation. Excluding elective terminations and stage V disease, 45% of cases progressed to a more advanced stage, and 18% progressed to a lesser stage. Of note, stage II was often temporary, with 20% of cases regressing, and 60% regressing to stage I. These observations notwithstanding, 78% of cases were at least stage III at some time during the pregnancy. Survival rates were 58%, 60%, 42% and 43% for stages 1–IV at presentation, respectively, with no statistically significant influence of stage on survival. On the other hand, the major finding was that survival was clearly poorer when the stage increased, as opposed to diminished (27% vs. 94%). Thus, staging may be more useful for monitoring disease progression than for absolute risk assessment[60].

At Queen Charlotte's and Chelsea Hospital, our group now uses a modified staging system that incorporates the antenatal finding of an AA anastomosis indicating some, albeit insufficient, compensatory countertransfusion, and thus improved prognosis[52]. If an AA anastomosis is noted, stage is postscripted with an 'a' as opposed to 'b' when none is detected. Thus, stage III disease is substaged as IIIa in the presence of an AA anastomosis and IIIb in its absence. In an analysis of 96 TTTS pregnancies, overall survival was better in the presence of an AA anastomosis on antenatal ultrasound (83%) compared with its absence (52%). The presence of an AA anastomosis conferred a stage-independent survival advantage to fetuses in stages I–III (overall survival (stage of treatment): Ia 100%, Ib 63%, IIa 100%, IIb 59%, IIIa 83%, IIIb 44%, IVa 25%, IVb 50%). Interestingly, survival in stage IIIa was better than Ib. Thus it would appear that the AA anastomosis modification of the Quintero classification improves prognostic stratification and may be an important variable in treatment selection.

## NEUROLOGIC INJURY

TTTS survivors are at risk of neurologic injury, not just as a consequence of preterm delivery, but also from antenatally acquired insults. Bejar and colleagues[61] reported that five of nine TTTS survivors undergoing neonatal intensive care had evidence of pre-existing white matter lesions. In a more recent study from our group, 35% (11 of 31) of double survivors delivered preterm showed evidence of antenatally acquired white matter lesions on day 1–3 neonatal cranial scans[62]. However, all but one of these lesions was minor and comprised mild ventriculomegaly, subependymal pseudocysts, small white matter cysts, basal ganglia echogenicity or lenticulostriate vasculopathy. Such lesions are not uncommon in preterm infants and are not necessarily associated with long-term impairment. Indeed, 6% of 177 unselected, well, term neonates investigated at the same institution showed evidence on scan of some antenatally acquired brain insult[63].

The number of formal studies of long-term outcome in cohorts of TTTS survivors is scant, and interpreting published case series is problematic because these are small, use unstated or imprecise assessment methods, have variable and sometimes insufficient follow-up periods and often confuse abnormalities on imaging with disability. However, more recent series with detailed neurodevelopmental follow-up of more than 40 survivors suggest a handicap rate of 9–23%[64–66]. The likely pathogenesis of antenatally acquired lesions is ischemia attributable to hemodynamic imbalance secondary to placental vascular anastomoses. Polycythemia and vascular stasis in the recipient, and anemia and hypertension in the donor, are plausible mechanisms for such neurologic insults. Most series show equal distribution of neurologic lesions between donors and recipients[46,62,66], with death of one twin associated with an increased risk of neurologic sequelae in the co-twin[39,42,47]. Poorly controlled observational series suggested higher incidences of lesions on neonatal imaging after non-laser treatments[41]. However, despite the initial claims of infrequent neurologic sequelae after laser treatment, recent studies show substantial cerebral palsy rates in laser survivors, and have yet to demonstrate lower sequelae with any treatment modality discussed in the management section below. It is axiomatic that long-term follow-up studies are crucial, especially of cohorts enrolled in randomized therapeutic trials.

## FETAL PROGRAMMING

Offspring of TTTS pregnancies have abnormal vascular function in follow-up studies, including reduced arterial distensibility in donors compared with recipients[32,34]. As these findings are not present in similarly growth-restricted MC twins without TTTS, such differences in vascular function seem to be a consequence of discordant hemodynamic programming of fetal vasculature *in utero*, which has implications for cardiovascular disease in adult life as proposed by Barker[67]. Of note, these changes in vascular function are absent in double survivors after laser in which ablation of anastomoses curtailed further intertwin transfusion *in utero*. This observation suggests that fetal therapy can alter the long-term consequences of hemodynamic imbalance – the first time that any *in utero* technique has been shown to

prevent or at least modify fetal programming in humans.

## RENAL FAILURE

Acute neonatal renal failure is not uncommon in TTTS. A cohort study of 17 pregnancies described a 48% incidence of renal failure in survivors (donor more than recipient), compared with 14% in gestational age-matched control twins[38]. However, such renal failure is often transient, with long-term renal sequelae occurring in only 33% of survivors[38,46]. Abnormal perfusion in other vascular beds may also rarely result in fetal/neonatal complications. Reduced splanchnic perfusion can lead to congenital intestinal perforation from ischemic necrosis[38,46]. Spontaneous lower-extremity ischemia resulting in amputations has also been described[68–70].

## MANAGEMENT

The choice of management technique for mid-trimester TTTS is controversial, although consensus is beginning to emerge. Because of the high untreated perinatal mortality and morbidity, expectant management is only appropriate in a few mild and non-progressive cases. The main therapeutic options include serial amnioreduction, septostomy, laser photocoagulation of placental shunts, selective feticide and, after viability, delivery. Other treatments reported include digoxin, prostaglandin inhibitors, 'give and take' transfusion and sectio parvae, although none are in current use. Overall, comparing treatment modalities is confounded by differing selection criteria (severity, gestational age, etc.), the evolving nature of each technique, multiple therapies and use of historical rather than contemporaneous controls. The length of this list demonstrates how illusive the development of optimal therapy has proved to be. Regardless, sizable observational literature on the main therapeutic options now exists, and completed multicenter randomized control trials are awaiting publication.

### Medical therapy

Empiric medical treatments have been tried with little evidence of benefit. Maternal digoxin therapy to improve cardiac function in the recipient has only anecdotal success[71]. Even so, the ability of digoxin to cross the placenta and reach the recipient in therapeutic concentrations, especially in the presence of hydrops, is questionable. Indomethacin and other non-steroidal anti-inflammatory drugs to control polyhydramnios in the recipient are contraindicated in view of adverse effects on the donor's already compromised renal function.

### Amnioreduction

The principal aim of amnioreduction is to control polyhydramnios to allow prolongation of gestation. An 18-gauge needle is guided under ultrasound control into the recipient's sac, and amniotic fluid is removed, either by the use of a three-way tap and syringes or by a suction drainage system[72]. The risk of preterm labor and amniorrhexis associated with polyhydramnios is considered to be mediated through increased amniotic pressure, which proceeds linearly in relation to the degree of excess amniotic fluid, and exceeds the reference range when the amniotic fluid index rises above 40–45 or the deepest pool is 12 cm[73]. Accordingly, these thresholds have been recommended as indications for intervention, although they take no account of gestational age. Amnioreduction restores normal amniotic pressure[73,74]. Small volumes of fluid (less than 1 l) were removed in initial series in view of concerns regarding precipitation of abruption or preterm labor[75,76]. Although this intervention is sufficient to restore amniotic pressure, it seems likely that with rapid reaccummulation of fluid, pressure quickly rises again. Along this line, one American group advocated removing all the excess amniotic fluid (up to 5–10 l)[77,78]. Their low complication rates and the clinical improvements reported after serial procedures led to the widespread use of serial aggressive amnioreduction in the 1990s as first-line therapy for TTTS. A more recent series of 30 TTTS patients suggested that rapid removal of as much amniotic fluid as possible reduced the total number of amnioreductions required from a mean of 5.6 to 1.5 procedures[79]. Amnioreduction, also known as amniodrainage, may additionally improve fetal well-being by improving uteroplacental perfusion[80].

Polyhydramnios is associated with impaired uteroplacental perfusion as suggested by an inverse correlation between the degree of hydramnios and impairment in fetal blood gases[81]. Amnioreduction also leads to a 74% increase in uterine arterial flow, which suggests a mechanism for the improvement in fetal condition sometimes observed after amnioreduction[80].

One chief advantage of amnioreduction is that it is a relatively simple procedure to perform. Another is that it is the most widely available of the various treatments for TTTS[72]. Although a single procedure may suffice in 10–20% of cases, the procedure usually has to be repeated (median $n = 2$, range 1–23 in the Australian and New Zealand Registry[39]). Further, although serial amnioreduction controls

polyhydramnios, it does not address the underlying pathophysiology of TTTS.

Procedure-related risks of amnioreduction include preterm premature rupture of the membranes (PPROM) (about 6%), chorioamnionitis and placental abruption, although the incidence is low[46,72]. In a retrospective analysis of the literature to 2000, covering cases with severe TTTS before 28 weeks' gestation, serial amnioreduction led to an improvement in perinatal survival to 60%, which included 50% double and 20% single survival[1]. Results from two registries, Australian and International, give overall survivals of 60–62%[39]. Neurologic lesions were present on ultrasound in 18% of survivors[39,46], however.

## Septostomy

Amniotic septostomy creates an artificial hole in the septum to allow equilibration of amniotic fluid volume. A 22-gauge needle is used to puncture the intertwin membrane under ultrasound control. Its rationale is based on the observation that TTTS occurs extremely rarely, if ever, in monoamniotic twins, and on anecdotal improvement observed when the septum is inadvertently breached at amnioreduction. The mechanism by which this treatment might work is unclear, however, particularly in terms of normalizing polyhydramnios, although by allowing oral rehydration, the donor fetus may be able to correct its hypovolemia and/or remove fluid from the amniotic cavity.

Saade and associates' early pilot series[82], puncturing the septum with a 20–22-gauge needle in 12 cases, reported 83% perinatal survival, which prompted a multicenter randomized control trial comparing septostomy against amnioreduction. As reported to date only in abstract form, no difference in overall survival (70%)[83] was observed. However, the reported benefit was a decrease in the need to perform repeat procedures with septostomy (40% vs. 70% with amniodrainage). In terms of limitations, the procedure carries a theoretical risk of intertwin cord entanglement through extension of a defect in the dividing membrane, although the hole created is usually small (microseptostomy), and this potential complication was not observed in the trial.

Despite re-equilibrating amniotic fluid, however, it is difficult to see how septostomy addresses the underlying transfusional basis of the disease. In this light, computer modeling shows that merging the two amniotic compartments to allow swallowing of the redistributed fluid by the donor has minimal effect on donor blood volume or growth[84,85].

## Laser ablation

Interruption of the vascular anastomoses between the fetuses is the most logical of therapeutic approaches to date. The technique of laser coagulation of the placental vessels using a neodymium : yttrium–aluminum–garnet (Nd : YAG) laser was first developed in animals and later applied to humans. Typically, an endoscope is introduced transabdominally into the uterine cavity under ultrasound guidance, and the Nd: YAG laser applied via a 400–600 μm optic fiber introduced through the side channel[86,87]. The procedure is completed by concomitant amniodrainage via the same side channel.

### *Non-selective laser ablation*

The original technique involved the non-selective method of photocoagulating all surface chorionic vessels crossing the intertwin septum[88]. Ville and colleagues carried out laser ablation of placental anastomoses in a series of 132 patients with severe TTTS at a median gestational age of 21 weeks. Overall fetal survival was 55%, and the number of pregnancies with at least one survivor was 73%[89]. De Lia reported 69% overall survival and 82% of pregnancies with at least one survivor in a series of 74 patients, although seven patients were excluded from analysis owing to pre- or intraoperative complications[90]. A meta-analysis in the year 2000 of TTTS presenting before 28 weeks concluded that outcomes from non-selective laser ablation were similar to those after serial amnioreduction, with 58% overall survival and at least one survivor in 74% versus 70% of pregnancies after amnioreduction[1].

A likely explanation for the lack of improvement in survival with non-selective laser is that since the intertwin membrane bears little relationship to the vascular equator between the two fetoplacental circulations, a number of non-anastomotic vessels are also obliterated, thus devitalizing some normal cotyledons[91,92]. The excessive placental insult is substantiated by findings of full-thickness placental necrosis postpartum[86]. Such an insult is more detrimental to the donor with a lesser a priori placental share. This explains the high procedure-related fetal loss rate, which was as high as 42% in the first series but subsequently decreased to 15–20%[88,89]. In keeping with this, two-thirds of donors die if AEDF is present prior to laser[93].

Complications of all laser techniques of ablation include PPROM, chorioamnionitis, preterm labor and even reverse TTTS[94]. Rare findings, including aplasia cutis, limb necrosis, amniotic bands and microphthalmia, have been described, but their causal relationship to the procedure rather than

TTTS has not been established[90,95]. Anecdotal reports of maternal complications such as pulmonary edema, adult respiratory distress syndrome and maternal death are of concern, although the contribution of laser as opposed to the concomitant amnioreduction is unclear.

### *Selective laser ablation*

As a result of the lack of obvious improvement in survival with the original laser approaches, several groups have suggested that the therapeutic goal should be the selective ablation of those few AV anastomoses involved in the disease process[45,96–98], sparing uninvolved cotyledons in an attempt to minimize loss rates. The question is how to identify all of them. Currently, all vessels are traced endoscopically from their respective origins at each cord insertion to their termination to identify any unpaired vessels and thus AV anastomoses . Typically, all AV anastomoses are photocoagulated, including reverse ones from the recipient to the donor so as to prevent any reversal of the transfusional phenotype[98]. The anastomotic configuration can be complex and variable, making correct identification challenging. A recent validation study of laser against gold-standard placental injection studies shows that a mean of > 2 anastomoses per patient are missed at laser[99]. We quantified visual examination under optimal *ex vivo* conditions to identify only 45% of AV anastomoses present at injection study. The false-positive visual detection rate (28%) was also of concern (submitted for publication). AVAs can also be identified *in vivo* using color Doppler and three-dimensional ultrasound (Figure 65.5), which may facilitate planning of selected laser ablation and result in shorter procedure times, although sensitivity to date remains less than 50%[100,101].

A number of technical challenges arise with both types of laser treatment. Access to an anterior placenta is a particular problem. A lateral entry, use of flexible curved or side-firing scopes and even minilaparotomy to insert the cannula directly into the uterus have been utilized in attempts to overcome this problem[90,95,102]. Access may also be facilitated by maternal anesthesia, such as epidural or general, although not all groups find this necessary. Prior septostomy may occasionally render access to the chorionic plate problematic owing to chorioamniotic separation, and intra-amniotic bleeding secondary to iatrogenic vessel puncture may necessitate amnioexchange to restore visualization (Figure 65.6).

Using a selective approach, Quintero and coworkers reported survival of at least one fetus in 83% of patients versus 61% in a non-selective laser group and 67% with serial amniocentesis managed in the

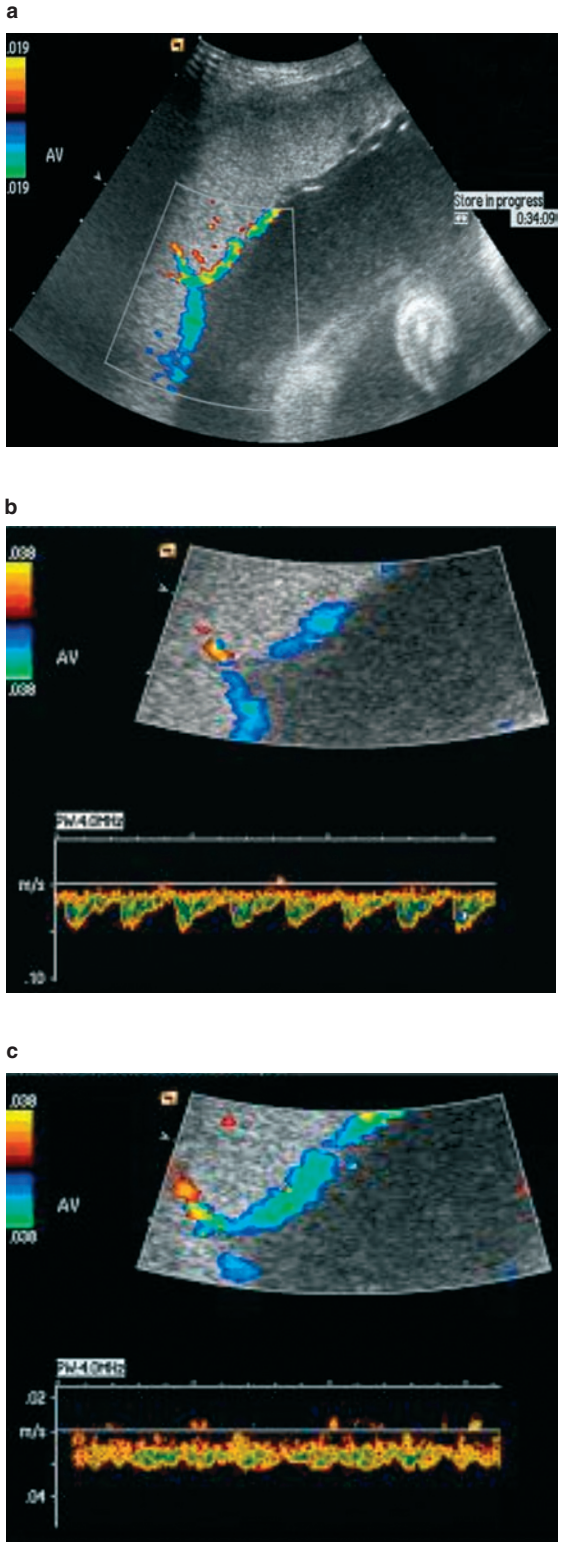



**Figure 65.5** Two-dimensional color Doppler appearances of an arteriovenous (AV) anastomosis. (a) A blood vessel is seen to enter the chorionic plate and a vessel emerge from the same cotyledon to continue towards the contralateral twin. Doppler waveforms confirm the pulsatile arterial (b) and non-pulsatile venous (c) components of the AV anastomosis[25]

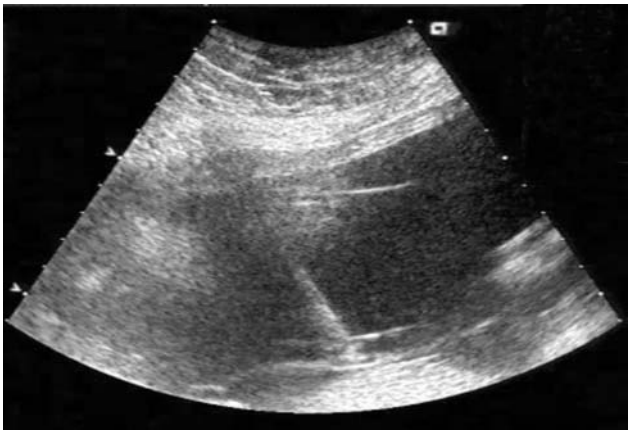


**Figure 65.6** Ultrasound immediately post-septostomy treatment of twin–twin transfusion syndrome. The inter-twin membrane, previously plastered over the 'stuck' donor twin, now floats freely and could potentially obstruct future endoscopic inspection of the placental surface

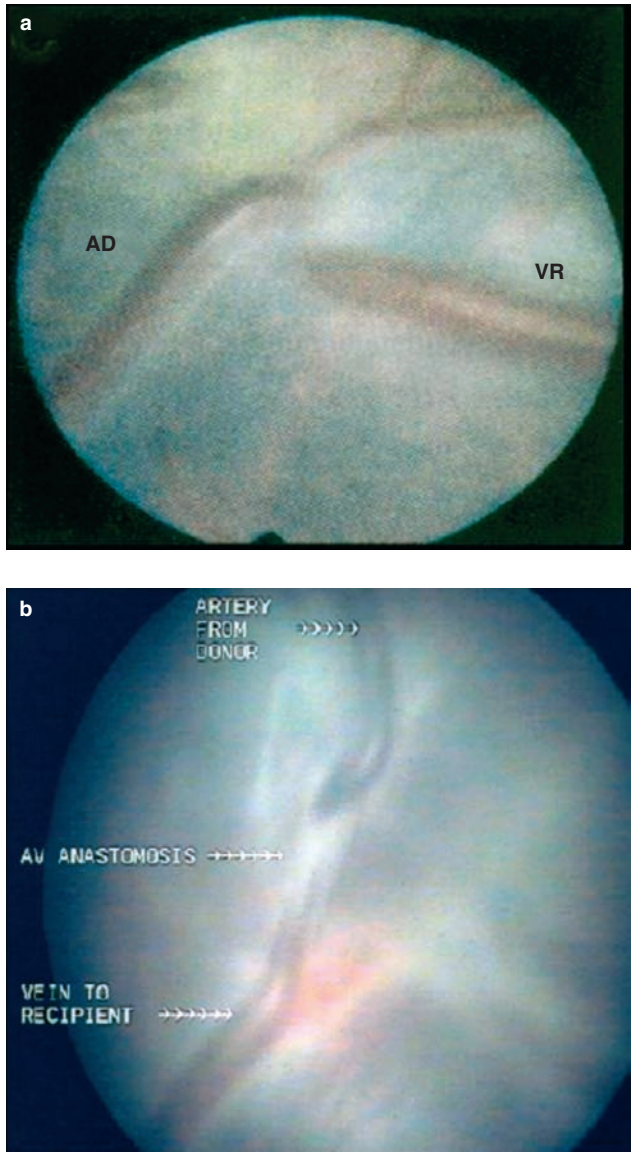



**Figure 65.7** Endoscopic appearance of an arteriovenous anastomosis before (a) and after (b) laser ablation. An unpaired artery (AD) from the donor enters the shared cotyledon and an unpaired vein (VR) emerges to run to the recipient twin. Reproduced with permission from reference 103

same center[58,97]. Similarly, Hecher and co-workers showed an improved overall survival of 68% with selective laser versus 61% in a non-selective laser group and 51% in non-contemporaneous amnio-drainage group from another center, with survival of at least one fetus in 81% (vs. 79% and 60%, respectively)[41,45]. However, a double survival rate of 54% indicates that even with the best treatment figures reported, almost half of affected pregnancies still lose one or more fetuses[45].

Quintero and colleagues suggested that laser led to a decreased incidence of neurologic morbidity (4% vs. 24% in the non-selective group), although without differentiating between ultrasound abnormalities and neurologic handicap[58]. Hecher and colleagues also suggested a lower incidence of abnormal cranial ultrasound findings with selective laser treatment (6% vs. 18% in an amnioreduction group managed earlier and elsewhere)[41]. However, a formal neurodevelopmental follow-up study of 89 TTTS survivors at 14–33 months by the same group subsequently showed a 22% incidence of neurologic sequelae in the selective laser group, including an 11% incidence of cerebral palsy[66]. The incidence was similar in recipients and donors. Ville and associates suggested a low 4% handicap rate[89] after laser; nonetheless, the same group, later detailing neurodevelopmental follow-up after non-selective laser, showed a 9% incidence of cerebral palsy[64]. Thus, the incidence of cerebral palsy with non-selective and selective laser is not obviously different from the overall incidence of cerebral palsy in TTTS, and in contrast to the poorly controlled observational series of cranial lesions seen on imaging, current follow-up data do not support an obvious improvement in neurologic outcome with laser therapy.

## Placental cast studies

Current understanding of chorionic plate angioarchitecture is based both on *ex vivo* injection studies (Figures 65.2 and 65.7) and on chorionic plate appearances at endoscopy, accepting the difficulty of

validating the latter[17,19]. Both superficial and deep anastomoses are seen to run along the surface of the placenta either in their entirety or for the most part. Arterial and venous components of AV anastomoses have been characterized with this technique by their meeting nose to nose before entering the shared cotyledon. Such descriptions form the basis for endoscopic identification of AV anastomoses. However, a recent cast study suggests that placental anatomy may not be so simple[104]. Casts allow the documentation of MC vasculature deep within the placental substance. Vessels are injected with colored resins and allowed to harden, before dissolving the placental substance by acid digestion. These resins are immune to acid so that the acid digestion removes everything except the vascular trees. In only half of the shared cotyledons in MC placentas were AV anastomoses characterized by co-termination of an artery and a vein on the chorionic plate. Instead, numerous deep anastomoses beneath the chorionic plate, which could not be visualized directly by chorionic plate inspection, were described (Figure 65.8). The implications for laser ablation are substantial. Both cast studies and standard placental injection studies of the placental surface suggest that a significant proportion of anastomoses go undetected for two reasons. First, they may lie beneath the chorionic plate and are thus invisible on surface examination of the placenta. Second, visual identification under optimal conditions misses small-diameter vessels in particular. Thus, functional dichorionicity seems an unlikely goal, although the physiologic significance of small, missed, atypical AV anastomoses may be less than that of typical AV anastomoses identified on the chorionic plate.

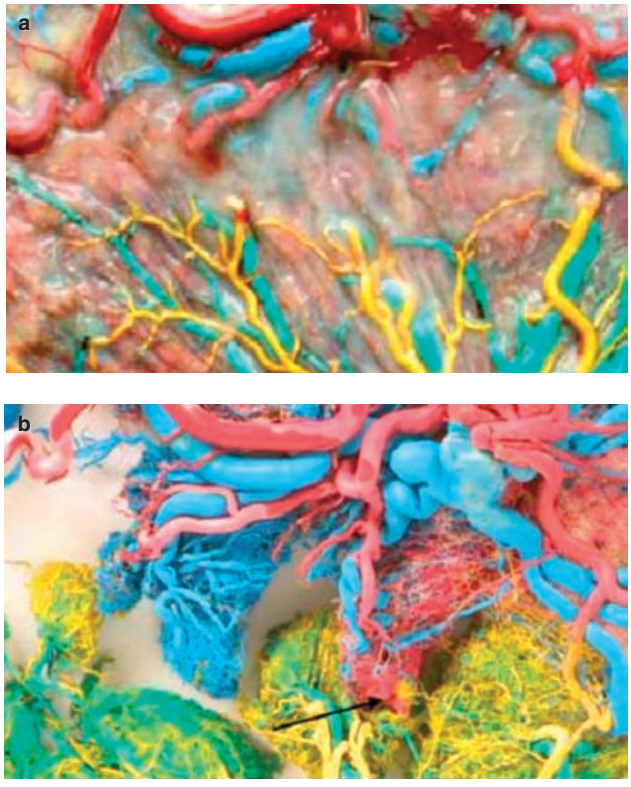



**Figure 65.8** Placental cast study of a monochorionic placenta. Two apparently normal (a) cotyledons on the surface are revealed by digestion (b) to be communicating beneath the chorionic surface (arrow indicates yellow vascular connection)

## Selective termination

The rationale for selective feticide is complete interruption of the transfusion process. One twin is terminated to allow survival of the other. The chief disadvantage is its inherent 50% perinatal mortality rate. Accordingly, most practitioners consider it appropriate only in the management of severe TTTS, whereby intrauterine death of one twin appears imminent, or once other treatment options have failed. More recently, it has been offered to patients with severe but not necessarily preterminal TTTS (stage III or IV) as an alternative to laser ablation, the rationale being that a better intact prognosis for one twin may be preferable to a guarded prognosis for both. However, ethical difficulties are also attached to this approach, for both staff and patients. In particular, some parents cannot sanction it, and others not unreasonably request to delay the operation until one twin is definitely preterminal, a process which entails the risk of unanticipated intrauterine death. Having said this, selective feticide is an appropriate strategy in the not uncommon occurrence whereby one fetus has a major anomaly, typically congenital heart disease or ventriculomegaly.

Although a variety of ultrasound-guided techniques have been described, safe feticide requires blockage of both umbilical arteries and the vein. Ultrasound-guided sclerosant injection[105,106] occludes only one vessel, which explains the failure rate of 67% reported using alcohol or enbucrilate[107]. Laser coagulation of the cord is usually not feasible after 18–20 weeks because the vessel diameter is too large[108]. Fetoscopy has been used to place a suture knot around the cord[109–111], although nowadays suture ligation of the cord is usually done less invasively entirely under ultrasound guidance[112]. Overall survival (of the non-terminated twin) with fetoscopic suture ligation of the cord is 63–71%, with an associated risk of preterm labor or preterm premature rupture of the membranes as high as 30–40%[109,111].

Currently, the preferred procedure for all selective termination procedures in MC twins is bipolar

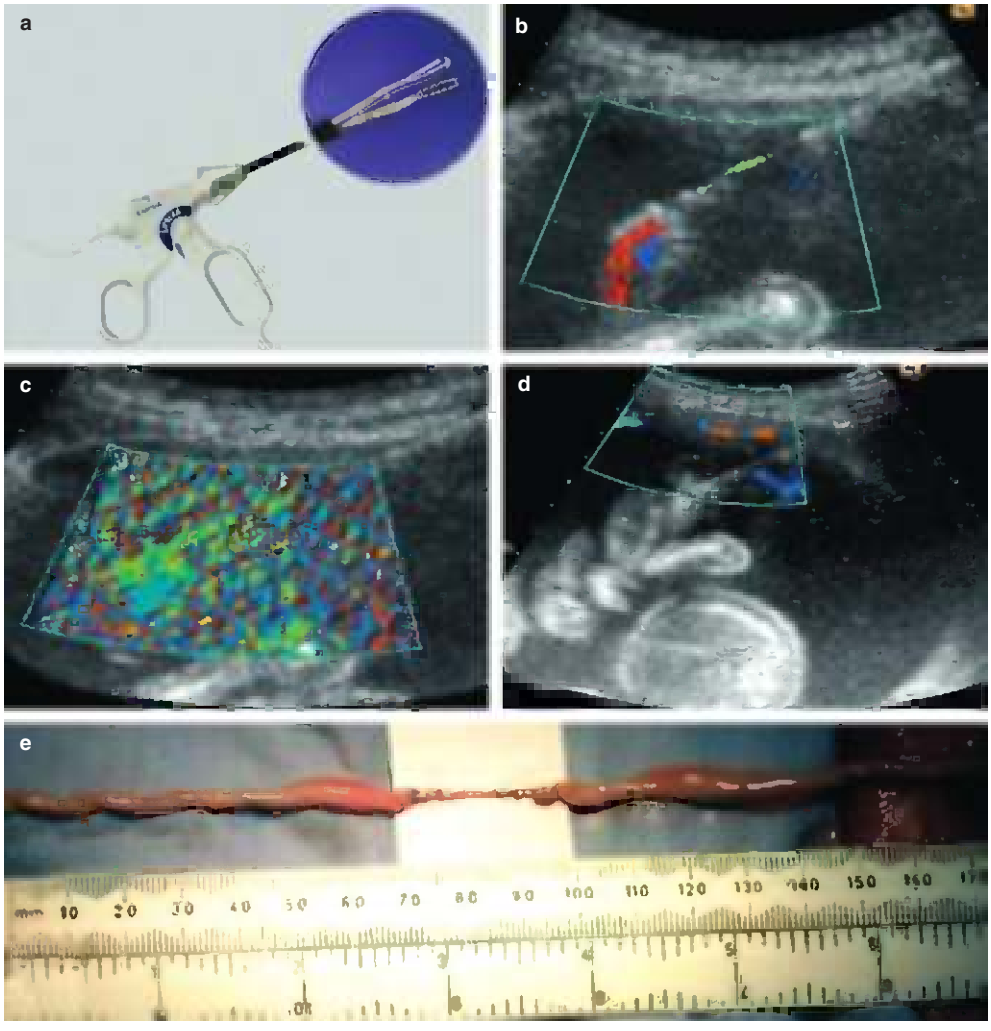



**Figure 65.9** Instruments and technique for bipolar diathermy of umbilical cord. A 3-mm diathermy forceps (Everest™) (a) is used to grasp the umbilical cord under ultrasound guidance after identification of the cord with color Doppler (b). Diathermy is applied (c), the cord is released and absence of blood flow through the cord is confirmed with color Doppler (d). Panel (e) shows the appearance of the umbilical cord of a selectively terminated recipient (cord occlusion by bipolar diathermy at 20 weeks) at delivery of the surviving donor at 35 weeks[114]. Reproduced with permission of John Wiley & Sons, Inc.

cord coagulation (Figure 65.9). Originally developed for use in acardiac or anomalous twins, the technique has also been applied to TTTS[113]. A single 3.3-mm port is introduced into the amniotic cavity under local anesthesia. A 3-mm bipolar diathermy forceps is advanced under ultrasound guidance to grasp a free loop of cord away from both the fetus and the uterine wall. Serial applications of coagulation lasting approximately 60 s are used with incremental power as needed (20–50 W) until the observed bubbling stops. Cessation of blood flow is confirmed by color Doppler. The principle disadvantage is the 12–20% incidence of PPROM[113–115]. An important aspect of this treatment, however, is the disparate legal status worldwide of termination of pregnancy after viability. Whereas this option may be feasible after 24 weeks in jurisdictions such as the United Kingdom, France and Israel, it is not widely available in other countries including most of the United States. In the best of hands, single survival rates of 90% can be achieved using selective feticide[113,116]. The choice of donor or recipient fetus for feticide is controversial. The presence of growth restriction, and abnormal umbilical arterial Dopplers along with net direction of anastomoses from donor to recipient (in the case of inadvertent incomplete cord occlusion), theoretically favor the donor as the choice for feticide. However, occlusion of the donor cord is technically challenging and often requires prior amnioinfusion[116]. On the other hand, recipients

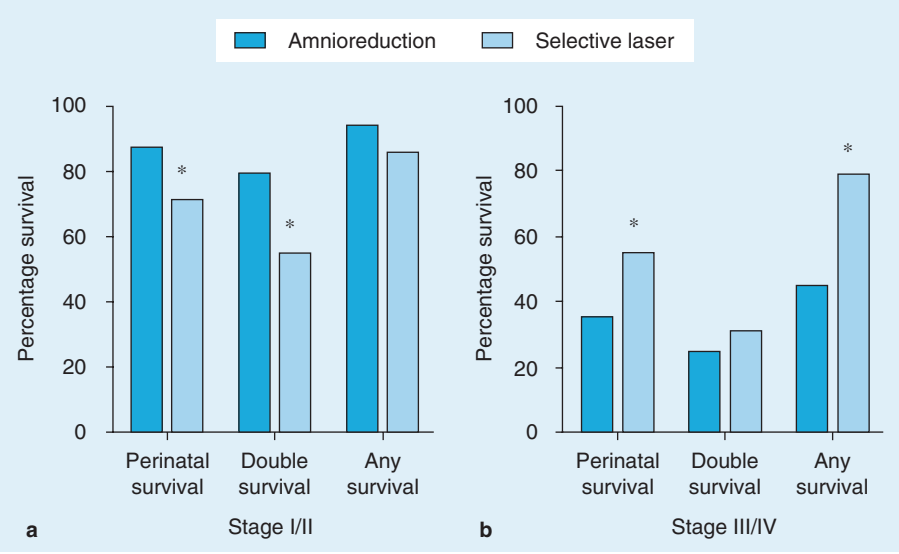



**Figure 65.10** Categorical reanalysis of stage-adjusted survival data from twin–twin transfusion syndrome (TTTS)-affected pregnancies treated with amnioreduction or selective laser[58]. (a) Perinatal (overall), double (both twins) and any (at least one) survival rates in mild (combined stages I and II) TTTS. (b) Survival rates in severe (combined stages III and IV) TTTS. *$p < 0.05$, versus amnioreduction (after Fisk and colleagues[120])

often have pre-existing damage (e.g. hydrops or cardiomegaly), and occlusion of the recipient cord is technically easier, except when too edematous (> 10 mm). Concomitant amniodrainage can also be performed. Fears of surviving donors succumbing to complications of uteroplacental insufficiency appear unfounded, as we have observed normalization of Doppler findings within 24 h in all cases where umbilical artery Dopplers were abnormal preprocedure, and postprocedure growth velocities were similar to those of surviving recipients[113].

Before 18 weeks, interstitial laser may be a useful alternative for selective termination[117]. This technique involves introducing a 20-gauge needle into the abdomen of the selected twin close to the vitilline arteries and intrahepatic vein under ultrasound guidance. A 400–600-nm laser fiber is advanced through the needle to protrude 4 mm beyond the needle tip, and short bursts of Nd:YAG laser (10–20 W) are fired until the area becomes echogenic. Here, again, cessation of umbilical blood flow is confirmed on Doppler. The advantage of this technique is that the use of a fine needle permits application earlier in gestation, when severe cases are increasingly being diagnosed. However, ensuring coagulation of all the cord vessels within the fetal abdomen can be challenging, and accordingly this method is restricted to earlier gestations. At the other extreme of gestational age, beyond 27 weeks, where the size of the umbilical cord precludes bipolar cord coagulation, selective feticide may rarely be carried out by ultrasound-guided suture ligation.

### Management of single intrauterine death

(See Chapter 70).

### Delivery

Unless earlier intervention is indicated on other grounds, our group recommends routine delivery in TTTS at 32–33 weeks after administration of steroids for fetal lung maturation. This is because survival at 32 weeks is similar to that at term, and because there remain empiric risks of deterioration as well as unexpected intrauterine death in the third trimester. In our view, cesarean section is indicated in view of the high likelihood of fetal intolerance of labor, and the possibility of acute intrapartum intertwin transfusion. Delivery earlier than 32 weeks may be indicated on fetal grounds, cognizant of the worse prognosis expected at earlier gestation compared with non-TTTS infants, both from prematurity-related complications and the sequelae of TTTS severe enough to prompt delivery, such as cardiac dysfunction in the recipient or renal compromise in the donor.

### Randomized control trials

Two randomized control trials, presented in abstract form, are awaiting full publication. In a multicenter randomized control trial comparing serial amnioreduction with septostomy[83], no difference in overall survival was shown, as discussed above. Serial amnioreduction was compared with laser coagulation in the Eurofetus trial[118] in pregnancies at less

than 26 weeks with TTTS. Survival, gestational age at delivery and birth weight were significantly higher and periventricular leukomalacia lower in the laser-treated group compared with amnioreduction, although power end-points for morbidity were not reached. The major finding of the trial, however, was the poorer survival in both study groups than in the literature, with one or both fetuses dying or having neurologic injury in two-thirds of cases even with the better of the two treatments. Patients in randomized trials generally experience better outcomes by virtue of participation. The lower than expected survival in the laser arm compared with selective laser series[45,58] might reflect the semiselective technique used. More pronounced was the discrepancy in the amnioreduction arm, with 41% survival compared with 65% in the amnioreduction arm of the randomized septostomy trial[83], which may have been due to a lack of standardization in perinatal care. Nevertheless, the authors concluded that laser is superior to amnioreduction for first-line treatment of TTTS. A National Institutes of Health (NIH) trial comparing serial amnioreduction and laser in stages II–IV TTTS is under way in the USA.

## STAGE-BASED TREATMENT

Although debate continues about the optimal treatment strategy in TTTS, what appears to be increasingly evident is that one treatment is not best used for all disease. In this respect, TTTS resembles many other conditions in that milder forms of therapy are reserved for milder disease.

Staging is increasingly used to guide management, with technically challenging procedures such as cord occlusion and endoscopic laser ablation of anastomoses, which are seemingly more effective but with a higher intrinsic risk of fetal loss, employed in poorer-prognosis cases. This approach is supported in a multicenter cohort comparison of survival by stage, which showed that laser had a higher perinatal death rate compared with serial amnioreduction (29% vs. 13%, odds ratio (OR) 2.7, 95% CI 1.1–7.0, $p = 0.02$) in stage I/II[58,119] but a lower rate in stage III/IV disease (45% vs. 65%, OR 0.4, 95% CI 0.2–0.9, $p > 0.02$) (Figure 65.10). Thus, every fourth use of amnioreduction produced an extra double survival[120] in stage I/II, particularly important when considering the 20–30% of cases which reduce in stage after one or two amniodrainage procedures[59, 60]. Furthermore, our suggested subcategorization of the Quintero stages, in which the presence or absence of an antenatally detected AA anastomosis is denoted 'a' or 'b', respectively, allows identification of not only good as opposed to bad-prognosis cases within each stage, but also an AA anastomosis-positive subgroup in stage III (IIIa) which is associated with better outcome than AA anastomosis-negative stages I and II (Ib and IIb) cases[52]. Incorporation of AA

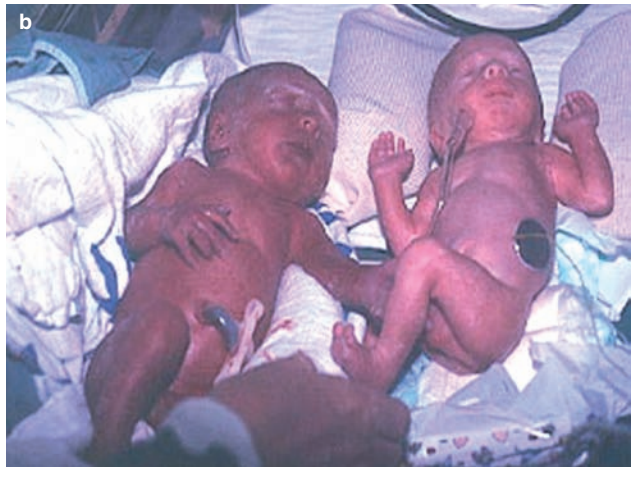




**Figure 65.11** The Wikkelkinderen of the De Graeff family, born April 7, 1617 (a). This painting, by an anonymous artist, depicts live-born (open eyes) twins with phenotypic characteristics of twin–twin transfusion syndrome (TTTS). The Rijksmuseum, Amsterdam, The Netherlands. Reproduced with permission. Compare with the appearance of twin neonates who experienced TTTS (b). Image courtesy of I. Blickstein, MD

anastomosis into a modified TTTS staging system should improve prediction of perinatal survival, and may facilitate treatment selection to optimize outcomes in TTTS. Thus, stages Ia, IIa and IIIa form a group with good survival prognosis, which can be managed conservatively or with temporizing measures such as amnioreduction and/or septostomy, and then delivered electively by 32–34 weeks. Stages Ib and IIb constitute a group with intermediate survival prognosis where amnioreduction or laser ablation may be considered, and technical considerations taken into account such as placental site, in order to select optimal therapy. Stages IIIb and IV form a group with the poorest potential survival, in which more invasive, definitive treatment such as selective laser or occasionally cord occlusion appear to be indicated. On the other hand, in about 20% of cases, one or two amnioreductions can result in regression of disease. In this group, survival is significantly greater than in those where stage increases (94% vs. 27%)[59].

Having said this, some arguments remain against the stage-based approach to treatment. First, a proportion of patients with early-stage disease will progress to require more definitive treatment, and membranous detachment after septostomy or, less importantly, intra-amniotic bleeding after amnioreduction may occasionally render laser technically more difficult, reducing the chances of success. Second, little information is available on neurologic sequelae by stage, although it is known that abnormal head scans are more frequent in more severe disease, as judged by greater hemoglobin discrepancy at birth[46]. Future studies will now need to stratify by modified stage. And, finally, in stage IV disease, the rare presence of an AA anastomosis seems to worsen prognosis, presumably by mediating acute transfusion with its sequelae when one twin dies *in utero*[51].

## CONCLUSIONS

Although the pathophysiology of TTTS is poorly understood, interplacental anastomoses and unbalanced intertwin transfusion form the etiologic basis of TTTS. Several therapeutic options are available, including amnioreduction, septostomy, laser ablation of vascular anastomoses and selective feticide, which together are responsible for an improvement in overall perinatal survival rates from 20% to around 60–70%. However, the majority of affected pregnancies still lose at least one baby, with significant long-term neurologic morbidity in around 10% of survivors. Current evidence supports a stage-based approach to treatment, with a further survival advantage conferred by an AA anastomosis. At present, palliative treatments such as amnioreduction and septostomy seem to be favored for early-stage disease, with selective laser or cord ligation conferring better outcomes in advanced disease. Two recently completed randomized trials, awaiting publication, appear to support septostomy as a useful adjunct to amnioreduction, and more importantly improved survival and reduced brain imaging lesions in patients treated with laser compared with amnioreduction. Outcomes, however, remain suboptimal, partly because of inherent limitations of the disease, such as deficient donor placentation and hidden arteriovenous anastomoses, and partly because of the difficulties in developing treatments in the absence of an animal model.

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# Pathophysiology of Twin–twin Transfusion Syndrome: a General Model

*M. J. C. van Gemert and A. Umur*


In our models[1,2], twin–twin transfusion syndrome (TTTS) is a consequence of normal growth of the anastomoses compared with normal growth of the fetal twins. Unfortunately, little is known about growth of anastomoses; therefore, we had to make the (reasonable) assumption that anastomoses grow at the same rate as the placental chorionic and umbilical blood vessels. Available data of serial measurements show:

(1) Arterioarterial anastomoses grow in diameter approximately proportional to gestational age[3]; we assume this behavior applies for all anastomoses.

(2) The length of umbilical veins (Figure 66.1) and diameter of the placenta grow approximately proportional to gestational age; therefore, we assume the length of anastomoses grows proportional to gestational age.

(3) The diameter of umbilical veins (Figure 66.2) also grows proportional to gestational age, confirming the assumed relationship between growth of umbilical and anastomotic vessels.

Because of these data, we assumed in our models that both the length and diameter of all anastomoses grow proportional to gestational age. This assumption has considerable consequences, relevant for the etiology and pathophysiology of TTTS: the laminar flow resistance (see below) of all anastomoses decreases significantly and at an increasing rate during gestation. Therefore, arteriovenous fetofetal transfusion from donor to recipient also increases significantly and at an increasing rate during gestation. In contrast, fetal growth increases only moderately. Thus, arteriovenous transfusion will affect fetal growth.

Significantly increasing arteriovenous transfusion versus moderately increasing fetal growth means donor twins effectively lose blood volume and recipients effectively gain blood volume, all at an increasing rate during gestation. Obviously, for unidirectional arteriovenous anastomoses, the well-known deleterious effects of TTTS develop with increasing severity without the possibility of recovery. However, if other, compensating anastomoses (opposite arteriovenous, arterioarterial, venovenous) are also present, part of the arteriovenous transfusion from donor to recipient will be returned back to the donor, the extent of which depends on the compensating capacity versus the arteriovenous capacity. Then, because arteriovenous and compensating anastomoses grow commensurately, TTTS will either not develop, or, if it does, has reduced severity. Consequently, the capacity (length and diameter) of arteriovenous anastomoses (donor to recipient) compared with the combined capacity of all compensating anastomoses (recipient to donor) determines whether TTTS develops or not, and the severity of TTTS. This mechanism explains why some but not all monochorionic twin placentas can develop TTTS.

The physics of this descriptive explanation, i.e. arteriovenous transfusion increases more rapidly than fetal growth, is simple and can be quantified as follows:

(1) First, arteriovenous blood flow is defined by Ohm's law. As such, it is driven by the pressure gradient over the anastomosis (press grad) and is inversely proportional to vascular resistance (resist), i.e. blood flow = press grad/resist.

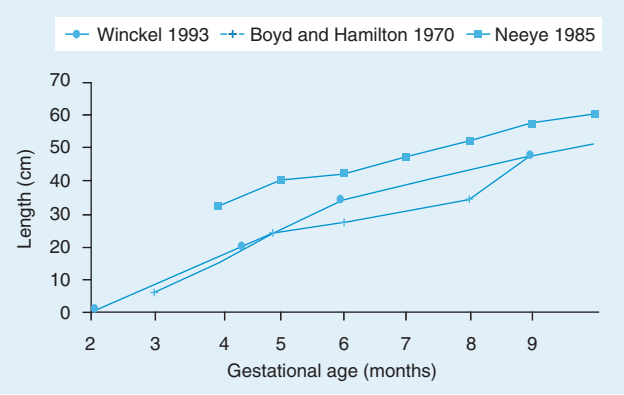


**Figure 66.1** Length of umbilical cord as determined in three studies (when exact numbers were not given, the approximate number was entered). From reference 4, with permission

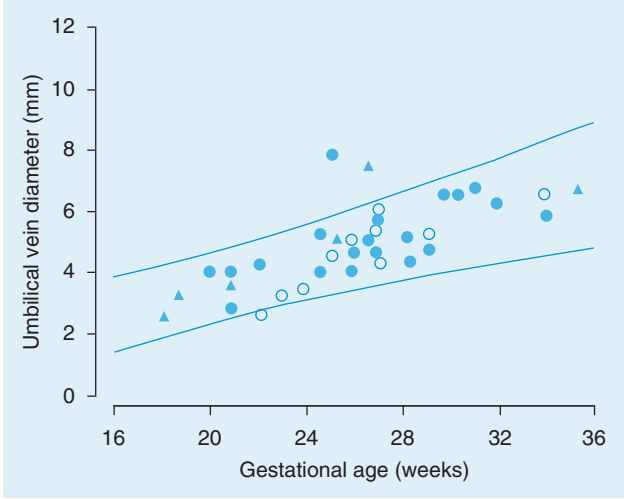


**Figure 66.2** Umbilical vein diameter before the first intravascular transfusion in 36 red-cell alloimmunized pregnancies. Lines indicate reference ranges (95% tolerance interval) in normal pregnancies. Open circles: moderate anemia (hematocrit deficit ≤ 20%); filled circles: severe anemia (hematocrit deficit > 20%); triangles: hydropic fetuses. From reference 5, with permission

(2) Second, 'press grad' (donor's arterial minus recipient's venous pressure) increases approximately linearly with gestational age, based on fetal lamb experiments.

(3) Third, because blood flow through these vessels is laminar rather than turbulent, Poiseuille's law dictates vessel resistances, i.e. 'resist' is proportional to vessel length divided by vessel diameter to the fourth power. Because vessel length and diameter increase linearly with gestation, it is elementary that 'resist' then is inversely proportional to gestational age to the third power. Therefore, also using that 'press grad' increases linearly with gestation (point 2), arteriovenous fetofetal transfusion is proportional to gestational age to the fourth power, an exceedingly strong increment of increasing flow. In contrast, normal fetal growth of twins, as is the case with any fetus, is approximately proportional to gestational age to the second power, which is a slower process than growth of arteriovenous anastomotic flow. TTTS pathophysiology then becomes simple and is explained above in the second paragraph.

Our models include overall fetal growth of donor and recipient twins' blood volumes as follows:

$$\text{Overall fetal growth} = \text{normal fetal growth} \pm \text{net fetofetal transfusion}$$

The minus sign refers to the donor, the plus sign to the recipient. The 'net fetofetal transfusion' (proportional to gestation to the fourth power for unidirectional arteriovenous anastomoses) starts slowly but can overrule the 'normal fetal growth', depending on capacity. However, if compensating anastomoses are also present, returning part of the transfusion back to the donor, the 'net fetofetal transfusion' will not overrule 'normal fetal growth' as strongly, or it remains so small that TTTS will not develop.

Our second model[2] also includes amniotic fluid dynamics. The minimal number of additional parameters needed are: fetal and amniotic fluid osmolality, and fetal blood colloid osmotic pressure, for both twins. For these parameters, standard growth equations have also been used and solved numerically, using type and size of anastomoses and degree of placental sharing as input parameters.

This latter model explains several things. First, in about 5% of cases, TTTS severity relates directly to gestational age at TTTS onset, because unidirectional arteriovenous anastomoses are present exclusively. If, on the other hand, additional compensating anastomoses are present as well, the time of onset has little bearing on TTTS severity[2]. Second, we proposed the mechanism of amniodrainage and septostomy[6]. Amniodrainage is suggested to be effective in milder forms of TTTS only. Septostomy is suggested to provide little therapeutic effect. Actually, the original rationale of 'converting' diamniotic into monoamniotic twins, derived from the rarity of TTTS among monoamniotic twins, turns out to be invalid, as the reduced TTTS incidence in monoamniotic twins is related to a different anastomotic

pattern, not to different amnion status[7,8]. Furthermore, we explain the clinical observation that arterioarterial anastomoses protect better against TTTS than the opposite arteriovenous type[9]. Unfortunately, our model also predicts that early assessment of TTTS severity is virtually impossible using fetal or amniotic fluid development. The reason is that the decreasing amniotic donor fluid volume before onset is similar for severe and milder TTTS, caused basically by arteriovenous flow, and the protective effects of the compensating anastomoses develop later, actually after TTTS onset.

In summary, our model has contributed to a better understanding of the underlying pathophysiology of TTTS but, unfortunately, less so to directly applicable management.

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# Monoamniotic Twins

*C. M. Bilardo and B. Arabin*

67



## INTRODUCTION

Monoamniotic (MA) multiples were first described by Boccalini in 1612. The condition is characterized by a single amniotic cavity, a single placenta and two umbilical cord insertions close to each other. The first review to emphasize the significantly higher morbidity and mortality (40–70%) and the low prevalence (2–5% of all monochorionic (MC) twin pregnancies) of MA twin pregnancies appeared in 1935[1]. The second survey of the American literature was published in 1959[2]. More recently, three review articles have appeared on prenatal diagnosis and management of MA twin pregnancies[3–5]. The pathology is well described in classical texts[6].

Modern technology, including high-resolution and three-dimensional ultrasound techniques, color Doppler and fetal monitoring, provides the potential to anticipate the diagnosis in the first trimester of pregnancy along with the possibility of closer surveillance and hopefully lower fetal loss.

## PATHOPHYSIOLOGY OF MONOAMNIOTIC TWINS AND NATURAL HISTORY OF CORD ENTANGLEMENT

Monoamniotic placentation is the result of the splitting of a single blastocyst after the ectodermal plate and amniogenic-committed cells emerge from the inner cell mass in the developing embryo, 8–9 days after fertilization (see Chapter 24). If the process of separation and amniogenesis is delayed until day 12 or 13, there may be incomplete separation of umbilical cords as well[6]. The stimuli and mechanisms of this late splitting are still unknown[6].

Current knowledge on the natural history of MA twins is mainly based on data derived from either postnatal studies or prenatal sonographic reports in which the diagnosis was made after 18 weeks[2,7–9]. Recently, we and other groups reported that cord entanglement in MA twins was visible in the first trimester[10–13]. Although it is not currently known how early cord entanglements occur, these observations support the conclusion that as early as 10 weeks the umbilical cord is long enough and the twins are capable of movements to 'produce' cord entanglement. It is speculated that this phenomenon more easily occurs at a stage when there is proportionately more amniotic fluid in relation to the small fetal body mass[12].

The proximity of cord insertions does not predict whether or not cords become entangled[6]. According to Benirschke, a remnant of a bilaminar amniotic membrane is noted in some MA twin pregnancies between closely adjacent cord insertions, suggesting that amniogenesis was in progress but was interrupted by the twinning process[6]. In most cases, however, there is no sign of a septum between the cord insertion sites, suggesting that twinning occurred and amniotic development was altered thereafter[14]. Female gender predominates in MA twins, and overall, the proportion of female like-sex pairs increases with proximity of the twins[15]. Whether the increased frequency of female sets reflects the effect of the mass of the X chromosome or some genetic factors on the inactivated X chromosome is unclear[6].

The umbilical cord complications seen in MA twins are associated with abnormally long and single-artery cords. It remains unclear whether these abnormalities are coincidental or causally related to

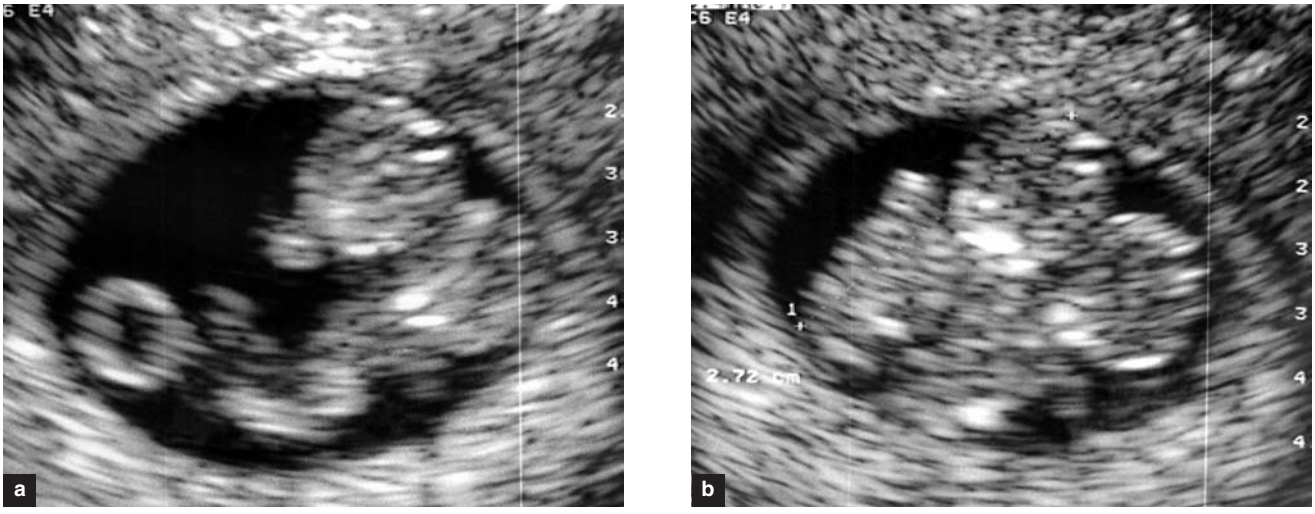


**Figure 67.1** (a) Transvaginal sonogram of a pair of monoamniotic (MA) twins with one yolk sac. (b) Transvaginal sonogram of a pair of MA twins with close proximity

cord entanglement and perinatal death. The increased contact between the members of a MA twin pregnancy might be a further reason why entanglement is facilitated, as neonates with long cords are relatively hyperkinetic compared with those with shorter cords[6]. In cases with sudden intrauterine death and cord entanglement, it cannot be ascertained how far the cord entanglement, in combination with other factors such as activity, caused hemodynamic interruption of blood supply, or whether previous changes of blood pressure might have facilitated a final obstruction of the entangled vessels.

## DIAGNOSTIC APPROACH

Improvement in ultrasonographic resolution is the basis for an increasing number of prenatally detected MA twins. Moreover, new diagnostic tools such as color-flow mapping combined with Doppler velocimetry and, more recently, three-dimensional (3D) ultrasound techniques have revolutionized the accuracy of the diagnosis of cord entanglement in MA twins from the first trimester of pregnancy onward (see Chapter 40).

### First trimester

When early transvaginal or transabdominal sonography (TVS/TAS) reveals two separate fetuses and no clear dividing membrane, MA twin pregnancy should definitely be suspected, especially if there is only one yolk sac (Figure 67.1a)[10–12,16–18]. The yolk sac is located in the chorioamniotic space which obliterates at the end of the first trimester. Whether MA twins have a single fused or two separate yolk sacs depends on the time of splitting of the germinal disk[16–18]. Therefore, visualization of two yolk sacs does not necessarily exclude a MA multiple pregnancy. If two yolk sacs and no dividing membrane are visualized before 9 gestational weeks, transabdominal (improved orientation) and transvaginal (improved resolution) scans should be repeated at a later stage (after 8 gestational weeks) when the dividing membrane should be clearly visible[18]. With the 3D technique, it is possible to differentiate between monochorionic–diamniotic (MC–DA) and monochorionic–monoamniotic (MC–MA) as early as 6 weeks[19,20]. However, we do not believe that this technique will have an important impact on further management.

If MA twins are suspected, a systematic diagnostic protocol should be followed, as outlined below.

#### *Detection of chorionicity and amnionicity (see also Chapters 39 and 40)*

(1) Absence of two separate chorionic sacs and absence of lambda sign: suspicion of MC multiple gestation;

(2) Absence of the intertwin membrane and absence of a T sign: suspicion of MC–MA multiple gestation;

(3) Single yolk sac (Figure 67.1a) with both allantoic vessels inserting into a single sac, single placenta with close insertion of the two umbilical cords and unusual intrauterine positioning of the two fetuses in close proximity to each other (Figure 67.1b): further confirmation of MC–MA pregnancy.

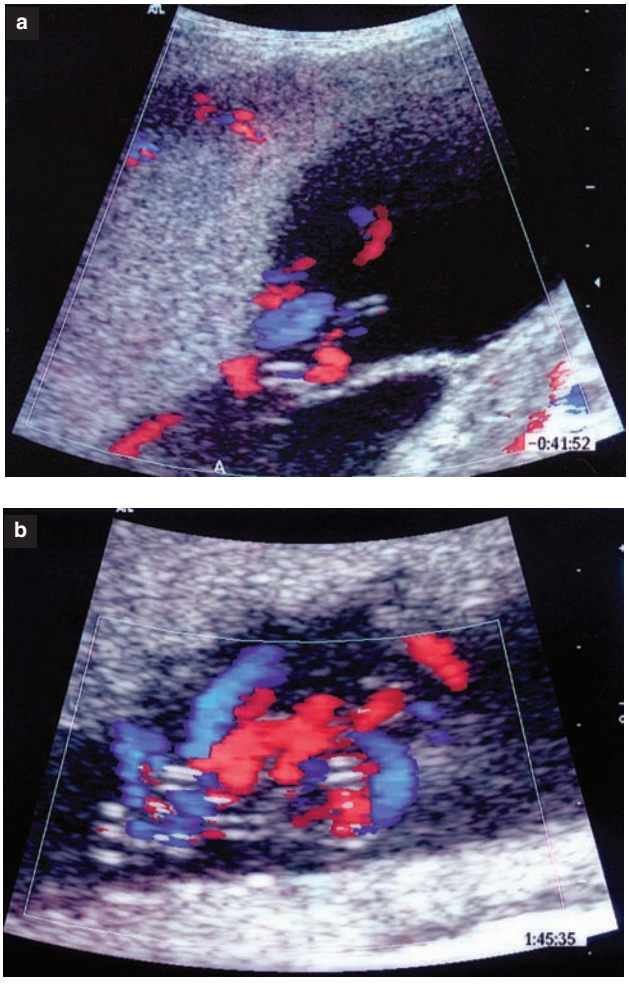


**Figure 67.2** (a) Transabdominal color ultrasound in a dichorionic–diamniotic triplet pregnancy at 14 weeks. Note the simple loop of cord entanglement close to the placental insertion of the two cords of the monoamniotic triplets and Doppler velocimetry of the same segment, confirming cord entanglement by two different heart rates of the involved umbilical arteries. (b) Transabdominal color ultrasound of the same case at 18 weeks. Note the increased braiding with overlapping vessels of the two crossing cords, suggestive of 'branching'

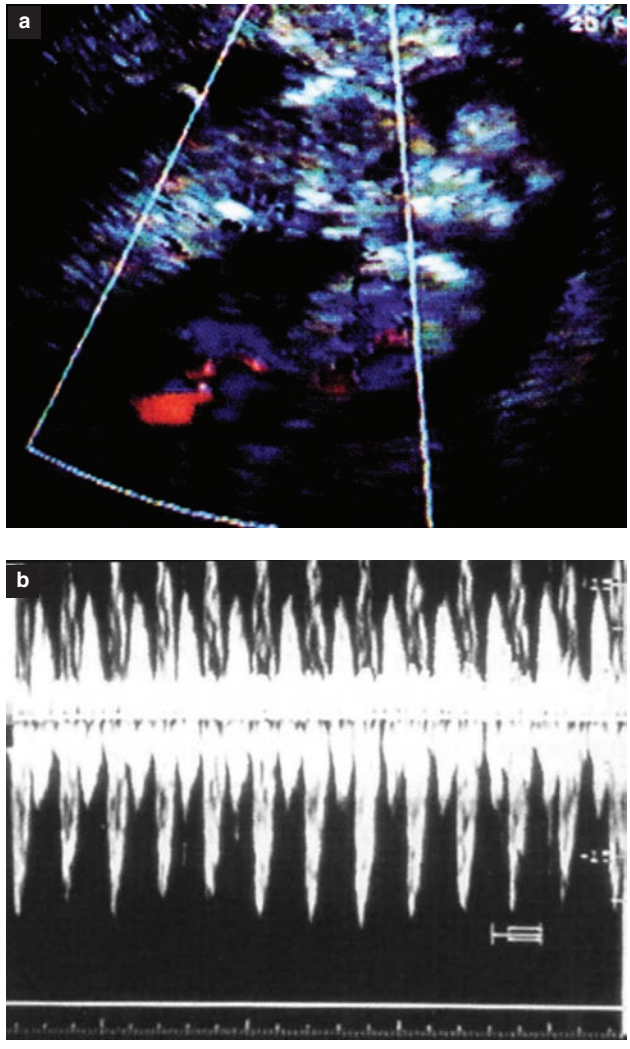


**Figure 67.3** (a) Transabdominal color ultrasound of a monochorionic–monoamniotic twin pregnancy at 14 weeks. Note the cord entanglement of the two cords close to the umbilical insertion. (b) Doppler velocimetry of the same segment showing the flow velocity waveforms of four different arteries with two different heart rates

### *Detection or exclusion of cord entanglement*

If only 2D real-time ultrasound is available, it may be possible to diagnose the quality and number of loops. This procedure should be repeated at each new scan. If color Doppler is available, on the other hand, cord entanglement can be diagnosed or excluded with more certainty and at an earlier stage (Figure 67.2a), the earliest diagnosis having been made at 10 gestational weeks[10–12]. Even in cases when cord entanglement is diagnosed, it is advisable to repeat the scan, as cord entanglement may worsen in the sense that more loops may become involved (Figure 67.2a and b), or alteration of the normal Doppler profile suggests that partial obstructions in the umbilical vessels may become detectable at a later stage in pregnancy[21–23]. Whether this finding might have implications for further management is not yet clear.

If Doppler velocimetry is available, the diagnosis can be further confirmed by demonstrating different fetal heart rate patterns in the same direction on umbilical artery Doppler analysis of a common mass of cord vessels visible by ultrasound between the ventral surfaces of the two fetuses (Figure 67.3a and b).

### *Detection or exclusion of gross structural anomalies*

Whenever the diagnosis of MA twin pregnancy is certain, detailed anatomic examination of both twins is very important, as structural anomalies occurring in only one of the twins or rarely in both are very common[12,24–30]. Major anomalies can be diagnosed even at this early stage (anencephaly, body-stalk anomaly, severe spina bifida, kyphoscoliosis and, last but not least, conjoined twins). Sebire and colleagues reported 12 cases (3.8%) of MC–MA pregnancy in a cohort of 315 MC pregnancies detected by ultrasound scan at 11–14 weeks' gestation. Four cases were conjoined twins, and in the remaining eight MA twin pregnancies, four cases showed structural anomalies confined to only one of the twins (anencephaly, body-stalk anomaly, diaphragmatic hernia, kyphoscoliosis)[12]. In all four remaining cases there were no signs of increased nuchal translucency (NT), but cord entanglement was demonstrated from the first trimester onwards. This is in agreement with our own experience[10]. Other anomalies described in MA twins involve central nervous system, urogenital tract[9] and cardiac anomalies[30]. Measurement of NT and ductus venosus (DV) flow patterns may play a role in identifying or ruling out those multiples with increased risk of chromosomal or congenital anomalies. However, owing to the rarity of MA pregnancy it has not been possible to clarify whether also in these pregnancies NT and DV measurement may be predictive of chromosomal anomalies or adverse fetal outcome[31].

## Second and third trimesters

When ultrasound examinations were not widely available, cord entanglement was only incidentally observed in the second or early third trimester and not uncommonly only at birth[7]. Suspicion of an MA twin pregnancy was confirmed by amniography and intra-amniotic injection of indigo carmine dye[32,33] and computed tomographic amniography[34]. It was even suggested early on that in the second and third trimesters, computed tomographic amniography might be more accurate than ultrasound in detecting MA twins[34]. However, transabdominal and transvaginal ultrasonography are clearly highly reliable tools to diagnose or exclude MA twin pregnancy. Therefore, we would not advise using other more invasive techniques[4,12,35].

The observation of a large and common mass containing umbilical cord vessels clearly demonstrates entanglement (Figure 67.2a and b). Color-flow Doppler may confirm the vascular nature of the mass, whereas pulsed Doppler analysis may show apparent 'branching' of the umbilical artery with evidence of two different heart rates in the two segments of the branches, another clear sign of cord entanglement[9].

A pseudo-MA pregnancy (see Chapter 68) can also be caused by disruption of the dividing membranes on the basis of external trauma whereby the amnion separates from the underlying chorion[36]. In other instances, accidental iatrogenic creation of a single amniotic compartment may be due to disappearance of the intertwin membrane in MC–DA, following intentional septostomy or, inadvertently, after repeated amnioreduction or at mid-trimester amniocentesis[37–42]. It is suggested that these artificial MA pregnancies carry the same perinatal mortality and morbidity as that of a 'true' MA pregnancy[36].

### *Diagnosis of cord entanglement and cord compression*

Cord entanglement is usually visualized as a loop of entangled umbilical cords interposed between the ventral surfaces of the two fetuses (Figure 67.3a) or at the placental insertion (Figure 67.2a). However, the umbilical cord can also wrap itself around other parts of the body of one of the multiples, for example it was even shown by color Doppler that the cord of one twin was tightly wrapped around the neck of its dead co-twin[43]. Cord entanglement may sometimes be confused with the clustering of segments of a single umbilical cord, sometimes referred to as a 'stack of coins' appearance[44]. Invariably, however, true cord entanglement shows each of the two cords lying in an orderly spiral fashion[43–45]. To date, there is only a single report whereby cord entanglement was correctly ruled out by ultrasonography in an MA twin pregnancy[45].

Doppler analysis of the umbilical artery flow patterns can reveal the presence of a notch indicative of a true knot, or abnormally elevated systolic/diastolic ratios up to absent end-diastolic flow[9,44,45]. The presence of a notch in the umbilical artery velocity waveform may reflect hemodynamic alterations in the fetal–placental circulation secondary to narrowing of the arterial lumen, with an increase in downstream resistance in the umbilical vessels involved in cord entanglement[44]. High blood flow velocities in the umbilical vein detected by velocimetry[7] and/or pulsation in the umbilical vein flow pattern are also indicative of tight entanglement[43]. The presence of pulsations in the umbilical venous flow profile are a poor prognostic sign because they suggest tight entanglement with the consequence of increased placental resistance with resulting cardiac overload[46,47].

In all our cases we searched for similar criteria, but we found no systematic patterns besides the characteristic knot with branching of the vessels seen

**Table 67.1** Diagnostic criteria for monoamniotic twin pregnancies

| |
|---|
| No observed dividing intertwin membrane |
| Single placenta |
| Single yolk sac |
| Same sex |
| Amniotic fluid surrounding each fetus |
| Unrestricted movement of both fetuses |
| Cord entanglement present (Doppler documentation of branching of double umbilical vessel signals) |

by color Doppler (Figure 67.2a and b), and the waveforms of umbilical arteries with different heart rates obtained from one segment (Figure 67.3b). The presence of pulsations in the umbilical venous flow profile are suggestive of tight entanglement, and may be the consequence of increased placental resistance resulting in cardiac overload, or be due to increased pressure in the constricted cord[44,45]. Umbilical cord complications seen with MA twins are considered to be associated with abnormally long cords and single-artery cord[9].

The diagnostic criteria for MA pregnancies are listed in Table 67.1.

### *Twin-to-twin transfusion syndrome (TTTS)*

No consensus exists as to whether TTTS occurs in MA multiple pregnancies[7,12,30,41]. When multiples are in separate gestational sacs, a change of amniotic fluid volume following even small feto-fetal transfusions results in intra-amniotic pressure differences that influence the picture of TTTS. In MA multiple pregnancy, on the other hand, the common amniotic cavity may function as a buffer for intertwin differences[6]. Nevertheless, when extensive polyhydramnios is observed in MA pregnancies, it must be explained by unbalanced perfusion, whereby the direction and passage of blood volume shifts remain unclear and may even occur in both directions[12]. Polyhydramnios was present in one case that we managed. Repeated amniodrainage, 2–3 l per week, was performed up to a total of 16 l. No signs of congestive heart failure or of tricuspid regurgitation were detected in either fetus. Doppler velocity waveforms of the ductus venosus and fetal arteries of both twins remained normal, and the neonatal outcome after elective cesarean section was uneventful. The postnatal computer angiogram of the placenta demonstrated deep arteriovenous (AV) anastomoses with cotyledon sharing, that may explain the twin–twin transfusion[10]. Collection of more data from MA placentas seems mandatory to determine the frequency and impact of unbalanced transfusion in MA twins. Prenatal Doppler velocimetry of arteriovenous anastomoses[48,49] and postnatal angiography[50] of the placenta might help to evaluate this issue in the future.

Sebire and colleagues suggest that acute TTTS more than cord entanglement may be responsible for sudden fetal demise in MA twins, because the close insertion of the two umbilical cords may be associated with large-caliber anastomoses between the two fetal circulations[12]. Consequently, an imbalance between the two circulations cannot be sustained for a prolonged period of time, as is the case in the classic TTTS, but would rather result in major hemodynamic effects causing sudden fetal death[12]. Although pathologic analysis of the twins and the placenta might help to find the answer, at this point it remains difficult, if not impossible, to detect the 'true' cause of early fetal demise from retrospective analysis alone.

### *Death of the co-twin*

This unwanted acute event may alter antenatal management. The most important factor in determining obstetric intervention is the gestational age at which the single fetal demise occurs. If the gestational age is less than 28–30 weeks, the general consensus is not to intervene, as the risk of cerebral damage as a consequence of prematurity in the surviving co-twin outweighs the risk of remaining *in utero*. However, if the event of single intrauterine death occurs later in gestation, some authors advocate urgent cesarean delivery, as the increased risk of neurologic damage and even death of the surviving twin may be as high as 20%[50,51]. This is much higher than the gestation-specific reported neurologic morbidity in twins, and may be attributable to the transient, but severe, hypovolemia and hypotension in the surviving twin which can lead to cerebral damage and renal ischemia[50]. Other suggested mechanisms that may explain cerebral damage in the surviving co-twin are disseminated intravascular coagulation, as a result of the release of thromboplastic material, or infarction due to embolism from the dead co-twin[52,53]. It is not yet known if prompt delivery of the surviving co-twin can prevent neurologic damage, or whether cases where the co-twin does not suffer any damage are a result of different kinds of anastomoses, capable of protecting the surviving twin from acute pressure changes[54]. In conclusion, the diagnostic approach in the second trimester should comprise:

(1) In referred patients, when the early diagnosis of MC–MA multiple gestation is uncertain, careful evaluation to determine whether there is an intertwin membrane: transvaginal ultrasonography

may be of help in cases of doubt. Diagnosis may be more difficult in cases with suspicion of TTTS when the amniotic membrane might be attached around the body of the donor.

(2) Detection or exclusion of cord entanglement: the same criteria apply as in the first trimester. If cord entanglement is confirmed, one should look for signs of branching, notch and cord compression, high blood flow velocities in the umbilical vein or pulsation in the umbilical vein, any one of which would alter the management in cases of fetal viability.

(3) Signs of TTTS such as polyhydramnios should be excluded or confirmed by additional techniques such as echocardiography and venous Doppler.

(4) Detection or exclusion of abnormalities should follow standard protocols, with specific attention to echocardiography by skilled staff. From 16–20 weeks onwards, we recommend TVS of the cervix to detect the risk of preterm birth (see Chapter 55). This should not be forgotten in cases of MA multiple gestation. Placenta previa is more likely to occur in multiple gestation, and MA multiple gestations are no exception to this rule.

(5) Growth monitoring and Doppler flow velocity assessment: in cases of poor intrauterine growth and signs of fetal demise the protocol includes early intervention, since blood pressure changes might increase the risk of cord entanglement. Up to viability, we recommend ultrasound examinations at 2-week intervals. If the patient is in the third trimester, the diagnostic approach should follow the same protocol. In cases of viability, the diagnosis will have an impact on the management (e.g. frequency of surveillance, elective delivery, see below). Nevertheless, the third trimester is the most difficult time to establish the diagnosis of MA twins, because the relative ratio of fetus to amniotic fluid is high and the multiples create shadowing that impairs visualization of membranes or entanglement.

The usual complications observed in MA twin pregnancies are listed in Table 67.2.

**Table 67.2** Complications commonly observed in monoamniotic twin pregnancies

| |
|---|
| Congenital anomalies (of one or both) |
| Cord entanglement |
| Cord accidents |
| Twin–twin transfusion syndrome |
| Intrauterine growth restriction |
| Polyhydramnios |
| Premature delivery |
| Single or double intrauterine death |

## CLINICAL MANAGEMENT AND OUTCOME

Traditionally, 95% of cases of reported fetal demise are attributed to fatal umbilical cord complications. The incidence of fetal demise due to umbilical cord complications increases by 2–5% every week after 15 weeks' gestation and total 30–40% by 30 weeks. In the case of survival, perinatal morbidity is high[55–60].

A Medline search on MA twins from 1968 to January 2001 revealed 105 articles with a total of 230 sets of MA twins[3]. In 144 sets, MA pregnancy was not diagnosed prenatally; in 86 sets of twins, MA membranes were diagnosed. In articles from the past 10 years, a total of 39 MC–MA twin pregnancies are reported with a survival of 54 fetuses and an incidence of morbidity and handicap varying between 20 and 40%[3–5,55,56]. Many clinical reports of MA twins focus on cord entanglement and the resultant risk[44,45]. However, as MA twins are rare, a management consensus has not yet been achieved independent of whether or not cord entanglement is identified prenatally[9,42–44,55–60]. Statistical validity of the findings is limited by the small sample sizes and the variety in management protocols, such as early admission versus out-patient management, or elective versus emergency cesarean section. Vaginal delivery of MA twins has been reported in cases of cephalic presentation of both twins, but should not represent the standard practice[7,61–63].

A series from one center of 13 cases delivered during the past 10 years reported cord entanglement at delivery in all sets of MA twins, and knots in eight sets[8]. In all 13 cases, the monoamniotic condition, but not the cord entanglement, had been diagnosed prenatally[8]. Timing of delivery is also controversial. Some authors recommend delivery at 32 weeks of gestation, while others state that the risk of cord accidents declines with advancing gestation, thus questioning the usefulness of routine delivery at 32 weeks[23]. A search of records from 1967 to 1988 at one center including 138 232 live births revealed 24 sets of histologically confirmed MA twins. Among the 17 sets of MA twins that reached 30 weeks' gestation with at least one twin still alive, there were no additional fetal deaths[64]. A retrospective review of the most comprehensive articles finds conflicting opinions on whether the risks of early delivery outweigh the risks of fetal death as a result of monoamnionicity[7,64]. In fact, looking carefully at the cases where cord entanglement was diagnosed prenatally, the decision for surveillance and timing of delivery varied according to what the obstetrician thought

about continuation of pregnancy[9,42–44,55–60]. Only 4/15 mothers were primarily admitted for surveillance. Three cases where cord entanglement had been diagnosed were treated with sulindac to reduce amniotic fluid volume and thereby the risk of excessive movements[65]; all six fetuses survived. Another study reports less promising results after sulindac administration: of two sets of MA twins, one pregnancy resulted in a single intrauterine death at 30 weeks and delivery of a normal co-twin, the other in intrauterine death of both twins at 31 weeks[12]. The presence of a notch in the umbilical artery velocity waveform should indicate prompt intensive cardiotocographic monitoring, as it is reported to precede the onset of pathologic fetal heart rate tracing[23]. In these cases, there is no consensus on whether or not a primary cesarean section should be performed[7,64], not even within the studies when cord entanglement was diagnosed. Apart from cord entanglement, sudden fetal distress may occur and indicate a cesarean delivery. In our small series of seven cases with MA twins continuing beyond 26 weeks, other reasons than cord entanglement prompted cesarean delivery. After counseling the parents about the data known from the literature, we performed a cesarean section when lung maturity was established. Nevertheless, we have doubts whether weekly out-patient examinations until 32 weeks or the continuation of pregnancy up to 35 weeks is justified based on such a small number of reported cases with prenatally diagnosed cord entanglement.

As far as we know, laser therapy has not yet been performed in MA multiple pregnancies, and there are only a few reported cases with therapeutic serial amniocentesis. Specific interventions, such as attempts to untie the entanglement, have not yet been reported. Moreover, current monitoring techniques for multiple pregnancies should be applied in MA twin pregnancies[66].

Based on the diagnostic approach (see above), we would recommend the following interventions in cases of fetal viability:

(1) Increased surveillance at 1–2-week intervals from 25–30 weeks onwards and then weekly, including detection of amniotic fluid volume and Doppler velocimetry of the two cords, fetal arterial and venous flow, seems advisable.

(2) Lung maturity assessment prior to cesarean section by amniocentesis for detection of fetal lung maturity should be performed from 30 weeks onwards at about 2-week intervals, although it reflects the sum of the pulmonary secretions of both twins. When lung maturity has been proven, cesarean delivery should be considered in the presence of any sign of deterioration (discordant growth, polyhydramnios, notches in the umbilical artery waveforms or pulsations in the umbilical vein). The management of cases with acquired lung maturity and normal fetal condition of both twins is still controversial, but increasingly elective delivery is chosen.

(3) Admission, surveillance and delivery in the case of 'notches' in the umbilical arteries, venous pulsations or increased velocities in the umbilical veins, admission and surveillance by ultrasound, Doppler, CTG monitoring, administration of corticosteroids and delivery is recommended. Fetal heart rate monitoring should be performed at frequent intervals – if not continuously. The parents and the management team should each be counseled individually, and be familiar with her/his role in the surveillance, delivery and postnatal care.

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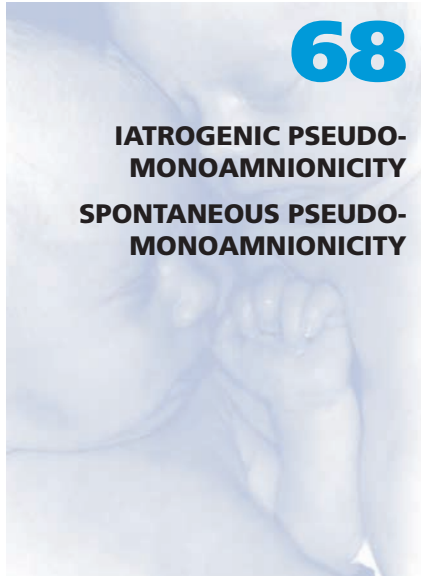
# Pseudo-monoamniotic Twins

*I. Blickstein*




> *'And when her days to be delivered were fulfilled, behold, there were twins in her womb. And the first came out red, all over like a hairy garment … And after that came his brother out and his hand took hold on Esau's heel;'*
>
> *Genesis 25:24–6*

The detailed description of the birth of these biblical twins is by no means simple to understand. For instance, how are we to interpret the description of Jacob grasping the heel of Esau during birth[1]? The first, and most common, explanation for this situation is that these twins must have been monoamniotic, and as such, Jacob could grasp Esau's heel *in utero* (Figure 68.1a). Yet, the biblical narrator meticulously describes the different phenotypes of the twins, which would suggest dizygotic twinning. The second possibility is that the twins were pseudo-monoamniotic (PMA), that is, the dividing membrane ruptured before birth (Figure 68.1b). However, the biblical scholar Ibn Ezra commented, as early as the 12th century, that this is an extremely unusual event[2]. The fact that PMA twins were known in ancient times clearly suggests that the existence (with or without rupture) of an intertwin membrane was discussed in relation to the remarkable birth of Jacob and Esau. This chapter discusses this rare entity.

## IATROGENIC PSEUDO-MONOAMNIONICITY

Iatrogenic PMA refers to inadvertent or intentional creation of a hole in the intertwin septum. Megory and colleagues[3] reported PMA twins with cord entanglement following genetic funipuncture, in 1991. In that case, cell growth failed twice following amniocentesis and the authors opted for a funipuncture at 24 weeks. The spatial anatomy of the uterine content dictated needle entry into the cord of one fetus through the sac of the other fetus. This procedure produced PMA with cord entanglement, which was noticed only at birth[3]. In 1998, Feldman and associates[4] reported inadvertent membrane puncture and creation of a PMA gestation following amnioreduction for twin–twin transfusion syndrome (TTTS), and cautioned against the adverse outcome. In the same year, however, Saade and co-workers[5] published the first series of intentional septostomy to alleviate severe TTTS (see Chapter 65).

Iatrogenic PMA twins should be suspected whenever significantly different amounts of amniotic fluid, such as would be the case in the poly–oligohydramnios sequence, equalize abruptly following amniocentesis. When the diagnosis of a PMA gestation is made, the pregnancy should be followed as any other pregnancy with a monoamniotic placenta (see Chapter 67).

## SPONTANEOUS PSEUDO-MONOAMNIONICITY

The frequency of spontaneous PMA is unknown, and extensive literature research has failed to reveal any description of this occurrence. We have recently-managed a monochorionic twin pregnancy in which a dividing membrane was not seen at first-trimester sonogram, but was clearly visualized on a subsequent scan. Both twins developed significant polyhydramnios, and the membrane was no longer seen

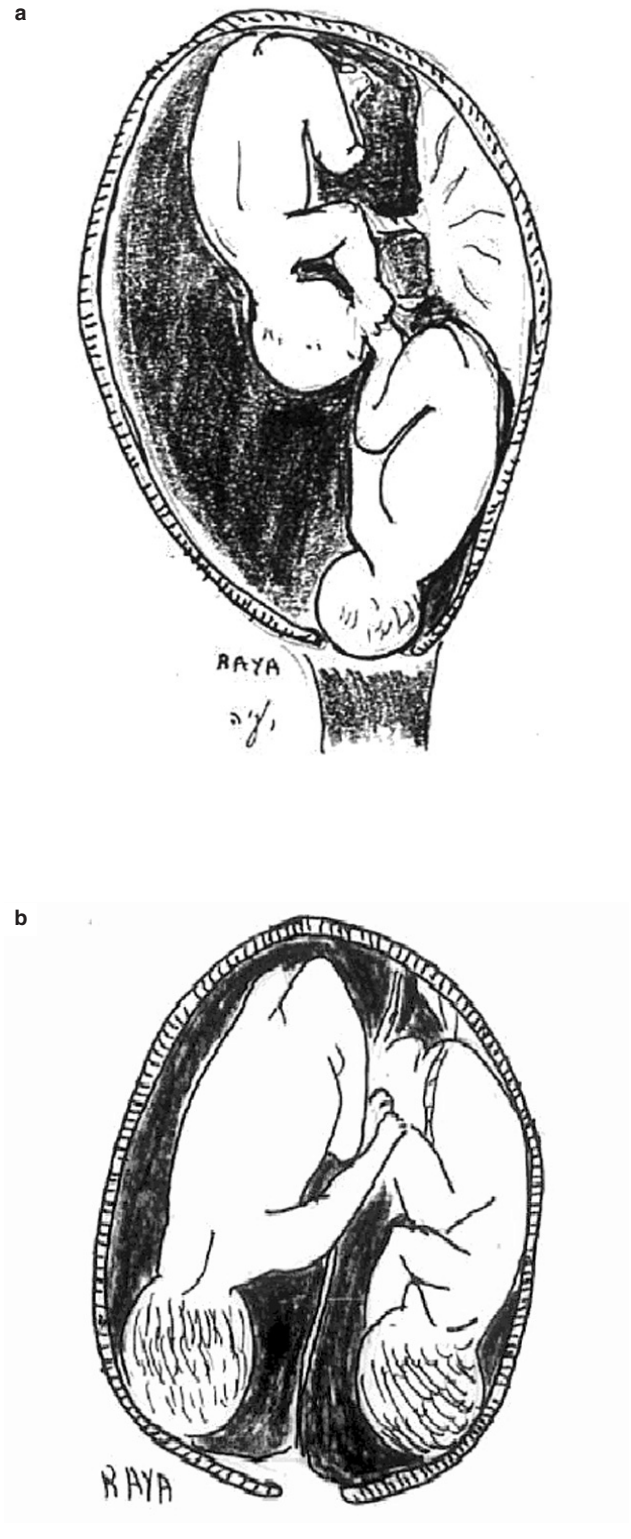



**Figure 68.1** (a) Monoamnionicity and (b) pseudo-monoamnionicity as an explanation of the delivery of Jacob and Esau. Illustrations: Raya Gabai, chief midwife, Kaplan Medical Center

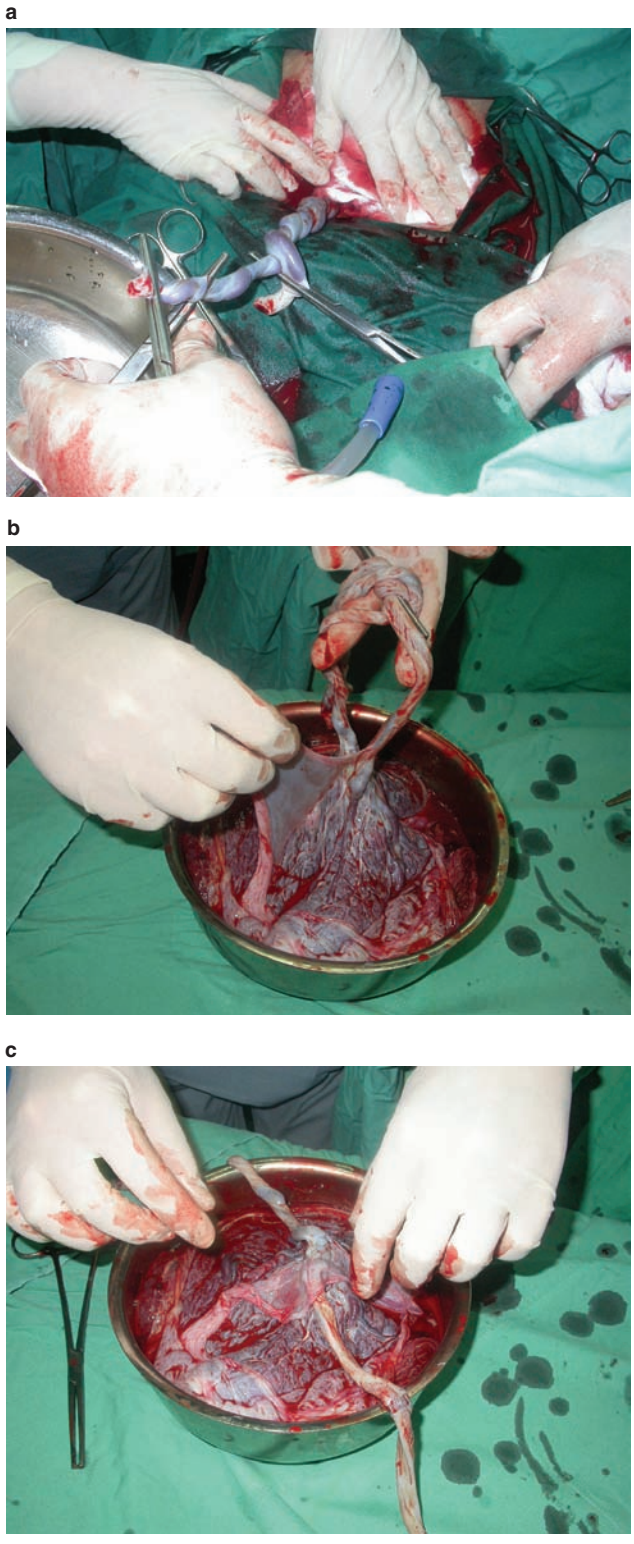



**Figure 68.2** (a) Cord entanglement of a case believed to be monochorionic–diamniotic. (b) After the cords were untwisted, a thin, diamniotic membrane was found. (c) Membrane between the two juxtaposed cords: the proximity of the cords suggests a monoamniotic, rather than a diamniotic placenta

on subsequent scans. During cesarean delivery at 33 weeks, cord entanglement was found (Figure 68.2a). When we untwisted the cords, a diamniotic membrane was evident, pushed down by the entangled cords (Figure 68.2b). The proximity of the cords, however, so characteristic of monoamniotic twins (Figure 68.2c), cast serious doubt on the possibility of spontaneous PMA in this case. Rather, it is possible that this represents a monoamniotic placenta with a remnant of an intertwin membrane, suggesting that amniogenesis was in progress but was interrupted by the twinning process[6].

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# Placental Vasculature in the Pathogenesis of Fetal Mortality and Morbidity in Multiple Pregnancies


*M. J. C. van Gemert and P. G. J. Nikkels*

If a monochorionic (MC) twin dies *in utero*, its co-twin may experience a variety of clinical outcomes, ranging from no sequelae to severe neurological damage or death. It is likely that the existing anastomotic pattern on the shared MC placenta primarily determines outcome. Sequelae are assumed to result from: exsanguination of the survivor into the dead twin's circulation along anastomoses; transfusion of active compounds such as clotting factors or interleukins from the dead twin into the survivor's body; or other causes. If no such sequelae develop in the co-twin, either the MC placenta lacks anastomoses (about 4% of cases) or, more important, exsanguination of the survivor remains limited because there is a favorable return anastomotic path from the dead twin to the survivor.

**Table 69.1** Predicted response of the surviving twin to the demise of its co-twin

| | | *Predicted hemodynamic response of survivor* | | |
|---|---|---|---|---|
| *Anastomoses* | *Demised twin* | *Exsanguination* | *Intertwin circulation* | *Transfusion from demised twin into survivor's body* |
| AV | donor | no | no | no |
| | recipient | yes, but slowly, due to high resistance of the cotyledon | no | no |
| AA | either twin | yes | no | no |
| VV | either twin | not likely, driving blood pressure is small | no | if the demised twin's filling pressure exceeds the survivor's venous pressure |
| AA + VV | either twin | yes | yes | yes |
| AV + VA | donor | yes | yes | yes |
| | recipient | yes | yes | yes |
| AV + AA | donor | yes | no | no |
| | recipient | yes | no | no |
| AV + VV | donor | no | no | if the demised twin's filling pressure exceeds the survivor's venous pressure |
| | recipient | yes | no | no |

AV, arteriovenous; AA, arterioarterial; VV, venovenous; VA, venoarterial

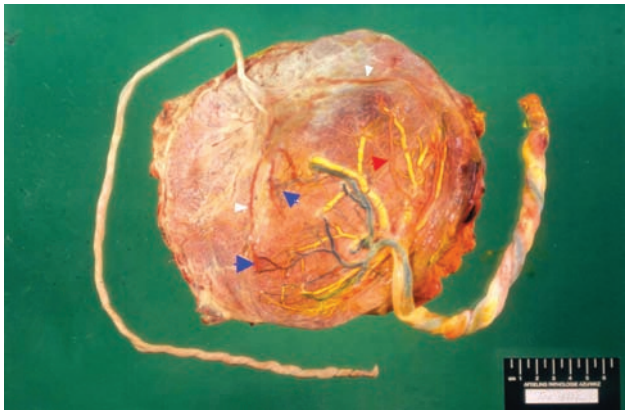

**Figure 69.1** A 33-week placenta that includes a functioning venovenous anastomosis, despite intrauterine fetal death of one twin at 24 weeks

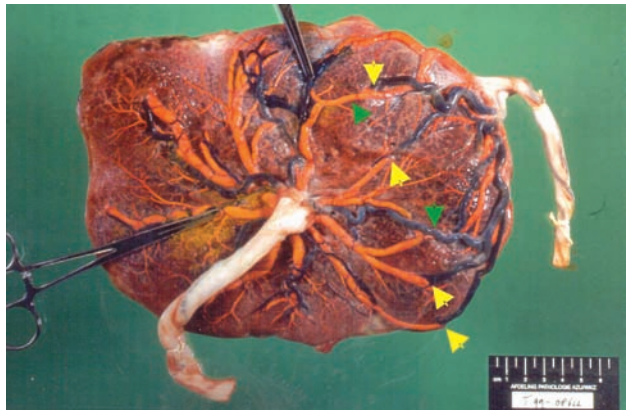

**Figure 69.2** Post-natal dye-injected placenta with a velamentous cord insertion of a case of intrauterine fetal death that occurred at 36 weeks and was followed by emergency cesarean section

Table 69.1 summarizes the predicted hemodynamic response of the surviving co-twin in relation to placental anasatomoses[1]. Exsanguination through an arterioarterial anastomosis is completed within a period that varies from minutes to several hours, depending on the vessel's diameter. Using our previous model[2], an arterioarterial diameter of 0.5 mm takes about 2 h to complete the exsanguination process, versus 0.5 h for a 1-mm diameter anastomosis. If an arterioarterial anastomosis is lacking (20% of non-twin–twin transfusion syndrome (TTTS) cases versus 70% of TTTS cases), exsanguination through an arteriovenous anastomosis (cotyledon) can take about 16 times longer (i.e. from a few hours to a day), because the estimated arteriovenous resistance is 16 times larger than the arterioarterial resistance in the presence of feeding and draining vessels of identical diameter and length[3]. It has also been suggested that venovenous anastomoses are associated with intrauterine death[4]. The reason for this observation is unclear. However, because venovenous anastomoses occur virtually always together with other anastomoses, particularly arterioarterial and bidirectional arteriovenous, we submit that a hemodynamic origin for sequelae relates merely to the other anastomoses. We also submit that the concept of transfusion of active compounds (the so-called thromboplastin-rich material) from the dead twin into the survivor's body will not cause many sequelae to the survivor as, to our best knowledge, such material has not been identified to date.

Figure 69.1 shows a postnatal dye-injected placenta at 33 weeks, which includes a functioning venovenous anastomosis, despite intrauterine fetal death (IUFD) of one twin at 24 weeks. A clear return path is present, consisting of two arteriovenous anastomoses from the survivor to the dead twin (two left dark triangles) connected to the venovenous anastomosis (white triangles), which protected the survivor from significant blood loss at the time of fetal death and kept the venovenous anastomosis perfused. Interestingly, Hyrtl's (i.e. the deep intracotyledonary) anastomosis[5] was lacking in this case (right dark triangle shows a chorionic artery originating from the other umbilical artery), implying that more arteriovenous connections from the survivor to the dead twin might have been present. Without this return path, the venovenous anastomosis would have been thrombosed and could not have been identified.

Figure 69.2 shows a postnatal dye-injected placenta with a velamentous cord insertion of an IUFD case that occurred at 36 weeks and was followed by an emergency cesarean section. The time between fetal death and delivery was less than 12 h, but otherwise uncertain. In this case also, the survivor, with the central cord insertion, had at its disposal various return paths through the arterioarterial (dark triangle, dark dye), venovenous (dark triangle, light dye) and arteriovenous (from the dead to the surviving twin, light triangles) anastomoses. The dead twin had only a small part (30%) of the placenta, but survived during pregnancy by blood received from its co-twin through the arterioarterial and another arteriovenous anastomosis (from the survivor to the dead twin, top forceps).

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# Management of Single Fetal Death

*I. Blickstein*

**70**



*If, in a woman pregnant with twins, either of her breasts lose its fullness, she will part with one of her children; and if it be the right breast which becomes slender, it will be the male child, or if the left, the female.*

Hippocrates, *Aphorisms*, Section V, 400 BC
(translated by Francis Adams)

## INTRODUCTION

Stillbirth is much more frequent among multiples than among singletons, and single fetal demise in multiples is different from singleton stillbirths, in terms of etiology, fetal–maternal problems and feto-fetal effects. Population-based series reporting on stillbirth rates among twin or higher-order multiple pregnancies usually include cases of single fetal demise as well as stillbirth of the entire set[1]. Several important aspects of single fetal death in multiple pregnancies are discussed in detail elsewhere in this volume (Chapters 97 and 103). This chapter focuses specifically on the management of this rather common complication.

## FACTORS INFLUENCING MANAGEMENT

### Management by etiology

The etiology of single fetal death in a multiple pregnancy can be classified under three subheadings:

(1) Single fetal death can occur because of *discordant fetal conditions*, such as discordant anomalies, discordant growth or abruption of one placenta. Rare conditions such as blunt trauma to the abdomen[2] or umbilical vein thrombosis[3] can also affect only one twin.Y

(2) In some instances, single fetal death stems from *conditions that may affect both twins*, such as severe pre-eclampsia or chorioamnionitis. In these cases, the pre-existing insult may also endanger the surviving co-twin.

(3) Single fetal death can occur as a result of a particular condition related to *twin-specific syndromes*, such as twin–twin transfusion syndrome (TTTS) and twin reverse arterial perfusion. In such cases, the intertwin anastomoses endanger the survivor twin via the mechanism(s) described elsewhere (Chapters 65, 69 and 93).

Management according to the etiology-based approach is usually aimed toward eliminating the condition that caused fetal demise. If such a condition does not exist after fetal death (e.g. anomaly), no further intervention is necessary. Conversely, if the insult that caused fetal demise still exists (e.g. chorioamnionitis), intervention, in the form of delivery of the surviving fetus, is indicated.

### Management by chorionicity

Monochorionicity is the single most important determinant of the sutvivor's outcome. The so-called twin embolization syndrome – death or damage to a twin after death of its monochorionic (MC) co-twin – was supposedly explained by transfusion of an (as yet) unidentified thromboplastin-like material from the dead to the live fetus, via the transplacental

anastomoses. This 'embolic' theory for increased risk in the survivor has been discarded over the past decade. Instead, it is currently held that vascular resistance significantly and abruptly decreases around the time of death of the twin, and shunting of blood, hypotension and ischemia of vital organs causes damage to the other (the so-called 'ischemic' theory) (see Chapters 65 and 93). Nicolini and colleagues[4] sampled blood from five twin fetuses immediately before death and from four of their co-twins, and also from four surviving fetuses within 24 h after death of the co-twin. Blood samples of four of the five fetuses who subsequently died showed acidosis and three of these showed hypoxemia, whereas none of these fetuses or their co-twins were anemic at that time. All survivors sampled within 24 h of the death of each co-twin had low hematocrits. This observation supports the concept that fetal anemia, probably a consequence of acute blood shunting just before the time of death of the co-twin, may play a role in the high mortality and morbidity found in the surviving twin.

### Management by timing of occurrence

Single fetal death in a multiple pregnancy very rarely occurs under direct monitoring. In the common clinical scenario, the diagnosis is made only some time after fetal death, and the time interval is entirely unknown. It has been speculated that if, by chance or otherwise, death is diagnosed immediately, prompt intervention may save the co-twin. However, it is unclear whether damage in the co-twin occurs immediately before death or within minutes, hours or days after death. For example, the study of Nicolini and colleagues described above[4] supports the notion that it is unlikely that immediate delivery of the survivor, after death of its co-twin, could practically affect outcome.

Timing of intervention also relates to the gestational age at which death occurred. Obviously, delivery of an apparently healthy co-twin, remote from term, and at an unknown time interval from the death of its co-twin, has little logical justification. Because the risk of serious damage to the survivor is high, with estimates of around 20–30%, single fetal death in an MC pair *before viability* needs special consideration. Although the survivor may seem unharmed, the parents should be counseled about the risk of permanent damage, and the option of termination of the entire pregnancy should be discussed.

### Management by maternal effects

As pointed out above, single fetal death in a multiple pregnancy may be the result of serious maternal disease, such as severe pre-eclampsia or overwhelming chorioamnionitis. In such circumstances, termination of the pregnancy is indicated to save the mother's life. One should remember, however, that complete resolution of pre-eclampsia might occur following the death of a single fetus[5,6]. This possibility should be considered when single fetal death occurs remote from term and is related to a specific maternal condition. Thus, if maternal status permits, single fetal death should not be an absolute indication for prompt delivery.

More often, however, single fetal demise occurs in otherwise healthy mothers. Whereas fetal death in singletons may cause serious coagulation defects, this complication is, for an unclear reason, extremely rare in multiples[7]. Indeed, the cited reference is almost the only one available and it is 20 years old. Because large series of single fetal death in multiples do not document maternal coagulopathy, it is debatable whether these mothers need to be followed by regular coagulation studies.

## MATERNAL–FETAL VARIABLES

Before a management decision is reached, the clinician should have some essential information. The following steps may help at this stage.

*Step I: establishing chorionicity* The first step in the management of single fetal demise is to determine chorionicity. Ideally, this information should be available from early sonography performed in the first trimester of pregnancy (see Chapter 39). However, when sonography has not been done prior to the diagnosis of fetal death, a meticulous scan should be performed. Following this step, the clinician should be able to determine whether the pregnancy is MC or dichorionic (DC). In higher-order multiples, the clinician ideally should know if the dead fetus belongs to a MC or a DC subset.

*Step II: excluding serious maternal etiology* Careful clinical and laboratory assessment of the mother must exclude maternal conditions that may cause fetal death. When a probable diagnosis is made, the balance between the risks of continuing versus the risks of terminating the pregnancy should be established. In some situations, however, risk estimations are theoretical, and decision-making may have to be based on educated guesses rather than on evidence.

*Step III: considering gestational age or maturity of the survivor* Gestational age determines the risk to the survivor, and is an important factor whenever delivery is considered. For instance, the clinician may decide

more easily on delivery when the chance of fetal maturity is very high, or gestational age is advanced. Conversely, extreme prematurity is a strong argument against prompt delivery, even when the risk to the survivor is high, such as in MC twinning.

*Step IV: establishing the well-being of the survivor* In certain circumstances, the demise of one fetus may point to a precarious condition of its co-twin. It is therefore important to ensure that the survivor is doing well *in utero* before the option of expectant management is considered, unless the fetal condition is so grave that a choice of fetal sacrifice has been made.

## MANAGEMENT GUIDELINES

Despite the numerous factors that need be considered during decision-making, management of single fetal death follows a rather simple algorithm. Needless to say, 'no-win' situations exist in many instances, and these circumstances should be discussed with the parents. Their opinion about the management options should also be heard, respected and recorded in the case file.

### Fetal demise in DC twins

This is probably the most common situation because there are many more DC twins than MC twins, as a result of either iatrogenic or spontaneous conceptions. It is estimated that the incidence of MC twins in developed countries has decreased from 33% (in spontaneous pregnancies) to as few as 7–10% (following ovulation induction and *in vitro* fertilization). When maternal conditions that may have caused fetal death are excluded, and the survivor's well-being is established, no immediate measures should be taken. It is, however, recommended to follow such cases with weekly assessments of the biophysical profile (see Chapter 62). Bearing in mind that placental insufficiency is common in these instances, growth of the survivor should be followed as well. Fetal demise in DC twins is not, *per se*, an indication for abdominal delivery.

### Fetal demise in MC twins, timing unknown

Despite the unknown time of death *in utero*, it may be advisable to estimate the time of death by ultrasound. Regrettably, accurate timing is impossible, but a macerated fetus with overriding skull bones clearly suggests that death did not occur recently. Nevertheless, this is probably among the most serious situations for which clear-cut guidelines are often absent. These situations are discussed under the following subheadings:

(1) *Fetal demise at the beginning of the second trimester* Because the risk of damage to the survivor is significant, the option of termination of the entire pregnancy should be discussed with the parents. However, the patient should be informed that, despite the ominous prognosis, the chance of a favorable outcome is greater than that of an adverse outcome. The potential advantage of an early (i.e. 15–16 weeks) comprehensive sonographic scan should be emphasized, as damage or the lack thereof to the fetal organs, as visualized by ultrasound, may be the arbiter for or against pregnancy termination. The decision becomes more difficult when the survivor approaches viability. At this stage of pregnancy, some advocate complementing the sonographic scan with magnetic resonance imaging (MRI)[8,9]. With the current experience of this imaging modality, however, the clear value of MRI has yet to be proven. Finally, it should be remembered that several screening tests such as the 'triple test' (see Chapter 46) and inhibin A[10] may have spurious results after fetal demise, irrespective of chorionicity.

(2) *Fetal demise beyond viability but remote from term* When fetal death is diagnosed at 25–27 weeks, and the surviving fetus seems to be intact (as far as imaging is concerned), most clinicians will not intervene, as the real risk of prematurity is greater than the potential risk from the fetal embolization syndrome. Again, imaging is necessary to exclude visible end-organ lesions.

(3) *Fetal demise beyond viability but preterm* In this circumstance, and when delivery is considered, enhancing lung maturity with steroids, with or without amniocentesis to prove lung maturity, could be an option. However, when the survivor is apparently normal, there is little logic in a preterm delivery because the preterm neonate is not at an additional risk *in utero*, especially when the time since the death of the co-twin is largely unknown.

(4) *Fetal demise at term* In many of these circumstances, especially when the etiology of fetal demise is unknown, the clinician may opt for delivery instead of continued close monitoring of the pregnancy. As always, the mode of delivery should be tailored to the patient's condition and to the fetal size and presentation.

### Fetal demise in MC twins, timing known

The actual death of a twin is rarely seen in real-time. The only instance with a potential of prompt diagnosis is when the twin pair is under close supervision.

**Table 70.1** Important considerations in the management of single fetal death in a multiple pregnancy. Adapted from reference 14

| |
|---|
| Single fetal death should be considered a further complication of an already complicated case. |
| The counseling session should provide both information and support. Remember that grief is not less when the patient is 'left with something'. Empathy is the key. |
| Consider all guidelines as merely guidelines. Each pregnancy needs individualized management. |
| Acknowledge your limitations. Some cases need expert consultation, tertiary-care facilities and advanced imaging and surgical technology. |
| Do not construct a management plan without being sure about chorionicity. When in doubt, try to estimate the probable chorionicity. |
| Try to establish the etiology of fetal death, starting with the exclusion of 'external' causes (i.e. maternal conditions) that may affect both twins. |
| Assess the biophysical well-being of the survivor. In MC pregnancies, look for potential damage in the survivor's brain and kidneys. |
| Balance the risks versus benefits of either continuation or termination of the pregnancy. Accurate dating of the pregnancy is clearly imperative. |
| Whenever early delivery is contemplated, consider steroids to enhance lung maturity of the survivor. |
| Although cesarean birth is not absolutely indicated, consider that this may not be the case to show your manual dexterity in complex vaginal births. |
| The etiology of death should be further evaluated by postpartum pathological examination of the demised fetus and the placenta. |
| Introduce the parents to follow-up facilities. |

MC, monochorionic

The idea behind treatment is that if acute hemodynamic changes due to feto-fetal hemorrhage occur at the time of death of the co-twin, then intrauterine transfusion may save the anemic survivor.

Senat and colleagues[11] transfused *in utero* six of 12 surviving albeit anemic fetuses within 24 h after demise of the co-twin. Four of the six had normal neurological development at 1 year of age. A less optimistic observation comes from an English group who performed intrauterine rescue transfusion in seven anemic fetuses within 24 h after death of a co-twin due to TTTS[12]. Two severely acidemic fetuses at blood sampling died *in utero* within 24 h of the procedure, two surviving twins manifested abnormal sonographic findings of the brain and underwent late termination, two cases continued to an uneventful delivery with good neonatal outcome and one case was delivered a week after the procedure at 28 weeks, but died within the first day of life. Recently, the French group replaced diagnosis via cordocentesis by the measurement of middle cerebral artery peak systolic velocity, which was found to be a reliable non-invasive diagnostic tool to detect fetal anemia, and helpful in planning invasive assessment and rescue therapy[13].

## SUMMARY

Single fetal demise should be considered a further complication of an already complicated case, a situation calling for vigilance in every step taken. Table 70.1 lists some important points in caring for these cases[14].

Single fetal death in DC twins or in trichorionic triplets is not associated with feto-fetal effects, and the risk for the survivor is negligible. Such pregnancies could be managed expectantly. In contrast, it appears that even the most heroic measures to rescue the survivor after death of an MC co-twin are often futile. A serious confounder of this pessimistic statement is the unknown time interval between fetal death and irreversible damage to the survivor, and the timing of rescue efforts in relation to this. Based on the few successful cases reported in the literature[11,12], it is possible that rescue, in the form of intrauterine transfusion or prompt delivery, can be performed in some instances at a reversible phase of the hypovolemic insult to the survivor. Because currently there is no practical way to diagnose and to intervene before the damage has occurred, even prompt intervention cannot alleviate the situation.

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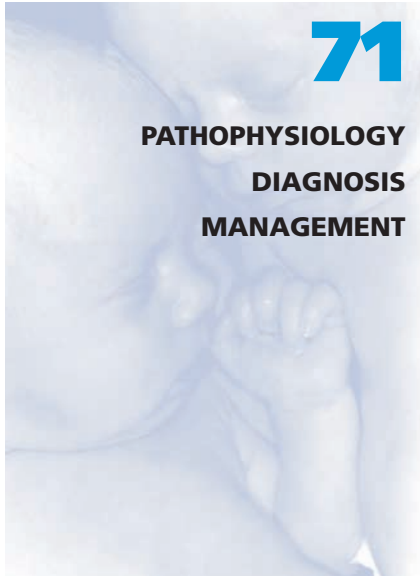
# Twin Reversed Arterial Perfusion (TRAP) Sequence

*I. Blickstein*




## PATHOPHYSIOLOGY

Abnormal placental vessels are common in monochorionic (MC) twinning. In the usual setting, blood from the placenta enters the fetal circulation through the umbilical veins and exits via the umbilical artery. Very rarely (1% of MC twins or 1 : 35 000 births), retrograde or reversed arterial perfusion takes place, from the placenta through the umbilical artery of one of the twins. Because the circulations of the twins are connected by arterioarterial and venovenous placental anastomoses, the twin with the reversed flow receives all of its blood supply from a normal co-twin who gains circulatory predominance – the so-called 'pump' twin. This vascular abnormality is currently termed the twin reversed arterial perfusion (TRAP) sequence.

Whereas the 'pump' twin is usually anatomically normal, the heart of the recipient twin is unable to support perfusion of the upper body, thereby causing decreased oxygen tension and altered fetal physiology in the twin with the reversed perfusion. Severe reduction anomalies of the upper part of the fetal body are the usual result. Often, these twins lack a heart (acardiac) and head (acepahalic), except for a few cases with a rudimental heart ('hemicardiac'). Based on these observations, the TRAP sequence is also characterized as chorioangiopagus parasiticus, and as acardiac twinning (Figure 71.1).

Although the TRAP sequence and the twin–twin transfusion syndrome (TTTS) share some similarities, they differ in several important aspects (Figure 71.2). First, whereas both share a trans(MC)placental shunt from a donor to a recipient twin, in TTTS the shunt is via an arteriovenous anastomosis and in TRAP, on the other hand, the shunt is via an arterioarterial connection. Second, the twins in TTTS are usually anatomically normal, whereas in TRAP, the recipient twin is grossly malformed. Finally, the strain on the fetal heart in TTTS is usually present in the recipient who suffers from cardiac overload, whereas the heart problem in TRAP is present in the donor, who needs to provide for both twins.

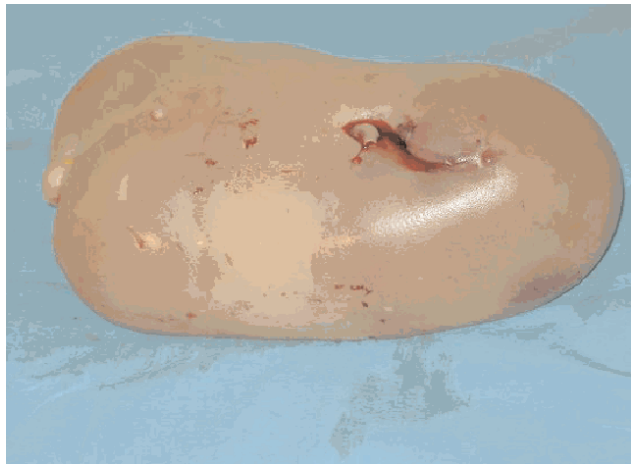


**Figure 71.1** Edematous ellipsoid mass of an acardiac–acephalic twin. Image courtesy of Dr Luis Graca, Lisbon, Portugal

The embryogenetic background of the TRAP sequence is still controversial. Opinions differ whether the underlying pathology is primary cardiac agenesis or cardiac dysmorphogenesis secondary to the reversed flow[1]. Some authors maintain that although TRAP might be a key diagnostic element for the acardiac

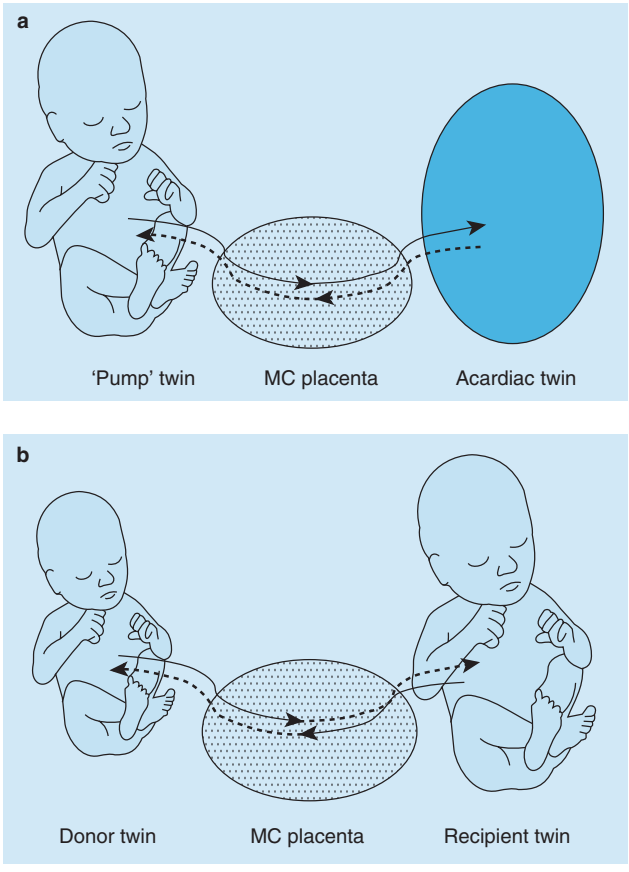



**Figure 71.2** Schematic representation of vascular connections in twin reversed arterial perfusion (TRAP) and in twin–twin transfusion syndrome (TTTS). (a) In TRAP, the vascular connection is via a transplacental arterio-arterial anastomosis; (b) in TTTS, the vascular connection is via a transplacental arteriovenous anastomosis. MC, monochorionic

condition, it need not necessarily be the primary cause[2]. A lethal heart malformation in early organogenesis – the so-called 'cardiac regression sequence' – seems more likely[2]. The alternative view holds that inadequate perfusion of the recipient twin is responsible for the development of the characteristic anomalies. In one recent report, TRAP sequence was diagnosed several weeks after demonstrating independent embryonic heart rates by ultrasonography performed at 5–6 weeks[1]. The unique aspects of this case suggest that the pathogenesis of acardia involves an arterioarterial shunt with retrograde blood flow, and not a primary arrest in cardiac development. It is difficult to distinguish the fetal heart from the large pulsating mediastinal vessels which can be present in these fetuses and this may lead to difficult diagnosis of death in an acardiac fetus in early pregnancy[3]. Therefore, given the availability of first-trimester sonography, the last word has almost certainly not been said regarding the pathogenesis of TRAP[4].

In 1981, Bieber and co-workers[5] identified two maternally derived chromosome sets and both maternal histocompatibility antigen haplotypes in the tissues of an acardiac twin. These findings were explained by proposing independent fertilizations, by two different spermatozoa, of a normal haploid ovum and its diploid first-meiotic-division polar body. More recently, however, Fisk and colleagues[6] performed polymerase chain reaction (PCR) on DNA extraction from nine twin sets with the TRAP sequence. Based on DNA fingerprinting patterns, Fisk and colleagues calculated that the chance that any of the acardiac twins resulted from fertilization of either the first or second polar body was < 4%, and the chance that they all resulted from polar body fertilization was < 1 : 100 000[6].

The anomalies associated with TRAP are categorized according to the site of maldevelopment:

(1) Acardius anceps: a body and extremities are present, but the head and face are partially developed (Figure 71.3a and b);

(2) Acardius acephalus: there are developed pelvis and lower limbs without a head, thorax or arms (Figure 71.3a);

(3) Acardius amorphus: this is an amorphous mass without recognizable organs, but with some form of axial structure (Figure 71.4);

(4) Acardius acormus: there is some cranial development.

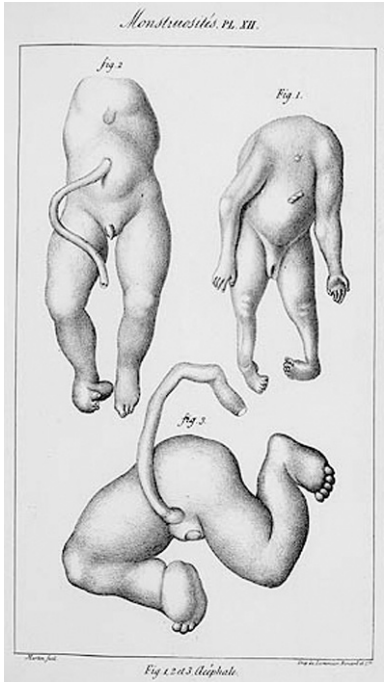
Figure 71.5a–e shows a closer examination of an acardius amorphous twin, including an X-ray image as well as the main autopsy results.

Despite being anatomically normal, heart failure of the 'pump' twin is the primary cause of concern in TRAP sequence. This is because of the excess demand from the abnormal circulation, whereby the 'pump' twin maintains the shared circulation of itself as well as that of the acardiac co-twin (see Chapters 41 and 42). The imposed cardiac overload is a serious threat to the 'pump' twin and, if left untreated, it may die in as many as 50–75% of cases[1]. Frequent assessments of the cardiac function of the 'pump' twin are therefore a critical step in the management of these pregnancies.

## DIAGNOSIS

Sonographic imaging during the first trimester usually depicts MC twins, with absent or vague heartbeat in one. Unfortunately, many cases are erroneously diagnosed during early ultrasound as a missed abortion of one twin (Figure 71.6). However,

a

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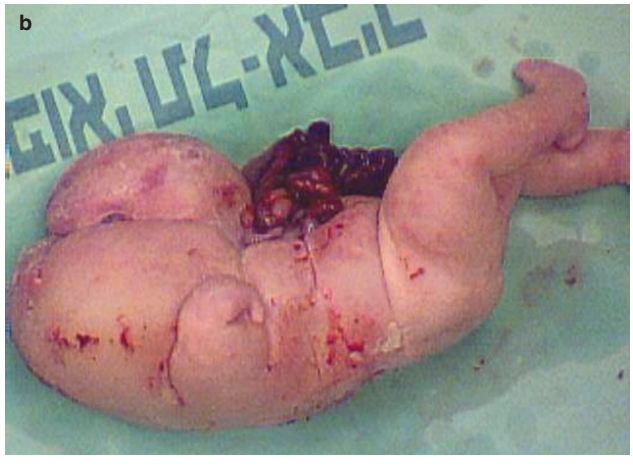


**Figure 71.3** (a) Lithographic depiction of acardius anceps (two upper images) and acardius acephalus (lower image). Reproduced with permission from Saint-Hilaire IG. *Histoire Générale et Particulière des Anomalies de l'Organisation chez l'Homme, et les Animaux*. Paris: JB Baillière, Plate XII; Figure 1, 2 et 3. History of Science QL991. G34, 1832. Courtesy of the Division of Rare and Manuscript Collections, Cornell University Library. (b) Acardius anceps. Image courtesy of the Department of Obstetrics and Gynecology, The Liss Maternity Center, Tel Aviv

in a typical missed abortion case, the size of the embryo/ fetus decreases with time. In contrast, the size of presumed missed twin is *increasing* in the TRAP sequence. Since no missed embryo can increase in size, the diagnosis of TRAP in such a circumstance should be straightforward. Color Doppler studies of the umbilical vessels show the characteristic reversed flow in the acardiac twin (see Chapters 41 and 42).

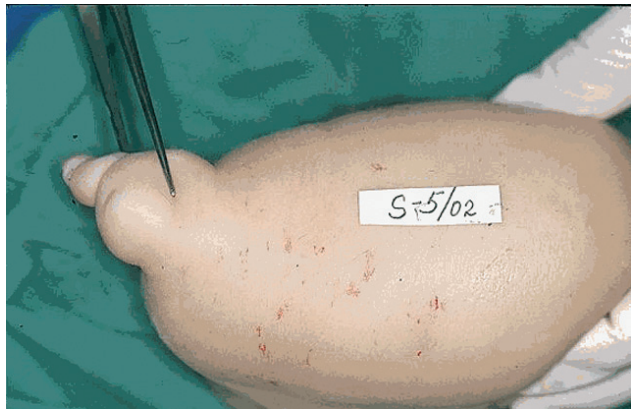



**Figure 71.4** Acardius amorphus. This amorphous mass has no recognizable organs, but has some form of a limb

Later in pregnancy, the lumpy phenotypic characteristics of the acardiac twin are easily recognized (Figure 71.7). When the diagnosis is made sufficiently early, potential interception of the acardiac's blood supply can be offered. Later, the size of the umbilical cord may be too large for simple procedures.

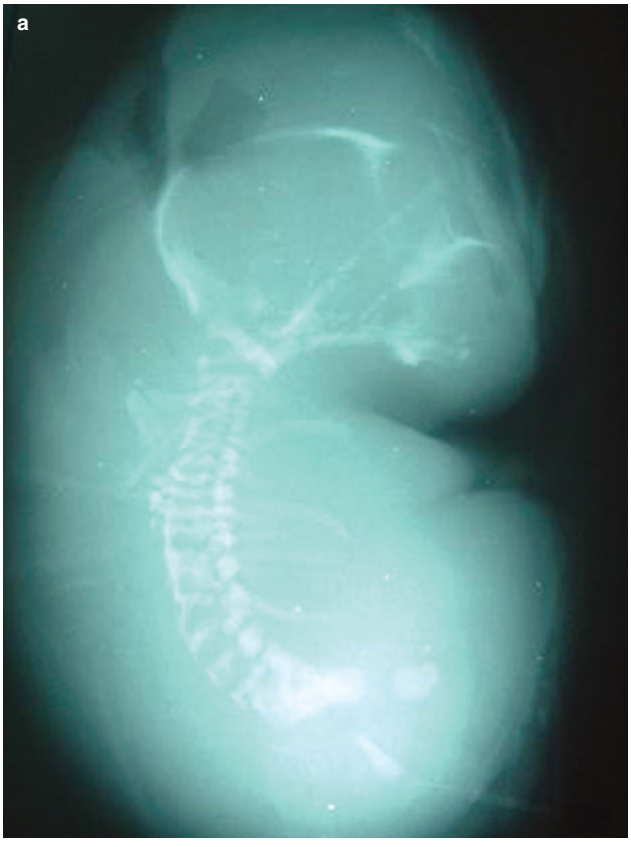
## MANAGEMENT

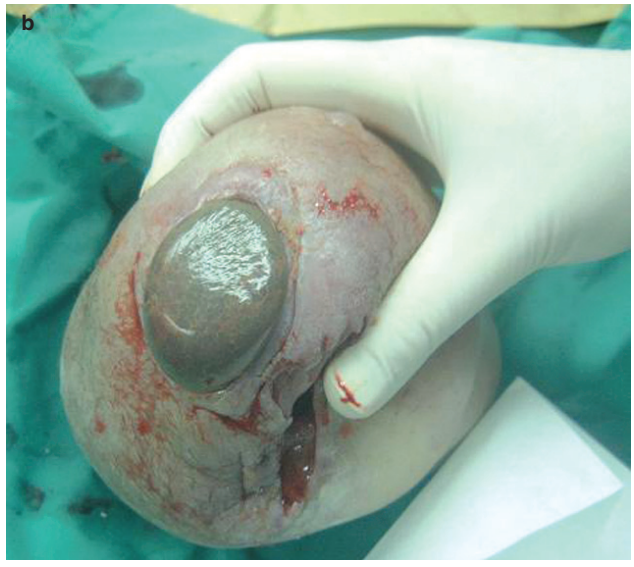
Clinicians have two management options – conservative and interventional. The following information should be known before any management decision is made:

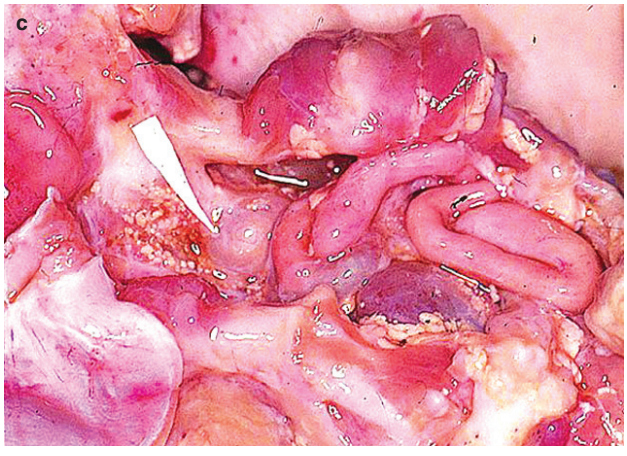
(1) Amnionicity: TRAP occurs in the diamniotic as well as in monoamniotic variants of the MC gestation. Monoamniotic twinning has been reported in only 25% of cases of TRAP sequence[7]. When TRAP occurs in monoamniotic pregnancies, treatment of the TRAP alone does not reduce the risks associated with monoamnionicity. It follows that umbilical cord occlusion with transection of the cord is necessary in patients with monoamniotic or 'pseudomonoamniotic' TRAP to avoid subsequent entanglement and demise of the 'pump' twin[8].

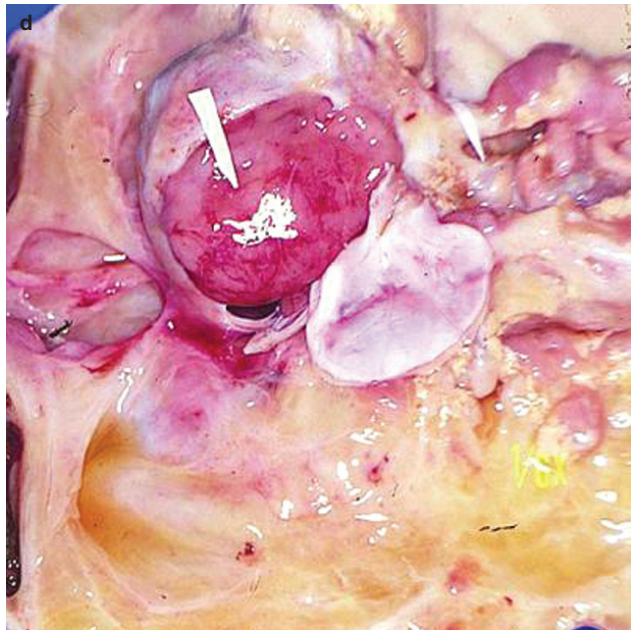
(2) Although 'pump' twins are in essence morphologically and chromosomally normal, anomalies are reported in these twins. It is therefore necessary to exclude malformations in order to avoid unnecessary invasive treatments. Van Allen and colleagues[9] reported that the incidence of chromosomal abnormality in the 'pump' twin may be as high as 9%.

(3) The well-being of the 'pump' twin, especially adequate cardiac function, should be established, and lack thereof may necessitate intervention.



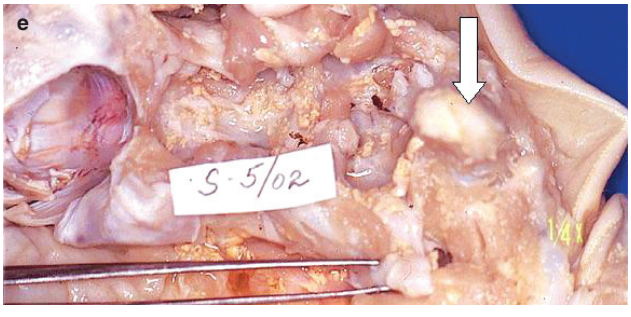




**Figure 71.5** (a) X-ray image of the acardiac twin shown in Figure 71.4. Note the underdeveloped skull, no facial contour and no limb bones. (b) Cephalic end of the acardiac twin shown in Figure 71.4. Note the porencephalic cystlike structure. (c) Autopsy of the acardiac twin shown in Figure 71.4. The arrow points to the remnants of a heart. The small intestine was 2 cm in length, the large intestine was 10 cm in length. (d) Autopsy of the acardiac twin shown in Figure 71.4. The arrow points to the remnants of a brain. This structure was contained within a cyst in the occipital area (b) lined by respiratory mucosa from the nasal cavity. (e) Autopsy of the acardiac twin shown in Figure 71.4. The forceps points to a dilated ureter emerging from a horseshoe kidney (arrow). Autopsy by Dr N. Sokolovskya-Ziv, Department of Pathology, Kaplan Medical Center, Israel

(4) The size of the acardiac mass and its umbilical cord in relation to the size of the 'pump' twin should be established in order to choose the most appropriate mode of therapy. According to some authorities (see below), if the estimated weight of the acardiac twin is less than one-quarter that of the pump twin, the prognosis is excellent without further therapy.

### Conservative management

When intervention is not performed, the target of follow-up is the 'pump' twin's congestive heart failure, which also leads to polyhydramnios and preterm birth. In one large series of 49 cases, the overall perinatal mortality was 55%, primarily associated with prematurity[10]. In this series, gestational age at delivery was 29 ± 7.3 weeks, and the birth weights were 1378 ± 1047 and 651 ± 571 g for the normal twin and the acardiac twin, respectively[10]. As noted above, follow-up is performed by serial echocardiographic assessments (Chapters 41 and 42). The purpose of follow-up is to determine when cardiac function begins to deteriorate.

Because polyhydramnios, the acardiac twin's weight and the occurrence of preterm labor are all related to the cardiac function of the 'pump' twin, perinatal outcomes are strongly related to the ratio of the acardiac and pump twins' weights. Specifically, the higher is the weight of the acardiac twin, the more likely is the development of cardiac insufficiency in the pump twin, with a risk of congestive heart failure increased to 94% when the acardiac twin's weight is more than half that of the 'pump' twin[10]. In the series described by Moore and associates, the mean overall ratio of the acardiac/normal twin weights was 0.52 ± 0.42; however, the ratio for patients delivered at < 34 weeks was 60 vs. 29% ($p < 0.04$). In one-quarter of the cases, the twins' weight ratio was > 0.7, and the incidence of preterm births in these cases was 90%. As the fetal indices used for sonographic estimations of fetal weight are not applicable to acardiac twins, the authors proposed the following equation:

$$\text{Weight (g)} = 1.2L^2 - 1.7L$$

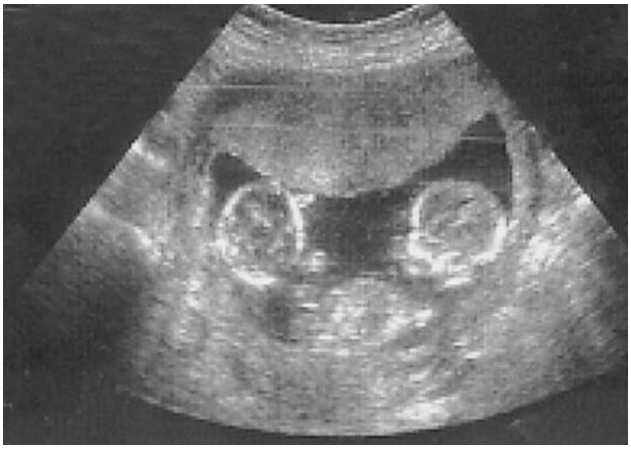


**Figure 71.6** First-trimester sonography showing twins. One of the twins was diagnosed as a missed abortion, but was, in fact, an acardiac twin

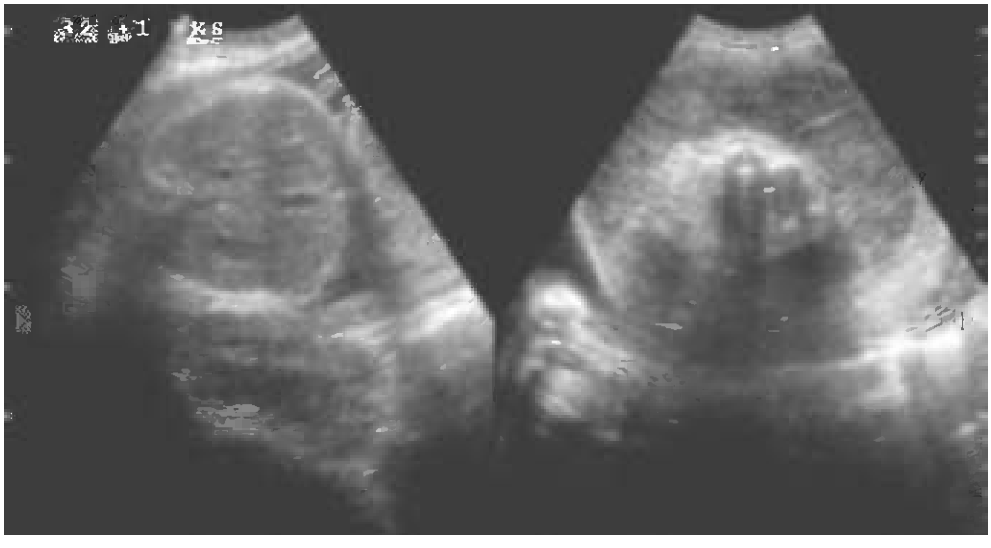


**Figure 71.7** Characteristic third-trimester sonographic image of an acardiac twin (right). Note the vertebral column shown in this sonographic plane. Compare with the image of the 'pump' twin in the plane of the fetal liver (left)

where $L$ = longest dimension of the acardiac mass[10]. Alternatively, approximate estimation of the weight of the acardiac twin can be made by comparing the abdominal circumferences of the twins, or by applying any formula that estimates the size of an ellipsoid.

Management, therefore, is guided by the associated risks of conservative treatment. When the acardiac/normal twin weights ratio is low, delivery at term or near term can be expected. In contrast, when the weights ratio is high due to massive edema of the acardiac twin, the cardiac dysfunction of the 'pump' twin may indicate early delivery.

In a recent publication concerning ten cases managed expectantly, Sullivan and colleagues[11] reported nine women who delivered healthy 'pump' twins (one neonatal death), at a mean gestational age of 34.2 weeks, and mean weights of the 'pump' and acardiac twins of 2279 and 1372 g, respectively. This observation suggests that when the diagnosis of TRAP is made antenatally, neonatal mortality of the 'pump' twin may be considerably less than previously reported.

Intrauterine prophylactic digoxin treatment, initiated after the sonographic diagnosis of fetal cardiac insufficiency, was reported by Simpson and coworkers more than two decades ago[12]. Sonographic signs of cardiac insufficiency disappeared completely after treatment over 6 weeks with survival of the 'pump' twin. It is not currently known how often this therapy is selected.

## Invasive procedures

In the past, treatment by selective delivery of the acardiac twin via sectio parvae (hysterotomy) was advocated[13]. This aggressive and potentially complication-laden modality has been replaced by less invasive procedures in the form of various interventions designed to interrupt the blood supply to the acardiac twin, a logical approach in such circumstances. Because of the arterioarterial shunt in TRAP, the artery must be interrupted, as simple thrombosis is quite difficult to achieve, and, if the vein is inadvertently thrombosed, the 'pump' twin may suffer from embolization related to the procedure.

Umbilical cord ligation was pioneered by Quintero and colleagues a decade ago[14]. In this procedure a knot is tied around the umbilical cord of the acardiac twin by a working instrument (with or without an endoscope) introduced into the amniotic cavity under ultrasound guidance. Although this procedure is associated with 70–80% success rate, it also entails risks of technical failure (7.6%), premature rupture of the membranes (10%) and bleeding. An alternative approach, first advocated in 1994 as well, is endoscopic coagulation of the umbilical cord vessels of the acardiac twin using a Nd : YAG (neodymium : yttrium–aluminum–garnet) laser[15]. Laser coagulation was successful in arresting blood flow to the acardiac fetus in cases treated at 17 and 20 weeks, but in pregnancies treated at 26 and 28 weeks, the umbilical cords were very edematous and laser coagulation failed to arrest blood flow[15]. These findings suggest that, during midgestation, endoscopic laser coagulation of the umbilical cord vessels of the acardiac twin is an effective method of treating the TRAP sequence. In later pregnancy, however, alternative methods of treatment are needed. Arias and coworkers[16] more recently reviewed 22 cases of acardiac twinning treated with invasive procedures, seven of which used endoscopic laser coagulation. 'Pump' twin mortality with endoscopic laser coagulation at ≤ 24 weeks and endoscopic or sonographic-guided umbilical cord ligation at > 24 weeks was 13.6%, in comparison with 50% mortality associated with expectant management. Still more recently, a tailored approach was proposed, whereby conservative treatment was offered to milder cases of TRAP sequence with a low weights ratio, whereas larger acardiac twins had invasive intervention and cord occlusion[17].

Recent attempts to minimize the nature of the therapeutic intervention were reported by Tsao and colleagues[18]. Under direct real-time sonographic guidance, the operators percutaneously inserted a 3-mm (14-gauge) radiofrequency ablation needle through the maternal abdominal wall into the intrauterine fetal abdomen at the level of the cord insertion site of the acardiac twin. Energy was applied until termination of blood flow to the acardiac fetus was documented by Doppler ultrasound scanning. No major maternal complications were reported in 13 cases, and 12 out of 13 'pump' twins remained alive and well. Average gestational age at intervention was 20.7 weeks, and average gestational age at delivery of the 'pump' twin was 36.2 weeks.

A recent review of 207 articles published in the English-language literature identified 32 reports involving 74 cases of acardiac twin treated by invasive techniques[19]. Seventy-one cases were included for analysis: 40 treated by cord occlusion (five embolizations, 15 cord ligations, ten laser coagulations, seven bipolar diathermy and three monopolar diathermy) and 31 by intrafetal ablation (five by alcohol, nine by monopolar diathermy, four by interstitial laser and 13 by radiofrequency). The overall median gestational ages at treatment and delivery were 21 and 36 weeks, respectively, with a median treatment–delivery interval of 13 weeks. The overall 'pump' twin survival rate was 76%. Intrafetal ablation was associated with increased gestational duration (37 vs. 32 weeks) and longer median treatment–delivery interval (16 vs. 9.5 weeks) compared with

cord occlusion techniques. It was also associated with a lower technical failure rate (13 vs. 35%), lower rate of births or rupture of membranes at < 32 weeks (23 vs. 58%) and higher rate of clinical success (77 vs. 50%) compared with cord occlusion techniques. No significant differences existed in terms of outcome between the fetoscopic- and ultrasound-guided cord occlusion techniques. This review suggests that intrafetal ablation is the treatment of choice for acardiac twins.

### Delivery considerations

The umbilical cord of the acardiac twin is usually very short, and the diameters of this ovoid mass may be larger than the pelvic outlet or even larger than the 10–12-cm uterine incision performed at cesarean section. Accordingly, because extraction of the acardiac–acephalic twin might prove traumatic and may cause rupture of the cord and exsanguination of the 'pump' twin, it seems reasonable to consider the welfare of the normal twin first. This may be accomplished only during a cesarean section. Thus, following the uterine incision, and after delivery of the normal twin, there is no rush to deliver the acardiac mass. Sometimes, and despite the elastic nature of the mass, extraction through a narrow incision may be difficult. It is advisable to have a good grip of the mass in order to perform a controlled slow delivery. Care must be taken to avoid lateral extension of the transverse uterine incision towards the uterine arteries. In one case at our hospital, the surgeon had to use a 'corkscrew' device attached to the mass in order to develop a firm grasp and ensure a safe extraction. Here, also, the use of a 'smile' incision into the lower uterine segment is warranted.

## SUMMARY

Diagnosis and management of the TRAP sequence has changed dramatically since the advent of sonography, echography, Doppler flow analysis and so-called 'minimally invasive' instrumentation. It is now possible to tailor the appropriate management to the individual case, based not only on intertwin size ratio, but also on direct echographic assessment of the cardiac function of the 'pump' twin. Thin endoscopes, introduced under fetoscopic or sonographic guidance, are currently available for ligation and/or ablation procedures to interrupt the blood flow to the acardiac twin. Expectant management, under close observation, is at present safer than ever before. Consequently, the chance of survival of the 'pump' twin has significantly improved with modern perinatal care.

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# Inhibition of Preterm Labor and Subcutaneous Terbutaline Therapy

*F. Lam and P. Gill*

72

PRETERM LABOR TREATMENT IN TWINS

BED-REST AND ACTIVITY LIMITATION

LOW-AMPLITUDE HIGH-FREQUENCY UTERINE ACTIVITY

CIRCADIAN PATTERNS

SUBCUTANEOUS PUMP THERAPY

AMBULATORY TOCOLYSIS

MANAGEMENT OF PRETERM LABOR IN THE HOME

## INTRODUCTION

Three decades ago, the inhibition of preterm labor was applicable to only a minority of women[1]. With the advent of preterm birth prevention programs, however, which emphasize patient and provider education, identify patients at risk, facilitate early diagnosis and provide for aggressive and expeditious therapy, increasing numbers of patients are now considered to be candidates for tocolytic management. Tocolysis is used to prolong pregnancy in the hope of avoiding or ameliorating the sequelae of preterm delivery. Delaying delivery allows time for the administration of steroids and (*in utero*) transfer of the mother, thereby enabling preterm infants to be delivered in obstetric units experienced in the care of high-risk pregnancies as well as having supportive neonatal intensive-care facilities. At early gestational ages, even a modest (48- to 72-h) prolongation of pregnancy can be greatly beneficial to the fetus and improve neonatal outcomes[2].

Since the early 1980s, many clinicians have appreciated the need to distinguish between the traditional but imprecise term of 'prematurity' and two additional terms: preterm labor and low birth weight (< 2500 g). The former terminology was used loosely for decades to describe, without distinction, preterm births and infants whose birth weights were less than 2500 g. As a result of this imprecision, present-day reading of the older literature and major textbooks is often limited by an inability to distinguish between these entities. Retrospective comparisons are often difficult, if not impossible.

In the 1990s, the term 'preterm labor' in a pregnancy between 20 and 36 weeks' gestation was characterized by the presence of regular uterine contractions of six or more per hour that resulted in cervical change[1]. This characterization was widely accepted by academicians as well as clinicians. Moreover, to strengthen the precision of this diagnosis, it was deemed appropriate that cervical change should be documented by the same examiner who would evaluate cervical dilatation, effacement, consistency, position and station of the presenting part at two examinations separated by a 2-h interval[1]. In this manner, a reliable and reproducible diagnosis of preterm labor could be established if progressive cervical change occurred in the presence of regular uterine activity. Additionally, the diagnosis of advanced preterm labor was established in the presence of cervical dilatation of ≥ 2 cm or effacement of ≥ 80%, although the likelihood of successful tocolysis was decreased in this latter circumstance[3].

In the past 30 years, a variety of tocolytic agents have been used to treat preterm labor. To date, no large prospective study has been published describing the use of systemic tocolytics in the management of preterm labor in multiple gestations, and the use of prophylactic oral tocolytic therapy in this population is of no proven benefit[4]. Most of the investigations of therapy for preterm labor have been conducted in singleton gestations and mixed (singletons and twins) populations, and such results must be extrapolated for twins. It is clear, however, that tocolytics alone are by no means a panacea for preventing preterm birth[5].

Individualization of tocolytic therapy is always critical for success as well as preventing complications. The management of preterm labor in multiple gestation presents several challenges, however. First, among

multiples, an increased frequency of premature labor occurs normally, along with onset at an earlier gestational age. Second, the latency period for tocolysis to be effective is greater than for singletons. Third, patients with multiple gestations are less likely to perceive their uterine activity, and often present with advanced cervical dilatation or preterm premature rupture of the amniotic membranes. Fourth, the risk of complications from tocolytic treatment is substantially higher[4], often because of the increased workload on the heart from the physiologic increased blood volume and anemia which renders patients more susceptible to fluid overload and pulmonary edema. The increased plasma volume and increased renal clearance present in multiples also makes tocolytic dosing and titration erratic. Fifth and finally, therapeutic failures result in two or more infants subject to the potential morbidity and mortality of preterm birth.

## THERAPEUTIC PRINCIPLES FOR PRETERM LABOR TREATMENT IN TWIN GESTATIONS

The early diagnosis of preterm labor in a twin gestation and an immediate subsequent intervention is the essential component in halting the preterm labor process. The following points represent the essential components of the therapeutic program. This program is based on our experience as well as that of other authors:

(1) Regard all twin gestations as high-risk for preterm labor and delivery.

(2) Enroll all patients with twin gestation in preterm labor/education programs by 18 weeks' gestation.

(3) Begin to evaluate cervical status at the first prenatal visit and increase frequency at 20–22 weeks.

(4) Consider the use of ambulatory tocodynamometry.

(5) Avoid prophylactic tocolysis with oral β-mimetic agents, as this only leads to down-regulation of the β-receptors.

(6) Advise bed-rest and moderate hydration if increased uterine activity is present.

(7) Hospitalize and treat aggressively with parenteral tocolytics if cervical change is documented. Do not wait for advanced cervical dilatation (≥2 cm).

(8) Rule out pathologic causes of preterm labor such as infection, abruption, polyhydramnios and congenital anomalies.

(9) Use intravenous (IV) magnesium sulfate as the primary tocolytic agent of choice, as it causes fewer maternal side-effects and does not down-regulate the β-receptors which may later be needed for long-term tocolysis.

(10) Consider ambulatory tocolysis only after the patient has been stabilized on parenteral tocolytics.

(11) Respect contraindications to tocolytic use.

(12) Select a tocolytic agent to maximize efficacy and minimize toxicity on a patient-specific basis.

(13) Titrate tocolytic dosage to end-organ effect (decrease of uterine activity) rather than toxicity (tachycardia or other side-effects).

(14) Monitor for signs of recurrent preterm labor.

(15) Provide close nursing support.

(16) Readmit patients with recurrent preterm labor for reinfusion with parenteral tocolysis.

(17) Use a sequential approach for tocolysis in recurrent preterm labor.

(18) Allow a 24–48-h IV magnesium sulfate 'drug holiday' in patients who experience a β-mimetic tocolytic breakthrough.

(19) Consider terbutaline pump therapy for patients with recurrent preterm labor or for those who cannot tolerate oral therapy.

(20) Continue all required prenatal testing on an ambulatory basis.

(21) Intensify maternal and fetal surveillance at 34 weeks to determine the best time for delivery.

## BED-REST AND ACTIVITY LIMITATION

Although prophylactic bed-rest in twin pregnancy remains ill-defined and controversial, few experienced clinicians question the wisdom of limiting daily activity in the patient with diagnosed preterm labor. Theoretically, bed-rest offers the advantage of improving uterine blood flow and relieving mechanical pressure on the cervix. More specifically, hospitalization provides the following theoretical advantages: enforced bed-rest, improved nutrition, access to maternal–fetal surveillance modalities, access to therapeutic modalities, exposure of the patient to educational programs and sequestration of the patient from a potentially hostile home environment. A program for home care should address each of these issues. With the cost of hospitalization rising rapidly and lengths of stay frequently restricted by third-party payors, home management of patients with preterm labor is an economic necessity as well as a clinical reality. The disadvantages of routine rest in the hospital include: considerable financial costs,

disruption to the life of the patient and her family and an increased risk of thromboembolism.

The concept of hospitalizing patients with multiple gestation near term probably started in 1952 when Jake Russell, noting that middle-class women generally delivered bigger and older (in terms of gestational age) twins than did working-class mothers, postulated that the more privileged patients 'had more leisure and consequently more rest during their pregnancies'[6]. It is not clear whether Russell was aware that Pinard had said almost the same thing about singletons at the Maternité Port-Royal in Paris about 50 years earlier. In any event, Russell proposed that consideration be given to hospitalizing all patients with twins at the 30th week in order to ensure their health during what was considered the danger period. As a result of this recommendation, hospital bed-rest in the third trimester in twin pregnancies became common practice in Britain. This recommendation may also have provided the basis of decisions in Eastern Bloc countries in the 1960s and in Western countries where cost concerns were not paramount.

Investigators have since vigorously supported or refuted the value of prophylactic bed-rest for these patients. The early questions in the bed-rest controversy included when to begin it, where it should take place and for how long it should continue[7]. Similar questions are valid today. In the only prospectively randomized study, patients were not hospitalized until 32 weeks or later[8]. Because more than 50% of the perinatal mortality associated with twin pregnancy occurs prior to 30 weeks' gestation, recent reports suggest that bed-rest should be instituted earlier, i.e. as early as 24–25 weeks' gestation[7]. Whereas bed-rest may reduce intrauterine growth restriction (IUGR) when initiated after 30–32 weeks, any impact on preterm labor can be achieved only with earlier intervention.

Empiric hospitalization of all patients with twins does not appear to be cost-effective. Hospitalization in such instances is expensive in developed countries, and is logistically impossible in underdeveloped or developing countries[9]. At present, prophylactic in-hospital bed-rest for twin gestation is not routinely practiced in the United States. Reduced activity at home, on the other hand, as well as time off work starting at 25 weeks' gestation, is reported to be sufficient, and hospitalization is recommended only when complications such as increased uterine activity or cervical change are noted.

## LOW-AMPLITUDE HIGH-FREQUENCY UTERINE ACTIVITY AND THE ONSET OF PRETERM LABOR

The guard-ring tocodynamometer introduced by Smyth[10] in 1957 became the scientific basis for the identification of a specific pattern of uterine activity in which contractions occur frequently, albeit with low amplitude (Figure 72.1). Previously, these low-amplitude, high-frequency (LAHF) contractions were characterized as 'uterine irritability', and their importance was minimized because they were regarded as physiologic. Often they were quite incorrectly characterized as 'Braxton-Hicks' contractions, but Braxton-Hicks in reality described the physiologic uterine contraction–relaxation palpable in the first and second trimesters. In terms of 'uterine irritability', several reports suggest that the LAHF contractility pattern may have a causative role in the occurrence of preterm labor[11–14].

Technical descriptions of LAHF contractions were first provided by Alvarez and Caldeyro[11]. Often later characterized as 'Alvarez waves', they are defined as uterine activity with an intensity of < 5 mmHg occurring at a frequency of 1–2 per minute[15]. Alvarez and Caldeyro ascribed LAHF uterine activity to asynchronic local contractions occurring randomly in different parts of the uterus, and characterized this activity as 'uterine fibrillation'. Although such contractions are generally not perceived by the woman, they can be detected by internal tocodynamometers[14] or external guard-ring tocodynamometers[10,13,14]. Many years later, Nakae classified each waveform of the external tocograph and described the circumstances in which 'small waves' increased in women with preterm labor and who were receiving tocolytic treatment[15].

The significance of the LAHF contraction has not always been appreciated. According to Warkentin, LAHF contractions account for 70–80% of the total contractions recorded in normal pregnancies. On this basis, he concluded that they were not associated with preterm labor or poor outcome[16]. However, after these contraction patterns were subject to intense clinical scrutiny, Creasy concluded that they served as prodromal events that lead to the development of more synchronous contractions of greater intensity and subsequently to preterm labor[12,17].

Newman and co-workers determined that parity and gestational age had no effect on the occurrence of LAHF contractions[13]. These authors based their conclusion on a study of 50 women at low risk and 92 women at high risk of preterm labor, including 20 twin pregnancies. Patients destined to develop preterm labor exhibited this contractility pattern significantly more than their counterparts who delivered at term (13.5 vs. 9.2%, respectively). Newman and co-workers subsequently studied the influence of fetal number on uterine activity. They concluded that although fetal number had no impact on the intensity of pre-labor contractions, triplet gestations had a significantly higher incidence of increased

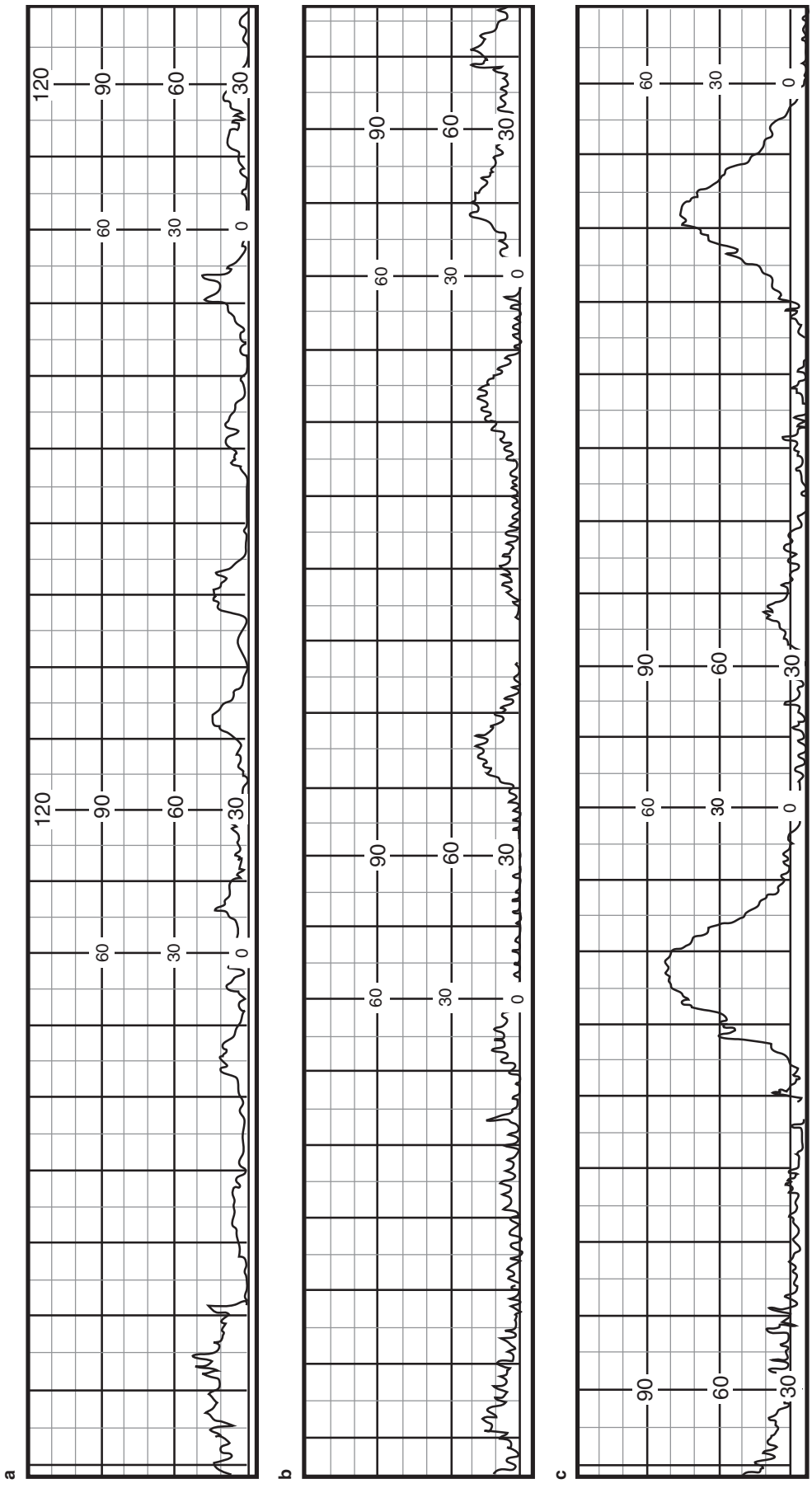


**Figure 72.1** Low-amplitude, high-frequency contractions (a,b) may be precursors to the organized uterine contractions (c) that can cause preterm birth

LAHF uterine activity[13]. These authors additionally suggested that LAHF contractions played a role in bringing about the 'silent' cervical changes so often present in triplet gestations[18].

Kawarabayashi and colleagues[14] studied 6363 cardiotocographs obtained from 578 patients and observed:

(1) The presence of small-wave (LAHF) activity in 7.5% of the patients;

(2) A decrease in the rate of LAHF activity as the pregnancy progressed;

(3) An increase in small-wave (LAHF) activity in 42.3% of patients in preterm labor;

(4) That patients with increased LAHF activity had relatively poor obstetric parameters and fetal outcomes.

Their observations suggest that small-wave LAHF activity is a real manifestation of a specific type of uterine contractility, and that its presence is ominous for the outcome of the pregnancy in general. Stated another way, LAHF activity may indicate the presence of a state of high excitability and poor coordination of the uterine muscle before the onset of large phasic contractions.

If LAHF contractions indeed are precursors of more organized, phasic contractions that lead to cervical change and preterm delivery, three important clinical questions immediately arise:

(1) Can the detection of increased LAHF wave activity be used as a screening tool to diagnose preterm labor at an earlier stage?

(2) Can LAHF contractions be suppressed with tocolytic agents?

(3) Can suppression of this activity be achieved with smaller doses of tocolytic agents?

With regard to the first question, the diagnostic role of LAHF activity has not been substantiated. In the study by Newman and co-workers[13], an analysis of the last 7 days before the onset of labor in the group of patients who developed preterm labor failed to show an increasing frequency of LAHF activity. The response to the second question is much more promising. Newman and co-workers observed a 50% decrease of LAHF contractions during tocolysis[13]. Moreover, Kawarabayashi and colleagues suggested that the appearance of LAHF activity does not lead to a poor prognosis in preterm labor if large phasic contractions can be abolished by $\beta_2$-stimulant treatment[14]. Finally, in response to the third question, preliminary studies suggest that LAHF contractions can be suppressed by low-dose subcutaneous infusions of terbutaline[19].

## CIRCADIAN PATTERNS OF UTERINE ACTIVITY

In 1982, Schwenzer and co-workers described a circadian pattern of uterine contractions in resting pregnant women who were monitored with a stationary tocodynamometer[20]. A nocturnal increase in uterine activity was noted between 23.00 and 03.00 in addition to a diurnal increase between 11.00 and 13.00. The period of least uterine activity occurred between 13.00 and 09.00. Zahn subsequently evaluated 57 women with normal pregnancies by continuous 24-h tocodynamometry[21]. He observed a circadian pattern of contraction frequency with peaks between 22.00 and 02.00, followed by a decrease in uterine activity. A similar pattern was also noted in normal women by Arakai[22], with a frequency of distribution similar to that of Zahn's. In patients with recurrent preterm labor, our group observed a nocturnal frequency distribution pattern of organized contractions, with 80% of all uterine activity occurring during a 6-h peak period in the late evening[17,19,23]. This nocturnal pattern of increased uterine activity was observed in singleton as well as in multiple gestations. Although individual patients exhibited different patterns, any given patient's pattern of uterine activity was usually consistent over time and repetitive. Most important, the appearance of LAHF contractions generally preceded the onset of organized uterine contractions.

The existence of a circadian pattern of uterine activity suggests that the treatment of preterm labor can be planned on an individual basis (Figure 72.2). The tocolytic dose can be increased during the nocturnal peak of uterine activity and decreased during periods of uterine quiescence. Such patient-specific regimens not only reduce overall medication requirements but also minimize the risk of tachyphylaxis and toxicity.

Prior to the initiation of patient-specific dosing, however, individual patterns of uterine activity should be determined by 24-h continuous in-hospital tocodynamometry. In addition, any perceived uterine activity detected by self-palpation should be recorded on a preterm labor log (Figure 72.3). Medication dosage or frequency can be adjusted accordingly, based on changes of uterine activity.

## SUBCUTANEOUS PUMP THERAPY

Subcutaneous pump therapy was developed as an alternative to intravenous tocolysis in patients who failed oral treatment due to recurrent preterm labor[19]. Subcutaneous pump therapy delivers a

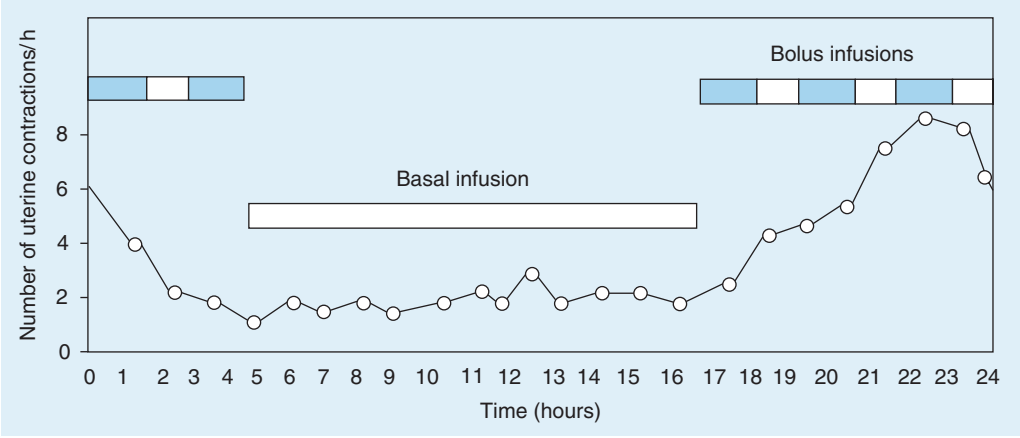


**Figure 72.2** Most preterm labor patients exhibit a circadian pattern of labor activity as shown. Over 80% of all contractions occur during a 6-h nocturnal period in the late evening. Subcutaneous terbutaline pumps are programmed to infuse a low-dose (0.05–0.09 mg/h) basal rate during periods of low-amplitude, high-frequency uterine activity. During the nocturnal period of organized contractions, intermittent boluses of 0.25 mg terbutaline are infused. The overall result is a low total daily dosage (3–4 mg/day) of terbutaline, reducing the chance of side-effects and tachyphylaxis

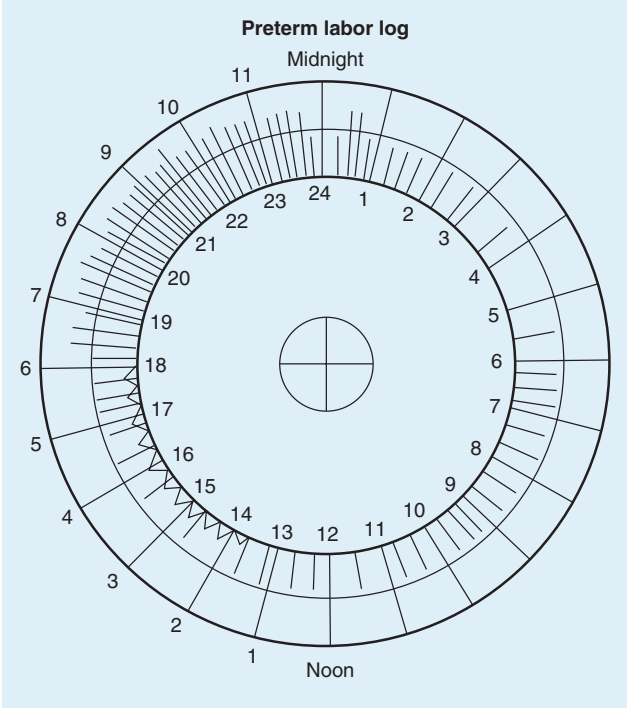


**Figure 72.3** Based on the 24-h clock, the preterm labor log provides a graphic record of uterine activity. Records are made daily based on tocodynamometry, palpation and self-perception of uterine contractions. The radial lines represent uterine contractions and the 'serrated' line represents periods of uterine irritability (low-amplitude, high-frequency uterine activity)

continuous low basal rate of terbutaline and scheduled boluses of 0.25 mg of this agent during identified periods of increased uterine activity. The total average daily dose (including basal and bolus infusions) is 3–4 mg/day, and this dose is titrated according to changes in uterine activity. Resensitization of the β-receptors is essential to the success of this therapy. Patients are first maintained on IV $MgSO_4$ for 24–48 h as a 'drug holiday' to allow the β-receptors to regain their sensitivity.

Patients who cannot otherwise be discharged to home care because of inadequate response to oral therapy may be successfully maintained on pump therapy. Not unexpectedly, nursing care plays a significant role in patient education prior to discharge and in the subsequent management of pump therapy in the home[24–26].

**Nursing interventions**

Nursing actions include those listed below for β-mimetic therapy at home, plus several interventions specific to subcutaneous terbutaline pump therapy:

- Educate the patient regarding the use and mechanics of the pump.
- Teach about care and changing of the infusion site.
- Monitor titration of the dose according to uterine activity as ordered by the physician. Deliver basal and bolus doses according to a specific protocol. Set criteria for notifying the physician of changes in contraction patterns.
- Instruct the patient to monitor her radial pulse rate prior to emergency bolus doses.

Basal infusion rates should be adjusted to minimize periods of low-amplitude, high-frequency uterine activity. Our dose–response studies demonstrated

that continuous basal terbutaline infusion rates of 0.05–0.08 mg/h are most effective in suppressing LAHF waves and subsequent uterine contractions. In triplet gestations, basal infusion rates of 0.06–0.09 mg/h may be required, because of the higher maternal blood volume. Higher basal infusion rates should be avoided, not only because they result in more medication than necessary to control LAHF waves, but also because they fail to provide significant additional suppression of organized uterine contractions.

Bolus schedules are determined according to the patient's individual contraction pattern. Bolus doses of 0.25–0.30 mg are given to suppress organized uterine contractions. They are scheduled every 2 h during the established peak period of uterine activity, and less frequently during the periods of minimal uterine activity. The typical patient will require 6–8 bolus doses over a 24-h period, resulting in a total infusion of less than 4 mg/day[19,23]. This dose level compares very favorably to the typical oral dosages of 40–60 mg/day and typical IV dosages of 60–80 mg/day.

We start the majority of our patients with multiple pregnancy who are in preterm labor on a standard dosage schedule: a basal infusion of 0.06 mg/h and boluses of 0.25 mg at 9 a.m., 12 noon, 3 p.m., 6 p.m., 8 p.m., and 10 p.m.[19]. Patients are instructed to use supplemental demand boluses if they experience more than 4–6 contractions per hour, and to record them on their preterm labor log. Demand bolus histories are of value in making adjustments to the patient's routine bolus schedule. Boluses should not be given if the maternal pulse rate is greater than 110 beats/min, and in any case, no more frequently than every hour. Whereas the currently accepted practice for titrating dosage levels of oral β-mimetic agents relies on measuring maternal tachycardia (a secondary $\beta_1$ cardiac effect), patient-specific dosing with the terbutaline pump is directed toward reduction of uterine activity (a direct $\beta_2$ end-organ effect)[23].

The schedule of intermittent boluses can be adjusted if the patient's pattern of uterine activity changes, either during the hospital stay or after discharge home. Adjustments may include increasing the frequency of boluses, adding additional boluses, increasing the individual bolus doses up to a maximum of 0.3 mg or shifting the cluster of boluses to coincide with a shift in the period of peak uterine activity.

The basal infusion rate may be increased if there is an increase in uterine LAHF waves or a persistent increase in uterine contractions of greater than 4–6/h despite repeated boluses. It is best to maintain the basal infusion at the lowest rate possible, however, to prevent $\beta_2$ receptor site desensitization. When the patient is stable on terbutaline pump therapy, she can be discharged home on bed-rest and monitored intermittently with a portable tocodynamometer.

Monitoring is scheduled for 1 h during the peak period of contractions, and 1 h during the 'quiet' period to determine LAHF wave activity. Additional monitoring may be needed if periods of increased uterine activity occur. A home-care perinatal nurse should visit the patient on a weekly basis to check blood pressure, pulse rate, fundal height and fetal heart rate, perform a urinanalysis and perform cervical examinations as indicated.

Our studies of recurrent preterm labor in patients with singleton or multiple pregnancies who are receiving β-mimetic therapy demonstrate the following patterns (Figure 72.4): a return of excessive levels of low-amplitude, high-frequency (LAHF) contractions; a return of a circadian, generally nocturnal pattern of organized high-amplitude uterine contractions; a rapidly increasing need for increased frequency and dosing of terbutaline or ritodrine[23]; and a 'crescendo' effect or acceleration of the frequency of uterine contractions 48–72 h prior to the episode of active recurrent preterm labor[27].

Although infrequent, breakthrough does occur in patients receiving terbutaline pump therapy. If it does, the patient should be readmitted to hospital and stabilized on intravenous $MgSO_4$ for 24–48 h. Terbutaline pump therapy should be discontinued (both basal and bolus infusions). This 'drug holiday' will allow the myometrial receptors to regain their sensitivity to terbutaline (Figure 72.5). When stable, the patient can be restarted on terbutaline pump therapy and discharged home. Tocolytic therapy is generally discontinued at 36–37 weeks.

## EVIDENCE FROM CLINICAL STUDIES USING THE SUBCUTANEOUS TERBUTALINE PUMP

In 1988, we described our initial experience using a microinfusion pump to administer a low-dose basal rate and scheduled bolus doses of subcutaneous terbutaline in nine women with recurrent preterm labor[19]. Pregnancies were prolonged by an average of 9.2 ± 4.3 weeks in this population. In a randomized fashion, we later reported 69 patients who received either continuous subcutaneous terbutaline or oral terbutaline, following stabilization with intravenous tocolysis. In this study, those receiving subcutaneous terbutaline had their pregnancies prolonged by a mean of 8.6 weeks, compared with a mean of 2.4 weeks in the oral terbutaline group[28].

Other investigators have also compared continuous subcutaneous terbutaline with oral terbutaline for ongoing tocolysis following recurrent preterm

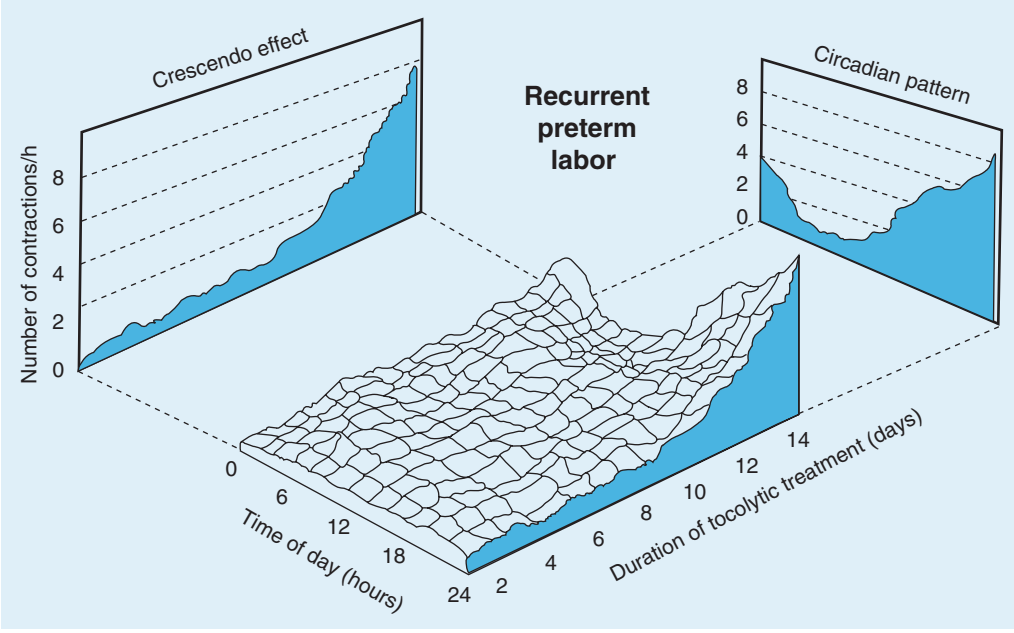


**Figure 72.4** Three-dimensional plot of uterine activity in a twin gestation leading to recurrent preterm labor: continuous monitoring of a patient on oral terbutaline therapy. Recurrent preterm labor is characterized by a return of excessive levels of low-amplitude, high-frequency (LAHF) precursor uterine activity patterns, a return of a circadian, generally nocturnal pattern of organized high-amplitude uterine contractions, a rapidly increasing need for increased frequency and dosage of terbutaline and a 'crescendo' effect of acceleration of the frequency of uterine contractions 48–72 h prior to the episode of active recurrent preterm labor

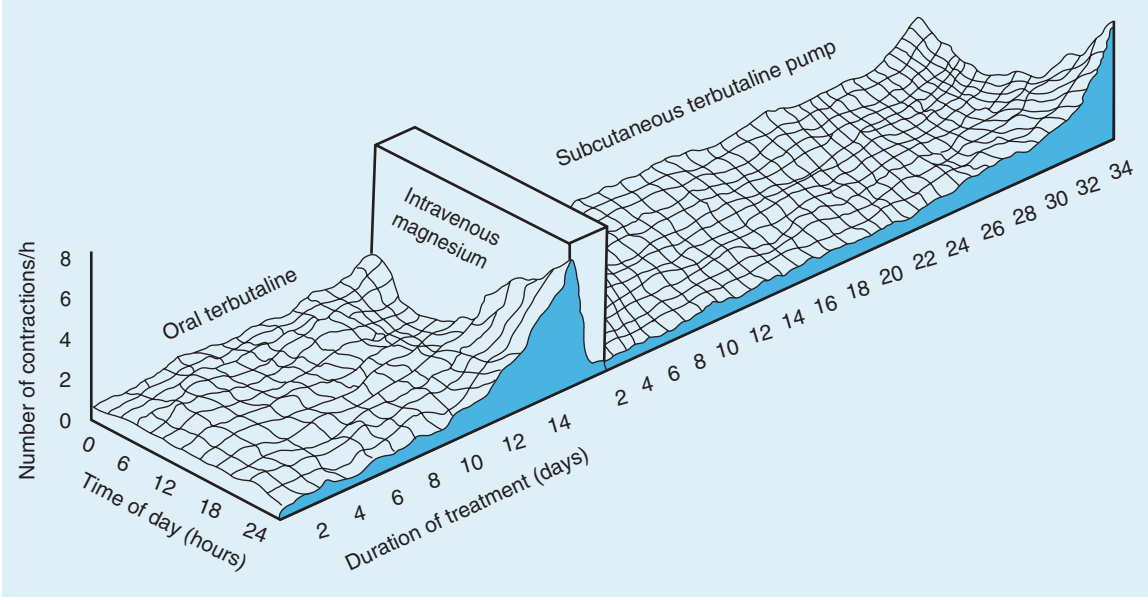


**Figure 72.5** Recurrent preterm labor may be secondary to down-regulation of the uterine β-receptors. Intravenous magnesium sulfate is initiated in a sequential fashion to provide a 'drug holiday'. At least 24–48 h is required for the uterine β-receptors to up-regulate and regain their sensitivity to terbutaline. At this point, subcutaneous terbutaline pump therapy can be started to prevent the recurrence of preterm labor

labor. In a matched-study design, Allbert and colleagues compared 32 patients who received subcutaneous terbutaline infusion with 32 patients who received oral therapy[29]. Singleton and multiple gestations were combined. Women achieved 72% of desired prolongation with oral therapy compared with 86% of desired prolongation among those receiving subcutaneous therapy. A descriptive analysis of

992 high-risk patients, including 206 twin pregnancies receiving continuous subcutaneous terbutaline infusion, also reported by Allbert and co-workers, showed a mean pregnancy prolongation of 38 ± 23 days[30].

Adkins and associates[31] reported 51 patients with preterm labor (including four with twins) who received subcutaneous terbutaline therapy after stabilization with intravenous magnesium sulfate. Subcutaneous administration of terbutaline was successful in 98% of patients, prolonging pregnancy by a mean of 6.6 weeks. Mean gestational age at delivery was 37 weeks, and the mean infant birth weight was 3035 g, with 85% of neonates weighing > 2500 g. Only 22% of infants went to the neonatal intensive-care unit (NICU), with a mean stay of 7 days. Three patients reported adverse effects and had their bolus dosages decreased. No serious adverse events were reported.

Wenstrom and colleagues[32] during a 4-year period enrolled 42 patients having the diagnosis of preterm labor to evaluate subcutaneous infusion therapy. In this three-arm study, patients were randomized to receive oral terbutaline, subcutaneous terbutaline infusion or subcutaneous saline infusion. Subcutaneous drug therapy was not adjusted for patient weight or volume of distribution. Electronic home uterine-contraction monitoring was not used. Terbutaline boluses were adjusted for patient-reported contractions. Patients received a mean of 1.5 ± 2.4 scheduled boluses per day in the terbutaline subcutaneous infusion group, which is considerably less than standard practice. All patients in the Wenstrom study were administered a basal rate of 0.05 mg/h, which was not titrated to the level of uterine irritability, as is customary. Patients were permitted to cross over between treatment arms if initial therapy failed. This study parameter resulted in 25% of the women initially enrolled in the placebo saline group ultimately to receive subcutaneous terbutaline. Outcomes for patients were compared only by the treatment group to which patients were originally assigned. Even with the unblinding of the assigned treatment group, the authors concluded that the three interventions were equally efficacious.

Guinn and co-workers reported 52 women randomized to either terbutaline or placebo via subcutaneous infusion[33]. Patients did not receive daily nursing contact or home uterine-activity monitoring, as is generally prescribed in obstetric practice for women receiving continuous subcutaneous terbutaline infusion in the home setting. In 50% of the participants, the cervix was 3 cm or more dilated and at least 50% effaced at enrollment. Patients were enrolled at a mean of 31 weeks, which made the hypothesized 6-week prolongation for the treatment group unlikely. In addition, patients were not treated for recurrent preterm labor occurring at or beyond 34 weeks. Tocolytic dosing was not individualized or titrated to uterine activity, and the bolus schedule employed in the study allowed a 7-h lapse during the nighttime, a period during which there is a likelihood of increased uterine activity[34]. Using this protocol, the authors reported only a 1-day difference in pregnancy prolongation between the groups, with the subcutaneous terbutaline group achieving a 28.8 ± 22.0-day prolongation.

In 1998, Lam and colleagues reported the efficacy of subcutaneous terbutaline infusion therapy in 256 singleton pregnancies with recurrent preterm labor while on oral terbutaline[35]. Pregnancy prolongation was found to be greater for subcutaneous versus oral administration of terbutaline (4.4 vs. 2.7 weeks). The pregnancy prolongation index for subcutaneous therapy was 74%, compared with 31% for oral therapy. In a similar fashion, Lam and colleagues reported 386 women with twin gestations[36] in preterm labor who were treated with oral terbutaline, versus a like number who used subcutaneous terbutaline. Those treated with parenteral therapy in the home gained significantly more days *in utero* (34.0 ± 19.8 vs. 19.3 ± 15.3 days) with a higher pregnancy prolongation index (79% vs. 33%, $p < 0.001$). Patients gained a mean of 53.4 ± 21.4 days overall, with a mean gestational age at delivery of 35.2 ± 1.9 weeks. These women gained 2.8 weeks with oral terbutaline and 4.9 weeks with subcutaneous terbutaline prescribed sequentially.

Elliott and Radin[37] reported subcutaneous terbutaline infusion therapy use in higher-order multiple gestations. Fifteen triplet and six quadruplet pregnancies were treated with individualized dosing protocols. Triplet patients remained on infusion therapy for 58 days and delivered at a mean gestational age of 33 weeks. Quadruplet patients were on subcutaneous infusion therapy for 77 days and delivered at a mean gestational age of 33 weeks. Only two of 15 (13%) of triplets and one of six (17%) of quadruplets were delivered because of tocolytic failure. No one in the study had subcutaneous terbutaline discontinued owing to side-effects.

Angel and associates described a clinical protocol whereby triplet and quadruplet pregnancies underwent a transition to subcutaneous terbutaline after intravenous magnesium sulfate treatment for the first episode of preterm labor[38]. Overall, 87% ($n = 20$) of women with triplet gestations experienced preterm labor. The mean gestational age at delivery for triplets was 32.3 ± 0.5 weeks.

Elliott and colleagues assessed the gestational gain in triplet pregnancies treated with oral terbutaline followed by continuous subcutaneous terbutaline therapy[34]. One hundred and four triplet pregnancies

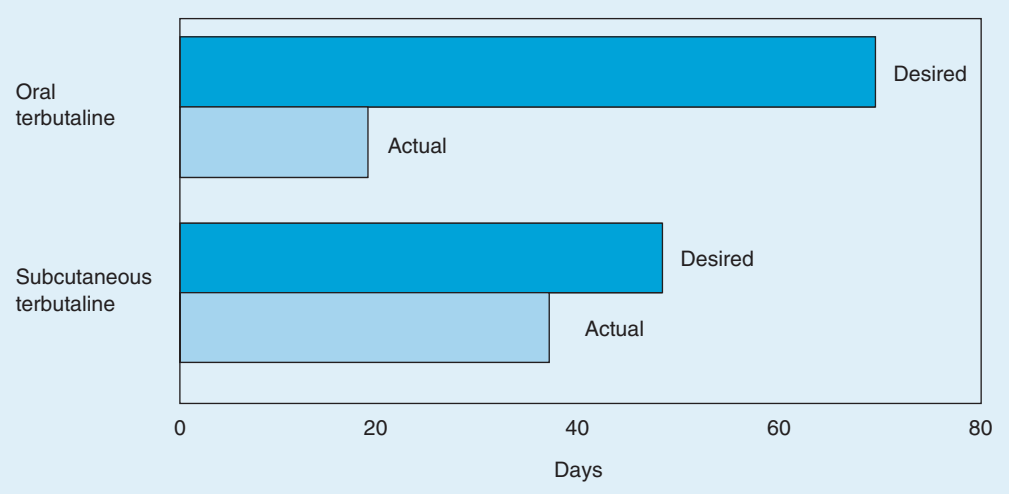


**Figure 72.6** In 104 women with triplet gestations experiencing threatened preterm labor, pregnancy was prolonged 52% more when terbutaline was administered via continuous subcutaneous infusion as compared with oral ingestion. Overall, patients gained a mean of 8.2 ± 3.1 weeks' gestation with oral and subcutaneous terbutaline[34]

were studied (Figure 72.6). The mean gestational age at enrollment was 22.0 ± 2.7 weeks. The study showed that these pregnancies were prolonged 52% more (mean 5.4 ± 3.4 vs. 2.8 ± 2.2 weeks) when terbutaline was administered via continuous subcutaneous infusion compared with oral administration (Figure 72.6). Overall, patients gained a mean of 8.2 ± 3.1 weeks' gestation with oral and subcutaneous terbutaline. The mean gestational age at delivery was 33.2 ± 2.2 weeks. The authors concluded that in women with triplet gestation, greater pregnancy prolongation was achieved with subcutaneous administration than with oral administration of terbutaline.

Morrison and colleagues[39] compared 15 women with singleton pregnancies and recurrent preterm labor (RPTL) at less than 32 weeks' gestation and who were treated with subcutaneous terbutaline with 45 matched control patients (3 : 1) treated with no tocolytic therapy after hospitalization. Gestational age at delivery more than 37 weeks (53% vs. 4%), percentage delivered at less than 32 weeks overall (0% vs. 47%) and pregnancy prolongation (49.8 ± 19.2 days vs. 24.5 ± 12.8 days) were all significantly better in the study group. Also, the total number of maternity hospital days, duration of NICU stay and the total cost for newborn care favored the subcutaneous therapy patients. The authors concluded from this small study that the use of subcutaneous terbutaline significantly prolongs pregnancy, decreases serious neonatal complications and reduces the duration of hospitalization for both mother and infant, as well as neonatal costs. For every dollar spent on subcutaneous terbutaline therapy, there was a saving of 4.67$US in newborn hospital costs for control patients.

Elliott and colleagues[40] presented the first report of the incidence of subcutaneous terbutaline-related adverse side-effects. A total of 9359 patients with singleton, twin and triplet pregnancies were studied. Data were obtained from the national network of Matria Healthcare patient service centers. Transient medication side-effects were reported by 1447 (15.5%) patients. Severe adverse events were identified in 12 patients either during treatment with subcutaneous terbutaline ($n = 4$) or following discontinuation of therapy ($n = 8$). The most frequent, serious side-effect was pulmonary edema ($n = 9$). There was no maternal mortality in this study, although mortality has been reported in women receiving subcutaneous terbutaline. In one case reported in 1993[41], a patient pregnant with twins had been receiving subcutaneous terbutaline for 1 week before reporting severe chest pain and shortness of breath. The death was attributed to cardiac arrhythmia. Another woman died in the hospital from a ruptured iliac artery aneurysm during treatment with intravenous $MgSO_4$ after subcutaneous terbutaline was discontinued. In Elliott's report, the overall incidence of severe adverse events in women receiving subcutaneous terbutaline was low and the therapy was generally well tolerated. Patients with co-morbidity (i.e. infection, pre-eclampsia, cardiac conditions) and/or concomitant tocolysis with IV magnesium sulfate should be closely assessed for the development of serious events.

Lam and co-workers[42] also compared the clinical and cost-effectiveness of utilizing continuous subcutaneous terbutaline versus oral tocolytics following recurrent preterm labor. In all, 558 women with

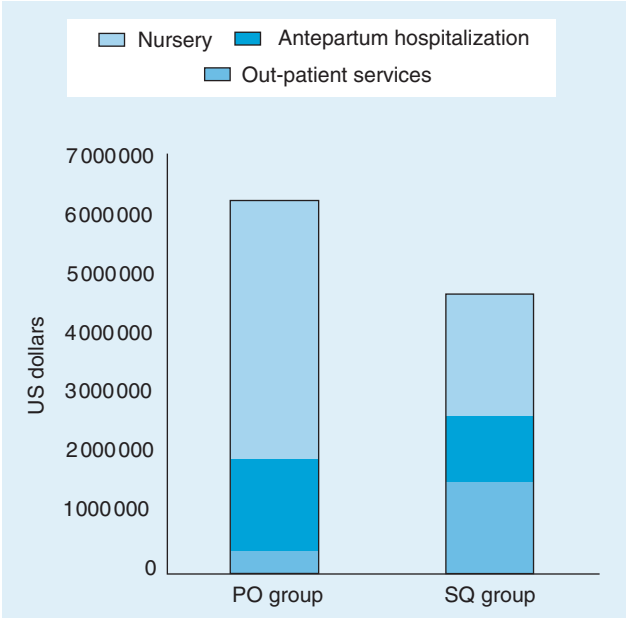


**Figure 72.7** Costs of oral terbutaline (PO group) versus subcutaneous terbutaline (SQ group). Overall costs for those in the SQ group were $5286 less per pregnancy compared to the PO group

singleton pregnancies were studied (279 per group). The oral treatment group had less gestational gain following RPTL than did the subcutaneous treatment group (28.4 ± 19.8 days vs. 33.9 ± 19.0 days, $p < 0.001$). The subcutaneous terbutaline group had fewer per-patient charges for antepartum hospitalization ($3986 ± 6895 vs. $5495 ± 7131, $p = 0.009$) and nursery ($7143 ± 20 048 vs. $15 050 ± 32 648, $p < 0.001$). Out-patient charges were less for the oral treatment group ($1390 ± 1152 vs. $5520 ± 3292, $p < 0.001$). Overall costs for those in the subcutaneous treatment group were $5286 less per pregnancy compared with the oral treatment group (Figure 72.7). In this population, continuous subcutaneous terbutaline infusion was both a clinically beneficial and cost-effective treatment following recurrent preterm labor.

## AMBULATORY TOCOLYSIS

The early diagnosis of preterm labor and immediate intervention is the essential component in halting the preterm labor process. Initial interventions for preterm labor include bed-rest, left lateral position, assessment of signs and symptoms, electronic monitoring of uterine activity, obtaining a urine sample for analysis, culture and sensitivity, cervical culture, evaluation of hydration, and cervical examination if not contraindicated. Several scenarios may occur when patients enter labor and delivery. First, the patient's complaints of uterine contractions or other symptoms may not be substantiated by regular uterine activity as documented by electronic monitoring. If the cervical examination indicates no change over time, the patient may return home, but be encouraged to continue to observe for symptoms and to notify her health-care provider if they recur. Second, regular uterine contractions may be documented, despite that no cervical change is found after a period of monitoring. Sedation and hydration are indicated to decrease uterine activity, and monitoring may continue over the next 24 h. This patient may be discharged once uterine activity returns to normal limits. Finally, if regular uterine activity and progressive cervical change are documented and cannot be controlled with bed-rest and hydration, then tocolytic therapy may be initiated.

As currently practiced, diagnosed preterm labor is promptly treated with parenteral tocolytics. The utility of administering a labor-inhibiting agent after successful suppression of an acute episode is controversial. The limited published data suggest that oral magnesium salts, calcium channel blockers and prostaglandin-inhibiting agents are not effective in preventing preterm birth or prolonging pregnancy[43]. There is evidence, albeit weak because of sample size issues, that maintenance therapy with β-adrenergic receptor agonists can reduce the number of preterm labor recurrences or the time to a recurrence[44]. Despite this controversy, the majority of clinicians in the United States continue to transition preterm labor patients who are stable to an oral tocolytic agent for long-term maintenance until either term gestation is reached or recurrent preterm labor occurs. In this scenario, the goal of ambulatory tocolysis becomes the detection and prevention of recurrent preterm labor.

Three principal indications dominate the use of tocolysis in the treatment of preterm labor in multiple pregnancies:

(1) Prophylaxis: that is, therapy based on the presence of a risk factor or uterine activity alone (in the absence of documented cervical change), in an effort to prevent preterm labor;

(2) Therapy: that is, administration of parenteral agents for prompt control of the acute episode of preterm labor for durations varying between 24 and 72 h;

(3) Maintenance: that is, the use of oral or subcutaneous medications for long-term tocolysis after cessation of preterm labor to prevent the recurrence of uterine activity.

Of the three principal indications cited above, the use of β-sympathomimetic drugs for prophylaxis in

**Table 72.1** Indications and contraindications for tocolysis

| |
|---|
| *Indications* |
| Gestational age between 18 and 36 weeks |
| Fetal weight less than 2500 g |
| Documented fetal lung immaturity |
| Regular uterine contractions |
| Labor progressing with documented cervical change |
| Positive fetal fibronectin |
| *Contraindications* |
| Active vaginal bleeding |
| Eclampsia or severe pre-eclampsia |
| Fetal demise or conditions incompatible with life |
| Intrauterine infection |
| Any obstetric or medical condition that is a contraindication to the prolongation of pregnancy |
| Conditions limiting the chance of success, e.g. cervical dilatation greater than 4 cm, rupture of membranes |

twin gestations has received the most rigorous scientific evaluation[8]. Double-blinded randomized studies using placebo controls have evaluated oral feneterol[45], terbutaline[46] and ritodrine[47,48]. All trials failed to demonstrate a significant increase in the length of gestation or increased birth weight in the treated patients. The initiation of tocolytic therapy was predicated upon the assessment of its potential benefits versus the possibility of adverse maternal or fetal complications. The general criteria which support or refute this basic decision are listed in Table 72.1.

## β-ADRENERGIC RECEPTOR STIMULATORS (β-MIMETICS)

### Physiology

β-Mimetic agents stimulate the β receptors of the sympathetic nervous system. Interactions with the receptor sites cause an increase in intracellular production of cyclic adenosine monophosphate (cAMP). This phenomenon results in the reduction of intracellular calcium concentration in the smooth muscle. The lower level of calcium inhibits activation of the contractile proteins actin and myosin which in turn results in relaxation of the myometrium. Two types of β receptors exist: $\beta_1$ and $\beta_2$ (Table 72.2). Because terbutaline possesses $\beta_2$-specific properties, it is the drug of choice when uterine relaxation is desired. Table 72.3 lists the major adverse effects from $\beta_1$ stimulation. Ritodrine (Yutopar®; Astra Pharmaceuticals) was approved for use in preterm labor in 1980. During the ensuing 22 years, no other drug was approved for use as a tocolytic by the Food and Drug Administration (FDA). Subsequent to a

**Table 72.2** Receptor stimulation by β-mimetic agents

| |
|---|
| $\beta_1$ |
| Heart rate increased |
| Heart force increased |
| Lypolysis increased |
| Intestinal motility decreased |
| $\beta_2$ |
| Uterine relaxation |
| Arteriole relaxation |
| Bronchiole relaxation |
| Muscle and liver stimulation: glycogenolysis |
| Pancreas stimulation: hyperinsulinism |
| Cell stimulation: hypokalemia |

**Table 72.3** Side-effects of β-mimetic agents

| |
|---|
| *Maternal* |
| Minor |
| nausea and vomiting |
| tremors |
| anxiety |
| flushing |
| headache |
| palpitations |
| heartburn |
| constipation |
| Major |
| angina |
| dyspnea |
| pulmonary edema |
| myocardial ischemia |
| cardiac arrythmias |
| myocardial infarction |
| ileus |
| hyperglycemia |
| hyperinsulinism |
| ketosis |
| hypokalemia |
| *Fetal* |
| Tachycardia |
| *Neonatal* |
| Hypoglycemia |
| Hyperinsulinism |
| Hypocalcemia |
| Ketoacidosis |
| Ileus |

meeting of the FDA Fertility and Maternal Drug Advisory Committee in October 1992, oral ritodrine for maintenance therapy was removed from the United States market after presentation of the Canadian ritodrine trial[49]. The manufacturer has since also removed parenteral ritodrine from the United States market.

### Precautions

Prior to initiation of β-mimetic therapy for acute-onset preterm labor, baseline evaluation should include vital signs, electronic monitoring of the fetal heart rate and uterine activity pattern, laboratory assessment (total blood count, blood glucose, electrolytes, urinalysis with culture and sensitivity and cervical culture), electrocardiography (ECG) to identify any previously unrecognized cardiac irregularity and, finally, a thorough pulmonary auscultation.

### Therapeutic plan

Initial therapy may consist only of a fluid bolus (500 ml of isotonic crystalloid over 30 min) administered via an indwelling line (18 gauge). If hydration is unsuccessful, therapy with subcutaneous terbutaline can be started. The use of intravenous terbutaline is not advised because of unacceptable side-effects. Intravenous ritodrine is no longer available. Terbutaline 0.25 mg may be given subcutaneously every 2–4 h. The oral maintenance dose is 2.5–5 mg every 2–4 h. Oral therapy is generally initiated after 6–12 h of subcutaneous therapy.

**Nursing interventions**

Nursing care should aim toward achieving the desired effect as well as preventing or avoiding serious side-effects:

- Reinforce the physician's prior discussion about potential adverse reactions.
- Monitor vital signs every 15 min during initial intravenous titration and for 1 h after the optimal dose is reached; this activity may be reduced to every hour after stabilization is achieved.
- Use a cardiac monitor during the initial period of treatment. The maternal heart rate should not exceed 130 beats/min and any irregularities should be noted.
- Maintain the systolic blood pressure above 90 torr.
- Repeat the ECG 24 h after initiation of therapy.
- Monitor fetal heart rate and uterine activity closely. The fetal heart rate should not exceed 180 beats/min.
- Repeat pulmonary auscultation frequently. Pulmonary edema is a serious side-effect.

### Comment

Patients at highest risk for pulmonary edema include women with multiple gestations, those with fluid overload or those with underlying infection. Initial symptoms may include shortness of breath, coughing or wheezing. Maximum fluid administration should not exceed 3000 ml per 24 h. Monitoring of intake and output must be strictly maintained. Oral fluid intake should also be monitored, and a positive fluid balance should be avoided. Patients should be weighed daily. The monitoring of metabolic status during therapy includes repeated evaluations of glucose levels, total blood count and electrolyte status.

After successful treatment, patients with preterm labor can be discharged home on oral β-sympathomimetic therapy. The potential advantages of oral therapy at home include reduced risks, reduced costs, decreased stress and ease of administration.

Prevention of recurrent preterm labor is the goal of long-term tocolysis. During episodes of recurrent preterm labor, patients are at risk for premature rupture of the membranes, further cervical change and preterm delivery. Among the many potential causes of tocolytic failure are patient noncompliance, drug side-effects, premature rupture of the membranes (PROM) and the emergence of drug tolerance. In addition, oral medications are poorly absorbed during pregnancy.

Perhaps the major cause of recurrent preterm labor is the desensitization of myometrial $\beta_2$-adrenergic receptor sites by prolonged and continuous exposure to high-dose β-mimetic agents such as terbutaline and ritodrine. This down-regulation phenomenon may explain the failure of β-mimetic tocolytics for the prophylactic treatment of preterm labor[45,50–55].

If the diagnosis of recurrent preterm labor is made prior to advanced cervical dilatation (> 2 cm), tocolysis will be sucessful in 90% of cases if a sequential approach is taken[56]. Patients in preterm labor with tocolytic breakthrough from terbutaline or ritodrine should be treated with magnesium sulfate ($MgSO_4$). Because $MgSO_4$ acts differently from the β-mimetic agents, a β-mimetic-free period allows the myometrial receptor sites to recover their sensitivity[53]. Patients who are treated with a β-mimetic agent after a β-mimetic failure have a less than 25% chance of success[56]. The minimum period for this 'drug holiday' is 24–48 h; once stable, the patient can be considered a candidate for ambulatory tocolysis again[19].

## MAGNESIUM SULFATE

Alternative tocolytic agents such as magnesium sulfate ($MgSO_4$) have been proposed because of the high frequency of maternal side-effects and

tachyphylaxis associated with β-mimetic agents. With the adoption of a sequential approach in the use of tocolytic agents, the use of intravenous magnesium sulfate became increasingly popular. Subsequent to the withdrawal of ritodrine from the market in the United States, magnesium sulfate became the standard intravenous tocolytic agent for the treatment of acute preterm labor.

## Physiology

Magnesium sulfate is a major cation in the intracellular fluid. Elevated levels diminish the release of acetylcholine, thereby decreasing sensitivity at the motor end-plates. At the cellular level, magnesium competes with calcium leading to impairment of light-chain phosphorylation of myosin and decreased contractility of uterine smooth muscle. The inhibitory effect on skeletal muscle results in hyporeflexia and hypotonia primarily due to the inhibition of acetylcholine release at the neuromuscular junction. Magnesium acts directly on the central nervous system with resultant depressant effects.

## Precautions

The normal plasma concentration of magnesium is 1.5–2.25 mg/dl. Therapeutic levels effecting uterine relaxation are 4–8 mg/dl. After therapeutic levels have been delivered and before toxicity is reached, the patient may experience flushing, feelings of warmth, headaches, lethargy, drowsiness, blurred vision, decreased reflexes, decreased gastrointestinal motility, nausea and vomiting. Toxicity results in loss of patellar reflexes at 10 mg/dl, loss of respiration at 12–15 mg/dl and cardiac arrest at 15 mg/dl. Clinical studies demonstrate that $MgSO_4$ is as equally efficacious as IV terbutaline and IV ritodrine with fewer side-effects[56–60].

Magnesium sulfate passes the placental barrier and causes central nervous system depression in the fetus. This may manifest as changes in beat-to-beat variability. Neonatal depression is reflected by a lower Apgar score of 1–2 points due to loss of tone, decreased respirations and decreased reflex irritability. High magnesium levels and low calcium levels may be observed. Gastrointestinal motility may be decreased. Supportive care for the neonate may include intubation, intravenous fluids, intravenous calcium and exchange transfusion. These effects are transient and usually resolve within 3–4 days.

## Therapeutic plans

Baseline physical parameters should be assessed prior to the initiation of $MgSO_4$ treatment, as is the case with β-mimetic therapy. Magnesium is delivered intravenously and is mixed according to hospital protocol. An initial bolus of 4–6 g is given slowly over 20 min via an additive set, then followed by a maintenance dose of 1–3 g/h via an infusion pump. It is important to note that in twin pregnancies, there are greater volumes of distribution and renal clearance, requiring higher infusion doses. Oral maintenance on a β-mimetic agent can be initiated after stabilization on IV $MgSO_4$. Patients who did not previously tolerate intravenous β-mimetic therapy (i.e. diabetics, multiple gestations) and instead received $MgSO_4$ should be monitored carefully during transition to the oral agent. In a diabetic pregnancy, oral nifedipine may be better tolerated owing to terbutaline's greater hyperglycemic effects.

**Nursing interventions**

The nursing implications are similar to those of β-mimetic therapy with additional attention placed on neurologic assessment:

- Inform the patient of the expected side-effects prior to the initiation of therapy.
- Monitor vital signs every 5 min during the loading dose and every 15–30 min during the maintenance dose until stable, then hourly. Observe respiratory rate and notify physician if respirations are depressed or below 15/min.
- Evaluate the fetal heart rate. $MgSO_4$ can decrease the beat-to-beat variability.
- Evaluate deep tendon reflexes hourly.
- Check the IV site frequently. Magnesium is extremely irritating to the vein. If infiltration occurs, the needle site should be changed immediately. The preferred site is a large vein in the forearm, rather than the hand.
- Monitor intake and output. Magnesium is cleared almost entirely via the kidney. Fluid retention may result in magnesium toxicity, and pulmonary edema may occur. Notify the physician if the output is less than 30 ml/h. Daily weights will aid in evaluating fluid retention.
- Monitor bowel sounds and function. Gastrointestinal relaxation may develop into an ileus.
- Laboratory assessment includes frequent magnesium levels, total blood count with differential and electrolytes.
- Prepare emergency equipment and maintain a 10-ml syringe of calcium gluconate (10 ml of 10% solution) at the bedside to reverse magnesium toxicity.
- Provide additional emotional support owing to depressive effects of magnesium.

## Comment

Oral magnesium preparations have been used for long-term tocolysis. Magnesium gluconate can be

administered 1 g every 2–4 h or magnesium oxide 250–450 mg every 3 h. Some authors suggest that oral magnesium preparations may be as effective as oral terbutaline or ritodrine for the maintenance of tocolysis, with fewer side-effects and lower cost[61,62]. Therapeutic serum levels of magnesium have not been achieved, however, via oral administration[63].

## PROSTAGLANDIN SYNTHETASE INHIBITORS (INDOMETHACIN)

### Physiology

In pregnancy, prostaglandins $PGE_2$ and $PGF_{2a}$ stimulate uterine contractility by increasing free intracellular calcium levels in the myometrium. Prostaglandins stimulate the formation of gap junctions between myometrial cells, facilitating the synchronization of uterine contractions. They may also play a role in cervical maturation before the onset of labor. Prostaglandins are produced by synthesis and metabolism of the compounds of the arachidonic cascade. Prostaglandin synthetase inhibitors (nonsteroidal anti-inflammatory compounds) act by inhibiting the enzyme cyclo-oxygenase from converting arachidonic acid into $PGG_2$ and $PGH_2$, and then ultimately to $PGE_2$ and $PGF_{2a}$. Prostaglandin synthetase inhibitors also directly inhibit calcium influx into the cells and the storage of calcium within the sacroplasmic reticulum. The decrease in free intracellular calcium inhibits myosin light-chain kinase, thereby causing uterine relaxation[64].

### Precautions

Side-effects of prostaglandin synthetase inhibitors include gastric irritation resulting in nausea, vomiting, epigastric pain, rectal irritation and peptic ulceration. Inhibition of platelet aggregation may result in maternal bleeding. Water and sodium retention may occur. An increased pressor response to angiotension II may affect maternal blood pressure and cause headaches and dizziness. Transient elevations in the liver enzymes serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), bilirubin and alkaline phosphatase may occur during treatment.

Fetal effects are of primary significance, with possible increased pulmonary vasculature, ductal constriction and case reports of premature closure of the ductus arteriosis *in utero*[65]. Ductal constriction appears to depend upon both gestational age and duration of exposure[66]. Therefore, indomethacin is not recommended after 32 weeks' gestation or for treatment for > 72 h. Water excretion from the fetal kidney may be inhibited and result in oligohydramnios. Neonatal pulmonary hypertension may result from therapy and is usually associated with other causes, such as hypoxia, acidosis and hypovolemia.

No significant difference in the incidence of neonatal complications has been found when indomethacin is administered for tocolysis over a short period (1–2 days) and to infants less than 32 weeks' gestational age[65–68]. However, a relationship exists between total daily maternal indomethacin intake and fetal renal inhibition[69]. Oligohydramnios, transient neonatal anuria and renal insufficiency have been reported after maternal indomethacin administrations of 150–300 mg/day[70]. No significant adverse fetal or neonatal effects of maternal indomethacin exposure occurred when the daily maternal dosage was 125 mg or less per day[69]. Contraindications of therapy include hypertensive disease, renal disease, oligohydramnios, twin–twin transfusion syndrome, bleeding disorders and liver disease.

### Therapeutic plan

Indomethacin may be administered as rectal suppositories or in oral tablets. An initial dose of 50–100 mg is recommended, followed by 25 mg every 4–6 h for a maximum of 48 h. The medication should be titrated until uterine activity is reduced. The lowest effective dose (not greater than 125 mg/day) should be used for no longer than 48 h. The drug should not be administered at a gestational age greater than 32 weeks. Serial ultrasonographic evaluations of amniotic fluid volume are recommended. Indomethacin is of limited value for maintenance or out-patient tocolytic treatment because of these restrictions.

Indomethacin may be administered in conjunction with β-mimetic therapy. Alternating these drugs may aid in decreasing the risk of β-mimetic desensitization and the risk of fetal vascular effects during β-mimetic stimulation.

**Nursing interventions**

The nursing activities specific to indomethacin therapy include:

- Inform the patient of potential effects prior to the onset of treatment.
- Continuously monitor the fetal heart rate for signs of compromise. Observe for cardiac irregularities. Variable decelerations may be an indication of oligohydramnios.
- Assess for maternal side-effects, i.e. headaches, dizziness, intestinal disorders, bleeding.
- Monitor intake and output. Evaluate fundal height measurement weekly and observe for signs of decreasing amniotic fluid. Evaluate lung sounds and observe for signs of pulmonary edema.
- Monitor maternal blood pressure.
- Patients receiving indomethacin may also receive β-mimetic therapy.

## CALCIUM CHANNEL BLOCKERS (NIFEDIPINE)

### Physiology

Calcium blockers inhibit the influx of extracellular calcium across the cell membrane. As a result, calcium is not available as a component with myosin light-chain kinase. Nifedipine selectively inhibits uterine tension, making it the drug of choice among the calcium channel blockers. Nifedipine may also interact with calcium-binding proteins, thereby inhibiting uterine contractions[71,72].

### Precautions

Side-effects of calcium channel blockers include vasodilatation and direct cardiovascular effects, specifically slowed atrioventricular node conduction. Nifedipine exhibits little direct cardiac effect as compared with other, similar agents (e.g. verapamil). Its major side-effects are reflex tachycardia and hypotension secondary to the vasodilatory effect.

### Therapeutic plan

The recommended dose is nifedipine 30 mg orally, followed by 20 mg three times daily for 3 days, then twice a day during the remainder of treatment. An effect is noted 20 min after ingestion of the drug, with facial flushing, an increase in maternal heart rate of 10–25 beats/min and a decrease in uterine activity. The plasma half-life is 2–3 h with a duration of 6 h. As is the case with $MgSO_4$ and indomethacin, the mode of action of nifedipine is independent of interaction with the β-receptor, allowing for its use in sequential tocolysis.

**Nursing interventions**

Nursing considerations specific to calcium channel blockers include:

- Inform patients of potential side-effects prior to the onset of treatment.
- Nifedipine may be contraindicated in patients with a history of migraine headaches.
- Monitor maternal vital signs, specifically pulse rate and blood pressure.
- Observe maternal side-effects including headaches and flushing.
- Monitor fetal heart rate to assess fetal well-being.
- Position the patient in the lateral recumbent position to enhance uterine blood flow.

## MANAGEMENT OF PRETERM LABOR IN THE HOME

The success of hospital therapy for preterm labor provides a subset of patients who require long-term maintenance therapy. The need for home care is supported by the high cost of hospitalization and the emotional stress of being away from home and family[73]. Patients who achieve the most benefit from home care include those whose uterine contraction pattern is most affected by increased activity and in whom cervical change occurs with a minimal number of uterine contractions or increased pressure.

Preparation for discharge and continued home therapy should begin at the time of admission for treatment of preterm labor. Home therapy may not be feasible if the patient is in advanced preterm labor with a high degree of cervical dilatation and/or has undergone spontaneous rupture of the membranes and delivery is deemed inevitable. For home care to be successful, the patient must have a clear understanding of the potential adverse consequences of preterm labor, the nature of the management plan, including proposed tocolytic therapy, and the degree of activity restriction that she is expected to maintain. A teaching plan must be developed and followed; Table 72.4 gives an example of such a plan.

Prior to discharge, the home-care nurse should obtain a thorough medical and obstetric history and be knowlegeable of the treatment plan to be initially followed in the home. In addition, the home environment should be evaluated to determine whether adequate resources are available to make bed-rest or activity restriction feasible. *The entire family should be included in the plan of care. Without their cooperation and support, the chances of success are diminished*. Home visits should take place on a weekly or more frequent

**Table 72.4** Discharge teaching plan for patients with preterm labor for whom home-care is anticipated

| |
|---|
| Ongoing patient teaching |
| Signs and symptoms of preterm labor |
| Self-monitoring of preterm labor |
| Tocolytic therapy |
| dose schedule |
| potential side-effects |
| adjustment of therapy within specific guidelines, according to uterine activity and vital signs |
| Activity restriction |
| definition of bed-rest |
| activities to pass time while on bed-rest |
| physical discomforts associated with bed-rest |
| plan for finding help with child care, housekeeping, meal preparation, etc. |
| Points for emphasis prior to discharge |
| when to call the physician regarding problems |
| how to take the tocolytic agents at home |
| importance of maintaining bed-rest |
| how to contact members of the interdisciplinary team, e.g. social worker, nutritionist, nurse and physician |

**Nursing interventions**

All nursing care provided during the home visit should be performed according to specific protocols and physician orders:

- Vital signs: notify the physician if the pulse is consistently over 120 beats/min, the diastolic blood pressure is greater than 15 torr above baseline or systolic pressure is 30 torr above baseline.
- Lung assessment: notify physician at the slightest sign of congestion, regardless of whether it is in association with dyspnea or chest pain.
- Weight: refer for nutrition counseling if weight gain is inadequate. If weight gain is rapid, assess lung sounds and palpate for the presence of edema.
- Fetal heart tones/fetal movement: notify physician if fetal heart rate is less than 120 beats/min or greater than 160 beats/min and/or if decreased fetal movement is discerned.
- Fundal height: notify physician if fundal growth exceeds or falls behind expected growth.
- Urine dipstick for sugar, acetone or protein: if glucose is present, check serum glucose levels. A glucose loading test should be obtained in all patients at 28 weeks' gestation. Patients on oral β-mimetic therapy have a higher incidence of glucose intolerance and should have another glucose test after tocolytic therapy has been initiated. If acetone is present, the patient's nutritional status should be evaluated as well. If protein is present, the blood pressure should be evaluated.
- Deep tendon reflexes: if reflexes are greater than 2+, the patient should be examined for the presence of clonus, edema and elevated blood pressure.
- Uterine activity pattern: when the patient is resting in bed, the cervical status should be evaluated if more than four contractions per hour are present. The physician should be notified if the contraction pattern persists.
- Cervical status: the physician should be notified of any change in cervical status: dilatation, effacement, consistency, position or station of presenting part.
- Gastrointestinal/nutrition: the patient should be offered a bowel program of stool softeners, and a diet high in fiber and protein. Consultation with a trained dietician is beneficial.
- Bed-rest: activity reduction and therapeutic bed-rest are major components of the home management of preterm labor. The nurse must reinforce the importance of bed-rest, lying in a lateral position and possible elevation of the foot of the bed or the use of pillows under the hips to reduce pressure on the cervix. The guidelines regarding time allowed for activities such as showers and sitting up for meals should be clear, and depend on patient status and physician orders. The home environment should be comprehensively evaluated to determine if the patient is receiving adequate help with child care, meal preparations, housekeeping and shopping. If home help is required, the patient should be assisted in finding adequate service. If necessary, the patient should be referred to a hospital-based or independent social-service program. Rehospitalization may be required if the patient is not able to maintain adequate activity reduction and bed-rest at home.
- Oral tocolysis: the dosage of oral tocolytic agents and the uterine activity pattern should be assessed concomitantly to ascertain effectiveness of the maintenance dose. Adjustments should be made accordingly.
- Psychosocial: community services and parental support groups are often available to aid women on bed-rest and should be contacted. Insurance companies often cover costs for help in the home.

Properly planned and initiated, the home environment can provide an atmosphere conducive to meeting the specific needs of each patient. A major focus in home care is educating the patient and allowing her to participate in her care.

basis as dictated by the patient's status. The initial visit should be planned within 2 days after discharge to aid in the transition from hospital to home care.

## UTERINE-ACTIVITY MONITORING

All patients should be instructed in self-monitoring of uterine activity and observation of signs and symptoms of preterm labor as a part of their initial prenatal teaching. In addition, objective monitoring of uterine activity can provide two types of particularly useful information in assessing patient status at home: the identification of regular uterine contractions as soon as possible in order to make a prompt diagnosis of preterm labor and initiate effective tocolytic therapy[74], and the identification of recurrent preterm labor and the prompt adjustment of tocolytic treatment regimens[75]. Studies have shown that the home uterine-activity monitor is useful in titrating tocolysis at home and reducing unnecessary hospital admissions unless they are required to institute or reinstitute intravenous tocolysis[75,76].

In general, a home monitor is worn by the patient during two 1-h sessions per day and during periods of perceived increases in uterine activity. The monitor tracing is then transmitted via the telephone to a nursing service where the data is evaluated. Regardless of the level of uterine activity, the patient has daily contact with the nurse to discuss any of the other possible signs or symptoms of preterm labor or any problems or concerns. It remains unclear whether the device is more effective in the identification of preterm labor than the nursing contact. Interestingly, the two randomized clinical trials[32,33] that showed a lack of efficacy

for subcutaneous terbutaline therapy did not use home uterine-activity monitoring. Subsequently, the bolus therapy for terbutaline could not be tailored to the erratic patterns of contractions that occur during pregnancy[39]. Also, because uterine-contraction monitoring was not used, when preterm labor did recur the patient had no early warning of increased uterine activity.

## CONCLUSIONS

It is estimated that subcutaneous terbutaline administered through a programmable pump in an ambulatory setting has been used in tens of thousands of pregnancies with excellent safety profiles and good outcome statistics[40]. Of the 22 reports in the world literature, 20 demonstrate significant prolongation of the pregnancy compared with oral or no maintenance therapy[40]. Pregnancy prolongation averaged 6.4 ± 2.8 weeks, double that of the control group, which averaged only 3.2 ± 6.6 weeks after treatment. These composite results (see Appendix on p. 621) support our original findings[28]. The majority of these studies were in patients who were at very high risk for preterm delivery, with nine having populations with recurrent preterm labor and five involving multifetal gestations. Women with twin pregnancies at significant risk for preterm delivery constitute a select group for whom this comprehensive model of management may be most appropriate. The ultimate goal of achieving term delivery with a reduction in the incidence of low-birth-weight infants will provide the greatest contribution to improving perinatal outcome in the future.

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**Appendix** Evidence-based medicine and continuous subcutaneous terbutaline infusion: review of efficacy literature

| *Study* | *Research design* | *Quality of evidence* | *n* | *Population* | *Comments* |
|---|---|---|---|---|---|
| Lam *et al*. The impact of portable tocodynamometry and subcutaneous terbutaline pump therapy on preterm birth in a private obstetrical practice. Presented at the *ACOG Districts VIII and IX Meeting*, Las Vegas, Nevada, September 2, 1987 | observational cohort | II-2 | 1556 | RPTL | inclusion criterion: tocolytic breakthrough in high-risk population subset, results: PTD rate was reduced from 5.18 to 2.69% ($p<0.05$) |
| Lam *et al*. Use of the subcutaneous terbutaline pump for long-term tocolysis. *Obstet Gynecol* 1988;72:810–13 | descriptive case series | III | 9 | RPTL | pregnancy prolongation 9.2 weeks, mean GAD 39 weeks |
| Lam *et al*. Comparison of portable subcutaneous terbutaline pump and oral terbutaline treatment for long-term tocolysis: a randomized clinical trial. Presented at the *Eighth Annual Meeting, Society of Perinatal Obstetricians*, Las Vegas, Nevada, February 1988:abstr 400 | randomized controlled trial (RCT) | I | 68 | CPTL | weeks of pregnancy prolongation and PPI were 8.6 (0.93) and 2.4 (0.34) in the pump versus oral groups, respectively |
| Gianopoulos *et al*. SQ terbutaline pump for premature labor. *Am J Obstet Gynecol* 1991;164:426 | descriptive case series | III | 31 | RPTL | pregnancy prolongation 5.4±4.5 weeks and 34.2±3.8 weeks' gestational age at delivery |
| Jones *et al*. Continuous subcutaneous terbutaline infusion for the prevention of recurrent preterm labor. *Am J Obstet Gynecol* 1991;164:426 | descriptive case series | III | 50 | RPTL | pregnancy prolongation 6.3 weeks |
| Fischer *et al*. Continuous subcutaneous infusion of terbutaline for suppression of preterm labor. *Clin Pharm* 1991;10:292–6 | descriptive case series | III | 19 | CPTL | safe and effective in the treatment of preterm labor, average GAD 35.6 weeks |
| McGettigan *et al*. Prenatal β-mimetic exposure of the newborn: maternal oral versus continuous infusion therapy. *Pediatr Res* 1991;(Suppl):62A | observational cohort | II-2 | 28 | RPTL | average GAD 35.7 weeks, terbutaline pump prolongs tocolysis, reduces terbutaline dose significantly ($p<0.001$), reduces maternal side-effects and may reduce the newborn's total exposure to β-mimetic dosage |
| Wolfsen RN, Winn SK. Prolongation of twin pregnancy with magnesium sulphate/subcutaneous terbutaline pump therapy in the face of advanced cervical dilatation and effacement. *Am J Obstet Gynecol* 1992;166:366 | descriptive case series | III | 9 | twins with advanced cervical dilatation | 75% achieved >37 weeks or mature lung indices on amniocentesis |
| Allbert *et al*. Subcutaneous tocolytic infusion therapy for patients at very high risk for preterm birth. *J Perinatol* 1992;12:28–31 | descriptive case series | III | 992 | C/RPTL<br>206 twins<br>786 singletons | extended the gestation a mean of 38±23 days and average GAD 36.3±2.6 weeks |

| Study | Research design | Quality of evidence | n | Population | Comments |
|---|---|---|---|---|---|
| Lindenbaum *et al*. Maternal glucose intolerance and the subcutaneous terbutaline pump. *Am J Obstet Gynecol* 1992;166:925–8 | observational cohort | II-2 | 725 | CPTL | the incidence of gestational diabetes is not increased in patients receiving terbutaline via the subcutaneous pump |
| Moise *et al*. Continuous subcutaneous terbutaline pump therapy for premature labor, safety and efficacy. *South Med J* 1992;85:255–9 | descriptive case series | III | 13 | RPTL<br>10 singletons<br>2 triplets<br>1 twin | average GAD 35.3 weeks, pregnancy prolongation 5.0 weeks |
| Weinbaum *et al*. The effect of subcutaneous infusion on uterine activity in patients at risk for preterm delivery. *Am J Obstet Gynecol* 1993;166:362 | descriptive case series | III | 202 | CPTL | contractions were arrested and the mean gestational age at delivery was 36.2 weeks, only 9.6% of the patients were readmitted to hospital |
| Elliott *et al*. Quadruplet pregnancy: contemporary management and outcome. *Obstet Gynecol* 1992; 80:421–4 | observational case–control | II-2 | 67 | CPTL<br>67 quadruplets | mean GAD 32.5 weeks, mean infant birth weight 1534±429 g |
| Adkins *et al*. Prevention of preterm birth: early detection and aggressive treatment with terbutaline. *South Med J* 1993;86:157–64 | descriptive case series | III | 51 | CPTL | average birth weight 3000 g, average GAD 37 weeks, pregnancy prolongation 6.6 weeks |
| Regenstein *et al*. Terbutaline tocolysis and glucose intolerance. *Obstet Gynecol* 1993;81:739–41 | observational case–control | II-2 | 151 | CPTL | no difference in the incidence of gestational diabetes or glucose intolerance between subcutaneous and oral groups |
| Allbert *et al*. Tocolysis for recurrent preterm labor using a continuous subcutaneous infusion pump. *J Reprod Med* 1994;39:614–18 | observational cohort | II-2 | 64 | RPTL | pregnancy prolongation index was 0.86 and 0.72 for the pump and oral groups, respectively |
| Perry *et al*. Incidence of adverse cardiopulmonary effects with low-dose continuous terbutaline infusion. *Am J Obstet Gynecol* 1995;173:1273–7 | descriptive case series | III | 8709 | CPTL | continuous terbutaline infusion is associated with much fewer adverse effects than previously reported literature on intravenous terbutaline or ritodrine therapy would suggest |
| Elliott *et al*. Terbutaline pump tocolysis in high order multiple gestation. *J Reprod Med* 1997;42:687–94 | retrospective cohort | II-2 | 21 | CPTL<br>15 triplets<br>6 quadruplets | estimated $18 150 savings per pregnancy, only 2 of the 15 triplets (13%) and 1 of the 6 quadruplets (17%) delivered because of tocolytic failure, mean GAD 33.0 weeks for both groups |

| Study | Research design | Quality of evidence | n | Population | Comments |
|---|---|---|---|---|---|
| Wenstrom *et al*. A placebo-controlled randomized trial of the terbutaline pump for prevention of preterm delivery. *Am J Perinatol* 1997;14:87–91 | randomized control trial (RCT) | I | 42 | CPTL | three-arm study: 15 terbutaline pump, 15 oral terbutaline, 12 saline pump, significant methodologic flaw in that patients crossed over between groups while in study (patients on oral terbutaline or saline pump were switched to terbutaline pump if therapy failed), no electronic contraction monitoring or daily nursing contact, tocolytic therapy was not individualized for each patient, study underpowered in that it did not contain enough patients to show a difference between groups, no difference in outcomes between groups |
| Guinn *et al*. Terbutaline pump maintenance therapy for prevention of preterm delivery: a double-blind trial. *Am J Obstet Gynecol* 1998;179:874–8 | randomized control trial (RCT) | I | 52 | CPTL | overall drop-out rate 38%, 13 patients in the terbutaline group completed this study and 19 patients in the placebo group, advanced median cervical dilatation of 3 cm, effacement of 50% at start, tocolytic therapy was not individualized for each patient, no electronic contraction monitoring or daily nursing contact, study was underpowered and therefore showed no difference in outcomes between groups |
| Lam *et al*. Pregnancy prolongation and route of tocolytic administration in patients with singleton gestation. *Am J Obstet Gynecol* 1998;178:180 | observational cohort | II-2 | 256 | RPTL | patients served as their own control, subcutaneous terbutaline therapy prolonged pregnancy greater than oral terbutaline, 4.4±2.6 weeks compared to 2.7±2.2 weeks |
| Berkus *et al*. Effect of terbutaline pump on maternal glucose metabolism. *Am J Obstet Gynecol* 1999;180:S41 | descriptive case series | III | 7 | CPTL | low-dose, continuous SQ terbutaline infusion had no effect on insulin sensitivity in non-diabetic patients, in contrast to oral terbutaline |
| Hammersley *et al*. The use of continuous subcutaneous terbutaline in a private maternal–fetal medicine practice. *Obstet Gynecol* 1999;93:67–8 | descriptive case series | III | 70 | RPTL<br>52 singletons<br>11 twins<br>7 triplets | inclusion criterion: preterm labor or cervical shortening <3 cm and/or 50% funneling, mean cervical length 2.6±0.9 cm at initiation of therapy, 76% of desired pregnancy prolongation was achieved |

| Study | Research design | Quality of evidence | n | Population | Comments |
|---|---|---|---|---|---|
| Lam *et al*. A comparison of gestational days gained with oral terbutaline versus continuous subcutaneous terbutaline in women with twin gestations. *J Perinatol* 2000;20:408–13 | observational cohort | II-2 | 386 | RPTL<br>386 twins | 34.0±19.8 versus 19.3±15.3 days *in utero* gained with subcutaneous therapy compared to oral therapy |
| Ambrose *et al*. Clinical and economic outcomes of continuous subcutaneous tocolysis. *Obstet Gynecol* 2001;97:47 | observational case–control | II-2 | 180 | CPTL<br>76 twins | out-patient-administered subcutaneous terbutaline shown to be a cost-effective and viable alternative versus in-patient-administered subcutaneous terbutaline |
| Elliott *et al*. Expectant management of the quadruplet pregnancy: inpatient or outpatient? *Am J Obstet Gynecol* 2001;185:110 | observational case–control | II-2 | 144 | 144 quadruplets | out-patient therapy cost $30 270 less per patient and is associated with a statistically significant better chance of delivery ≥32 weeks than in-patient |
| Elliott *et al*. Pregnancy prolongation in triplet pregnancies: oral versus continuous subcutaneous terbutaline. *J Reprod Med* 2001;46:975–82 | observational cohort | II-2 | 104 | RPTL<br>104 triplets | mean pregnancy prolongation on pump 5.4±3.4 weeks versus 2.8±2.2 weeks for oral treatment |
| Fleming *et al*. The clinical and cost effectiveness of nifedipine versus terbutaline. *Am J Obstet Gynecol* 2001;185:148 | observational case–control | II-2 | 284 | RPTL | 37.3% of nifedipine patients delivered ≤35 weeks compared to 19.7% of subcutaneous terbutaline patients, subcutaneous terbutaline patients cost $6945 less per pregnancy |
| Lam *et al*. Clinical and cost effectiveness of continuous subcutaneous terbutaline versus oral tocolytics for treatment of recurrent preterm labor in twin gestations. *J Perinatol* 2001;21:444–50 | observational case–control | II-2 | 706 | RPTL<br>706 twins | total maternal and nursery charges were $17 109 less for patients treated with subcutaneous terbutaline compared to oral treatment |
| Elliott *et al*. Adverse events related to continuous subcutaneous terbutaline therapy. *Obstet Gynecol* 2002;99:63–4 | descriptive case series | III | 9359 | CPTL<br>7028 singletons<br>1946 twins<br>385 triplets | extremely low incidence of serious adverse events, GAD was 36.6 weeks in the singletons, 34.9 weeks in the twins and 32.8 weeks in the triplets, authors conclude therapy a viable and safe option for out-patient management |
| Hamersley *et al*. Delayed-interval delivery in twin pregnancies. *J Reprod Med* 2002;47:125–30 | descriptive case series | III | 6 | twins with delayed-interval delivery | the median pregnancy prolongation achieved following delivery of the first-born nonviable twin was 93 days |
| Viscarello *et al*. The effect of proactive dose acceleration in triplets receiving continuous subcutaneous tocolysis. *Obstet Gynecol* 2002;99:12 | observational case–control | II-2 | 40 | CPTL<br>40 triplets | proactive dose acceleration protocol achieved significantly better outcomes than standard dosing |

| Study | Research design | Quality of evidence | n | Population | Comments |
|---|---|---|---|---|---|
| Viscarello *et al*. Outpatient management of higher order multiples with a comprehensive careplan improves outcome. *Obstet Gynecol* 2002;99:71 | observational case–control | II-2 | 59 | higher order multiples: 56 triplets 3 quadruplets | a comprehensive clinical pathway (CCP) including subcutaneous terbutaline proved significantly better outcomes (35.1 ± 1.6 versus 31.6 ± 3.1 weeks GAD) compared to concurrent local standard of care, of the 12 patients whose GAD was < 32 weeks, 1 received the CCP including subcutaneous terbutaline, compared to 11 who received the concurrent local standard of care |
| Jones *et al*. Pregnancy prolongation after discontinuation of subcutaneous tocolysis in singleton gestations. *Obstet Gynecol* 2003;101:76 | descriptive case series | III | 1691 | RPTL | over 57% of women experienced PTD within 1 week of DC of SQT, early discontinuation of SQT places a pregnancy at risk for PTD |
| Morrison *et al*. Benefits of continuous subcutaneous terbutaline infusion in the management of recurrent preterm labor: a case–control study. *Am J Obstet Gynecol* 2003;188:1460–7 | observational case–control | II-2 | 60 | RPTL | among patients with recurrent PTL, the use of SQT infusion significantly prolongs pregnancy while decreasing the likelihood of the rate of low-birth-weight (2500 g) infants, the need for admission to NICU and duration of being hospitalized, for every dollar spent on SQT, there was a saving of $4.67 on the charges of newborn stay in the hospital |
| Lam *et al*. Managing perinatal outcomes: the clinical and cost-effectiveness of pharmacologic treatment of recurrent preterm labor. *Managed Care* 2003;12(7) | observational case–control | II-2 | 558 | RPTL | 70.6% of subcutaneous therapy patients reached at least 36 weeks compared to 56.6% of oral therapy patients, subcutaneous therapy patients cost $5286 less |
| Roman *et al*. Clinical and demographic factors associated with spontaneous preterm delivery in twin pregnancies diagnosed with preterm labor at < 34 weeks. *Am J Obstet Gynecol* 2004;189(Suppl 6):S123 | matched cohort | II-2 | 260 | twins in CPTL | > 7 days prolongation of pregnancy in over 86% of cases |
| Gaziano *et al*. Inpatient versus outpatient surveillance for singleton pregnancies following inpatient treatment with magnesium sulfate for preterm labor. Presented at the *Society for Gynecologic Investigation Year 2004 Annual Meeting*, Houston, Texas, March 24–26 | matched cohort | II-2 | 1079 | CPTL | out-patients obtained statistically better antepartum days, pregnancy prolongation, GAD, delivery < 35 weeks and cost, total average cost out-patient were $17 375 versus $39 040 in-patient |
| Rebarber *et al*. Factors associated with spontaneous preterm delivery in singleton gestations. *Obstet Gynecol* 2004;103(4):in press | matched cohort | II-2 | 783 | CPTL | 86% of patients had their pregnancy prolonged > 7 days |

CPTL, current preterm labor (an initial episode of preterm labor stabilized and subcutaneous terbutaline infusion started); RPTL, recurrent preterm labor (subcutaneous terbutaline infusion started at second occurrence of PTL after stabilization); GAD, gestational age at delivery; PPI, pregnancy prolongation index; SQT, subcutaneous terbutaline; PTD, preterm delivery; DC, discontinuation; NICU, neonatal intensive-care unit

# Preterm Delivery: a Review of the Evidence-based Literature

*D. J. Owen and Z. Alfirevic*

**73**



## INTRODUCTION

The etiology of higher rates of premature labor in multiple pregnancy is unknown. Some argue, rather simplistically, that it is primarily due to overdistension of the uterus and this in itself is the major cause. However, this is an observation, which is unfounded in any credible scientific basis. Sociologic and epidemiologic factors are also thought to be implicated in the etiology of premature labor, but the vast majority of studies concern singleton pregnancies, and it is widely assumed that such factors also apply to multiple gestation. Numerous epidemiologic studies show that socioeconomic deprivation, smoking, low body mass index (BMI < 19 kg/m$^2$) before pregnancy and young maternal age are associated with preterm delivery. Each of these variables carries a relative risk of 1.5–2.0, and attempts to predict risk of premature labor based on such factors alone yield low sensitivity and specificity[1]. The single most effective predictor of preterm delivery is previous preterm delivery (relative risk 2.3), but this is unhelpful in primigravidae.

More recently, the etiology of preterm delivery has been described as heterogeneous. No identifiable cause is found in the majority of cases although a number of medical factors have been identified, including antepartum hemorrhage, intrauterine growth restriction, chorioamnionitis, congenital uterine anomaly, maternal heart disease, diabetes mellitus, polyhydramnios and pyelonephritis.

Anatomic cervical 'incompetence' is a rare cause of premature labor. Classically defined as 'the history of painless dilatation of the cervix resulting in second or third trimester delivery and the passage, without resistance, of a size nine (9 mm) Hegar cervical dilator', more recent definitions include 'recurrent second or early third trimester loss of pregnancy caused by the inability of the uterine cervix to retain a pregnancy until term'. There is no reliable test for the condition which is based on history alone. In terms of multiple gestation, the incompetence related to early dilatation from the downward pressure of the uterine contents is 'functional incompetence' at best.

For many years, it was proposed that infections of the genitourinary tract causes preterm labor. Infectious etiologies are particularly likely in prelabor rupture of the membranes. Micro-organisms such as group B hemolytic *Streptococcus*, *Neisseria gonorrhoea*, *Chlamydia trachomatis*, *Trichomonas vaginalis*, *Myoplasma hominis* and *Ureaplasma urealyticum* have been implicated without conclusive evidence. Recent interest has focused on bacterial vaginosis (a vaginal overgrowth of the normal flora, predominantly *Gardnerella vaginalis*) and treatment of women with asymptomatic bacterial vaginosis with antibiotics, but clearly this normally present organism does not explain all preterm labor in multiples.

## PSYCHOSOCIAL STRESS

Increasingly, psychosocial factors are being implicated in the etiology of many adverse outcomes in pregnancy such as intrauterine growth restriction, low birth weight, miscarriage, congenital malformations and preterm delivery[2–6].

The results of experimental animal research leave little doubt that exposure to stressful conditions has adverse effects on the offspring, including smaller litter size, lower birth weights, premature labor and an increased incidence of congenital malformations[7–10].

Assuming that stress reactions in primates are comparable to those in humans, it is plausible that stressful stimulation can negatively impact on fetal development and precede the onset of human parturition.

Recent work looks at corticotropin-releasing hormone (CRH), a component of the hormonal pathway that regulates the response to stress, as a putative regulator of human parturition. In twin pregnancy, increased fetal–placental mass results in higher levels of placental hormones (including CRH) in the maternal circulation compared with singleton gestation. The maternal plasma levels of CRH also increase with advancing gestational age in twin gestation, and a rapid rise in CRH production precedes labor[11]. The same mechanisms initiating labor possibly pertain in multiple pregnancy, but the additional placental mass could theoretically boost the placental amplification of the endocrine response to stress. If women with twin pregnancy are much more susceptible to the effects of psychosocial stress, it is imperative that such stressful situations and the nature of psychologic symptoms associated with preterm delivery are identified precisely, in order to plan a future intervention study which would aim either to reduce the risk of preterm delivery or to prolong significantly the gestational length in twin gestation. Little is known about the prevalence of anxiety and depression in this high-risk obstetric group, and as yet no studies exist on the effects of psychosocial stress on outcome in twin pregnancy.

## IATROGENIC CAUSES

Approximately 30% of preterm births are iatrogenic. Induction of labor or recourse to cesarean section are due to maternal and fetal indications such as fulminating pre-eclampsia and severe intrauterine growth restriction. Management dilemmas related to iatrogenic preterm delivery (e.g. delivery versus conservative management in pre-eclampsia, delivery versus watchful waiting in the presence of monochorionic twins or discordant growth or dizygotic twins, management of twin-to-twin transfusion syndrome) are outside the scope of this chapter (see Chapters 40, 53, 65 and 81)

## PREVENTION OF PRETERM LABOR

It is axiomatic that prevention is better than cure. Numerous strategies are used in asymptomatic women aiming to reduce the risk of preterm labor. A search of the most recent issue of *The Cochrane Library* revealed clinical trials of a number of strategies attempting to reduce premature labor including: aerobic exercise (no multiple pregnancies included); antibiotics for preterm rupture of the membranes (no studies specifically of multiple pregnancies but multiple pregnancies included in references 12–16); hospitalization and bed-rest for multiple pregnancy (six randomized controlled trials but small numbers); hydration for treatment of preterm labor (no multiple pregnancies included); magnesium sulfate therapy for preventing preterm labor (one study included twin gestation but only two women entered the study); and support during pregnancy (no data on multiple gestation) (see Table 73.1).

### Routine vaginal examination

In continental Europe it is common practice to examine the cervix digitally at each antenatal visit, but a multicenter trial involving more than 5000 women failed to demonstrate any benefits to such an arbitrary policy[17]. No information is currently available from *The Cochrane Library* and a search of Medline found only one randomized controlled trial on this topic.

### Ultrasound

The use of ultrasound should, theoretically, be more accurate in determining cervical shortening than digital examination, which does not assess the internal os. There is now clear evidence that ultrasound is the best available predictor of imminent preterm delivery in multiple pregnancy[18,19] (see Chapter 55). Cervical length of 20 mm or less is found in about 8% of the population. This group contains about 40% of women with twin pregnancies delivering spontaneously before 33 weeks. Such good predictive values of a shortened cervix have prompted clinicians to conclude that ultrasound diagnosis of shortened cervix should be followed by cervical cerclage. However, data from singleton pregnancies suggest caution[20] at present as there is no evidence that cervical cerclage can reduce the burden of prematurity in multiple pregnancy.

### Fibronectin

Recent research has sparked interest in fibronectin. Fetal fibronectin is distinct from the maternal form of this protein and can be identified by the monoclonal antibody FDC-6. Initially, it was found that the presence of fetal fibronectin in vaginal secretions was predictive of premature labor, but this test is too nonspecific even if regular fortnightly samples are taken.

In a systematic review, Honest and colleagues[21] found 28 studies in asymptomatic women; among these, the best summary likelihood ratio for positive results was 4.01 (95% confidence interval (CI)

**Table 73.1** Interventions for prevention of preterm labor (PTL) tested in randomized trials. Adapted from *The Cochrane Library*, 2004, Issue 1

| *Intervention* | *Number of trials* | *Number of women* | *Multiple pregnancies included?* | *Overall relative risk or odds ratio (95% CI)* |
|---|---|---|---|---|
| Aerobic exercise | 10 | 688 | no | RR 2.29 (1.02–5.13) increased risk of PTL |
| Antibiotics | 19 | 6948 | included in five trials | but delivery within 48 h significantly reduced RR 0.71 (0.58–0.87) |
| Hospitalization and bed-rest | 6 | 259 | yes | RR 1.8 (1–3.3)? increases risk of PTL |
| Magnesium sulfate | 23 | 2036 | included in one trial | RR 0.85 (0.58–1.25) |
| Psychosocial support in pregnancy | 16 | 10 237 | no | RR 0.96 (0.86–1.07) |

CI, confidence interval; RR, relative risk

2.93–5.49). The review concluded that cervicovaginal fetal fibronectin is most accurate for women with symptoms of threatened preterm labor (before cervical dilatation) in predicting spontaneous preterm birth within 7–10 days of testing. There are very few studies investigating the use of such screening in multiple pregnancies, but in those undertaken the positive predictive values are not sufficient to justify its use as a routine screening test[22–24].

### Screening for infection

Treatment of bacterial vaginosis in pregnancy does not significantly reduce the risk of premature labor before 37 weeks (odds ratio (OR) 0.95, 95% CI 0.82–1.10; eight trials of 4062 women), before 34 weeks (OR 1.20, 95% CI 0.69–2.07; five trials of 851 women) or before 32 weeks (OR 1.08, 95% CI 0.70–1.68; three trials of 3080 women). However, none of these trials included women with multiple pregnancies and further research is required in this regard[25].

### Bed-rest

Although hospitalization for best-rest was advocated in the past, little evidence exists to support this practice, and the theoretical risk of higher rates of thromboembolism is ever present. Admission to hospital is often highly disruptive to a woman's life and can be a stressful experience not just for the woman but also for her family. In addition, it is an expensive option. Therefore, any benefits and potential harm should be carefully evaluated before such advice is given. A meta-analysis of four randomized controlled trials indicates that bed-rest for women with twin pregnancies may increase the chance of premature labor. There is very little evidence for higher multiples (one trial included only 19 women with triplet pregnancies), and further research is required for this group[26].

### Prophylactic tocolysis

Meta-analysis of seven randomized control trials shows the use of β-sympathomimetic therapy prophylactically has no benefit in preventing preterm delivery in twin pregnancies. Indeed, women with multiple gestation are at increased risk of complications from β-sympathomimetic infusion which include potentially fatal pulmonary edema.

### Mutiple courses of antenatal corticosteroids

The role of glucocorticoids in multiple gestation is also unclear, and although numerous studies have demonstrated a reduction in the incidence of fetal respiratory distress syndrome and its sequelae, the optimal prophylactic treatment regimen for multiple pregnancies has yet to be determined. Evidence of the use of routine serial corticosteroids in multifetal gestation remains controversial, and there is no apparent benefit over a rescue approach. Murphy and colleagues[27] in a retrospective cohort study demonstrated a reduction in birth weight resulting from the routine use of corticosteroids in twin gestation. Moreover, there is concern remaining over the repeated use of glucocorticoids on glial cell function and hippocampal development. Several

multicenter trials are now ongoing, and hopefully they will provide evidence in this area. The largest study (MACS) has randomized already more than 600 women and is expected to finish recruiting in 2004 (http://www.utoronto.ca/miru/macs/macs_dec2003.pdf).

## MANAGEMENT OF WOMEN WITH THREATENED PRETERM LABOR

The only certainty in diagnosis of preterm labor is when progressive dilatation of the cervix is established over time by repeated examination. However, at this point it may be too late to attempt any intervention, and therefore the diagnosis often rests with reported uterine contractions. Thus, the inherent difficulty in ascertaining the early stages of premature labor often leads to misdiagnosis, mistaken treatment and possible misadventure. It is perhaps better to use the term 'threatened premature labor' in the absence of objective evidence of cervical dilatation. A meta-analysis of 16 trials of the use of β-sympathomimetics in threatened preterm labor found that in women randomly allocated to a control group, and therefore not treated, almost two-thirds had not delivered in 48 h and a third went to term. Moreover, it is not uncommon for women with regular uterine contractions not to develop established labor. However, such data should not engender complacency, and the diagnosis of preterm labor should always be kept in mind when any pregnant woman is admitted with abdominal pain or vaginal discharge. It is mandatory to perform an examination of the vagina and cervix with a speculum and take swabs for microbiologic investigation. Digital examination should, of course, be avoided if there is any suggestion of ruptured membranes because of the attendant risk of introducing ascending infection.

In a search of *The Cochrane Library*, acute tocolysis included: the use of calcium channel blockers (two of seven complete reviews included women with twin gestation – 35 women with twin gestation were recruited in total); use of magnesium sulfate (one study included twin gestation but only two women entered the study); and terbutaline pump maintenance therapy for preventing preterm birth (no women with twin pregnancy recruited).

### Can antibiotics inhibit premature labor with intact membranes?

Meta-analysis of 11 trials (over 700 women including the ORACLE II 2001 trial)[28] fails to demonstrate any effect on neonatal outcome, and therefore the use of antibiotics in premature labor (with intact membranes) cannot be recommended in routine clinical practice[29]. However, only two of the 11 trials included women with twin gestation.

### Antibiotics for preterm rupture of membranes

In a systematic review of 19 trials (over 6000 women), the use of antibiotics is associated with a significant reduction in the numbers of babies born within 48 h after preterm premature rupture of the membranes (relative risk 0.71, 95% CI 0.58–0.87) and a decrease in neonatal morbidity[30]. No studies have looked exclusively at multiple gestation and only five recruited women with twin pregnancies.

## SUMMARY

Most research investigating premature labor has been conducted in women with singleton pregnancies. As yet, little work on high-risk multiple pregnancies is reported in the literature. In a search of twin gestation using the Cochrane database only three of 50 complete systematic reviews were directly related to multiple pregnancy. In part this is due to the balance of numbers, but also because historically there have been few specialist clinics for multifetal gestation. In Liverpool, as in most other large teaching hospitals, clinics for multiple gestation have been set up to optimize management and facilitate research in this high-risk group; to date, too much has been inferred from studies of premature labor in singleton gestation.

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# Preventing Preterm Birth in Twins and Triplets

*E. Papiernik*

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## INTRODUCTION

Prevention of preterm birth is an important aim in twin as well as triplet pregnancies. Risks in twin or triplet newborns, as well as singletons, decrease exponentially with each week of gestational age in terms of death, severe morbidity and hospital neonatal costs[1]. The same may be said for developmental delay and cerebral palsy[2].

Prevention of preterm birth seems impossible in the face of increases in the rate of twin births in the United States[3] as well as in Europe[4]. The major aim for prevention of preterm birth in twin pregnancies should focus on extremely preterm births, as the risk of death and lifelong disability is disproportionately high in these infants[5].

The problem of preterm birth prevention is different for twins or triplets as the risk for preterm birth in twins is 50% and is 90% for triplet pregnancies. Using US data, this means that the risk for severely preterm birth, i.e. before 32 weeks' gestation, is eight times higher for twins than for singletons, and the risk for triplets is 26 times higher than for singletons[6].

The global rate of preterm births in twins has increased. In the United States, for example, the rate of preterm births among twins rose from 40.9% in 1981 to 55.0% in 1997[7]. Moreover, twin births accounted for an ever-increasing percentage of all preterm births (8.3% in 1981 to 13.0% in 1997). The spontaneous preterm birth rate did not change for US twin births from 1989 to 1997 (Table 74.1), whereas the proportion of twin births after induction of preterm delivery showed a small but definite increase for births after scheduled cesarean section, at least in terms of 1995–97 data compared with figures for 1989–91 and 1992–94. This increase is more obvious for pregnancies of 32 weeks and more, as the proportion of preterm births between 32 and 36 weeks rose from 26.8 to 46.2% of all preterm births (a positive increment of 72.4%), whereas the proportion of preterm twin births from 20 to 31 weeks rose from 8.3 to 9.6% (a positive increment of 16%)[7]. During these years, the increase of preterm deliveries among twins took place alongside a remarkable improvement of infant mortality rates[7] for all twin births at all gestation durations.

Overall, twin newborns have not only benefited from transformations in neonatal intensive care, but have also benefited from improvements in obstetric practice. The same observations have been made in other developed countries[4]. French national figures show an increase in preterm births among twins[8] and, during the same time, an increase of twin births. The evolution of medical practice in terms of iatrogenic preterm births among twin and triplet pregnancies can be measured in France using the register (FIVNAT) of all pregnancies following *in vitro* fertilization (IVF) and related assisted reproductive technologies (ART)[9] (see Chapter 11) which records the reasons for preterm deliveries and the relationship with fetal growth restriction. The FIVNAT register shows the differences in rates of preterm births, comparing singleton with twin and triplet pregnancies, for gestation duration periods 22–27 weeks, 28–32 weeks, 33–35 weeks, 36 weeks and 37 weeks and more (Table 74.2). The major difference is in the rate of early preterm births, here defined as births at less than 33 weeks, with 2.3% in singletons, 8.4% in twins and 30.4% in triplets.

**Table 74.1** Spontaneous and medically indicated (i.e. induction of labor or elective cesarean section) preterm (< 37 weeks) US twin births 1989–97. Adapted from reference 7. Data are presented as % (*n*)

| *Type of preterm birth* | *1989–91* | *1992–94* | *1995–97* | *p Value* |
|---|---|---|---|---|
| Spontaneous | 25.3 (66 127) | 25.7 (69 836) | 25.5 (71 096) | NS |
| Induced | 2.0 (5159) | 3.2 (8678) | 4.7 (12 947) | 0.001 |
| Elective cesarean | 19.9 (55 137) | 21.5 (55 286) | 22.6 (62 979) | 0.001 |
| All preterm | 47.2 (126 423) | 50.4 (133 800) | 52.8 (147 022) | 0.001 |
| Births at 37+ weeks | 52.8 (135 085) | 49.6 (134 686) | 47.2 (131 489) | — |
| All twin births | 100.0 (261 508) | 100.0 (268 486) | 100.0 (278 511) | — |

NS, not significant

**Table 74.2** Percentages of pregnancies, by gestational age at birth and plurality, included in the FIVNAT register 1986–99. The distribution of gestation duration is different by plurality. See Chapter 11

| *Gestational age* (weeks) | *Singletons* (*n* = 12 112) | *Twins* (*n* = 8068) | *Triplets* (*n* = 1344) | *Total* (*n* = 21 524) | *p Value* |
|---|---|---|---|---|---|
| 22–27 | 0.6 | 1.7 | 3.3 | 1.2 | 0.0001 |
| 28–32 | 1.7 | 6.7 | 27.1 | 5.1 | 0.0001 |
| 33–35 | 3.5 | 20.0 | 46.9 | 11.8 | 0.0001 |
| 36 | 3.3 | 15.5 | 12.3 | 8.2 | 0.0001 |
| 37–38 | 22.9 | 40.9 | 7.6 | 28.8 | 0.0001 |
| 39+ | 63.3 | 13.5 | 2.1 | 41.2 | 0.0001 |
| <37 | 9.1 | 43.9 | 90.3 | — | 0.0001 |
| <33 | 2.3 | 8.4 | 30.4 | — | 0.0001 |
| Mean ± SD | 39.2 ± 2.3 | 36.7 ± 2.7 | 33.9 ± 2.8 | — | 0.0001 |

SD, standard deviation

In countries where a prevention policy for preterm deliveries is applied, as in all European countries including France, the rate of spontaneous preterm births among singletons has decreased, whereas the rate of iatrogenic preterm births has increased, with no change and no increase of the total preterm birth rate among singletons for the past 10 years[4]. In contrast, the rate of preterm births among twins has increased in all population-based registers. Because of this, it seems important to define the goals that might be reached by a preventive policy for preterm births in twin pregnancies, and whether prevention of preterm birth is even possible. To do this, it is useful to distinguish three periods of preterm birth, each with different risk status for twin infants, and to include new knowledge about the risk of cerebral palsy among twin infants. The risk of cerebral palsy is clearly higher for twin infants than for infants born from singleton pregnancies. The meta-analysis of Stanley and colleagues[2] yields an odds ratio of 5.5 (95% confidence interval (CI) 14.3–12.1). This difference is even higher for triplets, with an odds ratio of 18.2 (95% CI 8.7–31.1). The fact that the risk of cerebral palsy is not the same for the different segments of gestational age among preterm-born twins provides another strong argument to distinguish those three different periods in the description of preterm births in twin pregnancies.

For twins as well as singletons, the risk of neonatal death, severe morbidity, long-term developmental handicap and, specifically, cerebral palsy depends first and foremost on the severity of prematurity, measured by gestation duration. Even so, the risk might be higher for twin infants compared with singletons of the same gestational age[2,9], albeit the data on this point are conflicting[10]. Because the most important risk period for twin pregnancies is for deliveries at < 28 weeks, the rate of preterm births at < 28 weeks was proposed as the best criterion for the measure of quality of prenatal care[5]. In this period, from 22 to 27 weeks, the risk of cerebral palsy is higher for twin infants compared with singletons of the same gestational age, with an odds ratio (OR) of

**Table 74.3** Percentages of elective cesarean sections, by plurality and by six periods of gestation duration, in the cohort of women of the FIVNAT register 1986–99[9]. The rates of elective cesareans are high, but not different by plurality at gestational ages 20–27 and 28–32 weeks, although higher for triplets at 33–35 weeks

| *Gestational age* (weeks) | *Singletons* | *Twins* | *Triplets* | *p Value* |
|---|---|---|---|---|
| 20–27 | 18/32 (56) | 7/47 (15) | 4/10 (40) | 0.15 |
| 28–32 | 98/173 (57) | 124/255 (49) | 60/104 (58) | 0.86 |
| 33–35 | 201/420 (48) | 353/729 (48) | 173/211 (82) | 0.0001 |
| 36 | 151/386 (39) | 286/604 (48) | 47/56 (84) | 0.0001 |
| 37–38 | 1016/2742 (37) | 927/1658 (56) | 32/41 (78) | 0.0001 |
| 39+ | 2205/7772 (28) | 271/586 (46) | 7/11 (64) | 0.0001 |
| All | 3689/11 525 (32) | 1968/3879 (51) | 323/426 (76) | 0.0001 |

1.94 (95% CI 1.2–3.2)[2]. The proposed interpretation of this higher rate in twins is the specific contribution of monochorionic (MC) pregnancies, with the specific effect of the twin–twin transfusion syndrome (TTTS). Therefore, the aim of prevention would be to reduce the occurrence of extreme preterm births for cases not related to TTTS. In the period of early preterm births, from 28 to 32 weeks, the risk of cerebral palsy is the same for twin as for singleton infants, with an OR of 1.03 (95% CI 0.6–3.2)[2]. This period is the most important for a preventive policy, as a prevention program is not in competition with the need to consider fetal growth restriction, as in the subsequent period.

On the other hand, in the period of late preterm births, from 33 to 36 weeks, the risk of cerebral palsy is higher in twins than in singleton infants, with an OR of 2.2 (95% CI 1.3–3.7)[2]. The interpretation is based on the different proportions of fetal growth restriction, being much higher in twins than in singletons. This interpretation is valid for the higher risk of cerebral palsy among term-born twins, compared with singletons[2,9]. During this period from 33 to 36 weeks, therefore, prevention of preterm births should be exercised only if fetal growth restriction with its associated potential danger is excluded. This may be a good reason for termination of pregnancy by induction of labor or by elective cesarean section before the spontaneous onset of labor (Table 74.3).

## RECOGNITION OF WOMEN AT RISK FOR PRETERM BIRTH IN TWIN PREGNANCIES

The risk for preterm birth is high and is recognized concurrently with the diagnosis of twinning. Preventive measures can be proposed as soon as the first ultrasound scan is performed. However, the real problem is to estimate the risk of extremely (22–27 weeks) and of early (28–32) preterm births.

That late recognition of twin or multiple gestation is an important risk factor for preterm delivery and perinatal death was shown as early as 1990[11]. In this controlled trial comparing two policies (with or without a systematic ultrasound scan), the early recognition of twinning was associated with much better outcomes, and the rate of extremely preterm birth was higher in the absence of an early diagnosis. This difference had an impact on the neonatal mortality rate, being 27.8 per 1000 births for twins born to women with the scan compared to 105.8 per 1000 twin births for the group of women without the scan.

It is also of importance to recognize chorionicity, as MC twins show specific complications and a higher rate of extremely preterm births at < 28 weeks, particularly related to TTTS[12]. This risk was determined in a population-based study including all 551 twins delivered in a study of perinatal deaths (from 22 weeks' gestation to 28 days postpartum) among 67 819 births in the district of Seine-Saint-Denis (France)[13]. Complications due to monochorionicity explained 50% of all perinatal deaths, when the proportion of MC pregnancies was not different from the commonly recorded rate of 30%. MC pregnancies are more frequently present in complications of extreme preterm birth at < 28 weeks, mostly with the loss of both twins, often directly related to TTTS.

Lack of prenatal care remains a major risk factor for preterm birth before 37 weeks. In the case of twins, in the USA, white pregnant women without prenatal care had 57.2% preterm birth compared with 51.2% who had prenatal care. The respective figures for the black population were 70.3% and 61.6%[14]. At the same time, women with intensive prenatal care in twin pregnancies show the lowest infant mortality rates, compared with those with inadequate level of prenatal care[7] (Table 74.4).

Belonging to a high-level social group with good access to information and the capacity to choose

**Table 74.4** Infant mortality rate/1000 (IMR), by gestational age and by utilization of prenatal care, all twin births, United States 1995–97. Adapted from reference 7

| *Gestational age (weeks)* | *Intensive care* | *Adequate care* | *Less than adequate care* | *Total* |
|---|---|---|---|---|
| 20–31 | 108.0 (98.1–118.0) | 173.4 (166.5–180.4) | 190.6 (177.9–203.2) | 166.5 (161.2–171.8) |
| 32–36 | 7.2 (5.9–8.5) | 8.2 (7.4–9.1) | 14.4 (12.2–16.6) | 9.0 (8.3–9.7) |
| 37+ | 5.4 (4.3–6.4) | 3.9 (3.3–4.4) | 6.9 (5.9–7.9) | 5.1 (4.6–5.6) |
| Overall IMR | 17.8 (16.5–19.1) | 33.0 (31.9–34.1) | 32.8 (31.0–34.5) | 29.2 (28.4–30.0) |
| Number of deaths | 726 | 3350 | 1410 | 5486 |

**Table 74.5** Opinion of the mother (*n* (%)) about the risk related to a twin pregnancy, for the children or for the mother herself, by socioeconomic level (education and income)[16]

| *Opinion of the mother on risk related to twinning* | *Socioeconomic status* | | | |
|---|---|---|---|---|
| | *Low* | *Average* | *High* | *Total* |
| No specific risk | 57 (35.6) | 61 (27.1) | 27 (19.1)* | 145 |
| Higher risk for the children | 63 (39.4) | 100 (44.4) | 82 (58.2)* | 245 |
| Higher risk for the children and the mother | 40 (25.0) | 64 (28.4) | 32 (22.7) | 136 |
| All twin mothers | 160 (100.0) | 225 (100.0) | 141 (100.0) | 526 |

*Significant difference, compared with other socioeconomic categories

a well-qualified obstetric team to follow a twin pregnancy was shown to be a predictor for better outcome as measured by the study of perinatal deaths for all twin infants born from 1989 to 1991 in the district of Hauts de Seine (France)[15]. The social status of the mother, measured in years of education and level of income, is related to important differences in perception of risk related to a twin pregnancy (Table 74.5), and to the choice by the mother of the prenatal out-patient clinic to be attended and the maternity unit for delivery[16]. This study was population-based and included all 541 twin deliveries (250–300 twin births/year) of a population of 2 000 000 inhabitants (October 1st 1989 to September 30th 1991). Twin mothers from the 22 maternity units of this district completed a direct questionnaire within 2 days postpartum. Questions included the level of education (years of school attendance), the income of herself and her husband/companion, the perception of specific risks for the children related to the twin pregnancy, or for the mother herself, and the reason for the choice of maternity unit. In addition, the following were collected: gestational age for infants of ≥ 26 weeks or 500 g or more, fetal deaths and neonatal outcome up to 28 days. The perception of specific risk for the children or the mother was described in various terms and was less appreciated by women of low socioeconomic level. In contrast, the more educated women had a higher degree of concern ($p < 0.01$). A difference in attitude was also measured by the choice of maternity unit in which they decided to deliver. Women belonging to a higher socioeconomic level more frequently chose a level-3 maternity unit, in a perinatal center with on-site availability of neonatal intensive care.

Important progress in risk assessment is afforded by the measurement of cervical length using a transvaginal ultrasound scan (see Chapter 55). One prospective study showed that twin mothers whose cervical length at 24 weeks was 35 mm or more were at low risk of spontaneous delivery before 34 weeks[17]. A meta-analysis of 46 studies including 31 577 women confirms the importance of this technique. Cervical shortening and cervical funneling, alone or in combination, appear to be useful in predicting spontaneous preterm birth in asymptomatic women[18]. The change of cervical length measured by repeated systematic transvaginal ultrasound scans shows that shortening of the cervix and change in shape of the internal os, starting with funneling, can be recognized early in those women who deliver before 34 weeks. The median shortening rate for women was 2.9 mm (0.8–5.2) per week in women delivering preterm and 1.2 mm (0.8–2.4) per week

in those who gave birth at term[19]. Although the predictive value of cervical length measurement is well established, as yet no interventional studies have evaluated the importance of this measurement in the prevention of preterm birth.

Among clinical signs assessed at the prenatal visits, the cervical length and the orientation and station of the presenting part remain good predictors for the risk of early preterm birth in twins. In spite of the subjective assessment, lack of precision and lower reproducibility, clinical cervical assessment appears to be safe and may be effective in monitoring twin gestation, especially where transvaginal sonography is not available[20–22]. Whereas home uterine activity monitoring can be helpful in identifying women at increased risk of preterm labour before cervical dilatation occurs, this information has not resulted in a reduction in the incidence of preterm labor, of advanced cervical dilatation at presentation or preterm birth in controlled trials[23–26], but in all fairness, it was not designed to do so.

For the extremely premature period of 22–27 weeks, a specific risk factor is TTTS, especially in the presence of the polyhydramnios–oligohydramnios sequence, and therefore the risk of extremely preterm birth is related to the proportion of MC pregnancies. Hence, the risk of extremely preterm birth is expected to be lower in twin pregnancies resulting from IVF and related techniques, compared with spontaneous twin pregnancies.

## TECHNIQUES USED FOR REDUCING PRETERM DELIVERIES IN TWINS

Most of the techniques proposed for the reduction of prematurity in twin or triplet pregnancies have not been proved effective by controlled trials.

### Bed-rest

Bed-rest is perhaps the most widely cited and oldest method for the prevention of preterm deliveries in multiple pregnancies. However, a meta-analysis of six controlled trials[27] reviewed its effect in 600 women and 1400 babies. Systematic bed-rest in hospital did not reduce the risk of preterm birth or perinatal mortality, although a trend to decrease the number of low-birth-weight babies was noted, with an OR of 0.79 (95% CI 0.6–0.99). However, no difference in the number of very-low-birth-weight infants was present, nor was there any difference in neonatal outcome. On the other hand, bed-rest in hospital for women with an uncomplicated pregnancy increased the rate of very preterm (< 34 weeks) deliveries, with an OR of 1.8 (95% CI 1.0–3.3). The only positive outcome related to bed-rest was the reduced risk of pregnancy hypertension, with an OR of 0.55 (95% CI 0.3–0.97). For women with a triplet pregnancy, most of the comparisons suggest beneficial effects from routine hospitalization; however, the differences observed between the experimental and the control group are compatible with chance variation[27].

### Prophylactic cerclage

Prophylactic cerclage has not been shown to be effective in twins[28], as envisioned by a meta-analysis of six randomized controlled trials in a total of 2175 women, comparing cervical cerclage in low- or moderate-risk women for second-trimester pregnancy loss with expectant management during pregnancy. Four trials compared prophylactic cerclage with no cerclage, and two examined the therapeutic role of cerclage when ultrasound examination revealed a short cervix. Pooled results failed to show a significant reduction in pregnancy loss and preterm delivery, although a small reduction of births at less than 33 weeks was seen in the largest trial. Cerclage was associated with mild pyrexia, increased use of tocolytic therapy and more hospital admissions, but no serious morbidity. The conclusion of this meta-analysis was that prophylactic cerclage to prevent preterm deliveries in mothers with a low or medium risk for second-trimester pregnancy loss is unproven. The role of cerclage in women whose ultrasound scan reveals a short cervix remains uncertain.

### Prophylactic tocolysis

Prophylactic tocolytics have not been shown to be effective in twin or triplet pregnancies[29–32], but there seems to be renewed interest[33–35] in the use of progestins for high-risk singleton or twin pregnancies. A recent meta-analysis found a protective effect (OR 0.50, 95% CI 0.3–0.85) for women with a singleton pregnancy at very high risk of recurrent preterm birth[36]. This might prove important, although the only specific controlled trial to date in twin pregnancies has given a negative result[33]. Treatment of the mother with antenatal corticosteroids was not effective for improvement of outcome for twin neonates[36], with no reduction of respiratory distress syndrome (OR 0.7, 95% CI 0.2–2.0), but with a reduction in mean birth weight in term babies of 129 g. Similar results were obtained in more recent studies.

### Weight gain

Adequate weight gain during pregnancy might have a protective effect against preterm birth in twin

**Table 74.6** Access to the preventive proposal offered to all women with twin pregnancy in the district of Hauts de Seine, France (1989–91). Despite some differences at diagnosis of pregnancy, no difference by socioeconomic level was measured for the major preventive propositions. Adapted from reference 15

| | *Socioeconomic class* | | | |
|---|---|---|---|---|
| | *Low* | *Average* | *High* | *p Value* |
| Diagnosis of pregnancy (days of gestation) | 44 | 35 | 34 | 0.01 |
| First prenatal visit (days of gestation) | 48 | 43 | 41 | 0.01 |
| Mean number of prenatal visits | 7.2 | 7.3 | 7.9 | NS |
| Mean number of ultrasound scans | 5.5 | 6.1 | 6.5 | 0.01 |
| Seen by an obstetrician before 72 days (%) | 25 | 26 | 25 | NS |
| Prescription of work-leave (%) | 34.3 | 34.4 | 40.9 | NS |
| Day of prescription of work-leave (mean ± SD) | 138 ± 56 | 141 ± 48 | 151 ± 49 | NS |
| Prescription of reduced physical activity (%) | 74.9 | 72.5 | 73.0 | NS |
| Day of prescription of physical activity (mean ± SD) | 159 ± 56 | 162 ± 52 | 159 ± 48 | NS |

SD, standard deviation; NS, not significant

pregnancies. No controlled trial is available to estimate the possible effectiveness of higher weight gain, but this issue is of interest as mothers of twins who gained weight early in pregnancy, i.e. before 24 weeks, were less likely to have preterm births and low-birth-weight twins[37,38] (see Chapter 51).

### Work-leave

Work-leave prescription upon medical advice and lifestyle modifications by information given to the mother are the basic techniques of a policy for the prevention of preterm deliveries proposed to all French women by Papiernik and colleagues[39]. This program has been the basis for effectively reducing preterm births among singletons in this country. The same program has been proposed (work-leave for twin-pregnant women between 22 and 24 weeks) for twin pregnancies, but must be implemented early in pregnancy, as the major goal is the prevention of extremely preterm births. No controlled trial has been undertaken to test the potential effectiveness of this policy. Any such evaluation of this policy would measure whether its application among all twin pregnant women of a given population would reduce the commonly observed social differences in preterm deliveries and in perinatal mortality figures. One study measured the results of such a policy among all pregnant women with twins within the population of a French district (Hauts de Seine) in the years 1989–91. Here, 546 women for whom the mean gestation duration at prescription of work-leave was 22.6 weeks were evaluated[15]. The goal of the study was that this prevention proposal should be available for every pregnant woman, regardless of her social class. Effectiveness of action was measured by the mean gestation duration at the first prenatal visit, the mean gestation duration at the first ultrasound scan, the number of prenatal visits, the number of ultrasound scans and the gestation duration at the prescription of work-leave (Table 74.6). The study was not meant to measure the effect of work-leave itself, as this specific proposal was included in a much larger preventive policy. The reality of equal access for all women regardless of social class to the prenatal care proposal was determined by the fact that no difference was observed for gestation duration at the first prenatal visit, gestation duration at first ultrasound or the time for prescription of work-leave according to socioeconomic class. In addition, there was no difference in the distribution of gestation duration by socioeconomic level. The only difference between the socioeconomic groups was in the choice of maternity facility, whereby mothers who were best informed more often chose a level-3 maternity unit, with intensive neonatal care available on site.

The major outcome measure was the rate of preterm births from 26 to 32 weeks, in this case 6%. Available populations for comparison show higher figures, such as 11% of births before 32 weeks for all US twin births[40]. This low rate of early and extremely preterm births seems to explain the low rate of perinatal deaths at 22 per 1000, with a fetal death rate at 8/1000 (8/1082) and a low neonatal mortality rate at 15 per 1000 (16/1074 live births), lower than the perinatal mortality rates for all twin births in the USA during 1989–91 of 28.7 per 1000[6], with no significant difference by socioeconomic group (Table 74.7).

### Twin clinic

Several maternity programs describe special sessions in the out-patient department devoted to mothers

**Table 74.7** Results of a preventive policy proposed to all twin pregnant women[15]. No significant difference was observed for gestation duration, and the apparent differences in stillbirth and neonatal deaths do not reach statistical significance with these small figures and wide confidence intervals (CIs). Adapted from reference 16

| | Socioeconomic class | | | |
|---|---|---|---|---|
| | *Low* | *Average* | *High* | *p Value* |
| Gestation duration at delivery mean ± SD (days) | 257 ± 17 | 256 ± 18 | 256 ± 15 | NS |
| 26–32 weeks (%) | 6.6 | 6.0 | 3.6 | NS |
| 33–36 weeks (%) | 39.8 | 39.5 | 41.4 | — |
| 37+ weeks (%) | 53.6 | 54.5 | 55.0 | — |
| Stillbirths; rate/1000 (CI) | 4/334; 11.9 (3–27) | 2/466; 4.0 (0–12) | 2/282; 7.1 (1–20) | NS |
| Early neonatal deaths (to 6 days); rate/1000 (CI) | 3/330; 9.1 (2–24) | 2/464; 4.3 (0–13) | 0/280; 0.0 (0–3) | NS |
| Late neonatal deaths (7–28 days); rate/1000 (CI) | 5/327; 15.3 (5–34) | 5/462; 10.8 (4–24) | 1/280; 3.7 (0–15) | NS |

NS, not significant

with multiple pregnancies (see Chapter 85). They are conducted by a trained team of doctors, midwives and nurses who offer specific attention to these mothers, specific education on the risk factors and advice on the importance of limitation of physical activity and avoidance of heavy effort, as well as practical nutritional advice and other educational topics. Such a twin clinic also provides a meeting place for twin mothers and fathers and allows mutual support. The first description of such a clinic and of its results came from Germany in 1977[41], whereas the first historical comparison with a demonstration of the positive effect for all twin pregnant women of a region was reported in Scotland[42]. In this setting, the reduction of extremely preterm births below 28 weeks and of babies of less than 1500 g in the two last historical periods, 1976–80 and 1981–83, was compared with figures for four previous historical periods from 1956 to 1975. The improvement was in neonatal deaths, from a mean level of 60 neonatal deaths per 1000 twin live births to figures of 18.4/1000 and 16.2/1000 since the twin clinic became available for all twin pregnant women in Dundee, Scotland (Table 74.8). This type of care has been proposed in many other patient care settings[43].

A preventive proposal should not only be proposed at the out-patient clinic level of a specific obstetric department, but should be offered to all women with a twin pregnancy in the population at large. The difficult task of preventing preterm birth in twin pregnancies and the inability to reduce the preterm birth rate in triplet pregnancies effectively is a strong argument for the prevention of multiple pregnancies in IVF and related techniques, up to the point of almost preventing twins, by elective single embryo transfers[44–47].

## PREVENTING PRETERM BIRTHS IN TRIPLET PREGNANCIES

In triplet pregnancies, no improvement of gestation duration is observed when old and recent publications are compared. The mean pregnancy duration remained stable at about 33 weeks, irrespective of the remarkable reduction in perinatal death (PND) rates. For instance, older papers cite PND rates of 132[48] to 312/1000[49], whereas more recent publications cite 93[50], 66[51], 80[52] and as low as 47[53] and 40[54] PNDs per 1000.

The rate of preterm births in triplets is very different from that in twins or singletons. For example, the French register of all births following IVF (see Table 74.2), for the years 1986–99, describes a rate of extremely preterm births (< 28 weeks) of 3.3%, 1.9 times more than for twins, and 5 times more than for singletons. The rate of severely preterm births (28–32 weeks) was 27.1% of all triplet births, 3.9 times more than for twins, and 15.9 times more than for singleton pregnancies.

Few techniques used for the prevention of spontaneous preterm births have been tested by controlled trials, none of them with proven efficacy in triplet pregnancies. Bed-rest was tested by a controlled trial[55], comparing bed-rest beginning at 28 weeks with conventional care and normal physical activity at home. The trial found some advantage of bed-rest, but a meta-analysis did not confirm this difference[27]. Another study[56] compared hospital bed-rest from the end of the second trimester with hospital bed-rest at 28 weeks, by choice of the mother herself. This study showed that women accepting early bed-rest had a longer gestation duration, higher mean birth weight and lower perinatal mortality rate. However, the results for the study group were better because they

**Table 74.8** The preventive policy in Dundee (Scotland) established in 1975 and evaluated by a historical population-based study. Adapted from reference 42

| | *Gestation duration* (weeks) | | *Birth weight* (g) | | |
|---|---|---|---|---|---|
| *Years* | *< 28* (%) | *28–34* (%) | *< 1500* (%) | *1500–1999* (%) | *Neonatal deaths/1000* |
| 1956–60 | 2.9 | 16.7 | 7.7 | 15.5 | 51.6 |
| 1961–65 | 2.8 | 16.6 | 11.3 | 15.9 | 66.7 |
| 1966–70 | 4.9 | 13.6 | 10.6 | 14.7 | 59.5 |
| 1971–75 | 3.5 | 18.1 | 12.1 | 13.0 | 64.2 |
| 1976–80 | 0.0 | 16.4 | 3.9 | 15.7 | 18.4 |
| 1981–83 | 1.6 | 14.5 | 4.0 | 17.7 | 16.2 |

were compared with a 'normal care' group with a mean gestation duration as low as 30.0 weeks, a mean birth weight as low as 1228 g and a perinatal mortality rate as high as 430 per 1000 births. A more recent paper[57] claims an improved birth weight of the newborns in a historical comparison of women with or without hospital bed-rest. In the former group, fewer cases of intraventricular hemorrhage were observed, but no difference in gestation duration and no difference in perinatal mortality rates[57].

Prophylactic (i.e. without specific indication) cervical cerclage has been proposed for many years to reduce preterm births in triplets. However, this procedure has no proven efficacy for triplets[50,58,59], with some benefit for pregnancy duration but no effect on neonatal mortality rates[60]. Home monitoring as well as prophylactic tocolysis did not reduce the preterm delivery rates of triplets.

Finally, delayed-interval delivery of multiple pregnancy, in the absence of clinical signs of chorioamnionitis, should be considered as a salvage procedure when one of the multiples has been delivered remote from term. This procedure is described in detail in Chapter 75.

## SUMMARY

The prevention of preterm delivery in multiple pregnancies is as difficult today as ever. The problem is accentuated by the recent figures showing an increase in preterm delivery rates. The goal, as described in this chapter, is to reduce the 'dangerously' preterm birth rate (< 28 weeks). This goal can be achieved using various strategies including early diagnosis, intensive prenatal care and liberal use of work-leave.

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# Delayed-interval Delivery

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**75**



## INTRODUCTION

Multiple pregnancy is frequently complicated by preterm delivery, a major cause of perinatal mortality and morbidity[1,2]. The number of multiple pregnancies has increased rapidly in recent decades, primarily due to the use of assisted reproductive technologies (ART) and increased maternal age (see below). Arrest of labor often occurs after the premature delivery of one member of a multiple pregnancy. Traditionally, only a few attempts were undertaken to postpone delivery of the remaining fetus(es). In 1880, Carson reported an interval of 44 days between the birth of two babies from a woman with uterus didelphis and 'twin' pregnancy[3]. In 1957, Abrams reported an interval of 35 days between the deliveries of two babies, both alive at the time of birth[4]. At 23.3 weeks of gestation, the mother delivered a girl of 396 g, who died 3 h after birth at home. Five weeks later, she delivered a living boy weighing 1033 g. Unfortunately, neonatal outcome and further development were not stated. Over recent decades, several additional case reports and series have reported delayed-interval delivery in multiple pregnancies. Review of these studies, despite a large variation in treatment protocols, shows a very high success rate (93%), suggesting that mainly cases with successful outcomes are reported[5]. As a result of this selection bias, both prognosis and recommendations concerning treatment protocols based on these early studies are speculative. Recently, however, three larger studies have been published demonstrating a success rate of about 50%[5–7]. The objective of this chapter is to report techniques and the results of our attempts using a fixed protocol.

## OUR OWN POPULATION AND MANAGEMENT

A specific protocol of delayed interval was used in all 73 twin pregnancies complicated by delivery of the first fetus between 16 and 31 weeks of gestation since 1991 to the present. We excluded from further analysis those pregnancies in which a cesarean section had to be performed, labor progressed or specific contraindications such as ongoing infection were present. During this period, 41% of all these multiple pregnancies were included, resulting in a study population of 30 women with twin pregnancies. The mean maternal age of these patients was 30.4 (range 23–41) years. When preterm delivery was anticipated, women were asked to give informed consent and were treated according to a fixed protocol, in which four phases can be distinguished: phase 1, preparation; phase 2, delivery of the first baby; phase 3, period between the births of the first and remaining fetus(es); and phase 4, delivery of the last multiple including evaluation of placenta. Each phase is characterized by specific measures that have to be taken.

### Phase 1, preparation

The procedure starts with ruling out contraindications and obtaining informed consent. Contraindications include fetal distress or severe congenital abnormalities of the remaining fetus, chorioamnionitis, severe vaginal blood loss and other situations in which the maternal condition is compromised (e.g. pre-eclampsia, suspicion of abruption, infection). Membranes of the remaining fetus(es) must be intact, since early-onset long-term oligohydramnios is associated with pulmonary hypoplasia[8]. Considering the potential risks of the procedure versus the risks of

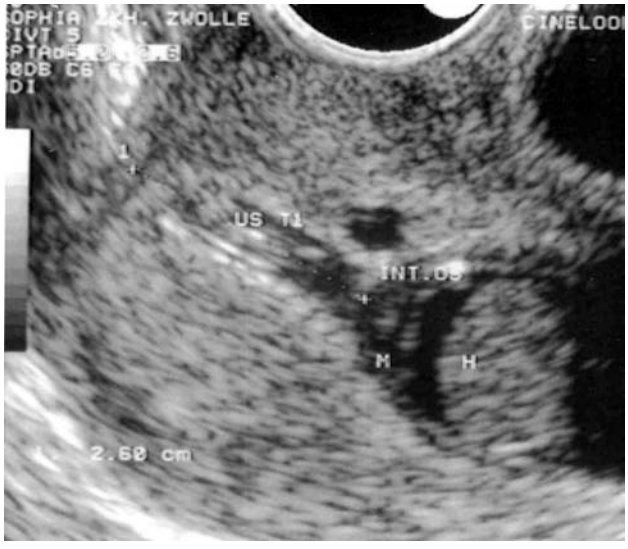


**Figure 75.1** Ultrasonic image of the cervix 2 days after delivery of the first baby, showing the umbilical cord of the first baby in the cervical canal which regained a length of 2.6 cm

perinatal mortality and morbidity, it is not appropriate to pursue delayed-interval delivery after 31 weeks of gestation, especially when corticosteroids have been administered to stimulate fetal lung maturation.

Informed consent includes a thorough explanation of the procedure, its limited success rate and the potential risks for mother and her unborn child(ren), such as chorioamnionitis, abruptio placentae and, although rare, maternal coagulation disorder. Side-effects of anticipated medication such as tocolytics should be discussed.

In The Netherlands, immature delivery before 25 weeks is practically always associated with neonatal death. However, parents should be made aware that if delivery of the remaining fetus takes place between 25 and 28 weeks, neonatal mortality may be reduced, but neonatal morbidity remains high. The latter may be considered an even greater and more costly burden in the long run, and may require hospitalization for several weeks. Motivation of the parents is an absolute prerequisite for starting a delayed-interval delivery procedure.

For tocolytic treatment, we have administered ritodrine or more recently atosiban intravenously or nifedipine orally and, if necessary, indomethacin suppositories. Fetal lung maturation is stimulated by 12 mg betamethasone intramuscularly between 25 and 32 weeks of gestation. Between 25 and 28 weeks we administer two doses of 12 mg betamethasone with an interval of 1 week, and after 28 weeks only one dose is administered. After cervical culture is obtained, antibiotics are administered intravenously for 1 week.

### Phase 2, delivery of first baby

The birth of the first baby deserves special consideration. Expulsion forces should be limited. During delivery of the first baby, administration of tocolytics and antibiotics is continued. As episiotomy is a source of infection, it should be avoided. After delivery of the first baby, no efforts should be undertaken to deliver the placenta. A culture is taken from the cervix and the vagina is disinfected. The umbilical cord is ligated near to the cervix, but cervical cerclage is not performed. In rhesus-negative women, 1000 IU of anti-D globulin is injected intramuscularly immediately after the first delivery.

### Phase 3, between births

After delivery of the first baby, digital examination is avoided. Cervical length, dilatation and funneling are monitored preferably by transperineal ultrasonography (Figure 75.1). Monitoring the maternal condition focuses on (early) detection of chorioamnionitis, recurrent preterm labor, abruptio placentae and coagulation disorders. Body temperature is measured four times daily. Cervical cultures are taken weekly and antibiotics are administered according to their results. Laboratory tests (infection and coagulation) are performed periodically. Fetal monitoring consists of very frequent biophysical assessment, including cardiotocography, Doppler flow velocimetry and real-time ultrasound. Fetal biometry and the amount of amniotic fluid are examined by ultrasound at regular intervals. The patient remains hospitalized as long as contractions are present.

### Phase 4, delivery of last multiple

After delivery of the remaining fetus(es), careful examination of the placenta prevents retention of the placenta of the first baby (Figure 75.2). Histologic examination is performed on all placentas for signs of infection and chorionicity. During the whole procedure parents are counseled regularly by our social worker and special attention is paid to the emotional state of the parents, which is frequently ambiguous in the situation when one baby is dead and the other may survive.

## OUR EXPERIENCE

Within our series of 73 multiple pregnancies, we treated 30 twin pregnancies according to the protocol described above. Data for all 30 twin pregnancies are provided in Table 75.1. The mean gestational age at delivery of the first baby was 24.8 (range 16–31) weeks. The mean birth weight was 746 (range

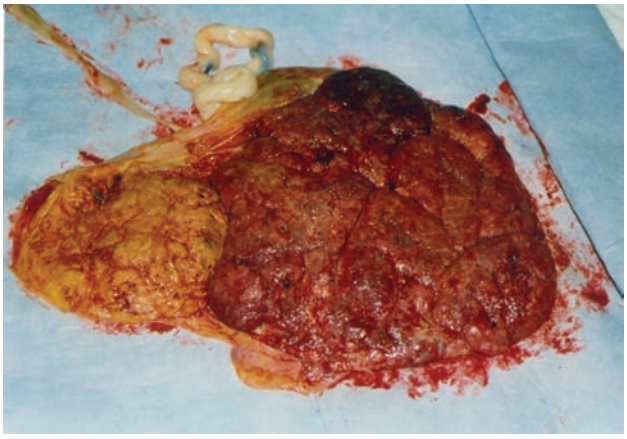

**Figure 75.2** Placenta showing the light smaller part of the first-born baby and the larger dark part of the baby who was born after an interval of 106 days

140–1660) g. Perinatal mortality of all first-born twins was 70%. All 17 first-born babies born before 26 weeks died perinatally and had a mean birth weight of 490 (range 140–1000) g. From 29 weeks onwards, all five first-born babies survived, but needed artificial ventilation in contrast to their later-born sibs. On average, delivery of the remaining fetus could be postponed for 20.2 days (range 0.5–106) (Figure 75.3). Four of the remaining fetuses were delivered by cesarean section, one instance for partial abruptio placentae, and in three others because of chorioamnionitis, once in combination with prolapse of the umbilical cord. One of these women had a second laparotomy because of a hemorrhage. This woman also developed a pulmonary embolism despite prophylactic use of anticoagulants. In 17 twin pregnancies in which the first baby was born before

**Table 75.1** Twin pregnancies ($n$ = 30): maternal age, gestational age at delivery, birth weight and sex, mode of delivery, outcome, placenta, mode of conception

| | | *Delivery* (weeks) | | | *Weight* (g) *and sex* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| *n* | *Maternal age (years)* | *1* | *2* | *Interval days* | *1* | *2* | *Mode of delivery* | *Outcome* | *Placenta* | *Mode of conception* |
| 1 | 25 | 16 + 2 | 20 + 2 | 28 | 140 m | 490 m | V/V | D/D | DC | spontaneous |
| 2 | 26 | 19 + 0 | 19 + 5 | 5 | 250 f | 300 f | V/V | SB/D | DC | ICSI |
| 3 | 33 | 19 + 1 | 20 + 4 | 10 | 235 m | 250 f | V/V | D/D | DC | spontaneous |
| 4 | 31 | 20 + 1 | 20 + 2 | 1 | 320 f | 360 m | V/V | D/D | DC | spontaneous |
| 5 | 32 | 20 + 1 | 31 + 4 | 73 | 350 f | 1890 m | V/V | D/A | DC | IVF |
| 6 | 37 | 21 + 1 | 21 + 6 | 12 | 300 m | 390 m | V/V | D/D | DC | IVF |
| 7 | 31 | 22 + 0 | 37 + 1 | 106 | 465 f | 2995 f | V/V | D/A | DC | ICSI |
| 8 | 36 | 22 + 4 | 26 + 6 | 30 | 410 f | 795 f | V/CS | SB/A | DC | spontaneous |
| 9 | 29 | 22 + 5 | 24 + 3 | 12 | 550 f | 620 f | V/V | D/D | MC–DA | IVF |
| 10 | 27 | 22 + 5 | 26 + 3 | 25 | 310 f | 710 m | V/V | D/D | DC | stimulation |
| 11 | 31 | 23 + 1 | 25 + 6 | 19 | 550 f | 740 m | V/V | D/SB | DC | IVF |
| 12 | 39 | 24 + 0 | 26 + 2 | 16 | 795 m | 860 m | V/V | D/A | MC–DA | ICSI |
| 13 | 23 | 24 + 2 | 26 + 2 | 14 | 615 f | 805 f | V/V | D/SB | DC | spontaneous |
| 14 | 27 | 24 + 4 | 25 + 1 | 4 | 680 m | 765 m | V/V | D/A | DC | ICSI |
| 15 | 26 | 24 + 6 | 25 + 4 | 5 | 670 m | 750 f | V/V | D/A | DC | IVF |
| 16 | 28 | 24 + 6 | 27 + 3 | 18 | 690 m | 1250 m | V/V | D/A | DC | spontaneous |
| 17 | 29 | 24 + 6 | 30 + 0 | 36 | 1000 m | 1530 f | V/V | D/A | DC | spontaneous |
| 18 | 29 | 26 + 1 | 26 + 4 | 3 | 875 m | 715 m | V/V | D/D | MC–DA | spontaneous |
| 19 | 29 | 26 + 2 | 26 + 5 | 3 | 780 f | 870 f | V/V | D/A | DC | stimulation |
| 20 | 35 | 26 + 2 | 29 + 6 | 25 | 940 f | 1470 f | V/CS | D/A | DC | IVF |
| 21 | 39 | 26 + 3 | 28 + 1 | 12 | 835 f | 1340 f | V/CS | A/A | DC | spontaneous |
| 22 | 33 | 26 + 3 | 32 + 3 | 42 | 850 m | 1690 m | V/CS | A/A | DC | spontaneous |
| 23 | 32 | 26 + 3 | 34 + 0 | 53 | 840 m | 2310 f | V/V | A/A | DC | stimulation |
| 24 | 28 | 28 + 1 | 30 + 3 | 16 | 865 m | 1470 m | V/V | D/A | DC | spontaneous |
| 25 | 32 | 28 + 6 | 29 + 1 | 2 | 1150 f | 1040 f | V/V | A/A | DC | spontaneous |
| 26 | 31 | 29 + 3 | 29 + 3 | — | 1305 m | 1580 m | V/V | A/A | DC | spontaneous |
| 27 | 26 | 30 + 1 | 32 + 1 | 14 | 1450 m | 1550 f | V/V | A/A | DC | spontaneous |
| 28 | 34 | 30 + 2 | 31 + 4 | 9 | 1220 m | 1945 m | V/V | A/A | DC | spontaneous |
| 29 | 26 | 30 + 5 | 31 + 2 | 4 | 1660 m | 1770 m | V/V | A/A | MC–DA | spontaneous |
| 30 | 28 | 31 + 0 | 32 + 2 | 9 | 1271 f | 1625 m | V/V | A/A | DC | stimulation |

m, male; f, female; V, vaginal; CS, cesarean section; D, perinatal death; SB, stillborn; A, alive; MC, monochorionic; DA, diamniotic; DC, dichorionic; ICSI, intracytoplasmic sperm injection; IVF, *in vitro* fertilization

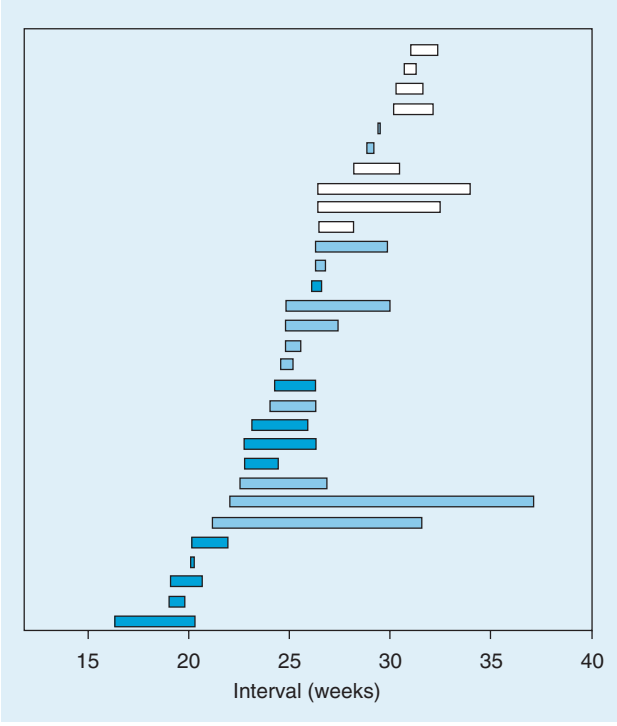


**Figure 75.3** Interval in weeks between delivery of the first and second babies. Dark blue bars indicate that both babies died, light blue bars indicate that one baby survived and white bars indicate that both babies survived

26 weeks, it was possible to delay the second delivery until at least 26 weeks in 47.1% of cases, resulting in a neonatal mortality of the second baby of only 25%. In contrast, in all 21 babies born after at least 26 weeks, neonatal mortality was 14.3%. In 80% of all women, it was possible to administer complete corticosteroid treatment. Histologic examination of the placenta showed 26 dichorionic and four monochorionic–diamniotic placentas. Nineteen placentas showed histologic signs of chorioamnionitis.

Nine women had clinical signs of developing chorioamnionitis and funisitis. In three, cesarean section had to be performed. In eight women the placenta had to be removed manually. Four women had a hemorrhage of more than 1 liter. Three women had prolapse of the umbilical cord, and in one it was necessary to perform a cesarean section. In the other two, a breech extraction was performed because there was full dilatation and the gestational age was 25 weeks or less. Two women had a partial abruptio. One of them delivered by breech extraction because there was full dilatation. One woman had an isolated transient elevation of liver enzymes, but serologic tests for viral infections were negative. One woman had a transient atrium fibrillation, which was successfully treated with digitalis and heparin.

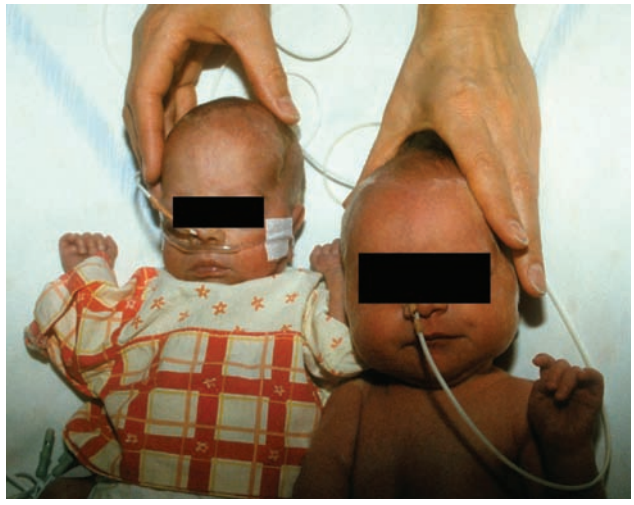

**Figure 75.4** Infants of patient 23 in Table 75.1, born with an interval of 53 days. On the left is the first-born infant

Short- and long-term neonatal follow-up was performed[9]. As expected, mean birth weight and gestational age were significantly higher in the second-born infants. Figure 75.4 shows the infants of patient 23 in Table 75.1, who were born with an interval of 53 days. Six out of ten first-born infants and ten out of 22 second-born infants needed assisted ventilation for an average period of 15 days and 7 days, respectively, which makes the difference in need and duration of assisted ventilation not significantly different. Idiopathic respiratory distress syndrome (IRDS) and patent ductus arteriosus (PDA) were more prevalent in first-borns, whereas second-born infants developed sepsis and bronchopulmonary disease (BPD) more often. However, these differences are not significant either. Specific data for the majority of these infants are published elsewhere[9]. Long-term follow-up at the corrected age of 1 and/ or 2 years is not yet known in children born after 2002, and is not available for those born before 1997. For the remaining 14 infants, 2/6 first-born infants and 1/8 second-born infants had abnormal neuromotor development (below two standard deviations on the Bayley scale) at the age of 2 years.

## DISCUSSION

Our study describes a large series originating from a single center. In this series, the survival rate of at least one remaining baby is comparable with those of two other large series by Arias[6] and Farkouh and colleagues[7], reporting 11 and 24 cases, respectively. In contrast to these two series, however, we never performed cervical cerclage. Our success rate depends on numerous criteria, including the length of

postponement, or merely whether time was obtained to give corticosteroids for lung maturation of the remaining fetus, or whether there was a reduction of mortality or morbidity. With respect to reaching viability of the remaining baby, the goal of our series was to postpone the second delivery until a gestational age of at least 26 weeks, resulting in a reduction of perinatal mortality of 85%. All remaining babies born after at least 29 weeks survived. Owing to the small number of infants available for follow-up, we could not find a significant difference between the two groups. If, however, we bear in mind that the reason for postponing the delivery of the second sib is the birth of a viable baby, and thus adverse outcome is defined as death or abnormal development, there was a significant difference. Nonetheless, it is important to recognize that delayed-interval delivery is associated with a relatively high degree of chorioamnionitis and manual delivery of the placenta. Besides the technical aspects of this procedure, it is important to consider psychosocial and emotional support to the patient and her partner.

## CONCLUSION

If twin pregnancies are complicated by immature or very premature delivery of the first baby, delayed-interval delivery results in a significant reduction of perinatal mortality of the second infant. Results from single case reports and smaller series show a higher success rate than those of larger series, suggesting selection bias, based on the fact that only successful results have been published. The significant reduction of adverse neonatal outcome has to be considered in relationship to the degree of complications and maternal morbidity. For further recommendations concerning treatment protocols and success rates, larger series reporting all attempts are needed in the future.

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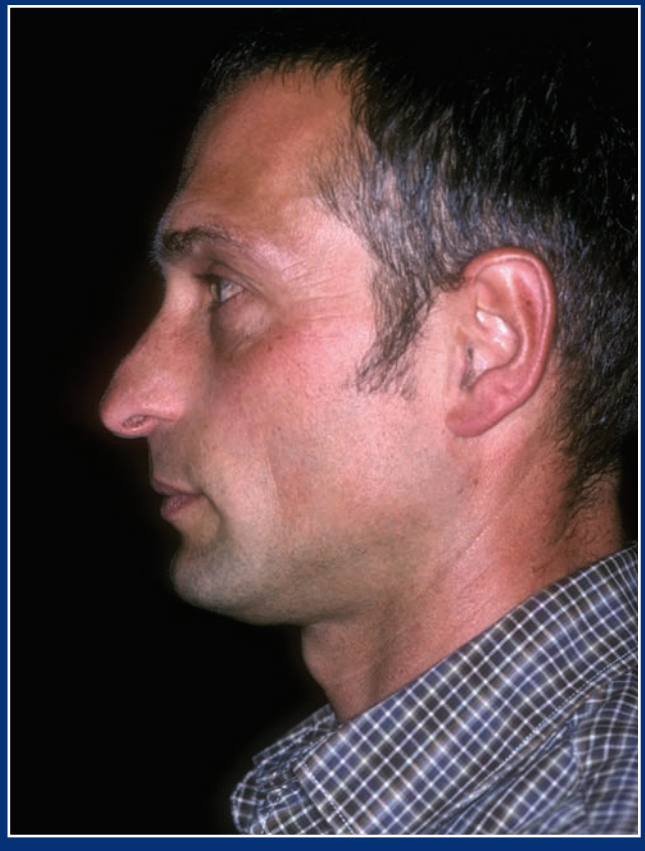
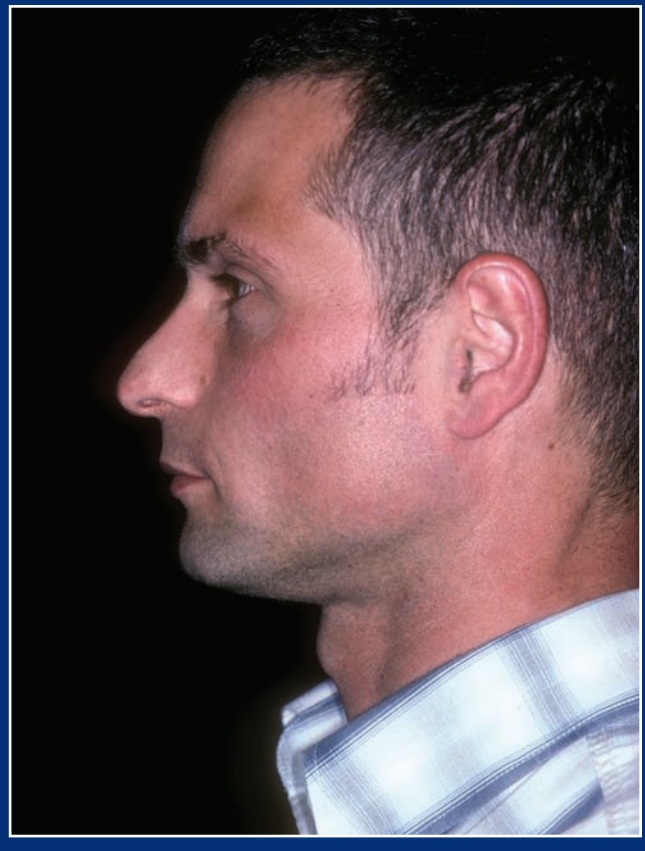
# SECTION VII
# PREGNANCY MANAGEMENT: DELIVERY





**39-year-old male monozygotic, dichorionic, non-mirror twins, Belgium, 2004.**

Participants since birth in the East Flanders Prospective Twin Study. Twin A left, Twin B right.

The delivery of the Biblical twins Jacob and Esau. Dutch medieval iconographic painting

Another important and common contributor to perinatal morbidity and mortality in multiple pregnancies is delivery complications. The Figure, an iconographic depiction of the delivery of Jacob and Esau, portrays the method of twin birth in ancient times, when no alternative to the vaginal route existed.

Admittedly, the prime focus of most studies related to multiple births is outcomes of the twins or higher-order multiples. Despite this, specific peripartum complications occur more frequently in mothers delivering multiples compared with their frequency in mothers of singletons, and result in disproportionate degrees of maternal morbidity. Indeed, when multiples are delivered under less than ideal conditions, as reported from developing African countries, disproportionately higher maternal mortality rates are not surprising (see Chapter 59 by Blickstein).

Over the years, however, the increasing safety of cesarean birth inevitably led to the ongoing controversies related to the optimal mode of delivery of multiples. This section presents the arguments for and against vaginal delivery of twins, and describes peripartum aspects such as anesthesia and hemorrhage.

*I.B. and L.G.K.*

# Contents of Section VII

# Timing of Delivery

*S. T. Chasen*

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## INTRODUCTION

Spontaneous preterm birth complicates nearly half of all twin pregnancies[1]. Maternal complications such as pre-eclampsia, and fetal complications such as intrauterine growth restriction are common in twins. In the presence of these conditions, early delivery may be indicated. Because of this, the timing of delivery may not be at the total discretion of the obstetrician. In the absence of spontaneous preterm birth or an indicated preterm delivery, however, the obstetrician may need to determine the optimal time for delivery.

In singleton pregnancies without complications, delivery prior to 39 weeks' gestation is not recommended, due to an increased risk of neonatal respiratory complications[2]. In the absence of the spontaneous onset of labor or a maternal or fetal indication for delivery, however, most authorities recommend delivery at 41 or 42 weeks' gestation for singletons[3].

In twin gestations, on the other hand, there is evidence that the optimal length of gestation is shorter than in singleton pregnancies[4]. Although the belief that pulmonary maturity is achieved earlier in twins[5] is widespread, this concept is controversial[6,7]. Epidemiologic evidence shows that the lowest rate of perinatal mortality in twins occurs at 37–38 weeks' gestation, and the increase in perinatal mortality after 38 weeks corresponds to that seen in singleton pregnancies after 41 weeks[8–10]. Luke and colleagues reviewed 163 women with twin pregnancy, and models for the 'ideal twin pregnancy' were developed. Using multivariate logistic regression, most women with an 'ideal twin pregnancy' delivered between 35 and 38 weeks' gestation[11].

Several large, population-based studies support the concept that better outcomes in twin pregnancies are seen earlier than in singleton pregnancies. One study compared the mortality of twins and singletons using data from the Swedish Medical Birth Registry from 1982 to 1995. Twins born between 29 and 37 weeks' gestation had lower rates of mortality than singletons at comparable gestational ages. After 37 weeks' gestation, although perinatal mortality continued to decline in singleton pregnancies, it increased in twins, and exceeded that of singletons[12]. Minakami and Sato reached similar conclusions based on birth data obtained in Japan between 1989 and 1993. In their study, the lowest rate of perinatal death was seen at 38 weeks' gestation, with the risk increasing later in gestation. The lowest risk of perinatal death in twins at 38 weeks' gestation (10.5/1000 infants) corresponded to the risk at 43 weeks for singletons (9.7/1000 infants) in the Japanese study[9].

In the United States, Hartley and colleagues reviewed birth-certificate data from Washington state from 1987 through 1997. A total of 9744 twin pairs were born. In these pregnancies, perinatal mortality declined with advancing delivery date from 24 to 39 weeks' gestation, and increased subsequently. Although the nadir occurred at 39 weeks, there was no statistically significant difference between outcomes at 38 and 39 weeks' gestation[13].

Although data from population-based studies have the advantage of describing large populations with the ability to discern small differences in outcomes, some limitations are present because population- based studies cannot assess the impact of obstetric management, which can vary widely. For example, lack of appropriate antepartum surveillance, such as ultrasound to assess fetal growth,

could account for much of the perinatal mortality noted with advancing gestation beyond 37–38 weeks. Although epidemiologic data suggest increased rates of adverse outcomes, the possibility that many perinatal deaths may have occurred due to suboptimal antepartum surveillance cannot be excluded.

A single randomized controlled trial comparing expectant management with induction of labor at 37 weeks in twin pregnancies has been published[14]. Thirty-six women were enrolled in the study, with 19 randomized to expectant management and 17 to induction of labor at 37 weeks' gestation. The primary outcome was the rate of cesarean delivery, which was not significantly different between the two groups. No changes in any maternal or neonatal outcomes were noted between the two groups. Although delivery at 37 weeks cannot be recommended based on this study, it was not designed to detect differences in neonatal outcome[14].

According to large population-based studies, it is apparent that trends in perinatal outcome in twin pregnancies based on gestational age differ from those in singleton pregnancies. Optimal outcomes are seen at earlier gestational ages, and the increase in perinatal mortality at term is noted several weeks prior to that seen in singleton pregnancies. Although the optimal timing of delivery in any individual pregnancy should be dictated by careful assessment of maternal and fetal status, a twin pregnancy should progress beyond 38 weeks only in the presence of reassuring fetal testing. The American College of Obstetricians and Gynecologists (ACOG) recommends delivering all twin pregnancies by 40 weeks' gestation[15], although available evidence does not identify a gestational age beyond which any individual twin pregnancy should not progress.

## ELECTIVE CESAREAN DELIVERY

A specific concern regarding the optimal timing of delivery in twins is the high rate of cesarean delivery prior to the onset of labor[16]. The reasons for this practice include a reluctance to attempt vaginal delivery of any non-cephalic-presenting fetus, as well as the perception that cesarean delivery is safer in many of these 'premium' pregnancies, which are often the result of assisted reproductive techniques[16].

Regardless, cesarean delivery before the onset of labor is associated with an increased risk of neonatal respiratory morbidity[17]. Although inadvertent delivery of a premature infant because of inaccurate gestational dating may contribute to this[18], some evidence exists to show that labor itself may have a protective effect. For example, increased catecholamine levels in the fetal lamb during labor led to decreased secretion and increased resorption of lung fluid[19]. Other mechanisms may include a slower decrease in pulmonary vascular resistance and lower levels of prostaglandins in neonates delivered before the onset of labor[20,21].

The ACOG issued guidelines for the timing of elective delivery in 1991[2]. Elective delivery before the onset of labor is not recommended before 39 weeks' gestation, which must be determined using precise dating criteria. In one series it was found that adherence to this protocol may have prevented the majority of respiratory morbidity seen in neonates delivered by elective repeat cesarean delivery before labor[22]. With reference to twin pregnancies, ACOG later stated that '[t]he ideal time of delivery for uncomplicated pregnancies is uncertain; however, if elective delivery is considered before 38 weeks of gestation, fetal lung maturity should be assessed'[15].

At the New York Hospital/Cornell Medical Center, we evaluated the risk of neonatal respiratory disorders in infants from 126 twin pregnancies. All women underwent elective cesarean delivery at ≥ 36 weeks' gestation before the onset of labor. Approximately two-thirds of cesarean deliveries were performed due to malpresentation of one or both fetuses. No maternal or fetal complications were present to require a medically indicated delivery. Monthly ultrasound examination to evaluate fetal growth had been performed in all cases, however, and non-stress tests were performed weekly starting at 32 weeks[23].

In this series, 15 infants from 11 pregnancies were diagnosed with either transient tachypnea or respiratory distress syndrome; all but one was delivered prior to 38 weeks' gestation. Twelve newborns required admission to the neonatal intensive-care unit, and three required mechanical ventilation. The rate of neonatal respiratory disorders was significantly higher among infants born at 36 or 37 weeks (13%) compared with those born at ≥ 38 weeks (2%) ($p = 0.04$). Based on these data, we concluded that elective cesarean delivery in a twin pregnancy should not be performed until 38 weeks' gestation or the spontaneous onset of labor[23].

## THE ASSESSMENT OF FETAL LUNG MATURITY IN TWIN PREGNANCIES

In some pregnancies, delivery may be desirable, although not imperative. If fetal lung maturity can be documented, the obstetrician can be confident that neonatal complications would be unlikely to occur. In a multifetal pregnancy, however, the use of amniocentesis to assess fetal lung maturity raises the question of whether sampling of both fetal sacs is necessary.

Small published series suggest a high degree of concordance in lecithin/sphingomyelin (L/S) ratios

from separate sacs in twin pregnancies, although some investigators have noted occasional biochemical or clinical discordance in fetal lung maturity[24–26]. The largest published series assessed L/S ratios in 58 diamniotic twin pregnancies. In 53 instances (91.4%), the L/S ratios of twin pairs were either both consistent or both inconsistent with pulmonary maturity. The disparity in L/S ratios was significantly greater at 32 weeks or less. In those cases with > 20% disparity in L/S ratios, the discordance was primarily the result of one twin having an L/S ratio advanced for gestation. There was no significant difference in L/S ratio between presenting and non-presenting twins or between the bigger and the smaller twins[27].

If amniocentesis for lung maturity is performed in a twin pregnancy, it is not clear whether sampling fluid from only one sac is appropriate. Although concordant results are seen in the vast majority of cases, biochemical tests consistent with lung maturity in one twin are not necessarily predictive of that of the other twin, particularly at earlier gestational ages. If sampling is going to be done for only one twin, it should be from the more accessible sac, as there is no evidence that the order of presentation or fetal size can reliably predict differences in results.

## MONOAMNIOTIC TWINS

Monoamniotic twins (see Chapter 67) represent a particularly high-risk subset of twin pregnancies. Delivery earlier in the third trimester may be indicated because of the high rate of perinatal mortality, primarily due to cord entanglement, described in these pregnancies[28,29]. Although prenatal diagnosis of monoamniotic twins and intensive antepartum fetal surveillance have reduced the perinatal mortality in these pregnancies, intrauterine death cannot be predicted in every case.

In one series, there were three fetal deaths among nine sets of monoamniotic twins who were monitored at least three times weekly[28]. Not every series has noted this, however; two studies, consisting of 37 monoamniotic pregnancies, reported no fetal deaths after 32 weeks, suggesting that early delivery may not be warranted[30,31]. Because monoamniotic twin pregnancies are uncommon, large series from single institutions are not available to determine the optimal time of delivery.

Outcomes after 32 weeks' gestation are excellent in most clinical settings. Consideration should be given to delivery of monoamniotic twins at 32–34 weeks to prevent perinatal mortality or morbidity due to cord entanglement, which cannot be predicted in some cases.

## CONCLUSION

Epidemiologic study suggests that the rate of perinatal mortality in twin pregnancies increases after 38 weeks' gestation, similar to that seen in singleton pregnancies after 40–41 weeks. Whereas delivery is not mandatory in either case after these gestational ages, pregnancy can only be continued in the context of reassuring fetal testing.

In the absence of a clear maternal or fetal indication for delivery of a diamniotic twin pregnancy, elective delivery is appropriate at 38 weeks' gestation. Cesarean delivery before the onset of labor prior to this gestational age may increase the risk of neonatal respiratory morbidity.

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# Impact of Obstetric Intervention on Trends in Perinatal Mortality

*C. V. Ananth and K. S. Joseph*

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## INTRODUCTION

The frequency of twin pregnancies is increasing because of aging of the maternal cohort and the use of assisted reproductive technologies[1]. Among the adverse outcomes associated with all multiple pregnancies are preterm birth, perinatal mortality and serious neonatal and maternal morbidity. Despite these general concerns, recent improvements in obstetric monitoring of fetal well-being, coupled with dramatic advances in neonatal care, permit greater flexibility with regard to obstetric intervention, especially in the case of preterm gestations. These changes have led to substantial improvements in perinatal outcomes in multiple pregnancies in the past decade.

This chapter reviews the role of obstetric intervention, particularly labor induction and cesarean delivery, in recent declines in stillbirths and neonatal and infant mortality among twins. For the purposes of this discussion, labor induction and cesarean delivery are viewed as representing the final common result of obstetric monitoring and surveillance, regardless of the specific pregnancy complication for which such intervention is used. The temporal increase in medically indicated labor induction and cesarean delivery thus subsumes increases in various diagnostic modalities, and, more generally, the enhanced effort aimed at identifying compromised fetuses.

The role of obstetric intervention is particularly important because of recent increases in the rate of preterm birth among twins and the simultaneous declines in infant mortality. In the USA, for example, preterm birth rates among twins increased from 41.9% in 1983 to 53.6% in 1995, while infant mortality among twins decreased substantially from 50.0 per 1000 live births in 1983–84 to 29.2 per 1000 live births in 1995–96[2–4]. In a similar fashion, preterm birth rates among twins in Canada increased from 42.5% in 1985–87 to 49.6% in 1994–96, while infant mortality rates decreased from 39.0 per 1000 twin live births in 1985–87 to 29.6 per 1000 twin live births in 1994–96[5]. The temporal decline in infant mortality rates combined with the simultaneous and unexpected increase in one of its most important determinants, namely preterm birth, initially led to speculation that the infant mortality decline among twins would have been larger but for the concurrent increase in preterm birth rates[6]. However, when the data are examined closely, the increase in preterm birth among twins appears to have been a consequence of increases in the numbers of obstetric interventions[5,7], and the latter being linked to declines in rates of stillbirth[5,7–9]. Given these circumstances, the need is urgent to clarify the role of obstetric intervention and to evaluate its potential impact on adverse perinatal outcomes including stillbirth and neonatal and infant mortality among twins.

Having said this, temporal trends in obstetric intervention and potential effects on perinatal outcomes among twins cannot be evaluated without first addressing issues related to practices in birth registration. Changes in the registration of stillbirths and live births weighing < 500 g, 500–749 g and 750–999 g are likely to affect trends in stillbirths and in neonatal and infant mortality rates. It is currently clear that as the limits of viability are steadily breached and as attitudes towards births at the borderline of viability change, numerous births that were previously unregistered are increasingly being

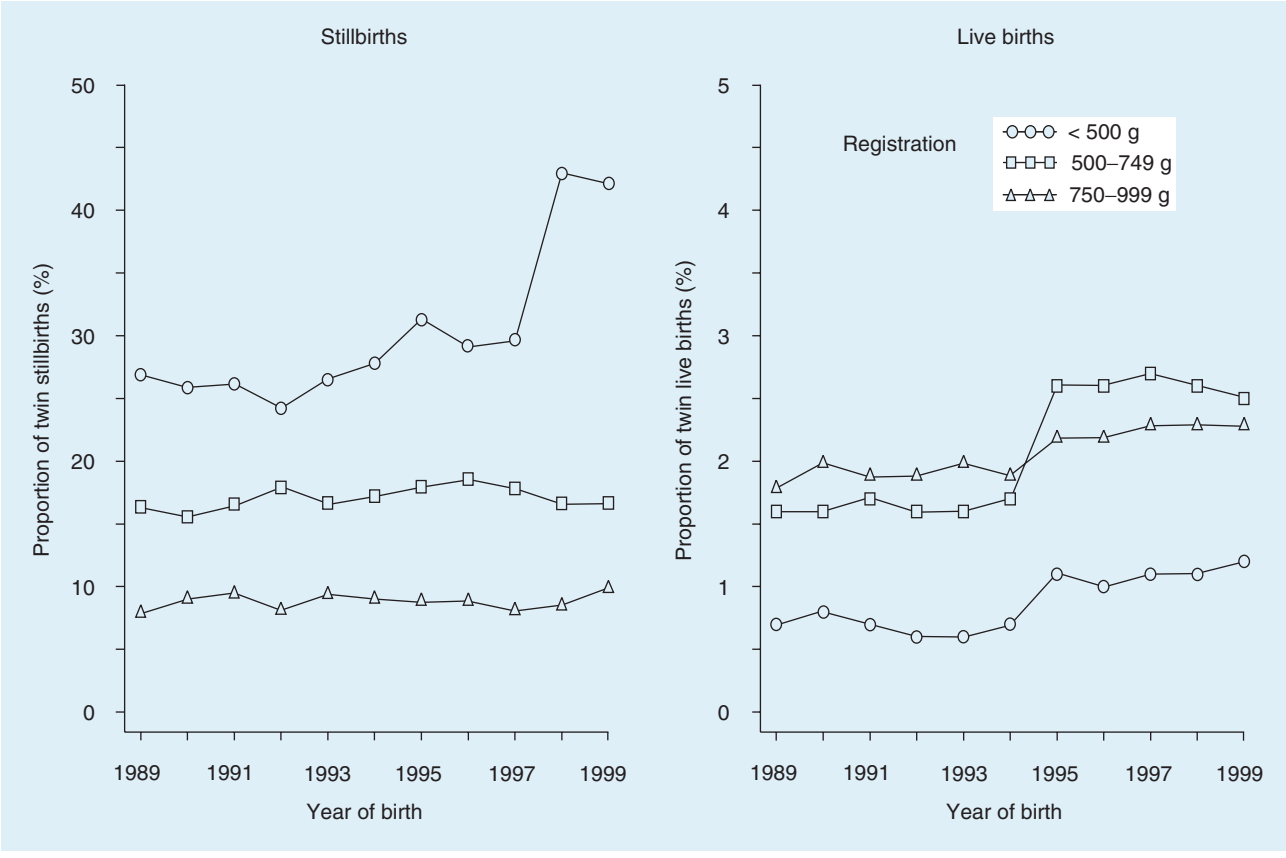


**Figure 77.1** Trends in the proportion of twin stillbirths (left panel) and twin live births (right panel) weighing < 500 g, 500–749 g and 750–999 g: United States twin births 1989 through 1999

registered as stillbirths or live births[10–12]. Such changes have the distinct potential for biasing temporal trends by leading to artifactual increases in stillbirth and infant (especially neonatal) mortality rates.

In this chapter, we first examine temporal trends in the registration of twin live- and stillbirths in the USA between 1989 and 1999. We then examine the extent to which labor induction and cesarean delivery were responsible for the recent decline in perinatal mortality among twins. The latter analysis was carried out after restricting the data to twin births delivered at ≥ 22 weeks' gestation and with a birth weight of ≥ 500 g, in order to exclude the potential effect of changes in birth registration (of births < 500 g or < 22 weeks).

Data from the USA were obtained from the natality records assembled and maintained by the National Center for Health Statistics of the US Centers for Disease Control and Prevention[13]. Canadian data used in these analyses were obtained from the Vital Statistics births and deaths databases maintained at Statistics Canada[14]. This latter database contains information obtained from birth certificates and includes all births in Canada.

## TRENDS IN THE REGISTRATION OF TWIN STILLBIRTHS AND LIVE BIRTHS IN THE USA

Previously defined limits of fetal viability are steadily changing, with dramatic improvements in neonatal care such as the introduction of surfactant[15], antenatal glucocorticoid therapy for fetal lung maturity[16] and assisted ventilation[17]. The subsequent changes in attitudes and birth registration practices, especially at the borderline of viability, affect regional and temporal comparisons of fetal and infant mortality in the United States and Canada[11,18–21]. Another important factor leading to increases in stillbirths at the borderline of viability is the recent increase in prenatal diagnosis and pregnancy termination for serious congenital malformations[22,23] (see also Chapter 34). This later consideration may play a larger role among singleton than among twin pregnancies, however.

The proportions of twin stillbirths weighing < 500 g, 500–749 g and 750–999 g, and infants weighing < 2500 g in the USA, as well as the corresponding proportions among twin live births, are shown in Figure 77.1. The increase in the registration

**Table 77.1** Trends in registration of twin stillbirths and live births: United States 1989–91 and 1997–99. All analyses are based on data aggregated across 49 states in the United States (excluding Louisiana)

| | *Proportion of twin births (%)* | | *Percentage change (95% CI)* |
|---|---|---|---|
| | *1989–91* | *1997–99* | |
| *Stillbirths* | | | |
| < 500 g | 26.3 | 38.1 | 73% (59–87%) |
| 500–749 g | 16.1 | 17.1 | 7% (–4–18%) |
| 750–999 g | 8.9 | 9.0 | 1% (–12–15%) |
| < 2500 g | 82.7 | 84.0 | 10% (0–21%) |
| *Live births* | | | |
| < 500 g | 0.7 | 1.2 | 79% (70–89%) |
| 500–749 g | 1.6 | 2.6 | 61% (55–67%) |
| 750–999 g | 1.9 | 2.2 | 18% (14–23%) |
| < 2500 g | 50.5 | 54.9 | 19% (18–20%) |
| *Stillbirths plus live births* | | | |
| < 500 g | 1.3 | 1.7 | 37% (32–43%) |
| 500–749 g | 2.0 | 2.8 | 43% (38–48%) |
| 750–999 g | 2.0 | 2.3 | 13% (10–17%) |
| < 2500 g | 51.3 | 55.3 | 18% (17–19%) |

CI, Confidence interval

of births weighing < 500 g between 1989–91 and 1997–99 was similar among twin stillbirths and live births (73% and 79%, respectively). The proportion of stillbirths with a birth weight < 500 g increased from 26.3% of all stillbirths in 1989–91 to 38.1% of all stillbirths in 1997–99 (Table 77.1). The rate of twin stillbirths that weighed 500–749 g increased marginally by 7% from 16.1% in 1989–91 to 17.1% in 1997–99. The proportion of twin stillbirths that weighed 750–999 g did not change. The proportion of stillbirths weighing < 2500 g increased by 10%.

The proportion of live births weighing < 500 g increased from 0.7% to 1.2% from 1989–91 to 1997–99 (Table 77.1), while the proportion of twin live births with a birth weight of 500–749 g increased from 1.6% to 2.6% over the same period (79% increase vs. 61% increase, respectively). The proportion of twin live births that weighed 750–999 g increased by 18% from 1.9% in 1989–91 to 2.2% in 1997–99. This differential increase in the proportion of live births < 500 g, 500–749 g and 750–999 g suggests small increases in birth registration at extremely low birth weights.

## TRENDS IN LABOR INDUCTION AND CESAREAN DELIVERY IN THE USA

Figure 77.2 shows the trend in rates of labor induction and cesarean delivery among twin births in the USA. The overall rate of labor induction more than doubled from 5.8% in 1989 to 13.8% in 1999, whereas the rates of cesarean delivery increased by only 15% from 48.3% in 1989 to 55.6% in 1999. Gestational age-specific changes in the rates of labor induction and cesarean delivery between 1989–91 and 1997–99 among twin births weighing ≥ 500 g and delivered at ≥ 22 weeks are shown in Table 77.2. These rates were calculated based on the 'fetuses at risk' approach[24,25]. In this analysis, the gestational age-specific labor induction rate was computed by dividing the number of pregnant women whose labor was induced at any gestational age by the number of pregnant women who were potential candidates for labor induction at that gestational age. Rates of labor induction among twin gestations increased by 34% at 22–27 weeks (from 3.9 per 100 fetuses at risk in 1989–91 to 5.1 per 100 fetuses at risk in 1997–99), 85% at 28–33 weeks (from 3.4 per 100 fetuses at risk in 1989–91 to 6.1 per 100 fetuses at risk in 1997–99) and by 140% at ≥ 34 weeks (from 7.3 per 100 fetuses at risk in 1989–91 to 15.8 per 100 fetuses at risk in 1997–99). As expected, the largest increase in the rate of labor induction occurred at ≥ 34 weeks' gestation.

Cesarean delivery rates also increased between 1989–91 and 1997–99 among twin births that were delivered at ≥ 22 weeks and weighing ≥ 500 g. Overall cesarean delivery rates increased by 13% (from 51.9% in 1989–91 to 55.0% in 1997–99). Among twin pregnancies that were delivered at 22–27 weeks',

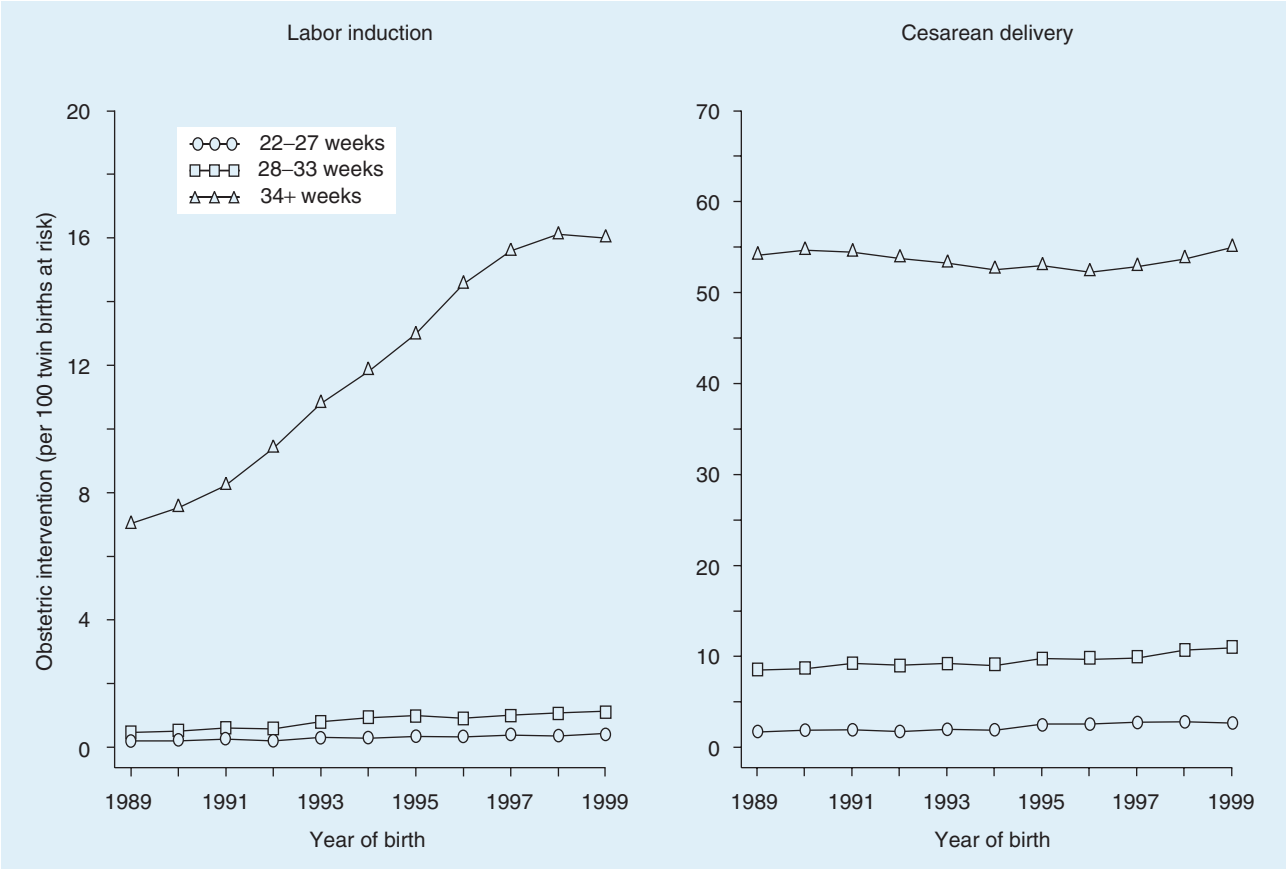


**Figure 77.2** Rate of labor induction (left panel) and cesarean delivery (right panel) among twin births delivered at 22–27 weeks, 28–33 weeks and at ≥ 34 weeks per 100 fetuses at risk: United States twin births 1989 through 1999

**Table 77.2** Trends in rates of gestational age-specific labor induction among twin births delivered at ≥ 22 weeks and weighing ≥ 500 g per 100 fetuses at risk: United States 1989–91 and 1997–99. All analyses are based on data aggregated across 49 states (excluding Louisiana) in the United States

| | *Rate per 100 fetuses at risk* | | *Percentage (95% CI)* |
|---|---|---|---|
| | *1989–91* | *1997–99* | |
| *Labor induction* | 6.6 | 13.7 | 132% (128–137%) |
| 22–27 weeks | 3.9 | 5.1 | 34% (19–51%) |
| 28–33 weeks | 3.4 | 6.1 | 85% (74–98%) |
| ≥ 34 weeks | 7.3 | 15.8 | 140% (135–144%) |
| *Cesarean delivery* | 51.9 | 55.0 | 13% (12–14%) |
| 22–27 weeks | 43.3 | 53.7 | 52% (45–59%) |
| 28–33 weeks | 55.2 | 61.1 | 28% (24–31%) |
| ≥ 34 weeks | 51.7 | 53.8 | 9% (7–11%) |

CI, confidence interval

28–33 weeks' and ≥ 34 weeks' gestation, the rate of cesarean deliveries increased by 52%, 28% and 9%, respectively, between 1989–91 and 1997–99. Although the rates increased to a greater extent at earlier rather than at later gestational ages, the absolute rates were higher at later gestational ages.

## TRENDS IN TWIN STILLBIRTH AND NEONATAL MORTALITY IN THE USA

As noted above, the assessment of temporal trends in twin stillbirth and neonatal mortality was restricted to mortality trends among twin births delivered

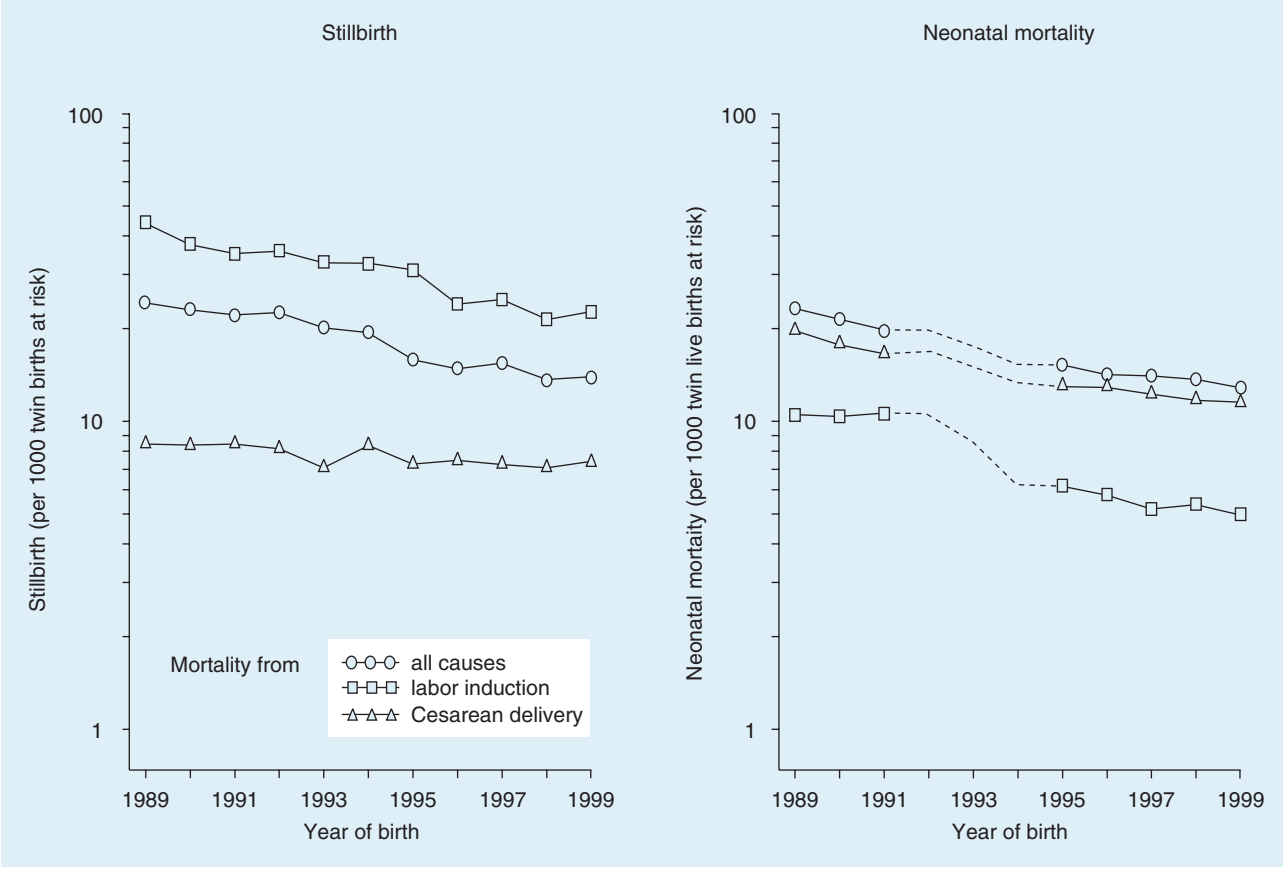


**Figure 77.3** Stillbirth (left panel) and neonatal mortality rates (right panel) per 1000 total births and per 1000 live births, respectively, among twins delivered at ≥ 22 weeks and weighing ≥ 500 g following labor induction and cesarean delivery: United States twin births 1989 through 1999

at ≥ 22 weeks, and with a birth weight ≥ 500 g. Stillbirth and neonatal mortality rates declined between 1989 and 1999, as did the overall rate of perinatal mortality (Figure 77.3). Stillbirth and neonatal mortality rates among twins delivered following labor induction, and to a lesser extent following cesarean section, declined as well (Figure 77.3). The overall stillbirth rate among twins in the United States decreased from 17.3 per 1000 total births in 1989–91 to 9.0 per 1000 total births in 1997–99, a relative decline of 48% (95% confidence interval 45–51%).

Ecologic multivariable logistic regression models[9] with sequential adjustment for labor induction and cesarean delivery reduced the observed decline in the stillbirth rate to 25% (95% confidence interval 21–28%), as shown in Table 77.3. Stated another way, the observed 48% decline in the twin stillbirth rate would have been only 25% if labor induction and/or cesarean delivery rates had not increased between 1989–91 and 1997–99. Thus, almost half the decline in the twin stillbirth rate between 1989–91 and 1997–99 (i.e. the difference between a 48% decline vs. a 25% decline) resulted from the increases in labor induction and/or cesarean delivery[9].

It is possible, however, that such obstetric interventions, while preventing stillbirths among compromised twin fetuses, led to an excess of neonatal deaths. If such a shift in the timing of death were to have occurred, it would have reduced the temporal decline in neonatal mortality among twins. We therefore examined the extent to which increases in such obstetric interventions may have attenuated the decline in neonatal mortality during the same period (Table 77.3). Overall, the neonatal mortality rate declined by 37% (95% confidence interval 35–40%) from 21.5 per 1000 twin live births in 1989–91 to 13.6 per 1000 twin live births in 1997–99[26]. When the temporal reduction in neonatal mortality was sequentially adjusted for labor induction and cesarean delivery, the neonatal mortality rate declined by 33% (95% confidence interval 31–36%).

**Table 77.3** Trends in twin stillbirth and neonatal mortality among twins delivered at ≥ 22 weeks and weighing ≥ 500 g: United States 1989–91 and 1997–99. All analyses are based on data aggregated across 49 states (excluding Louisiana) in the United States

| | *Twin still births* | | | *Twin neonatal deaths* | | |
|---|---|---|---|---|---|---|
| | *Rate per 1000 total births* | | *Percentage change (95% CI)* | *Rate per 1000 live births* | | *Percentage change (95% CI)* |
| | *1989–91* | *1997–99* | | *1989–91* | *1997–99* | |
| Crude trend | 17.3 | 9.0 | –48% (–51 to –45%) | 21.5 | 13.6 | –37% (–40% to –35%) |
| Sequentially adjusted for | | | | | | |
| labor induction | 15.5 | 11.0 | –29% (–33 to –26%) | 22.2 | 14.8 | –34% (–37% to –31%) |
| plus cesarean delivery | 14.7 | 11.1 | –25% (–28 to –21%) | 26.7 | 17.9 | –33% (–36% to –31%) |

CI, confidence interval

In other words, the observed 37% decline in the twin neonatal mortality rate would have been a 33% decline had labor induction and/or cesarean delivery rates not increased between 1989–91 and 1997–99. Although not nearly as large as the effect on stillbirth rates, labor induction and cesarean delivery contributed substantially to temporal reductions in neonatal mortality. In sum, these data provide compelling evidence that increases in obstetric intervention produced large declines in the stillbirth rate and have not adversely affected the temporal decline in neonatal mortality rates among twins in the USA[26].

## TRENDS IN OBSTETRIC INTERVENTION AND PERINATAL MORTALITY AMONG TWINS IN CANADA

As was the case in the neighboring USA, the rate of medical and surgical induction of labor increased substantially in Canada over the previous decade[27]. Not unexpectedly, these increases differed by risk status and occurred mostly at a gestational of ≥ 34 weeks[7]. For example, preterm labor induction rates among twins in Nova Scotia, Canada, increased from 3.5% in 1988–89 to 8.6% in 1996–97, while across the same period preterm cesarean delivery rates increased from 20.2% to 23.9%[5]. The increase in labor induction was due primarily to increases in labor induction for indications such as hypertension, premature rupture of the membranes, oligohydramnios and abnormal biophysical profiles. At the same time, labor induction rates for fetal growth restriction decreased between 1988–89 and 1996–97[5], suggesting that improved methods of assessing fetal well-being led to obstetric intervention before fetal growth was affected.

Labor induction rates among twin live births born at ≥ 37 weeks also increased substantially, from 18.1% in 1988–89 to 35.6% in 1996–97[5]. Although overall cesarean delivery rates did not increase significantly in Nova Scotia, Canada, the increase in obstetric intervention was responsible for a left-shift in the gestational age distribution of twin births. The preterm birth rate among twins increased from 42.6% in 1988–89 to 47.5% in 1996–97 in Nova Scotia, Canada. In Canada, increases in labor induction and/or cesarean delivery resulted in increases in the rate of preterm birth rate among twins from 42.5% in 1985–87 to 53.0% in 2000[6,8,27]. Temporal increases in labor induction and/or cesarean delivery were associated with reductions in perinatal mortality[8,27]. Stillbirth rates among twins ≥ 500 g decreased from 16.9 per 1000 total births in 1985–86 to 12.9 per 1000 total births in 1998–99[27]. Similarly, neonatal mortality rates among twins in Canada declined from 28.6 per 1000 live births in 1985–86 to 15.1 per 1000 live births in 1998–99[27].

Interestingly, stillbirths due to complications of the placenta, cord and membranes declined among twin births ≥ 500 g from 6.44 per 1000 total births in 1985–88 to 4.74 per 1000 total births in 1996–99 (Table 77.4), and stillbirths due to unspecified causes (International Classification of Diseases (ICD)-9 779.9)

**Table 77.4** Cause-specific rates of stillbirth and infant death among twin births weighing ≥ 500 g in Canada (excluding Newfoundland and Ontario) in 1985–88 and 1996–99

| *Cause of death* | *Stillbirths per 1000 total births/infant deaths per 1000 live births at risk* | | *Percentage change (95% CI)* |
|---|---|---|---|
| | *1985–88 (n = 18 055/17 749)* | *1996–99 (n = 19 847/9 592)* | |
| *Stillbirths per 1000 total births* | | | |
| Congenital anomalies | 0.8 | 1.2 | 46% (–24 to 177%) |
| Short gestation/low birth weight | 0.3 | 0.4 | 46% (–52 to 345%) |
| Complications of pregnancy | 3.4 | 3.3 | –3% (–31 to 37%) |
| Complications of placenta, cord, membranes | 6.4 | 4.7 | –26% (–44 to –3%) |
| Hypoxia/birth asphyxia | 1.6 | 0.8 | –51% (–74 to –9%) |
| Unspecified causes | 2.9 | 1.4 | –52% (–70 to –24%) |
| Total | 17.0 | 12.9 | –24% (–35 to –10%) |
| *Infant deaths per 1000 live births at risk* | | | |
| Congenital anomalies | 5.9 | 4.5 | –23% (–42 to 2%) |
| Short gestation/low birth weight | 2.5 | 1.1 | –55% (–73 to –24%) |
| Complications of pregnancy | 4.3 | 2.4 | –44% (–61 to –19%) |
| Complications of placenta, cord, membranes | 1.3 | 1.3 | –2% (–44 to 73%) |
| Hypoxia/birth asphyxia | 1.0 | 0.4 | –63% (–85 to –10%) |
| Respiratory distress syndrome | 7.2 | 2.5 | –65% (–75 to –52%) |
| Sudden infant death syndrome | 1.8 | 0.8 | –56% (–76 to –19%) |
| Total | 33.5 | 20.4 | –39% (–46 to –31%) |

CI, confidence interval

also decreased significantly from 2.94 to 1.41 per 1000 total births. The reduction in stillbirths due to intrauterine hypoxia and birth asphyxia was 51%. Among twin live births weighing ≥ 500 g, infant deaths due to intrauterine hypoxia and birth asphyxia declined by 63%, while those due to short gestation and unspecified low birth weight and respiratory distress syndrome decreased by 55% and 44%, respectively[27].

It is noteworthy that the magnitude of the temporal decrease in perinatal mortality was larger at later gestational ages, at which the largest increases in labor induction occurred[8,27]. For example, among twin births delivered at ≥ 36 weeks the reduction in stillbirth rate between 1985–88 and 1996–99 was 41% (95% confidence interval (CI) 20–57%); this was larger than the reduction in the stillbirth rate among twin births at ≥ 32 weeks' gestation (29% reduction, 95% CI 10–43%), which in turn was larger than the decline in the stillbirth rate at ≥ 22 weeks' gestation (24% reduction, 95% CI 10–35%). Similarly, among twin births delivered at ≥ 36 weeks, ≥ 32 weeks and ≥ 22 weeks, the reduction in neonatal mortality between 1985–88 and 1996–99 was 52%, 37% and 36%, respectively (Figure 77.4).

## CONCLUSIONS

Multiple pregnancy represents a serious and increasingly frequent obstetric challenge. Closer monitoring of these high-risk twin pregnancies has led to increased rates of obstetric intervention, with labor induction and cesarean delivery rates among twin gestations increasing in both the USA and Canada. These increases are particularly evident at 34 weeks' gestation and beyond. Although infant mortality among those born at mild preterm gestation (i.e. at 34–36 weeks) is not insignificant[28], supportive care available in contemporary neonatal intensive-care units clearly justifies iatrogenic

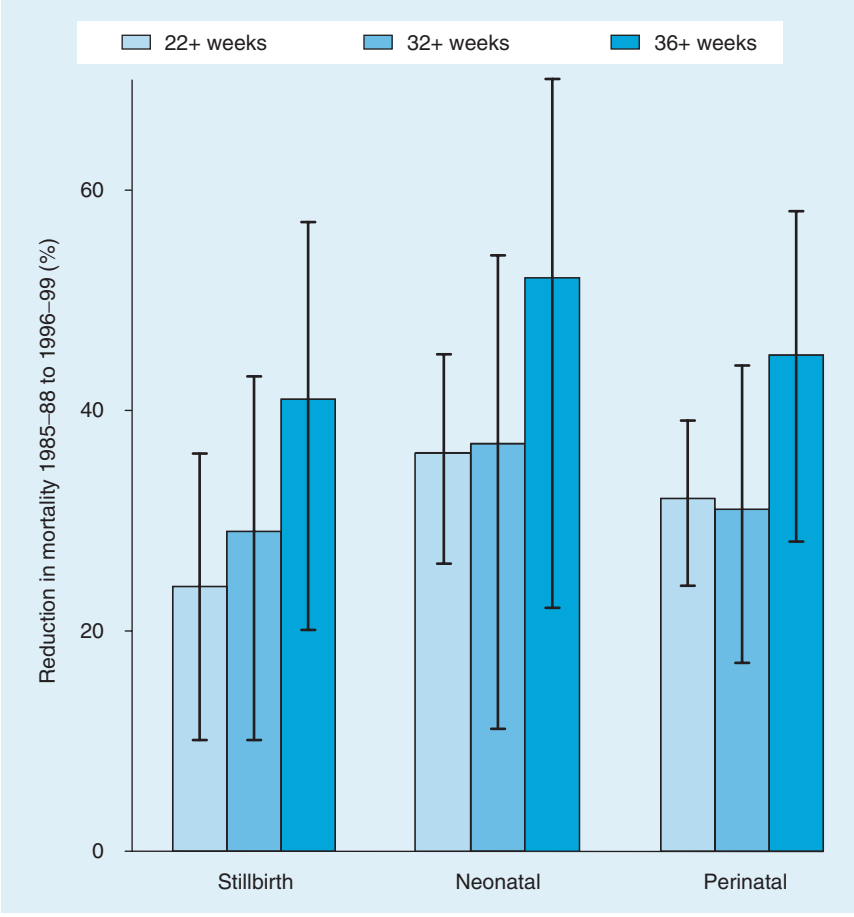


**Figure 77.4** Percentage reduction in stillbirths and neonatal and perinatal mortality among twin births, by gestational age, between 1985–88 and 1996–99, Canada (excluding Newfoundland and Ontario). Reproduced with permission from the Canadian *Perinatal Health Report 2003*[27]

preterm delivery of compromised fetuses at this age in order to prevent fetal death or serious neonatal morbidity. Despite the advantage of such a policy, increases in obstetric interventions, especially those performed at preterm gestational ages, lead to an increasing burden on the health-care system in terms of greater requirements for specialized obstetric services and neonatal care. Admittedly, temporal increases in such obstetric interventions have been accompanied by concurrent declines in stillbirth and neonatal and infant mortality rates among twin gestations in both the USA and Canada. The decline in fetal deaths has occurred owing to significant temporal reductions in the frequency of stillbirths due to intrauterine hypoxia and birth asphyxia and unspecified causes. Infant deaths due to intrauterine hypoxia and birth asphyxia, short gestation and low birth weight, complications of pregnancy, respiratory distress syndrome and sudden infant death syndrome have declined as well. Thus, the observed increases in medically indicated labor induction and cesarean delivery, supported by advances in neonatal care, contribute substantially to declines in fetal and infant mortality among twins.

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# The Optimum Route of Delivery

*R. B. Kalish and F. A. Chervenak*

78



## INTRODUCTION

The optimum route of delivery of multiple gestations has long been a matter of controversy[1,2]. Even in an era of emerging sets of population-based data, the role of elective cesarean delivery for certain subsets of twin gestation is still debated. Simply stated, any delivery plan for twins requires consideration of the varied possible presentations for twin A and twin B. Figure 78.1 illustrates these varied combinations, whereas Figure 78.2 illustrates a useful clinical classification of twin presentations. Here all combinations are classified into three groups[3]:

(1) Twin A, vertex with twin B, vertex (42.5%);

(2) Twin A, vertex with twin B, non-vertex (38.4%);

(3) Twin A, non-vertex (19.1%).

This chapter presents an intrapartum management plan for each group, based upon analysis of outcome, and discusses controversial issues associated with the choice of the route of delivery.

## TWIN A, VERTEX WITH TWIN B, VERTEX

In general, attempted vaginal delivery is appropriate for vertex–vertex twins with neonatal outcomes comparable to those of abdominally delivered twins[4]. In addition, although cesarean delivery has been proposed for vertex–vertex twins of < 1500 g[5], few data support this proposition. Rydhstrom evaluated the impact of cesarean section on neonatal outcomes in twins weighing less than 1500 g and found no significant impact of abdominal birth on the fetal outcome for low-birth-weight twins when twin A was in vertex presentation[6]. Thus, vaginal delivery of vertex–vertex twins may be appropriate for twins at any gestational age. In addition, in vertex–vertex twins, the estimated fetal weight of either fetus in relation to the other should not alter the management plan. In particular, Usta and colleagues evaluated the perinatal outcomes of vaginally delivered twins when twin B weighed ≥ 250 g more than twin A[7]. These authors found that when twin B was larger than twin A and both were delivered vaginally, the perinatal outcome was similar for both twins.

Previously, it was accepted clinical practice that the time interval between twin deliveries should be no more than 30 min to avoid asphyxia to the second twin, cord prolapse, placental abruption and retraction of the cervix[8]. Limited more recent evidence shows that an increased twin-to-twin delivery interval may be associated with increased risks of fetal acidosis in the second twin[9]. However, few studies have evaluated this circumstance in vertex–vertex presenting twins. Moreover, several studies using modern fetal monitoring equipment show that perinatal morbidity and mortality do not correlate with the time interval between twin deliveries[10–12]. Indeed, no acute urgency dictates delivery of twin B after delivery of twin A if electronic fetal heart rate monitoring or sonographic visualization of the fetal heart is reassuring.

Intervals between deliveries of multiples of up to several months have been reported (see Chapter 75)[13–20]. Most cases of delayed-interval twin deliveries occur in dichorionic twins, and are the result of preterm labor or preterm premature rupture of the fetal membranes of the first twin at

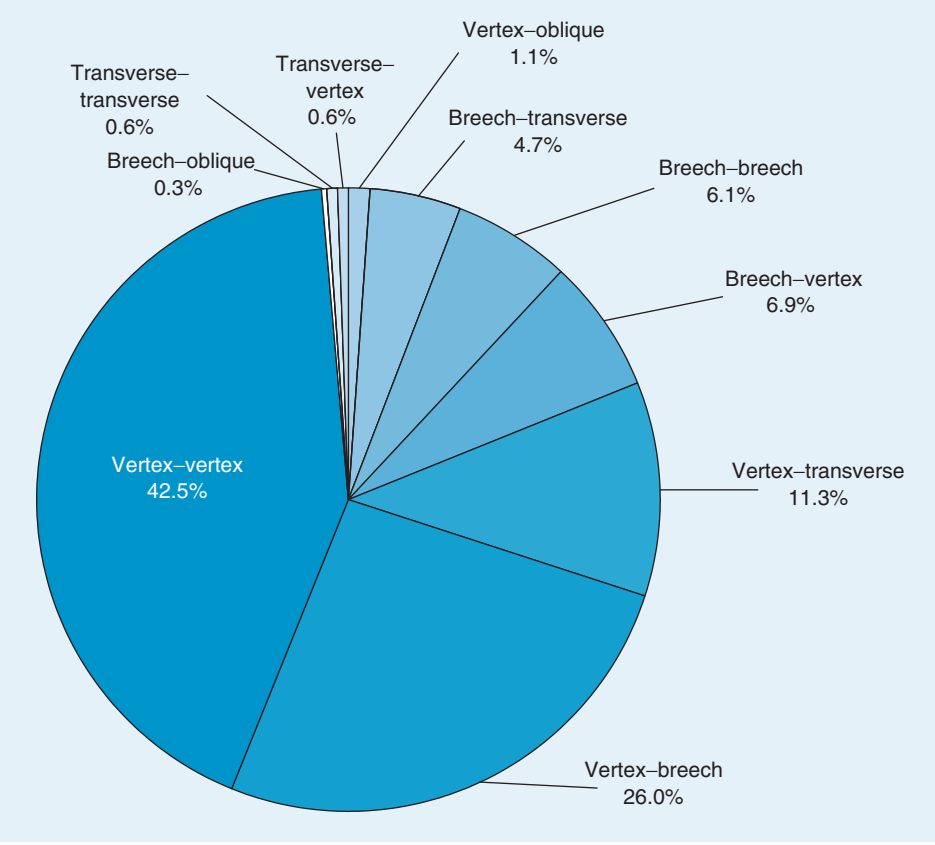


**Figure 78.1** Diagram showing occurrence of intrapartum presentations for 362 consecutive twin gestations (adapted from reference 1)

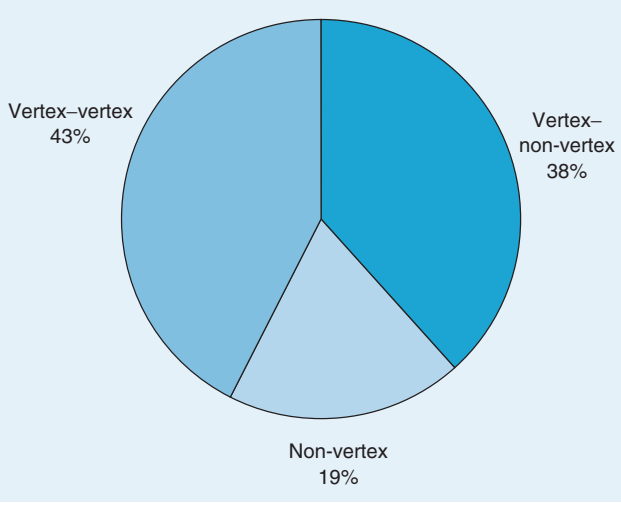


**Figure 78.2** Diagram showing occurrence of twin A, vertex with twin B, vertex; twin A, vertex with twin B, non-vertex; and twin A, non-vertex for 362 consecutive twin gestations (adapted with permission from reference 2)

previable or extremely premature gestational ages. Although favorable outcomes for the second twin have been reported in several series, high rates of perinatal mortality as well as maternal morbidity have also been reported[21]. Livingston and colleagues recently reported the outcomes of 14 instances of asynchronous multifetal deliveries, with only one of 28 neonates being discharged from hospital without any major neurologic sequelae. In addition, two cases of abruption, eight cases of maternal infectious morbidity and one case of maternal septic shock were observed. For delayed delivery of a second twin to be contemplated, the membranes of the second twin should be intact, and, if the placenta is retained, the umbilical cord of the first twin should be tied and cut as close as possible to the cervix. Despite that cervical suture and tocolysis have been reported as useful adjuncts in this setting to prolong interdelivery interval[22], the risks and benefits of this form of management need further evaluation. Currently, no consensus is present regarding what precise gestational age is appropriate to attempt delayed delivery of a multifetal gestation. If attempted, the risks and benefits of immediate delivery of the entire pregnancy versus delayed delivery should be clearly discussed with the family (see Chapter 75).

With vertex–vertex presentations, oxytocin augmentation with careful surveillance of fetal heart function may be useful if labor does not resume within 10 min of delivery of the first twin. Amniotomy is recommended only after the vertex of the second twin is in the pelvic inlet. No modern series demonstrates the safety of internal podalic version in

cases of fetal distress. If the fetal heart rate tracing of twin B deteriorates before atraumatic vaginal delivery is possible, in the authors' view, cesarean delivery is the management of choice. Because of this possibility, delivery of twins should always take place in clinical settings where it is possible to perform an immediate cesarean delivery. Indeed, such a setting should be considered the standard of care for all twins. Spontaneous conversion of a vertex second twin to a non-vertex presentation is a rare possibility. If this rare situation occurs, the intrapartum management of the second twin can proceed as described in the section that follows.

For both twins and singletons, a growing body of literature supports vaginal delivery of even the very-low-birth-weight (VLBW) fetus in the vertex presentation[6,23]. In the past, it was commonly believed that labor and subsequent vaginal delivery led to head compression and intraventricular hemorrhage (IVH) with its resultant complications. However, the incidence and severity of IVH are no longer thought to be affected by mode of delivery[24–26]. Although vaginal delivery is appropriate for the vertex–vertex twin gestation even in the VLBW group, this position is not universally accepted[5].

## TWIN A, VERTEX AND TWIN B, NON-VERTEX

The management of twin gestations in vertex–breech or vertex–transverse presentation is particularly controversial. Support is present for both cesarean and vaginal delivery. Several investigators advocate cesarean delivery as the management of choice when the second twin is in the breech presentation or transverse lie[27,28]. This approach was originally justified by early reports of increased perinatal mortality[25,29,30] and depressed Apgar scores with breech delivery of the second twin[30,31]. However, a substantial body of more recent evidence exists to demonstrate the safety of vaginal delivery in these cases[32–37]. The options of intrapartum external cephalic version and breech extraction of the second twin are analyzed next.

### Intrapartum external version

External cephalic version is a useful modality in singleton fetuses to allow for the possibility of a vertex vaginal delivery with a low risk of complications including cord accident or placental abruption[38]. Over the years, several reports also advocated external cephalic version of the second twin[39–42]. Kaplan and colleagues evaluated 142 cases of vertex–non-vertex twins. External cephalic version of the second twin with subsequent vaginal delivery was successful in 75% of cases with no complications reported[40]. In the series by Chervenak and associates, version was successful in ten of 14 (71%) transverse presentations and eight of 11 (73%) breech presentations, resulting in vertex vaginal delivery[39]. The success of version was not related to gestational age, birth weight or parity. In our hands, all eight versions attempted under epidural anesthesia were successful, suggesting that relaxation of the abdominal wall musculature may be helpful for success. In this series, the 5-min Apgar score was depressed in only two cases (Apgar of 6 in each case). Because the time interval between delivery of twin A and twin B was not related to either 1- or 5-min Apgar scores, the time spent in version apparently did not exert a detrimental effect. In this small series, maternal morbidity was not excessive, and consisted of two cases of endometritis requiring antibiotics and one case of uterine atony managed by uterine massage and oxytocin administration.

The following guidelines are recommended for performance of intrapartum external cephalic version of the second twin, beginning with an initial sonographic assessment of the size of each fetus. If twin B is larger than twin A and a great disparity exists, version with attempts at vaginal delivery is best avoided. Epidural anesthesia is advisable before delivery, to provide abdominal wall relaxation. In addition, intravenous nitroglycerin or inhalational analgesia will relax uterine muscle and may be considered if necessary[43]. Intact membranes are essential, and version should be performed only if immediate cesarean delivery is possible. The version should be attempted immediately after, or even during, delivery of the first twin while the uterus is most relaxed. A real-time ultrasound machine should be present in the delivery room to determine accurately fetal presentation after delivery of the first twin. The fetal heart rate should be monitored continuously. Gentle external abdominal pressure with the transducer may be used to guide the infant's head into vertex presentation above the birth canal (Figure 78.3). If this is not successful, external cephalic version can be attempted either as a forward or as a backward roll using the operator's hands on the abdomen in the traditional fashion. The shortest arc between the vertex and the pelvic inlet should be attempted first. Undue force should always be avoided. If version is unsuccessful, if the fetal heart tones of twin B show evidence of fetal distress or if twin B fails to descend after successful version, cesarean delivery or breech extraction is necessary.

Despite studies demonstrating high rates of successful vaginal delivery with low complication rates, some authors argue that external cephalic version should not be performed for a second non-vertex twin[44,45]. Chauhan and colleagues compared 23 twin pregnancies delivered by total breech extraction of

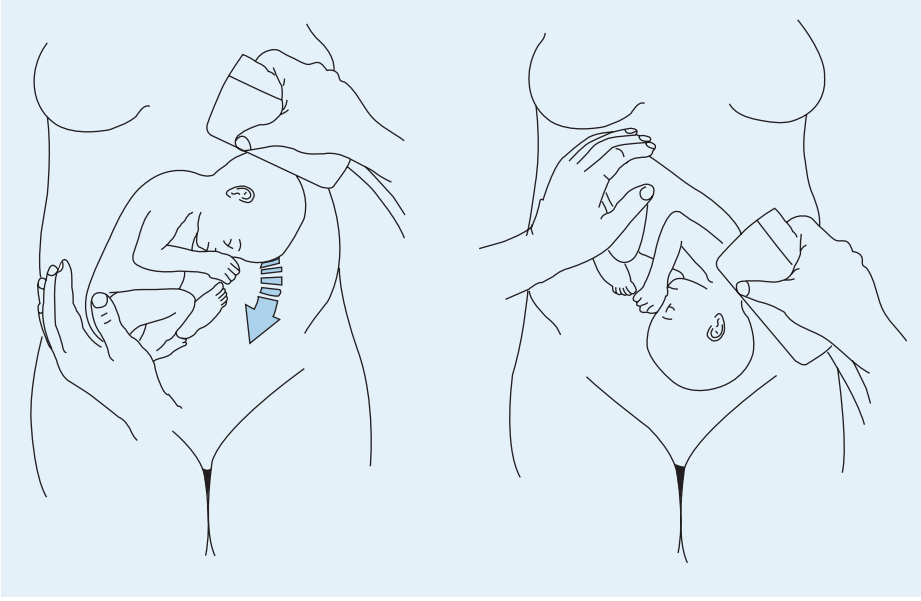

**Figure 78.3** Method of using ultrasound transducer to guide vertex into pelvis. (Reprinted with permission from reference 39)

the second non-vertex twin with 21 pregnancies that underwent external cephalic version of the second non-vertex twin. These authors found a significantly lower incidence of fetal distress and abdominal delivery with comparable neonatal outcomes in the total breech extraction group. Similarly, Smith and co-workers reported their series of 33 twin pregnancies undergoing external cephalic version for the second non-vertex twin and 43 undergoing primary breech extraction for the second non-vertex twin. Here, external version was associated with significantly greater incidence of cesarean section and fetal distress[45]. Of interest, both reports are recent, but it is not possible to state the level of experience of all operators. Indeed, it is quite possible that younger physicians will have little or no experience with total breech extraction. Moreover, such activities may become less favored as a result of the Term Breech Trial (see Chapter 79).

The obstetrician should always discuss the mode of delivery, possible maneuvers and potential risks with patients attempting to deliver vertex–non-vertex twins vaginally prior to the onset of labor (or at least prior to the second stage of labor). Of note, successful external cephalic version with subsequent vaginal delivery of a malpresenting twin A has been reported[46]. However, data regarding the safety and efficacy of this procedure have not been well documented and this procedure is not routinely recommended.

## Breech delivery

A recent Cochrane Review meta-analysis assessed the effects of cesarean birth compared with vaginal birth of a second twin not presenting cephalically using published randomized trials[47]. This review found no differences in neonatal outcome, despite an increased incidence of maternal febrile morbidity in women undergoing cesarean delivery. In particular, Rabinovici and colleagues randomized 60 twin deliveries with vertex–non-vertex presentation for either vaginal (31 pregnancies) or cesarean (27 pregnancies) delivery and found no difference in 1- and 5-min Apgar scores or incidence of neonatal morbidity between the second-born twins, irrespective of delivery route[36]. There were no cases of birth trauma or neonatal death.

The Cornell experience is in agreement with this[48]. In our series of 60 breech-delivered second twins with a birth weight of 1500 g or greater, no 5-min Apgar scores were recorded to be $< 4$. Three infants (5%) had scores between 4 and 6 and 55 infants (95%) had scores of $\geq 7$. Of the three pregnancies with Apgar scores $< 4$, one was an undiagnosed twin pregnancy, the second was a monoamniotic gestation with entangled umbilical cords and the third occurred in a 32-week gestation in which the first twin also had a depressed Apgar score. These data suggest that there is no excessive risk of asphyxia for the vaginally delivered breech second twin above 1500 g (Figure 78.4).

Further, examination of a large twin population in which 71% of 139 twins in vertex–non-vertex presentation delivered vaginally failed to document a high rate of birth trauma due to vaginal breech delivery[1]. The four cases of significant birth trauma for the entire twin population are summarized in Table 78.1. The one instance of neonatal death occurred in a 1000-g second twin of a breech–breech

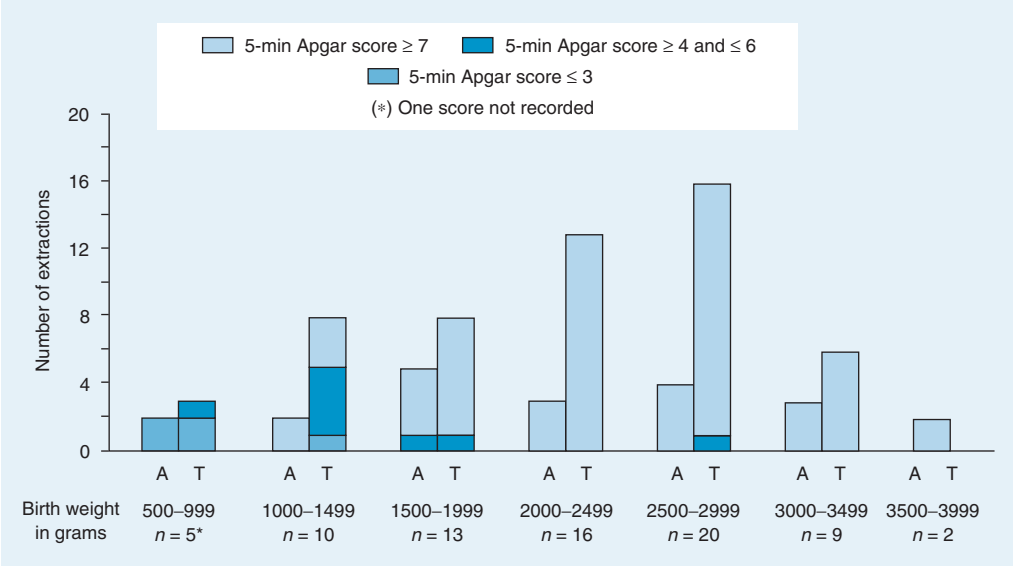


**Figure 78.4** Five-minute Apgar scores of extracted second twins by birth weight. A, assisted breech extraction; T, total breech extraction (reproduced with permission from reference 48)

**Table 78.1** Significant birth trauma for 362 consecutive twin gestations

| *Birth trauma* | *Presentation* | *Birth weight* (g) | *Mode of delivery* |
|---|---|---|---|
| Neonatal death, 12 h, perinatal asphyxia | breech–breech; twin B | 1000 | cesarean section with low vertical uterine incision |
| Erb's paralysis, paralysis left hemidiaphragm | vertex–vertex; twin A | 2100 | vertex vaginal delivery (mid-forceps, prolonged second stage of labor) |
| Greenstick fracture right clavicle; non-displaced fracture, right humerus | vertex–breech; twin B | 3420 | vaginal delivery; total breech extraction |
| Large cephalohematoma, resultant anemia and hyperbilirubinemia | vertex–breech; twin A | 2640 | vertex vaginal delivery (vacuum extraction, prolonged second stage of labor) |

pair. Both infants were delivered by cesarean section and neonatal death occurred at 12 h of life. The three remaining cases of significant birth trauma occurred during vaginal delivery. One was related to difficult total breech extraction of a second twin, and the other two were associated with operative vertex deliveries. In all three cases, follow-up examinations revealed no residual deficits in the surviving infants.

Blickstein and colleagues reported experience with 39 vertex–breech twin pairs delivered vaginally[37]. These authors found no difference in outcome between the breech second twin delivered vaginally and a control group of vertex second twins delivered by the same route. In addition, Acker and associates found no increase in perinatal mortality or depressed 5-min Apgar scores when the second twin was delivered vaginally as a breech[49]. Goecke and co-workers prospectively studied mode of delivery for the non-vertex second twin weighing > 1500 g[50], comparing three approaches: cesarean delivery, external cephalic version and breech extraction. Breech extraction had the best results with no increase in maternal or neonatal morbidity. Moreover, it was associated with the shortest postpartum stay. External version was successful in 46% of cases, but this procedure necessitated an emergent cesarean delivery in 6/41 cases. These authors concluded that breech extraction of the second twin was both safe and efficient. They also suggested that breech extraction was a reasonable secondary approach to vaginal delivery for the non-vertex second twin if version was unsuccessful.

The documented ill effects of vaginal delivery for low-birth-weight singletons in breech presentation[51–54], although controversial[55,56], should be considered in any plan of intrapartum management for

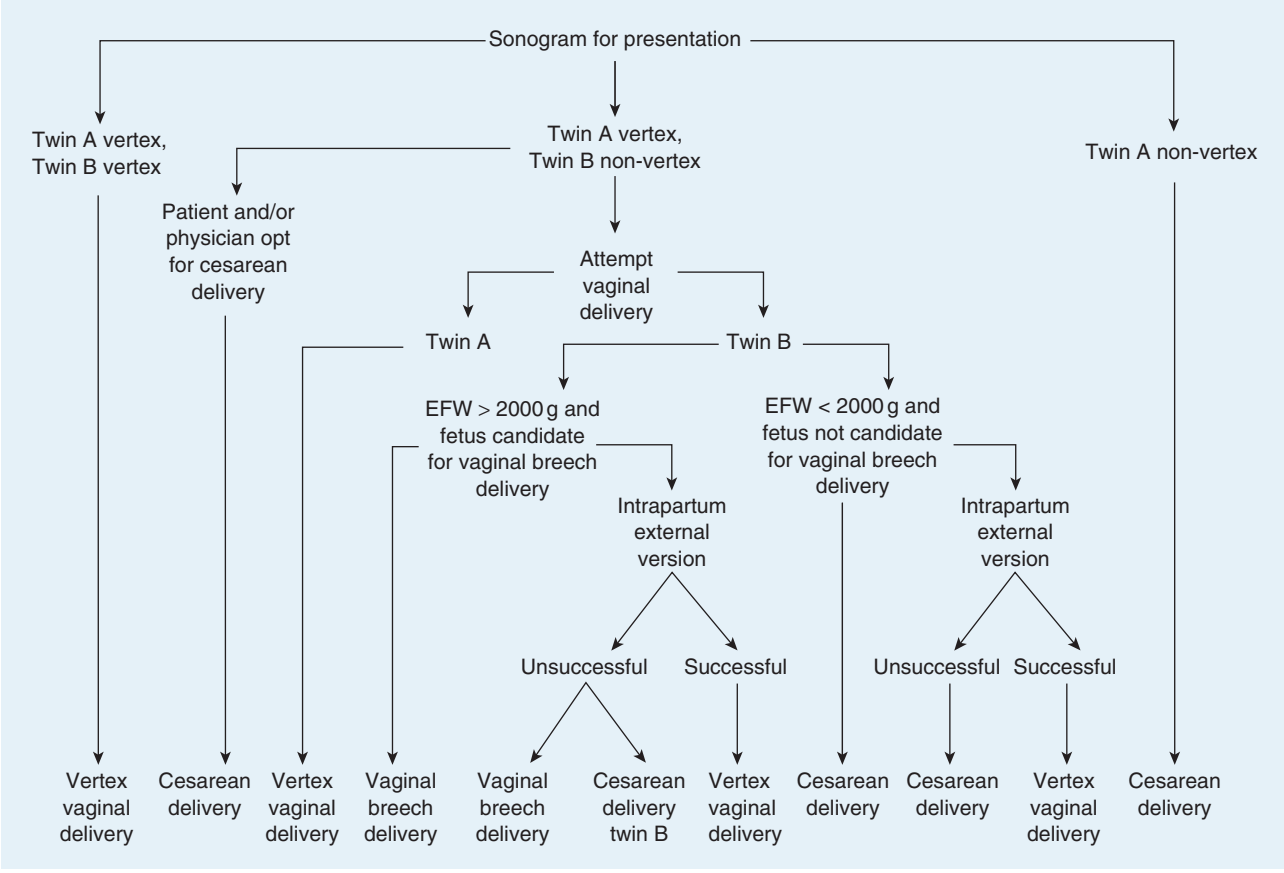


**Figure 78.5** Protocol for the intrapartum management of twin gestation. EFW, estimated fetal weight

vertex–non-vertex twin gestations. No published series has demonstrated any protection against the hazards of breech delivery for the low-birth-weight non-vertex second twin. Because of the lack of data demonstrating its safety, we believe that vaginal breech delivery is not warranted when birth weight is < 1500 g. Fortunately, the fetal weight can be estimated with fair reliability using antenatal sonography[57–59]. With current methods, sonographic estimations of fetal weight are accurate within ± 20% of actual weight. Under these circumstances, the use of a cut-off of 2000 g for estimated fetal weight would be highly unlikely to result in an infant with a birth weight of < 1500 g. A schematic plan for the intrapartum management of vertex–non-vertex twins is presented in Figure 78.5.

During the intrapartum period, it is possible and advisable to obtain sonographic estimation of fetal weight and to use this in the context of standard criteria for vaginal breech delivery (i.e. an adequate pelvis and a flexed fetal head)[60]. It is important to emphasize, however, that cesarean delivery is not a panacea and does not preclude the possibility of birth injury[61]. Indeed, Su and colleagues[53] demonstrated significant risk to vaginal breech delivery in singletons. Although the relevance of these data to vaginal breech delivery of the second twin is uncertain, we recommend that the potential risk of vaginal breech delivery is explained to all women who are considering breech delivery of the second twin.

## TWIN A, NON-VERTEX

Currently, cesarean section is the delivery method of choice when the first twin is non-vertex, as there are limited data to document the safety of vaginal delivery for this group of infants. External cephalic version of a non-vertex first twin would be difficult, if not impossible, in most instances. Interlocking of fetal heads is a potentially disastrous complication of vaginal breech delivery of the first twin[62]. It is not inconceivable that the second twin might also interfere with breech vaginal delivery of the first twin in more subtle ways, such as deflexion of the descending vertex. This view is not accepted by all practitioners, and vaginal delivery may be safe in specific cases. In particular, Blickstein and colleagues evaluated perinatal morbidity and mortality in breech first twins delivered vaginally and found no evidence that vaginal birth is unsafe[63,64]. Despite

this, Hogle and associates[65] recently suggested that elective cesarean section may decrease the risk of low 5-min Apgar scores if twin A is breech.

## FINAL CONSIDERATIONS

Special circumstances clearly occur for which the plan of management cited above is not appropriate. For example, monoamniotic twin pregnancies have such a high risk for cord entanglement and subsequent intrauterine death (see Chapter 67) that elective cesarean delivery should be performed in all cases[66]. Likewise, conjoined twins for whom there is some hope of survival, or for whom dystocia is likely, should be delivered by cesarean section.

Growth restriction frequently occurs in a twin pregnancy. Some fetuses are unable to withstand the stress of labor. Cesarean delivery is then necessary. Rarely, the position of a dead twin or of an acardiac fetus may affect the mode of delivery. In addition, some indications for cesarean delivery, such as placenta previa, prolapsed umbilical cord and dysfunctional labor of cephalopelvic disproportion, occur with increased frequency in twins.

Finally, in the rare instance when three or more fetuses are present, cesarean delivery is judicious (see Chapter 81). Although Locopoulos and Jewelewicz[67] and others[68] years ago suggested that cesarean delivery does not improve outcome in multifetal pregnancies, both reports are now more than 20 years old. Clearly, the difficulties associated with intrapartum surveillance and atraumatic vaginal delivery demand that only the most experienced operator should attempt vaginal delivery for higher-order multiples[67,68].

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# Delivery of the Term Twin: A Canadian Perspective

*J. F. R. Barrett*

**79**



## INTRODUCTION

The incidence of twins continues to increase worldwide[1] despite the recent modest success in reducing the incidence of higher-order multiples[2,3]. Among these latter gestations, many are reduced to twins, whose numbers continue to augment those that occur as a result of a maternal cohort who choose to conceive at later ages[4]. The end result of these diverse circumstances is reflected at the author's hospital, a university center in Toronto, Canada, where 6% of all deliveries were twins in 2001–02, compared with 2.3% just 4 years ago.

Because many of these *in vitro* fertilization/ assisted reproductive technologies (IVF/ART) conceptions have increased complications during pregnancy compared with spontaneous conceptions (see Chapter 19)[5], a thorough understanding of twin delivery techniques is essential. The Term Breech Trial demonstrated fetal benefit for the delivery of the term singleton breech presentation by cesarean section without a major increase in maternal risk[6]. The findings of this singular investigation are currently being extrapolated to many other 'at-risk' circumstances, especially twins in which the second twin is nonvertex.

This chapter focuses on the specific risks of term twins and presents a guideline for the current 'standard' of practice. It then discusses these data, suggesting that this 'standard' be re-evaluated in the form of a randomized controlled trial.

## ARE TERM TWINS AT HIGHER RISK COMPARED WITH TERM SINGLETONS?

The risk of death for twins has decreased over time in Canada, but still continues to be high (Table 79.1)[7]. Moreover, over the past 10 years, this risk has not decreased at the same rate in more mature twins (34–37 weeks) and in those at 32–34 weeks. This difference clearly implies that whereas our neonatal medicine colleagues are improving the outcome result of preterm infants, the obstetricians are not making similar improvements in fetal loss.

It is particularly noteworthy that among twins weighing > 2500 g at birth, the risk of death is higher than among singletons of the same birth weight.

**Table 79.1** Gestational age-specific risk of stillbirth and infant death among twin births in Canada: rates of stillbirth are expressed as per 1000 fetuses at risk, infant death rates are expressed as per 1000 live births

| *Gestational age* (weeks) | *1985–87* | | *1994–96* | |
|---|---|---|---|---|
| | *Stillbirth rate* | *Infant mortality rate* | *Stillbirth rate* | *Infant mortality rate* |
| 32–33 | 2.1 | 30.5 | 2.4 | 20.8 |
| 34–36 | 4.3 | 13.1 | 2.7 | 9.9 |
| 37–41 | 7.7 | 7.5 | 4.5 | 4.8 |

This sobering reality was first recognized when Kiely reviewed the data on 16 831 multiple births from the New York City Department of Health's computerized vital records for the period 1978–84[8]. The neonatal mortality rate for twins versus singletons at 2501–3000 g and ≥ 3001 g was 4.3/1000 vs. 3.8/1000 (relative risk, RR 1.12) and 7.4/1000 vs. 2.2/1000 (RR 3.32), respectively. Even more cause for alarm is the suggestion that the intrapartum fetal death rate for twins is higher than that for singletons. In the same study, Kiely reported that the intrapartum death rate for twins at ≥ 2501 g was 1.22/1000 vs. 0.34/1000 in singletons (RR 3.54, 95% confidence interval 1.82–6.88). More recent studies have repeatedly confirmed this higher risk of fetal and neonatal death in twins versus singletons if the pregnancy is at or near term or above 2500 g in birth weight[9–16]. Neonatal seizures, respiratory morbidity and low Apgar scores at 1 and 5 min are also higher for twins compared with singletons at birth weights > 1500 g and > 3000 g[14–16].

There are two possible explanations for the data discussed above. The first relates to a possible increase in the risk of stillbirth; the second relates to increased risk of labor and delivery compared with that of singletons.

### The risk of stillbirth in term twins

Overwhelming cohort and epidemiologic data support the increased risk of stillbirth in twins at more than 37–38 weeks' gestation compared with that of singletons[10,17–21].

In the absence of a randomized controlled trial, but extrapolating from the trial addressing the management of post-term singletons, many authorities including the International Society for Twin Studies and the Society of Obstetricians and Gynecologists of Canada (SOGC) now recommend delivery before the end of the 38th week of gestation[22]. Failing that, very intense fetal surveillance, such as twice-weekly biophysical profile (BPP), should be undertaken. A word of caution is necessary, however. One should not extrapolate these data to delivery by lower-segment cesarean section too early, as ample evidence shows that the risk of neonatal respiratory problems increases if elective cesarean section is undertaken prior to 38 weeks[23]. Thus, the ideal time to schedule an elective cesarean section is at 38 weeks' gestation[1]. If there is uncertainty about the gestational age, consideration must be given to confirming fetal maturity by checking the amniotic fluid lecithin/sphingomyelin (L/S) ratio or managing the pregnancy expectantly using serial fetal monitoring (twice-weekly nonstress and/or BPP tests) until one is confident that the fetuses are mature.

## WHAT ARE THE CURRENT 'STANDARDS' OF TERM TWIN DELIVERY?

### Indications for elective cesarean section

There are few absolute indications for elective cesarean section and certainly no good clinical studies on which to base strong recommendations. It appears reasonable that cesarean section without a trial of labor should be performed in cases of conjoined twins and monoamniotic (MA) twins, as each condition poses special as well as extraordinary risks. Case reports and even some older series describe MA twins being delivered vaginally without complication[24]. My personal experience with undiagnosed MA twins consists of delivering them vaginally with only the occasional variable deceleration noted throughout the labor, despite intense intertwining of both umbilical cords! Most authorities currently agree that elective cesarean section is the preferred route of delivery, although the timing of delivery is still in question[25–27].

The other indications for elective cesarean are not dissimilar to those of a singleton pregnancy, and include placenta previa and antenatal evidence of significant fetal compromise likely to be exacerbated during labor.

Cesarean section is also the recommended method of delivery in twin gestations when twin A is non-vertex[28–30]. In one study in which 31% of the twins were breech–breech and 36% were breech–vertex, the investigators found excessive morbidity in vaginally delivered breeches which caused them to suggest cesarean section for non-vertex first twins[30].

When the first twin presents as a breech, this gives rise to a situation long regarded as a relative contraindication for vaginal delivery. One of the major stated concerns with breech–vertex twins, which occurs in about 20% of all twins during labor[31–34], is the risk of locked twins[35]. However, this complication is uncommon (with an estimated frequency of 1/645 twin births, and only 147 cases reported in the world literature between 1958 and 1987). Regardless, the mortality associated with fetal entanglement is extremely high at between 30 and 43%[36–38]. Despite this, two recent studies challenged the need to perform a cesarean section for all twins with the first fetus in a breech presentation[38]. In a total of 141 twin pairs, all of whom had a non-vertex twin A, there was no difference in neonatal mortality or morbidity between the groups.

Unfortunately, mortality is not the only concern, as shown by the recent randomized controlled trial on singleton term breech delivery. This trial found that whereas in developed countries the chance of an infant dying as a result of a policy of planned vaginal birth was 1/300, the chance of significant handicap

**Table 79.2** Presentation combinations

| *Authors* | *n* | *Vertex–vertex (%)* | *Vertex–non-vertex (%)* | *Non-vertex–other (%)* |
|---|---|---|---|---|
| Chervenak *et al.*[31] | 119 | 42 | 45.4 | 12.6 |
| Caspersen[33] | 213 | 45.1 | 35.2 | 19.7 |
| Kelsick and Minkoff[34] | 2364 | 47.3 | 33.7 | 19 |
| Thompson *et al.*[39] | 341 | 38.4 | 33.4 | 28.2 |
| Laros and Dattel[32] | 174 | 43.7 | 36.2 | 20.1 |

was 1/20[6]. This well-conducted study provided grade-A evidence that a policy of planned lower-segment cesarean section reduced morbidity and mortality among neonates without a significant increase in immediate maternal complications. It seems difficult, therefore, to recommend vaginal birth in the similar twin circumstance which has the additional risks discussed above and in the rest of this chapter.

With consensus attained with respect to the appropriate delivery route for a singleton breech gestation, cesarean section for a twin gestation with twin A in a non-vertex presentation seems to be the appropriate recommendation.

## How should a twin delivery be conducted?

### *Twin A vertex, twin B vertex*

The vertex–vertex twin combination occurs in about 41% of twins during labor (Table 79.2). Widespread consensus supports the contention that attempted vaginal delivery is appropriate for vertex–vertex twins, unless other obstetric circumstances mitigate against it. Most series reveal a 17–25% incidence of cesarean section in planned vertex–vertex deliveries[31,39]. Although these data are encouraging, it should not lull the physician into a false sense of security. Several pitfalls await the unwary, and readers are strongly urged to consider the labor and delivery guidelines suggested by the SOGC Consensus Group as given below:

(1) It is necessary to have timely attendance by a physician competent to manage a twin birth.

(2) The presence of additional antenatal risk factors should be reviewed at the onset of labor. Intrapartum risk factors should be assessed on an ongoing basis and changes attended to appropriately.

(3) When participating in a call system, the replacing physician should be of similar competence and informed of all facts pertaining to a case when care is transferred.

(4) The diagnosis of twins is usually antenatal. Therefore, arrangements for delivery and/or transfer should be set in place. This may include antenatal consultation with a high-risk center.

(5) The assessment of lie and presentation of each fetus on admission in labor should be carried out, preferably by ultrasound.

(6) Intravenous access should be secured, and blood sent for group and antibody screen.

(7) Oxytocin augmentation may be used before the delivery of the first twin and/or between twins for hypotonic contractions.

(8) For either twin, the indication(s) for any intervention should be convincing, compelling and documented at the time of the event(s). However, for the cephalic second twin, vaginal delivery should be expedited should fetal distress occur.

(9) Documentation of all aspects of labor and delivery should be clear, contemporaneous and consistent amongst all involved health-care providers.

(10) Progress of labor should emerge clearly from the documentation.

(11) Continuous electronic fetal heart rate monitoring of twins A and B should ensure that both twins are being monitored individually. The presence of an ultrasound machine in the delivery room is advantageous.

(12) For attempted delivery by midforceps, vaginal breech delivery and multiple pregnancies, cesarean section should be available immediately. Immediate availability means the presence in the hospital of an anesthetist and nursing staff trained in cesarean sections. A note should be dictated describing all operative deliveries and complicated labor and delivery events. The time difference between the delivery of each baby should be noted.

(13) Cord blood samples should be taken at the time of delivery.

(14) The third stage of labor should be managed actively, with oxytocin being administered with the delivery of the second twin.

(15) Placentas should be sent for pathological examination.

(16) We suggest that twin deliveries be planned in level II and level III hospitals (II-C).

The recommendation for continuous electronic monitoring is not evidence-based, as no good studies on the use of intermittent monitoring in twin gestations exist. However, practical experience, common sense and, unfortunately, the medicolegal climate all contribute to the warning that intermittent auscultation does not ensure that each fetus is separately auscultated. Twin monitors are widely available. In order to increase maternal comfort, the author prefers a fetal scalp electrode on the leading twin, to reduce the number of straps on the maternal abdomen.

Ultrasonographic examination is a useful adjunct after delivery of the first twin in order to establish the fetal lie and presentation of the second twin. Depending on the gestational age, up to 20% of second twins will spontaneously change presentation once the first twin is delivered. In the case of vertex–vertex births, breech extraction will be required in between 0.8 and 3.9% of cases, and intrapartum cesarean for fetal distress/cord prolapse or failure of engagement in up to 10% of cases[20,39]. These data emphasize the need for all the precautions listed above, as the situation can change from a relatively low-risk delivery to one fraught with complications for mother and baby instantaneously should the practitioner be unprepared.

### *Twin A vertex, twin B non-vertex*

The optimal mode of delivery of vertex–non-vertex twins is widely disputed in obstetrics. When one of the editors of this book (L.G.K) was delivered as a second twin breech, cesarean delivery was not a realistic option. As recently as 1986, however, cesarean delivery was advocated if the second twin was non-vertex, citing increased perinatal morbidity and mortality in non-vertex twins delivered vaginally[34,40–43].

Numerous subsequent reports emphasize the fetal safety of vaginal delivery if limited to infants with birth weights greater than 1500–2000 g[28,44–49]. Rabinovici and colleagues published the only randomized control trial investigating this issue. Vertex–non-vertex twins after the 35th gestational week were randomly allocated to vaginal or abdominal delivery according to a protocol. Twenty-seven women were delivered by cesarean section and 27 were delivered vaginally (14 assisted breech extractions, five total breech extractions and eight internal podalic versions and total breech extractions). There were no statistically significant differences in fetal outcomes. Maternal febrile morbidity, however, was significantly higher in the cesarean-section group than in the vaginal-delivery group (40.7% vs. 11.1%, $p < 0.05$)[46].

Barrett and colleagues found that breech-extracted second twins with birth weights of less than 1500 g had lower Apgar scores and increased neonatal morbidity, compared as a group with their first-born siblings[50]. This difference was not found among twins delivered by cesarean section. Comparisons between second twins delivered vaginally and by cesarean section were not made. These authors, however, recommended routine cesarean section for the second non-vertex twin expected to weigh less than 1500 g. Chervenak and co-workers reported 76 breech-extracted second twins, of whom 16 weighed less than 1500 g[28]. Although delivery mode was not associated with any difference in outcome, they also recommended routine cesarean delivery for non-vertex second twins with birth weights of less than 1500 g.

### *External cephalic version versus breech extraction*

In 1983, Chervenak and colleagues advocated an alternative approach for delivery of the second non-vertex twin after delivery of the first using external cephalic version (ECV) in order to achieve delivery of the second as a vertex presentation. ECV was attempted in 25 sets of twins after successful delivery of the first vertex twin. This was successful in 18 of the cases (72%) and was not associated with increased perinatal complications[28,51]. On the basis of this report, the American College of Obstetricians and Gynecologists recommended ECV as a reasonable option for delivery of the second non-vertex twin[44]. Subsequent to Chervenak's report, numerous other investigators published similar findings[52,53].

In an effort to illuminate this area of potential controversy, four retrospective studies have been published reporting the success rates and cesarean section rates in second non-vertex twins delivered by ECV versus breech extraction. Overall, breech extraction was associated with higher success rates and lower cesarean section rates than ECV (Tables 79.3 and 79.4). There was also significantly less intrapartum fetal distress attributed to breech extractions than to ECVs (Table 79.5). Analysis of neonatal and maternal outcomes concluded that there was no significant difference between the two groups[54–57].

Our group reviewed the management of 206 vertex–non-vertex twin deliveries in major obstetric

**Table 79.3** Successful* vaginal delivery of second twin with external cephalic version (ECV) and breech extraction (BE)

| *Study* | *ECV* | *BE* |
|---|---|---|
| Gocke *et al.*[54] | 19/41 (46%) | 53/55 (96%) |
| Wells *et al.*[55] | 11/23 (48%) | 42/43 (98%) |
| Chauhan *et al.*[56] | 10/21 (48%) | 22/23 (96%) |
| Smith *et al.*[57] | 13/33 (39%) | 42/43 (98%) |
| Total | 53/118 (45%) | 159/164 (97%) |

*Note: not all 'failures' result in lower-segment cesarean section as some ECV failures will be delivered

**Table 79.4** Cesarean section rates of methods of delivery: external cephalic version (ECV) versus breech extraction (BE)

| *Study* | *ECV* | *BE* | *p Value* |
|---|---|---|---|
| Gocke *et al.*[54] | 16/41(39%) | 2/55 (4%) | <0.001 |
| Wells *et al.*[55] | 11/23 (48%) | 1/43 (2%) | <0.001 |
| Chauhan *et al.*[56] | 10/21 (48%) | 1/23 (4%) | 0.001 |
| Smith *et al.*[57] | 8/33 (24%) | 1/43 (2%) | 0.008 |
| Total | 45/118 (38%) | 5/164 (3%) | <0.001 |

**Table 79.5** Incidence of fetal distress in second non-vertex twins delivered by external cephalic version (ECV) versus breech extraction (BE)

| *Study* | *ECV* | *BE* | *p Value* |
|---|---|---|---|
| Gocke *et al.*[54] | 5/41(12%) | 0/55 | <0.001 |
| Wells *et al.*[55] | 4/17 (24%) | 0/43 | <0.001 |
| Chauhan *et al.*[56] | 4/21 (19%) | 0/23 | 0.001 |
| Smith *et al.*[57] | 8/33 (24%) | 1/43 (3%) | 0.008 |
| Total | 21/118 (18%) | 1/164 (1%) | <0.001 |

units in Toronto, Canada, in order to compare the different methods of delivering the second non-vertex twin following vaginal delivery of the first. Delivery was attempted by primary breech extraction with or without internal podalic version in 183 patients. This was successful in all but two patients (98.9%), who were delivered by cesarean section for failed breech extraction. External cephalic version was attempted in 23 second twins. This was successful in only six (26.1%), resulting in vertex vaginal delivery. In 12 patients, secondary breech extraction was performed and successful in all but one patient who required delivery by cesarean section.

Intrapartum complications including placental abruption, fetal distress and cord prolapse occurred more frequently in the ECV group (30.4% vs. 6.0%, $p = 0.001$). Despite that there were no differences in the 5-min Apgar score and incidence of neonatal trauma, there were more neonatal intensive-care unit admissions and a greater incidence of respiratory distress syndrome (RDS) and intraventricular hemorrhages (IVH) in the ECV group. There were no significant differences in maternal outcomes including postpartum hemorrhage or infection.

The following guidelines for the performance of ECV of the second twin are recommended:

(1) Ultrasonographic assessment of estimated fetal weights of both fetuses should be performed. If twin B is larger than twin A and a great disparity exists, ECV with attempted vaginal delivery should be avoided.

(2) Epidural anesthesia is advisable prior to delivery to provide abdominal wall relaxation.

(3) The procedure should be performed only if immediate access to cesarean section is possible.

(4) The fetal heart rate should be monitored throughout delivery.

(5) A real-time ultrasound machine must be present in the delivery room to ascertain accurately the fetal presentation of twin B after delivery of the first twin. Gentle pressure with the ultrasound transducer is used to guide the infant in the vertex presentation into the birth canal. If this fails, forward or backward rolls are used to convert the malpresenting fetus to the vertex presentation. The shortest arc between the vertex and the pelvic inlet should be attempted first.

(6) If ECV is successful, amniotomy should be performed and oxytocin augmentation may be used as necessary.

(7) If version is unsuccessful, if monitoring of twin B reveals a non-reassuring fetal heart rate, or if twin B fails to descend after a successful ECV, secondary breech extraction or cesarean section is necessary[58].

### *Time interval between delivery of twins*

It was previously believed that the time interval between twin deliveries should be no longer than 30 min, as a prolonged interval placed the second twin at risk of asphyxia from decreased placental circulation[38,41]. This time limit was widely adhered to in the days when electronic fetal monitoring and ultrasound were not routinely used. More recent literature, however, shows no correlation between 5-min Apgar score and the time interval between twin deliveries[38,59–61]. Rayburn and colleagues found that perinatal morbidity was lowest with expectant therapy and subsequent spontaneous delivery regardless of fetal presentation. One study based on a small sample size reported a six-fold increase in the risk of cesarean section for the second twin with a delivery interval greater than 15 min[62].

## WHAT IS THE EVIDENCE THAT A POLICY OF PLANNED CESAREAN SECTION MIGHT BE BENEFICIAL FOR TWINS AT OR NEAR TERM?

I should now like to draw the reader's attention to the crucial question in this field, that is: should vaginal delivery be attempted at all?

There are three ways to examine the evidence that a policy of planned cesarean section might be beneficial for twins at or near term. The first is to compare outcomes for second twin versus first twin and compare these outcomes in twins delivered vaginally compared with those delivered by lower-segment cesarean section.

In a recent study of 1305 twin pairs delivered between 1988 and 1999 in Nova Scotia, in which second-born twins were compared with first-born twins at ≥ 1500 g birth weight, the risk of adverse perinatal outcome (intrapartum fetal death, neonatal death, moderate–severe respiratory distress syndrome, asphyxia, trauma and complications of prematurity) was significantly increased (RR 2.1, 95% confidence interval (CI) 1.4–3.1) for second-born twins[15]. There is also evidence that the second twin is at greater risk of adverse perinatal outcome compared with the first twin if delivery is vaginal, but the same has not been shown if delivery is by cesarean section. Arnold and colleagues undertook a matched case–control study of preterm twin pairs[14]. The risk of respiratory distress syndrome was increased for the second twin compared with the first if delivery was vaginal (odds ratio (OR) (95% CI) 14.2 (2.5–81.1)) but not if delivery was by cesarean section (OR (95% CI) 0.90 (0–17.8)).

The second method is to compare outcomes for twins delivered vaginally versus by cesarean section. These data also show higher rates of adverse perinatal outcome for the twin at or near term if delivery is vaginal, compared with by cesarean section. In the Kiely review, for example, for twins in vertex presentation weighing more than 3000 g at birth, the neonatal mortality rate was 12.3/1000 vs. 2.9/1000 (RR 4.22) if delivery was vaginal versus by cesarean section[8]. These data are possibly strongly affected by selection bias, and therefore the best method is to compare outcomes for twins delivered by planned vaginal birth (actual vaginal birth plus emergency cesarean section) versus planned cesarean section.

As mentioned above, there has been only one randomized controlled trial of planned cesarean section versus planned vaginal birth for twins, in which 60 pairs of twins were enrolled[47]. There were no perinatal deaths or cases of serious neonatal morbidity in either group. The sample size was too small to answer the question of the better approach to delivery. A Cochrane Review, incorporating this one trial, has recommended that a larger randomized controlled trial be undertaken[63].

Because of the limited information from randomized controlled trials, we undertook a systematic review of studies that compared the policies of planned vaginal birth and planned cesarean section for the delivery of twins weighing at least 1500 g or reaching at least 32 weeks' gestation[64]. The meta-analysis did not find significant differences between the two approaches to delivery in terms of mortality or neonatal morbidity, although low Apgar score at 5 min was reduced with a policy of cesarean section. This finding, however, was confined to the twins in

which twin A presented as a breech. After this analysis was undertaken, a further cohort study of 2890 pairs of twins at ≥ 36 weeks found that in those delivered by planned cesarean section ($n = 454$) there were no deaths of either twin, but in those undergoing planned vaginal birth ($n = 2436$) there were no deaths of the first twin but nine second twin deaths[65].

## WHERE DO WE GO FROM HERE?

It seems that many physicians are in equipoise on this most fundamental of all aspects of twin research relating directly to obstetric practice, that is, what is the best way to deliver twins?

In 2001, Hutton and colleagues undertook a survey of Canadian practitioners to determine their views toward different delivery options for twins[66]. Most respondents indicated that for twins at 32 or more weeks' gestation in which twin A was vertex, they would usually recommend a planned vaginal birth, with the recommendation of planned vaginal birth being as high as 100% for the vertex–vertex combination at term to as low as 78% for the vertex–footling breech combination at 32–36 weeks. However, respondents to the survey were not convinced that planned vaginal birth was the best approach to delivery, as 64% indicated that they would be willing to enroll their patients with twin pregnancies in a well-designed randomized controlled trial comparing planned vaginal birth with planned cesarean section. The interest in a large twin delivery trial was greater for twins at term (55%) and for twins presenting vertex–non-vertex (58%). However, 48% were willing to enroll women with twins at 32–36 weeks' gestation, and 42% were willing to enroll twins presenting vertex–vertex.

The high number of physicians willing to enroll vertex–vertex twins likely reflects the following. First, up to 20% of vertex second twins will change presentation spontaneously after twin A is delivered[67]. Second, it was for the twin in vertex presentation that Kiely found better outcomes if delivery was by cesarean versus vaginal[8]. Third, it is the view of practitioners experienced in the management of labor and the delivery of twins that a substantial number of those presenting vertex–vertex will have serious acute intrapartum problems following the delivery of twin A (e.g. conversion to transverse lie, cord prolapse, prolonged interval delivery of twin B), which may lead to emergency cesarean section, perinatal death and neonatal morbidity. Last, if there are benefits to avoiding labor, both twins regardless of presentation should benefit.

Many policies in obstetrics have been accepted as the standard of care without adequate evidence to support them. A prime example is the widespread use of intrapartum fetal monitoring. Once a policy of management has been accepted and implemented into practice, it is very difficult to undertake research designed to determine the effectiveness of the practice. Although the Term Breech Trial emphasized the relative safety of a policy of planned cesarean section for the mother[6], the recently updated Cochrane Review found a higher risk of serious maternal morbidity following a policy of planned cesarean section if the fetus is a singleton breech, and the longer-term impact of a policy of planned cesarean section for the mother is not known[68].

The focus among practitioners has moved away from keeping cesarean section rates low and more toward supporting maternal choice for method of delivery. When the Term Breech Trial was conducted, practice had already shifted toward planned cesarean section. Recruitment to this study was therefore confined to a minority of practitioners who had maintained their skills and confidence in vaginal breech delivery. We believed that a large randomized controlled trial of planned cesarean section for twins must be conducted before practice is changed.

The Canadian Institutes of Health Research agreed with this premise, and funded in 2003 The Twin Birth Study. This international multicentered randomized controlled trial will enroll and follow 2400 twins and their mothers who have been randomized to deliver vaginally or by lower-segment cesarean section between 32 and 38 weeks' gestation.

### The twin birth study

This study will be a multicentered international randomized controlled trial of planned cesarean section versus planned vaginal birth for twins at ≥ 32 weeks' gestation in which twin A is presenting vertex. Proposed inclusion criteria are: twins at ≥ 32 weeks in which twin A is presenting vertex, both twins alive and estimated fetal weight between 1500 and 4000 g. Exclusion criteria include MA twins, lethal anomaly of either twin or other contraindication to labor or vaginal birth. Women with a twin pregnancy at 32–35 weeks' gestation who meet the selection criteria and consent to participate in the trial will be randomized from 32 weeks onward. Because of data mentioned above showing an increase in stillbirth rate at 38 weeks, trial participants will be delivered at 38–39 weeks' gestation. Vaginal delivery will be conducted in accordance with the SOGC guidelines, as discussed above, by experienced personnel. If twin B is non-vertex, the options for delivery will be spontaneous or assisted vaginal breech delivery (if breech), total breech extraction with or without internal podalic version, external cephalic version and vaginal delivery of the fetus as a vertex or lower-segment cesarean section.

The proposed primary outcome will be a composite of perinatal/neonatal mortality and/or serious neonatal morbidity (excluding lethal congenital anomalies) that has a prevalence of 4% from retrospective data. The proposed secondary outcome will be problematic urinary or fecal/flatal incontinence at 3 months and 2 years. Other outcomes that will be evaluated will be death or serious maternal morbidity within 28 days following delivery, maternal satisfaction with method of delivery (3 months), maternal quality of life (3 months and 2 years) and death or poor neurodevelopmental outcome of the children at 2 years of age (corrected for gestational age at birth). The sample size is 2400 women, designed to detect a difference in the primary outcome of 2%.

It is the author's contention (and probably bias) that a properly conducted twin delivery is safe for both mothers and babies. By the time that this chapter is in print, we will hopefully be well on the way to defining the most optimal method of twin delivery.

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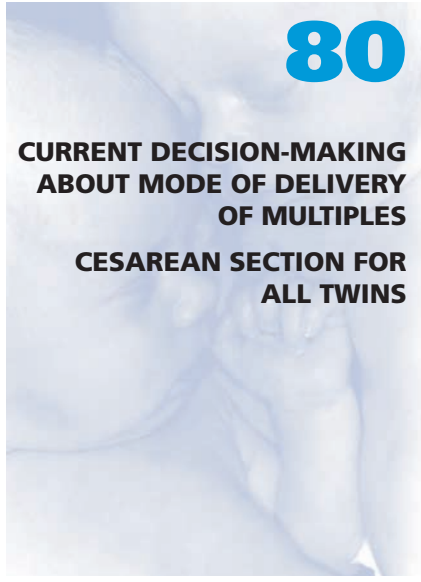
# Delivery of Multiples: a Dissenting View

*I. Blickstein*




## CURRENT DECISION-MAKING ABOUT THE MODE OF DELIVERY OF MULTIPLES

The previous chapters (78 and 79) related to the delivery of multiples come from important centers that influenced management. The first comes from authorities that pioneered a seemingly revolutionary approach to the vaginal delivery of the non-vertex second twin, and the second comes from an institute that pioneered a global change in the approach to vaginal birth of the breech-presenting infant. Reading these chapters, the clinician understands how distinguished authorities who review the same studies may differ in their opinion about the validity of their conclusions.

Yet, another opinion should be heard. This view is based on two important changes in the epidemiology of multiple pregnancies that may directly influence the mode of delivery of twins. The first is the dramatic increase in the frequency of multiple births and its impact on preterm deliveries[1]. The 2002 US vital statistics show that the twin birth rate reached a remarkable 3.1% of all live births, representing a 65% increase over the past two decades and a 38% increase since 1990[2]. Moreover, the 2002 incidence of triplets and higher-order multiples was 1.84 per 1000 live births, compared with about 1 : 10 000 births following spontaneous conceptions[2]. These increased rates of multiple birth are associated with inevitable increased rates of preterm births because 12% of twins, 36% of triplets and 60% of quadruplets are born before 32 weeks' gestation[2]. Such striking figures result from the widespread implementation of assisted reproductive technologies (ART). According to the US Centers for Disease Control and Prevention, the main reason for the increase in preterm births is multiple gestation secondary to ART, with 16% of all preterm deliveries in the USA being due to multiple births[2].

The second change refers to the increasing age of the mother of multiples[3] (see Chapter 93). In the past, pregnancies at an older age were primarily unintended, and women usually delivered their last baby. At present, however, many women intentionally postpone childbirth until they achieve personal milestones. Because of the reduced fecundity associated with older age, there is a significant need for ART to achieve the desired pregnancy. Loos and colleagues[4], using data from the East Flanders Prospective Twin Survey, noted that in 1976 there was one induced twin maternity for every 32 spontaneous twins. In contrast, by 1996, this ratio was 1 : 1.02. These figures reflect the facts that ART is associated with increasing frequencies of *iatrogenic* pregnancies and the proportion of previously infertile women delivering twins is increasing. Collectively, these changes lead to higher rates of so-called 'premium pregnancies', for which any mode of delivery except a cesarean (justified or not) may be declined[5].

Additional considerations also merit discussion. First, recent publications demonstrate reduced risks of elective cesareans, mainly in terms of maternal mortality, and describe the potential benefits of elective cesareans to both mothers and children in terms of reduced morbidity[6]. It could be inferred that if a cesarean section upon a woman's request is medically[6] and ethically[7] justified, it might be also a valid option for the delivery of multiples, although the indication may seem subtle or unfounded by evidence.

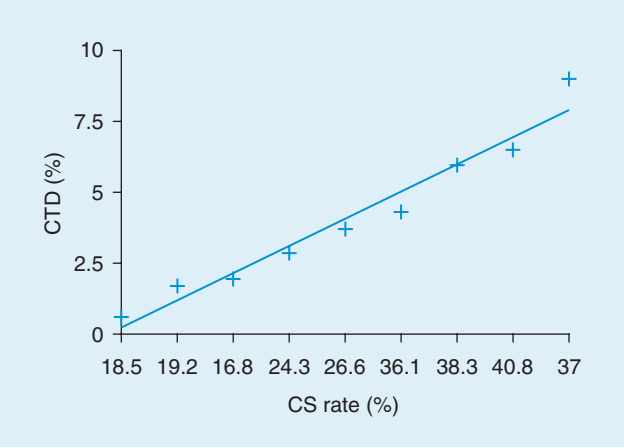



**Figure 80.1** Combined twin delivery (CTD) as a function of overall cesarean section (CS) rate in twins[10]

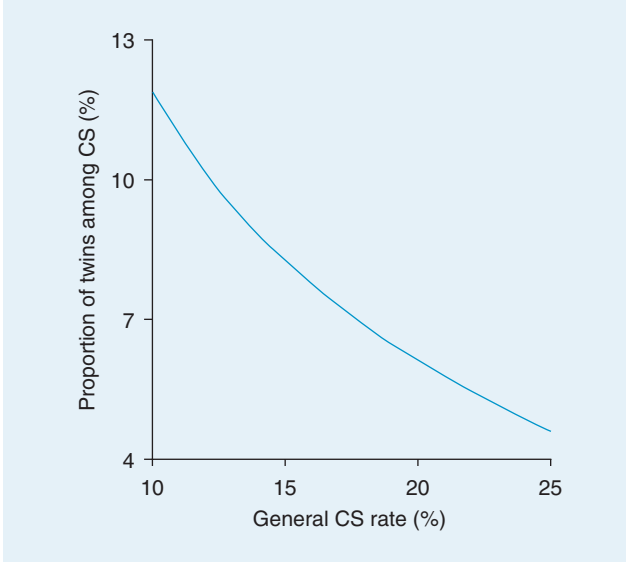



**Figure 80.2** Correlation between the proportion of twins (all delivered by cesarean section (CS)) and the overall cesarean rate[5]. The higher is the overall cesarean rate, the smaller is the contribution of twins to that rate

The second consideration comes from the Canadian Term Breech Trial documenting the advantage of a planned cesarean section for the term fetus in breech presentation[8]. As a result of this landmark study in singletons, many centers extrapolated its conclusions to twin births, and no longer deliver breech presentations by the vaginal route, irrespective of plurality. Consequently, many young residents currently lack adequate training, experience and manual dexterity required for breech delivery. Indeed, a secondary analysis of the Term Breech Trial cited the presence of an experienced clinician at delivery among the significant factors that reduced the risk of adverse perinatal outcome among vaginal breech deliveries[9]. Because twin pairs include at least one breech or transverse-lying twin in 50–60% of cases, assisted or operative deliveries are the rule rather than the exception. Indeed, a direct relationship exists between the cesarean section rate in twins and the combined delivery rate, suggesting that those who perform more abdominal deliveries in twins, and are apparently less experienced in vaginal deliveries of twins, are more likely to decide on a cesarean for the second twin (Figure 80.1)[10].

## CESAREAN SECTION FOR ALL TWINS

The United States cesarean delivery rates increased 13% (from 51.9 to 55.0%, 95% confidence interval (CI) 12–14) between 1989–91 and 1997–99 among twins delivered at ≥ 22 weeks and weighing ≥ 500 g[11]. This value represents the average increase of 52, 28 and 9% among twin pregnancies delivered at 22–27 weeks', 28–33 weeks' and at ≥ 34 weeks' gestation, respectively. Although the rates increased to a greater extent at earlier rather than at later gestational ages, the absolute number of cesareans was much higher at later gestational ages[11]. Of interest, these rates do not include the period after the publication of the Term Breech Trial. Nonetheless, they are quite similar to commonly cited rates of 50–60% abdominal births among twins and nearly 100% among triplets[5]. In the UK, the 2001 cesarean rate for twin deliveries was 59%[12].

Obviously, the higher is the overall cesarean rate in a given obstetric service (including half of the twins), the lower is the contribution of twins to the overall cesarean rate. Moreover, the best-fit theoretical correlation (Pearson's $R^2 = 0.99$) between the proportion of twins among all cesareans and the overall cesarean rate follows an inversely exponential curve (Figure 80.2), suggesting that with increasing overall cesarean rates, the contribution of twins to that rate becomes negligible[5]. Accordingly, performing cesarean sections for all twins would increase the overall rate by 10% in a service with an overall 10% cesarean rate but will add only 3.3% to a service with an overall 30% cesarean rate.

The conclusion from the previous discussion is quite simple. The issue is not the reduction of the overall cesarean rate but avoiding unnecessary cesareans. To this extent, one should be able to reply whether there are specific maternal risks associated with the abdominal delivery of twins. Regrettably, the first question has not been adequately addressed in the literature. Suonio and Huttunen[13] evaluated the infectious complications of 122 consecutive

abdominal twin deliveries. The incidence of endometritis was nearly three-fold higher after twin deliveries and the incidence of abdominal wound infections nearly two-fold higher compared with singleton abdominal deliveries. Multiple regression analysis indicated that only maternal age < 25 years and an interval >6 h from rupture of membranes to delivery were risk factors as regards puerperal endometritis among twins[13]. However, the distinction between cesareans performed before labor and those performed after the initiation of labor was not clearly defined. Goldberg and colleagues[14] at Evanston Northwestern Hospital found that mothers of multiples reported substantial rates of fecal (10%) and flatal (25.2%) incontinence, and that delivery by cesarean section was not significantly protective (see also Chapter 87). Again, elective cesareans were not separately assessed. Data from sub-Saharan and other African countries show that cesarean section increased maternal mortality when performed in emergency situations such as delivery of a retained second twin or bleeding, but was lifesaving when available during a vaginal birth of twins[15]. It follows that there are no data to show that planned cesareans for twins have specific risk associated with delivering more than one fetus.

## SUMMARY

Generally speaking, cesarean section is the simplest and most efficient way to deliver multiples. This statement is especially true when one considers the likelihood that this gestation indeed represents a 'premium' pregnancy, characterized by events that either preceded it (infertility) or the birth (pregnancy complications). In a particular case – for example a case of vertex–breech twins – the fact that vaginal delivery is *permissible* makes little sense if the operator is inexperienced in breech delivery. Even if the results of a randomized study would support the safety of vaginal birth, the clinician in such circumstances must rely on his/her own judgment and skills. It follows that the decision to perform a cesarean delivery in twins, intentionally or not, may emerge from quantitative variables that are difficult to interpret and from qualitative variables that are impossible to quantify.

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# Special Situations in Labor and Delivery of Multiples

*I. Blickstein*

**81**

**COMBINED TWIN DELIVERY**

**VAGINAL BIRTH AFTER A CESAREAN**

**LABOR INDUCTION AND AUGMENTATION**

**DELIVERY OF TRIPLETS**

This chapter discusses the following special situations in labor and delivery of multiples: combined twin delivery, vaginal birth after a cesarean (VBAC), induction of labor and the delivery of triplets.

## COMBINED TWIN DELIVERY

Combined twin delivery refers to cesarean section performed for twin B following the vaginal delivery of twin A. In an electronic letter to the Editor of the *British Medical Journal*, Jill Walton described this situation as 'the worst of both worlds – a tiring and often risky pregnancy, a tiring labour, a major abdominal operation, two lots of stitches and two new babies to care for' (*Br Med J*, November 5, 2002). Following this colorful, albeit provocative description, one may wonder if such a circumstance represents misfortune or mismanagement[1]. In a typical case, such a delivery occurs unexpectedly following the delivery of twin A when an emergent situation arises, and the clinician, in his/her best clinical judgment, considers an emergency cesarean for twin B to be the safest option for delivery. Retrospective audits of such cases may conclude one of the following:

(1) The emergency situation could not be expected, for instance placental abruption, umbilical cord presentation/prolapse, etc.;

(2) The emergency situation could be predicted, but the operator thought he/she could handle it, for instance inability to perform an internal version of a dorsoinferior transverse presentation;

(3) Failure to diagnose the complication before the situation became emergent, for instance failure to diagnose a dorsoinferior transverse presentation.

The first situation could be considered as misfortune, the third as mismanagement and the second could be either. Wolff described an excessive use of cesarean section for the second twin – 11% – and found that two-thirds of these procedures were considered potentially avoidable[2].

In the United States, the frequency of combined twin deliveries is estimated to be 9.5%[3]. Interestingly, but not surprisingly, a direct, linear, correlation was found between the frequency of combined deliveries and the frequency of cesareans in twins[1]. This could be explained by less experience gained in managing complicated deliveries of twin B when more cesareans are performed for both twins. Persad and colleagues[4] demonstrated a statistically significant increase in combined vaginal–cesarean and elective cesarean deliveries in the United States, with a decrease in vaginal deliveries during the period 1980–99.

Combined twin delivery may occur in all combinations of presentation in which vaginal delivery is planned[1]. Using data from the large US multiple birth file, Wen and colleagues[3] found that the cesarean rate for twin B was increased when the mothers had medical or labor and delivery complications. Breech and other malpresentations were the most important predictors of emergent combined deliveries (population attributable risk 33.2%). Indeed, the need for emergent cesarean delivery of the second twin after vaginal delivery of the first twin

in such combinations was increased four-fold. Operative vaginal delivery of the first twin was associated with a decreased risk of cesarean delivery for the second twin. Prediction of emergent cesarean for the second twin by clinical factors was stronger in term births than in preterm births. Kurzel and associates[5] noted that the risk for cesarean for the second twin increased 7.6-fold if twin A was vertex rather than breech, and that the prime reason for a combined delivery varied with the presentation of twin B.

It is important to remember that a prolonged interval between the vaginal delivery of twin A and the abdominal delivery of twin B may cause the uterus to contract around the malpresented fetus and lead to difficult extraction during cesarean section. In this circumstance, nitroglycerin is the agent of choice in managing the so-called 'entrapped' second twin during cesarean section (see Chapter 82).

In summary, it is not possible to avoid combined deliveries entirely unless cesarean section is performed in all twins. The operator must acknowledge the limits of his/her manual dexterity. If – for whatever reason – a safe vaginal delivery of twin B cannot be entirely anticipated, there is no need to test one's ability to handle cataclysmic situations.

## VAGINAL BIRTH AFTER A CESAREAN

As a result of current cesarean rates, there is at least a chance of 1 : 3 to 1 : 6 that a given multipara carrying twins had a previous cesarean. The combination of a uterine scar with a multiple pregnancy and its associated uterine overdistension and fetal malpresentation constitutes a contraindication for vaginal birth after a cesarean (VBAC) in the minds of many clinicians. However, existing evidence does not entirely support this policy. As early as 1989, Strong and colleagues[6] found no significant differences in maternal or neonatal morbidity or mortality rates in trial of labor versus no trial of labor groups, and reported a 4% dehiscence rate among women with twin pregnancies who attempted a trial of labor compared with 2% in women with singleton pregnancies. More recently, Sansregret and co-workers[7] reviewed their series of 26 cases collected over a 12-year period, in which 22 (85%) had successful VBACs, no uterine ruptures and no significant differences in maternal and neonatal outcomes between trial of labor for VBAC and elective cesarean. Trial of labor, however, was associated with 27% combined deliveries. Delaney and Young[8], also in 2003, reported the same maternal and neonatal outcomes, a somewhat lower successful VBAC rate – 74% – but a much lower combined delivery rate (7.1%). The fact that combined deliveries seem to be higher than in the general population should be included in the counseling process.

In summary, as long as a VBAC is not a contraindication for singletons, VBAC can be accomplished in carefully selected cases of twins. However, when manipulations to deliver the second twin are anticipated, cesarean section seems to be a more appropriate choice.

## LABOR INDUCTION AND AUGMENTATION

About 20% of twin gestations may require induction of labor for both fetal and/or maternal reasons. However, the overdistended uterus is a relative contraindication for labor induction by means that may cause uterine hyperstimulation. Despite the fact that pregnancy is often terminated by cesarean section, it seems that unfavorable cervical conditions are no longer impediments for trial of labor in appropriate candidates. Case series describe the use of an intrauterine balloon catheter[9] and of the prostaglandin $E_1$ analog misoprostol[10] in such circumstances. Both appear to be safe and effective to induce labor in twin gestations with an unripe cervix. Once the Bishop score is >5, the membranes may be artificially ruptured.

The conflicting[11,12] results present in the older literature related to oxytocin induction or augmentation in twin labors were questioned in a more recent study of 62 parturients with twin gestations who were matched with singleton controls[13]. Labor of twin pregnancies and that of singletons responded similarly regarding maximum oxytocin dosage, with similar interval from oxytocin to delivery, and similar successful vaginal delivery (90% in both groups).

## DELIVERY OF TRIPLETS

Because triplets' delivery is more complex than the delivery of twins, it may be intuitively understood why the abdominal route is preferred by most centers. In many other centers, however, the option of vaginal delivery of triplets has never been discarded.

Older reports, from the Baragwanath Hospital, South Africa, and Asaf-Harofe Hospital, Israel, document impressively good outcomes for vaginally born triplets[14,15]. The high frequency of vaginal birth during this period might be attributable to failure to diagnose triplets antepartum. Indeed, as many as 45% of triplet sets were diagnosed during the first or second stage of labor before the era of sonography[16]. Favorable outcomes of triplets were also observed in East Flanders, where 81% of 16 sets were delivered vaginally[17]. Whereas the East Flanders group maintained that better outcome was not expected with more cesarean births, Feingold and colleagues[18]

advocated a more liberal approach toward abdominal delivery of triplets.

With the increasing frequencies of triplets worldwide, more centers gained experience with more triplets during a shorter time span. Eventually, it became clear that gestational age was a more important determinant of outcome than mode of delivery[19]. The recent literature seems to demonstrate a general agreement that in terms of fetal and early neonatal outcomes, vaginal delivery of triplet gestations is an acceptable management option in selected cases, and may significantly decrease maternal hospital stay and postoperative morbidity[20–25]. Having said this, delivery of triplets, by either route, is a logistic endeavor, with as many as 15–20 persons necessary for delivery and neonatal care. The logistics involved in recruiting the necessary staff is often very difficult, and a planned, daytime, elective cesarean section may be the simplest solution to overcome logistic obstacles.

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# Pregnancy Management: Anesthesia

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**82**



## INTRODUCTION

The intrapartum management of multiple gestations poses unique challenges to the perinatal team. Good anesthesiology management may assist in the obstetric management of women with multiple gestation, as well as improve both maternal and neonatal outcome. Anesthesiologists should have an understanding of the unique problems associated with multiple gestation, and obstetricians should have an understanding of the anesthetic issues surrounding labor and delivery in these instances. The anesthesiologist should be notified whenever a woman with multiple gestation is admitted to the hospital for labor and delivery.

## PHYSIOLOGICAL CHANGES OF PREGNANCY AND ANESTHETIC IMPLICATIONS

Many of the physiological changes associated with pregnancy are exaggerated in multiple gestations. These changes are discussed in detail elsewhere in this text (see Chapter 52), but are reviewed here in the context of anesthetic care. Although the anesthetic implications of the exaggerated physiological changes associated with multiple gestation have not been well studied, it is probably safe to assume that the implications of these changes are also exaggerated. The major physiological changes and their anesthetic implications are summarized in Table 82.1.

### Circulation

Pregnancy is a hyperdynamic state. Cardiac output is increased approximately 45% during singleton gestation pregnancies and 60% in twin gestation pregnancies[2]. Plasma volume at term increases by an average of 67% in twin compared with 49% in singleton pregnancy[3]. Blood volume increases by 59% versus 43%, respectively.

The obstetric/anesthetic implications of this hyperdynamic state are numerous. As a consequence of hypervolemia, pregnant women or women immediately postpartum can lose large volumes of blood and still remain asymptomatic. Whereas non-pregnant individuals become symptomatic after losing approximately 20–25% of their circulating blood volume, pregnant women can lose as much as 30–35% of their blood volume before symptoms appear[4].

Increased cardiac output results in increased capillary perfusion, leading to engorgement of the oral, nasal, pharyngeal and tracheal mucosa. This may contribute to a markedly increased incidence of difficult tracheal intubations in obstetric patients (see below)[5].

Cardiac output decreases by 10–20% at term when pregnant women assume the supine position secondary to aortocaval compression[6]. The effects of aortocaval compression may be exaggerated in the presence of sympathetic blockade induced by neuraxial (spinal, epidural or combined spinal–epidural) analgesia/anesthesia. The adverse effects of aortocaval compression may be more profound in women with multiple gestation because of the sheer size and weight of the uterine contents.

### Metabolism and respiration

The risk of hypoxemia is likely to be greater in women with multiple gestation. Functional residual capacity (FRC) is decreased to a greater extent

**Table 82.1** Physiological and anatomical changes during pregnancy: anesthetic implications. Adapted from reference 1

| *Physiological change* | *Anesthetic implication* |
|---|---|
| *Circulation* | |
| Increased cardiac output | alters pharmacokinetics |
| Increased blood volume | alters response to hemorrhage |
| Capillary engorgement, airway edema | increased incidence of difficult airway |
| Aortocaval compression | decreased cardiac output and uteroplacental blood flow in supine position; may be exacerbated by neuraxial anesthesia-induced sympathetic blockade |
| *Metabolism and respiration* | |
| Decreased functional residual capacity | less oxygen reserve and greater risk of hypoxemia during induction of general anesthesia |
| Increased oxygen consumption | greater risk of hypoxemia during induction of general anesthesia |
| *Gastrointestinal system* | |
| Change in position/angle of gastroesophageal junction causing decrease in gastroesophageal barrier pressure | increased risk of pulmonary aspiration |
| Increased intra-abdominal pressure causing decrease in gastroesophageal barrier pressure | increased risk of pulmonary aspiration |
| *Endocrine* | |
| Increased progesterone levels causing relaxation of gastroesophageal sphincter | increased risk of aspiration |

because of the larger uterus, while at the same time, closing capacity and oxygen consumption are increased to a greater extent[7]. FRC is further decreased when the pregnant woman assumes the supine position, and further still when the mother is anesthetized (both general and neuraxial anesthesia). Accordingly, pregnant women should be encouraged to avoid the supine position, particularly when in labor. Supplemental oxygen should be administered to women who are forced to assume the supine position while anesthetized, even in the presence of left lateral tilt (e.g. during cesarean delivery).

## Airway management

The decreased FRC and increased oxygen consumption have profound implications for the induction of general anesthesia. Because of concerns of pulmonary aspiration (see below), parturients are almost never ventilated by face mask during the induction of anesthesia. Mask ventilation may introduce air into the stomach and increase the risk of pulmonary aspiration. Oxygen is administered via a tight-fitting face mask before the induction of anesthesia, resulting in an oxygen partial pressure ($pO_2$) close to 500 mmHg. An intravenous sedative hypnotic (e.g. thiopental) is administered, immediately followed by a neuromuscular blocking agent (e.g. succinylcholine). Patients remain apneic until the endotracheal tube is placed. If there is no difficulty with intubation, the apneic period lasts approximately 1 min. During this time, the $pO_2$ in the parturient falls at more than twice the rate of that in non-pregnant women. Hypoxemia ensues after 3 min of apnea, compared with 7 min in non-pregnant women[8]. In all likelihood, women with multiple gestation have an even shorter grace period.

To compound the problem, women with multiple gestation are at increased risk for failed intubation. The risk of failed intubation, estimated at one in 280 intubation attempts in the obstetric population, is approximately eight times higher than that in the general surgery population[9]. The physiological changes that contribute to an increased risk of failed intubation include pharyngolaryngeal edema, enlarged breasts (interfering with the laryngoscope handle during insertion of the blade into the mouth) and weight gain (increased airway soft-tissue mass). These changes are likely to be exaggerated in multiple-gestations.

## Gastrointestinal system

Failed intubation and pulmonary aspiration were responsible for 48% of anesthesia-related maternal mortality in the United States between 1979 and 1990[10]. The incidence of failed intubation was

1 : 280 in obstetric patients compared with 1 : 2230 in non-pregnant patients[5]. Several changes in the gastrointestinal system place pregnant women at increased risk for pulmonary aspiration (Mendelson's syndrome). Increased progesterone levels cause decreased gastric mobility and relaxation of the lower esophageal sphincter. Women with multiple gestation have higher circulating progesterone levels than women with singleton gestation[11]. The gravid uterus displaces the stomach cephalad, causing distortion of the angle between the stomach and esophagus, thus leading to functional incompetence of the lower esophageal sphincter. The gravid uterus also increases intra-abdominal pressure, and therefore intragastric pressure. Again, these changes are exaggerated in women with multiple gestation because of the larger uterus, larger placental mass and increased quantity of amniotic fluid.

Drugs that decrease the risk of pulmonary aspiration, or mitigate the sequelae of pulmonary aspiration, should be administered to pregnant women undergoing anesthesia. These include an oral, non-particulate antacid and histamine ($H_2$) blocking agents (e.g. ranitidine) to increase gastric pH, and metoclopramide to increase gastric motility.

### Pharmacokinetics

Pregnancy alters the disposition of drugs by several mechanisms. The volume of distribution may be altered. Plasma protein concentrations decrease, leading to decreased drug binding and an increased concentration of free drug[12]. Maternal protein concentration is decreased still further in twin compared with singleton pregnancies[13]. Increased renal blood flow and glomerular filtration, and altered hepatic microsomal activity, additionally contribute to changes in renal and hepatic drug clearance[14]. Alterations in cardiac output and minute ventilation affect the uptake, distribution and elimination of inhaled anesthetic agents. Based upon these considerations, it is likely that drug disposition is further altered in multiple compared with singleton gestation.

Vallejo and Ramanathan studied maternal vein and umbilical cord blood lidocaine concentrations after lidocaine epidural anesthesia in twin compared with singleton cesarean deliveries[15]. Maternal vein lidocaine concentrations were not different. However, umbilical vein and artery lidocaine concentrations were higher in both twins compared with singleton neonates. There was no difference in neonatal outcome in this small study, and the authors speculated that alterations in maternal plasma concentration of free lidocaine, and differences in neonatal birth weight and acid–base status, might explain these results.

## OBSTETRIC COMPLICATIONS AND ANESTHETIC IMPLICATIONS

Women with multiple gestations are at increased risk for a number of obstetric complications that potentially impact on anesthesia care. The details of these disease states are discussed elsewhere in this text (see Chapters 53 and 54). The anesthetic implications are discussed here.

### Incompetent cervix: cervical cerclage

Women with multiple gestation, particular higher-level multiple gestation, are more likely to require cervical cerclage. Spinal anesthesia is an excellent choice for women undergoing prophylactic cerclage. Some obstetricians prefer general anesthesia for emergency cerclage when the cervix is dilated or the membranes are bulging, believing that general anesthesia decreases intra-abdominal pressure and increases uterine relaxation, thus decreasing the risk of membrane rupture and facilitating replacement of bulging membranes. However, coughing on the endotracheal tube during emergence from general anesthesia, and vomiting (more likely to occur with general anesthesia), both acutely increase intra-abdominal pressure. Outcome differences between regional and general anesthesia have not been well studied, although one retrospective study found no difference in the incidence of inevitable abortion or low-birth-weight babies between the two techniques[16].

### Pre-eclampsia/eclampsia

Women with multiple gestation pregnancies are at increased risk for pre-eclampsia and eclampsia (see Chapter 53). Several aspects of the pathophysiology of pre-eclampsia are of particular concern to the anesthesiologist. Coagulation deficits may preclude neuraxial analgesia/anesthesia because of the increased risk of spinal/epidural hematoma. Additionally, pre-eclamptic parturients may have increased airway edema, increasing the risk of a difficult airway when intubation is required. Finally, magnesium therapy may interact with anesthetic techniques and agents. Magnesium sulfate resulted in more profound maternal hypotension after the initiation of neuraxial anesthesia to the T10 level in gravid ewes[17]. In addition, magnesium markedly prolongs the duration of action of non-depolarizing neuromuscular blocking agents[18].

There are several reasons to encourage neuraxial analgesia/anesthesia in the pre-eclamptic parturient. These patients have an exaggerated hypertensive response to sympathetic stimulation and pain, and this undesirable response is blunted by effective epidural analgesia[19]. Moreover, pre-eclampsia is

associated with uteroplacental insufficiency, and epidural analgesia improves intervillous blood flow in patients with severe pre-eclampsia[20]. Finally, pre-eclamptic parturients are at increased risk for an urgent or emergency cesarean delivery. The early initiation of neuraxial labor analgesia allows for conversion to epidural anesthesia should a cesarean delivery become necessary.

Neuraxial anesthesia for cesarean delivery has several advantages compared with general anesthesia, particularly in the parturient with pre-eclampsia and multiple gestation. Airway manipulation is avoided, as is the associated risk of inability to intubate. Compared with epidural anesthesia in severely pre-eclamptic parturients, general anesthesia is associated with significant systemic and pulmonary hypertension[19] and decreases in intervillous blood flow[20].

Controversy exists as to whether spinal anesthesia is appropriate for the parturient with severe pre-eclampsia[21]. There is concern that the sympathectomy induced by spinal anesthesia may place severely pre-eclamptic parturients with possible intravascular volume constriction at increased risk for profound hypotension. The onset of sympathetic blockade is much faster with spinal compared with epidural anesthesia. Although no randomized studies have directly compared the two techniques, results of recent observational studies suggest that spinal anesthesia is safe in this patient population[22]. Some anesthesiologists prefer spinal anesthesia in parturients who have a low platelet count because of the decreased risk of epidural/spinal hematoma associated with spinal compared with epidural anesthesia (smaller needle, no catheter)[23].

A small number of pre-eclamptic parturients have thrombocytopenia, and a subset of these have coagulation factor deficiencies. There are no data to support the use of a specific platelet count, above which it is 'safe' to initiate neuraxial analgesia/anesthesia. Epidural/spinal hematoma is a rare complication of neuraxial anesthesia. Most anesthesiologists feel comfortable initiating neuraxial anesthesia if the platelet count is greater than 100 000/mm$^3$, but not if the platelet count is below 50 000/mm$^3$ (reference 24). For pre-eclamptic parturients who have a downward trend in their platelet counts, the early insertion of an epidural catheter is recommended, before the platelet count is unacceptably low. Epidural/spinal hematoma may also occur at the time of epidural catheter removal. Therefore, the coagulation status should be acceptable at the time the catheter is removed. It may be necessary to wait for several days after delivery to remove the catheter if the platelet count or other coagulation tests are abnormal immediately postpartum.

### Antepartum hemorrhage: abruptio placentae and placenta previa

Women with multiple gestation are at increased risk for placental abruption and placenta previa (see Chapters 83 and 84). This circumstance has several implications for the anesthesiologist. Neuraxial anesthesia is relatively contraindicated in the presence of hypovolemia. The acute sympathectomy associated with neuraxial blockade may cause profound hypotension in the hypovolemic patient. An additional consideration in patients with placental abruption is the development of disseminated intravascular coagulation (DIC). Coagulation parameters, including platelet count, prothrombin time, activated partial thromboplastin time, fibrinogen level and D-dimer level should be measured prior to the initiation of neuraxial blockade. Patients with placental abruption and previa who are hemodynamically stable and have normal coagulation status are candidates for neuraxial anesthesia.

### Intrauterine fetal demise

Maternal DIC may occur after the intrauterine fetal death of one or more fetuses[25]. As neuraxial analgesia/anesthesia is contraindicated in the presence of DIC, coagulation parameters should be measured before the initiation of neuraxial blockade in these patients.

### Postpartum hemorrhage: uterine atony

Women with multiple gestation are at increased risk for uterine atony and postpartum hemorrhage for several reasons (see Chapters 84 and 86). These include a larger uterus, an increased incidence of polyhydramnios, an increased risk of pre-eclampsia and magnesium therapy and an increased risk of preterm labor and tocolytic therapy. Therefore, all parturients with multiple gestation should have large-bore intravenous access, and a sample of blood should be sent to the blood bank to type and screen or cross maternal blood when they arrive on the labor and delivery unit.

## LABOR ANALGESIA

Neuraxial labor analgesia may be advantageous to the parturient with multiple gestation. The only randomized study comparing epidural analgesia with no analgesia for twin deliveries was small ($n = 52$)[26]. No difference in neonatal outcome was found between the two groups. However, 46% of the women in the no-analgesia group required general anesthesia for intrauterine manipulation of twin B, versus none in the epidural group. Crawford reported the largest

($n = 200$) and most recent retrospective study of twin deliveries[27]. For babies delivered vaginally, there was no difference in neonatal outcome (as assessed by Apgar scores and umbilical cord gases) between twins A and B in women who had epidural analgesia. In contrast, twin B did worse in women who did not have epidural analgesia. Women who had epidural analgesia had fewer cesarean deliveries for twin B than women who did not have epidural analgesia.

A recent retrospective survey of 967 consecutive twin deliveries performed over a 10-year period between 1990 and 1999 found that the risk of a cesarean delivery for twin B after a vaginal delivery for twin A was decreased in the presence of epidural analgesia (relative risk 0.38, 95% confidence interval (CI) 0.163–0.883)[28]. Between 1980 and 1999, a survey of 1565 twin deliveries found that vaginal–cesarean delivery was associated with a 22-fold higher use of general anesthesia compared with a vaginal–vaginal delivery (95% CI 5.4–88.5)[29].

Presentation of twin B in a non-vertex position was also a risk factor for cesarean delivery of twin B[28]. If twin B presents as a transverse lie, intrapartum version and total breech extraction may reduce the cesarean delivery rate. Intrapartum version is painful and is facilitated by epidural analgesia[30]. Traditionally, uterine relaxation for the version was achieved with the use of general anesthesia or β-adrenergic agonists. More recently, intravenous nitroglycerine (NTG) has been used for both external cephalic[31] and internal podalic[32] version of twin B. NTG has a rapid onset, is short-acting and has few side-effects. Maternal hypotension is short-lived and often asymptomatic. In addition, NTG has been used for cervical relaxation in the presence of head entrapment during vaginal breech delivery[33]. NTG doses as high as 1000 μg have been described[34], although doses between 50 and 250 μg, administered as an intravenous bolus, are more common.

Grobman and colleagues reviewed the records of 134 women with twin gestation who underwent a trial of labor, and compared selected variables in women who were ultimately delivered by cesarean compared with women who delivered vaginally[35]. Multivariate analysis identified nulliparity and initiation of epidural analgesia at cervical dilation ≤ 3 cm as factors associated with cesarean delivery. These authors suggested that the timing of epidural analgesia is a modifiable risk factor for cesarean delivery. However, an association of early epidural analgesia initiation with cesarean delivery does not necessarily mean cause and effect. An equally plausible explanation for this association (also found in singleton pregnancies) is that the request for early epidural analgesia is marker of a risk factor for cesarean delivery, e.g. dysfunctional labor, and that the early initiation of epidural analgesia is not the risk factor *per se*. Further study is warranted.

## Technique of neuraxial analgesia for multiple gestation

Neuraxial analgesia should be initiated for women with multiple gestation as is routine for singleton labors. Special care should be taken to labor women with multiple gestation in the full lateral position to minimize the effects of aortocaval compression. Analgesia can be maintained with continuous epidural infusion, patient-controlled epidural analgesia or intermittent injection of a local anesthetic combined with opioid, e.g. bupivacaine with fentanyl. The addition of an opioid allows a low concentration of anesthetic to be used, thus decreasing the risk of motor block and subsequent operative vaginal delivery. A recent randomized study in nulliparous women with singleton gestation found that low-concentration local anesthetic epidural analgesic techniques were associated with a lower risk of forceps deliveries compared with a traditional, higher-concentration technique[36].

Prior to delivery, the mother should be transferred to an operating room capable of supporting a cesarean delivery (Table 82.2). NTG should be prepared, as well as a solution of concentrated local anesthetic solution (3% 2-chloroprocaine or 2% lidocaine). Drugs to induce general anesthesia, e.g. thiopental and succinylcholine, should be immediately available. Supplemental oxygen, as well as a non-particulate antacid, should be administered shortly before the delivery of twin A. Several minutes before the delivery of twin A, 5–10 ml of the concentrated local anesthetic solution can be administered via the epidural catheter. This deepens the analgesia/anesthesia in anticipation of intrauterine manipulation, and decreases the time necessary to extend the block for surgical anesthesia if cesarean delivery of twin B is required.

Intrauterine relaxation for internal podalic version can be accomplished with intravenous or sublingual NTG. If this is not successful, induction of general anesthesia followed by administration of a high concentration of a volatile anesthetic agent, e.g. sevoflurane, may be necessary.

Anesthesia for the urgent/emergency cesarean delivery of twin B can usually be accomplished by deepening and extending the epidural block. General anesthesia should be necessary only if time does not permit adequate surgical epidural anesthesia.

Occasionally the parturient with multiple gestation presents with imminent delivery. In this case,

**Table 82.2** Anesthetic preparation for vaginal delivery of multiple gestation

| *Procedure* | *Timing* |
|---|---|
| Transfer patient to delivery room that is set up with capability for general anesthesia and cesarean delivery | during 2nd stage of labor |
| Check anesthesia equipment and drugs, including:<br>(1) Drugs for induction of general anesthesia<br>(2) NTG<br>(3) Concentrated, rapidly acting local anesthetic solution (e.g. 3% 2-chloroprocaine, 2% lidocaine)<br>(4) Drugs for pulmonary aspiration prophylaxis | during 2nd stage of labor |
| Anesthesiologist present in delivery room:<br>(1) Monitor vital signs<br>(2) Consider administration of supplemental oxygen<br>(3) Administer non-particulate antacid<br>(4) Administer small epidural bolus of concentrated local anesthetic (about 5 ml) | crowning of infant A |
| If infant B is non-vertex:<br>(1) Assess analgesia for version and augment as necessary<br>(2) Watch clock and obstetrician<br>(3) Administer NTG for intrauterine relaxation or head entrapment<br>(4) Preoxygenate and induce general anesthesia if NTG is not successful<br>(5) Administer high dose of volatile anesthetic agent at high gas flows | version and delivery of infant B (and/or C) |
| If cesarean delivery of infant B is necessary:<br>(1) Preoxygenate with 100% oxygen by face mask<br>(2) Augment epidural block with 10–15 ml concentrated local anesthetic<br>(3) Be prepared to induce general anesthesia if surgical anesthesia is not adequate | cesarean delivery of infant B (and/or C) |
| Be prepared to treat uterine atony | 3rd and 4th stages of labor |

NTG, nitroglycerine

time may permit the administration of combined spinal–epidural analgesia or spinal anesthesia. Onset of analgesia occurs within several minutes. Even if neuraxial analgesia is not induced for vaginal delivery of twins or triplets, the anesthesiologist should stand by during the delivery.

## ANESTHESIA FOR CESAREAN DELIVERY

The majority of anesthesia-related maternal deaths occur during general anesthesia as a result of failed intubation, failed ventilation and oxygenation and pulmonary aspiration of gastric contents[10]. During the past several decades, the number of women who receive general anesthesia for cesarean delivery has declined significantly[37]. During this same period there has also been a significant decrease in the incidence of anesthesia-related maternal mortality[10]. Obstetric anesthesiologists generally believe that neuraxial anesthesia is safer for the mother, and therefore safer for the fetus/neonate, compared with general anesthesia. Therefore, in most situations, neuraxial anesthesia is the anesthetic of choice, including most women with multiple gestations. An additional benefit of neuraxial analgesia is the ability to provide postoperative analgesia via spinal or epidural opioid administration.

There are a few situations in which neuraxial anesthesia is contraindicated (e.g. maternal hypovolemia, coagulopathy, failed neuraxial anesthesia) and when general anesthesia is indicated, especially for an emergency cesarean delivery when time does not allow for initiation of neuraxial anesthesia.

### Elective cesarean delivery

Spinal anesthesia is the most frequent choice for elective or urgent cesarean delivery in women

without pre-existing epidural labor analgesia. The advantages of spinal anesthesia compared with epidural anesthesia include rapid onset of a dense block, higher success rate, lower drug dose and a simpler technique using a smaller needle. A disadvantage is the inability to prolong anesthesia if the surgical procedure takes longer than anticipated. If a long surgical procedure is anticipated, however, either combined spinal–epidural anesthesia, or epidural anesthesia in which an epidural catheter is introduced into the epidural space, should be performed.

No prospective study has compared spinal with epidural anesthesia for the cesarean delivery of multiple gestations. A single retrospective study of 96 triplet deliveries found a higher incidence of hypotension in women who received spinal compared with epidural anesthesia[38]. However, blood pressures remained within the physiological range and neonatal outcome was not different between the two groups.

Pregnant women require less intrathecal local anesthetic than non-pregnant women to obtain the same degree of sensory blockade. Mechanical as well as hormonal factors are likely to contribute to this phenomenon. Patients with increased intra-abdominal pressure (including pregnant women and obese patients) may have higher cephalad spread of intrathecal local anesthetic because of decreased cerebral spinal fluid volume[39]. Increased progesterone levels may increase the sensitivity of nerve fibers to local anesthetic blockade[40]. Compared with women with singleton gestation, women with multiple gestation have a greater increase in intra-abdominal pressure and a greater increase in progesterone levels.

Indeed, the onset of spinal anesthesia and maximal sensory cephalad blockade was higher in women with twin compared with singleton gestation undergoing spinal anesthesia[41]. The incidence of hypotension did not differ between the two groups, however. In contrast, several groups of investigators found no difference in the dose of epidural lidocaine necessary for epidural anesthesia for women with twin[15] or higher-order pregnancies[42], compared with singleton pregnancies.

### Urgent and emergency cesarean deliveries

The appropriate anesthetic for urgent and emergency cesarean deliveries depends on the circumstances and indications for the delivery. Laboring women with indwelling epidural catheters placed for labor often achieve satisfactory surgical anesthesia within 5 min of injecting the epidural catheter with concentrated local anesthetic solutions. Thus, timely notification of the anesthesiologist, when an emergency operation is first contemplated, is imperative. In patients without epidural labor analgesia, spinal anesthesia can often be performed quickly with the ability to make an incision within 4–5 min of the intrathecal injection. Supplemental oxygen should be administered in all instances.

If time does not allow the extension of epidural analgesia, or the initiation of spinal anesthesia, induction of general anesthesia will be necessary. As discussed earlier, the induction of general anesthesia is associated with an increased risk of hypoxemia during periods of apnea. Awake fiberoptic intubation by an anesthesiologist experienced in this technique is indicated for women with an anticipated difficult intubation. Techniques of general anesthesia do not differ from those used for singleton deliveries. For both neuraxial and general anesthesia, care should be taken to avoid aortocaval compression, and appropriate personnel should be available to resuscitate the neonates.

### Post-cesarean delivery analgesia

Many studies demonstrated superior postoperative cesarean delivery analgesia with neuraxial compared with systemic (either intramuscular or intravenous) analgesia. The total opioid dose is less and mothers are less sedated[43,44]. Neuraxial opioid analgesia may be supplemented with non-opioid systemic agents such as non-steroidal anti-inflammatory drugs[45] or acetaminophen[46]. This allows the use of lower neuraxial opioid doses, resulting in fewer side-effects.

No specific studies have addressed postoperative analgesia after delivery of multiples, but there is no reason to believe that existing study results would not apply equally to women with multiple compared with singleton gestation.

Patient-controlled intravenous analgesia (PCA) is an option for patients who have not received neuraxial opioids. The inherent safety of the PCA technique (patients only receive as much opioid as they need) is diminished if a continuous infusion is added[47]. Therefore, a basal-PCA infusion is not recommended for patients recovering from cesarean delivery[48].

## SUMMARY

Women with multiple gestation are at higher risk for maternal, fetal and neonatal complications during labor and delivery. The intrapartum medical care of these women should involve a team approach. Anesthesiologists should be involved in their care throughout the peripartum period.

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# Epidemiology of Bleeding and Hemorrhage in Multiple Gestations

*D. Levin and R. Levy*

**83**



## INTRODUCTION

Hemorrhage associated with pregnancy remains one of the most serious complications affecting parturients and their yet-to-be-born children. Along with thromboembolic phenomena and hypertensive disorders, hemorrhage contributes to the 'deadly triangle', causing 64–68% of maternal deaths in the second and third trimesters of pregnancy and peripartum, half of the maternal deaths being postpartum. Whereas overall maternal obstetric morbidity is estimated at 12 cases per 1000 deliveries, hemorrhage accounts for slightly over half of recorded morbidity[1]. The adjusted odds ratio (OR) for severe hemorrhage in multifetal pregnancy was 2.29 (95% confidence interval (CI) 1.2–4.37)[2]. In Europe the maternal mortality rate in 1994 was estimated at 5.2/10 000 live singleton births versus 14.9/10 000 live multiple births[3]. Stated another way, the maternal risk of death was triple in multiple gestations (OR 2.9, CI 1.4–6.1)[3]. It is logical to postulate that a substantial part of these deaths must be due to maternal hemorrhage in multifetal gestations.

In one older study, the incidence of antenatal and postpartum hemorrhage in multifetal gestations was 6.1% and 3%, respectively[4]. In more recent studies, which assessed postpartum hemorrhage, the relative risk in multifetal gestations ranged from 2 to 4.5[5–8].

In triplet pregnancies alone, the incidence of postpartum hemorrhage was 9–12%, and anemia was noted in 27–58% of these pregnancies[9,10]. In quadruplet pregnancies the incidence of postpartum hemorrhage was 21% (CI 11–31%)[11].

Table 83.1 lists several risk factors for bleeding and hemorrhage associated with multiple pregnancy. The majority are not unique to multifetal gestations, but their prevalence and severity are increased in such cases. Some may increase gravid women's risk for hemorrhage and are unique to multifetal gestations, including single fetal demise or its iatrogenic counterpart fetal reduction, heterotopic pregnancy and multifetal gestations with one conceptus being molar (see Chapters 18 and 23). In the majority of instances, hemorrhage during pregnancy is of maternal origin, but attention must also be paid to fetal hemorrhage, which may be more prevalent in multifetal gestations due to cord abnormalities such as vasa previa or velamentous insertion of the cord, which is more prevalent in multiple gestations[12,13].

**Table 83.1** Potential causes of pregnancy-associated hemorrhage that are more often encountered in multiple pregnancies

| |
|---|
| *All pregnancies* |
| First trimester |
| threatened abortion/abortion |
| Second and third trimesters |
| placenta previa |
| placental abruption |
| vasa previa |
| Postpartum |
| uterine atony |
| overdistended uterus |
| spontaneous |
| rupture of scarred uterus |
| traumatic delivery |
| operative vaginal delivery |
| *Conditions unique to multifetal gestations* |
| Vanishing twin phenomenon |
| Single fetal demise |
| Heterotopic pregnancy |
| Coinciding normal and molar pregnancy |

Assisted reproductive technologies (ART) pregnancies, in particular, and/or the techniques used to achieve them, create additional circumstances that may increase the rate of pregnancy-associated hemorrhage[14]. Also, the special hematological situation of the gravid woman is of crucial importance. Iron-deficiency anemia, for instance, is much more common in multifetal gestations than in singletons (see Chapter 51 on 'Nutrition'); furthermore, the unique entity of single fetal demise in multifetal gestations may potentially endanger the gravid woman with coagulopathies.

The management of the various entities causing hemorrhage is discussed elsewhere.

## THREATENED ABORTION

Abortion is one of the most common causes of bleeding associated with pregnancy. Do twin or high-order multiple pregnancies (HOMPs) have an inherent greater predisposition to abortion? Until the implementation of sensitive human chorionic gonadotropin (β-hCG) assays it was difficult to estimate the incidence of pregnancy loss before the first missed menses. Likewise, it was an almost impossible task to quantify the frequency of early absorption of one or more fetuses in a multifetal gestation, the so-called 'vanishing twin' phenomenon (see Chapter 17). Only with the development of high-resolution ultrasound has light, or, more accurately, 'sound', been 'shed' on this question.

It is well known that bleeding in the second and especially the first trimester may be a sign for impending abortion. In addition, bleeding is the only significant clinical sign suggestive of the vanishing twin phenomenon. Are multifetal gestations at greater risk for abortion? In three early studies, completed in the early 1980s, fetal loss rate was evaluated[15–17]. All concluded that the rate of pregnancy loss in twin gestations was significantly higher, up to three-fold, than in singletons. A gross calculation of the 'real' twinning rate was 1/30–1/76 conceptions, figures that, most probably, underestimate the twinning rate.

In order to estimate the true loss rate of twin pregnancy, pre-missed period losses and the 'vanishing twin' phenomenon must also be considered. In two studies assessing the rate of preclinical pregnancy loss in women attempting natural conception, by using sensitive β-hCG assays, the early pregnancy loss was found to be between 21.7 and 32.9%[18,19]. In patients undergoing ART, the preclinical pregnancy loss was 28.2%[20]. Actual preclinical losses may be even higher owing to loss before detection by highly sensitive β-hCG assays. Boklage estimated the rate of premenstrual abortion at 65% of singleton conceptions[21], and extrapolated that as many as 74.6% of twin conceptions are lost before the first missed period. A majority of multifetal pregnancies that survive beyond the first missed menses are also lost completely or partially, thereafter resulting in first-trimester bleeding. This rate was assessed in various studies with various methodological problems. First-trimester loss of twin pregnancies assessed by ultrasound scan of 1000 pregnancies[22] showed 24 twin pregnancies with distinct double cardiac activity. Only one patient had a complete pregnancy loss and seven others had a vanishing twin. The overall twin pregnancy loss was 33% in the first trimester. This may also be an underestimate if the ultrasound scan was done in some cases later in the first trimester.

Taking into account the rate of twin pregnancy loss before clinical diagnosis (75%) and the rate of first-trimester twin pregnancy loss (33%), the overall early to first-trimester loss is about 83%. This again may be an underestimate, and it is possible that less than 17% of all conceived twin pregnancies result in viable second-trimester gestations. Second-trimester twin pregnancy loss, as in singleton pregnancies, is by far less common than first-trimester loss. In a 1998 review, it was estimated that approximately 3–7% of viable twin pregnancies will be partially or fully lost during the second trimester[23].

## PLACENTA PREVIA

Several studies have attempted to answer the question whether placenta previa, a major cause of antepartum hemorrhage, is indeed more prevalent in twin pregnancies and HOMPs. In the earlier publications of hospital series, twin gestations were associated with an elevated risk for placenta previa, compared with singletons[24,25]. Eight cases occurred in 1464 (0.55%) twin pregnancies, significantly higher than the incidence of 0.31% in singleton pregnancies[24]. In a 1990 case–control study of 1253 twins delivered between 1982 and 1987, the incidence of placenta previa in twin pregnancies was not different from that of singletons[26], in contrast to other complications that were more prevalent in twin gestations compared with singletons (hypertension, abruption and anemia: OR 2, 95% CI 2.1–3.1; OR 3.0, 95% CI 1.9–4.7; and OR 2.4, 95% CI 1.9–3.0, respectively). This observation has been questioned in more recent studies[27,28], and still remains unsettled. The most recent publication on this topic, relating to a historical cohort study between 1997 and 2000, compared the occurrence of placenta previa at delivery between singleton and multifetal gestations[27]. A total of 28 372 singleton and 896 multiple births were recorded. Placenta previa occurred in 51 (0.18%) singleton gestations

and four (0.45%) multiple gestations ($p = 0.09$), whereas singleton and multiple gestations with placenta previa had similar maternal demographic variables, prior uterine surgery (excluding cesarean section) and gestational age at delivery. Multiple gestations with placenta previa were more likely to have had a prior cesarean section ($p < 0.001$). No differences were noted between singleton and multiple gestations with placenta previa and the need for cesarean hysterectomy and blood transfusion. The final word on this topic comes from a cohort study based on the US natality data files comparing nearly 38 million singleton births with about one million twin births[28]. The rate of placenta previa was 40% higher among twin births (3.9 per 1000 live births) than among singleton births (2.8 per 1000 live births). Comparison between the singleton and twin births revealed fairly similar risk factor profiles. Another study compared perinatal outcome and peripartum complications between twin and singleton pregnancies. A study group of 435 pairs of twins (870 neonates) was compared with a group of 4754 singletons. The co-authors concluded that outcome was better and complications were fewer (except cesarean section rate) in twin pregnancies. Among the complications studied, placenta previa rate was also lower in twin gestations compared with singletons (0.9 vs. 2.9%, $p < 0.01$)[29].

## PLACENTAL ABRUPTION

The second major cause of antepartum hemorrhage is placental abruption, for which twin gestation is considered a significant risk factor[30]. Different theories propose to explain this condition, including uterine overdistension and the simple fact that the placental area in contact with the endometrium is much larger in twin compared with singleton gestations. None are proven, and recent large studies question whether multifetal gestations are indeed at higher risk for placental abruption. For example, in a study cited above, Mizrahi and colleagues[29] showed that preterm twin gestations had significantly lower rates of placental abruption compared with preterm singletons (1.8 vs. 5%, $p < 0.01$).

The same authors who investigated the US population-based data on placenta previa used a similar methodology to investigate placental abruption[31]. In this instance, a retrospective epidemiological study evaluating risk factors for placental abruption in singleton versus twin pregnancies was based on data derived from the US linked birth/infant death files for 1995–96. This file comprised 7.5 million singleton births and nearly 200 000 twin births. Abruption was recorded in 5.9 per 1000 singleton births and twice as frequently (12.2 per 1000) in twin births. Another interesting observation in this study was the variable influence of different risk factors for abruption on singleton and twin births. The adjusted relative risks for abruption in singleton and twin births were: preterm premature rupture of the membranes (adjusted odds ratio, AOR 4.89 and 2.01, respectively), eclampsia (AOR 3.58 and 1.67, respectively) and hydramnios (AOR 2.04 and 1.69, respectively). Whereas chronic hypertension and pregnancy-induced hypertension were risk factors for abruption in singletons, this was not the case in twin births. The authors concluded that abruption was twice as likely to occur in twins as in singletons but with differing risk profiles, suggesting that abruption in twins may result from a different pathophysiological process.

A prospective analysis of twin and singleton pregnancies from the National Institute of Child Health and Human Development Network of Fetal–Maternal Medicine Units compared rates and severity of gestational hypertension and pre-eclampsia as well as perinatal outcomes[32]. As these complications developed more often in women with twin gestations, the incidence of placental abruption was, not unexpectedly, higher (but not significantly) in the twin group (4.7 vs. 0.7%, $p = 0.07$).

A far smaller study comparing 41 triplet gestations with twins showed a two-fold increase in the incidence of abruption in the triplet group; however, this difference was not found to be statistically significant owing to the small sample size of the groups[33].

## SPECIFIC PLACENTAL AND CORD ABNORMALITIES LEADING TO ANTEPARTUM BLEEDING

Vasa previa is a rare cause of antenatal bleeding. The origin of bleeding is from blood vessels of the umbilical cord traversing the membranes at or near the internal cervical os. When amniorrhexis occurs, blood vessels may be severed along with the membranes, thus causing fetal hemorrhage that can lead to exsanguination and fetal death within minutes. *In vitro* fertilization (IVF) has been found to be a risk factor for vasa previa in multiple as well as singleton pregnancies[12]. Vasa previa is usually associated with abnormal cord insertions such as velamentous or marginal insertions. Velamentous cord insertion (Figure 1) is noted in around 1% of singleton pregnancies, but is more frequent in twin pregnancies and is found in as many as 28% of triplet pregnancies[13]. Other placental pathologies that may cause antepartum hemorrhage are succenturiate and membranaceous placentas. Although it seems logical that these placental findings are more common in multiple gestations, the incidence in singleton and multiple pregnancies is unknown.

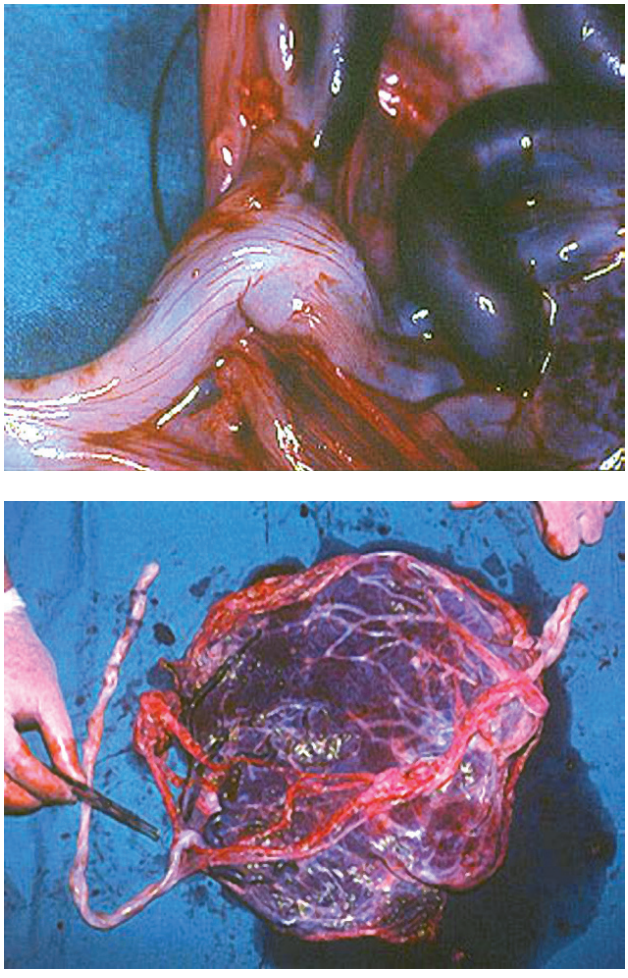

**Figure 83.1** Velamentous cord insertion

## ASSISTED REPRODUCTIVE TECHNOLOGIES

When addressing the question of hemorrhage in multiple pregnancies achieved by ART, one must first address the general question: 'Does any pregnancy achieved by ART have higher rates of hemorrhage?' In a retrospective comparison of obstetric outcomes of 335 singleton pregnancies achieved artificially with those of a control group of 643 natural pregnancies, the frequency of gestational hypertension, placenta previa and cesarean section was increased in ART gestations[34]. In an analysis comparing outcomes of 58 multiple pregnancies following IVF and intracytoplasmic sperm injection procedures with those of 58 singleton pregnancies following the same procedures[14], there was a significantly higher incidence ($p < 0.01$) of first-trimester bleeding and placental abruption in triplet pregnancies compared with twin and singleton pregnancies (40.9%, 6.4% and 6.9%, respectively for first-trimester bleeding and 33.3%, 0% and 6.9%, respectively for placental abruption). A retrospective study[35] comparing pregnancy outcomes of 104 ART and 193 spontaneous twin pregnancies delivered at or after 24 weeks found an increased incidence of gestational hypertension, uterine bleeding, premature contractions, intrauterine growth restriction and fetal death in the ART group. In this group, 10.4% of twin pregnancies were complicated by uterine bleeding, compared with 3.1% of the controls. Further stratification revealed that uterine bleeding occurred in 1.4% of twin pregnancies conceived after ovulation induction and 4.1% of spontaneous twin pregnancies ($p < 0.05$). In a recent study, only dizygotic twins were included (the study group encompassed only opposite-sex twin pregnancies), to remove confounding by monozygotic twins[36]. The study group of 514 IVF dizygotic twin pregnancies had a 5% antenatal bleeding rate, whereas the non-IVF group was complicated by antenatal hemorrhage in only 3% ($p = 0.03$). In addition, placenta previa was found to be more prevalent in IVF than non-IVF twin pregnancies (2.1 vs. 0.7%, $p = 0.01$). Such findings warrant further investigation of the yet-unknown factors in ART twin pregnancies which may increase the risk of maternal and perinatal morbidity. Finally, in a population-based study in northern Finland including 225 women who had delivered following IVF conception and 671 control pregnancies, the relative risk for vaginal bleeding during pregnancy was 4.1 (95% CI 2.5–6.7) for singletons and 6.9 (95% CI 2.5–19.2) for twins[37].

Another issue that arises in comparing obstetric outcomes between singletons and twins is that of the maternal milieu. The obstetric outcome of 232 pregnancies following ovum donation was retrospectively analyzed[38]. The overall incidence of vaginal bleeding was 12%, 1.5% and 2% in the first, second and third trimesters, respectively, figures which are similar to usual IVF statistics. The postpartum hemorrhage incidence, however, was 12%, which is significantly higher than the 3% incidence stated earlier[2].

## POSTPARTUM HEMORRHAGE

As stated above, the incidence of postpartum hemorrhage is significantly increased in multifetal pregnancies[6–11]. The majority of these cases are due to an overdistended uterus during the later stages of pregnancy, resulting in an atonic uterus after delivery. Other causes are placental pathologies or trauma to the birth canal during delivery. The latter is avoided by careful selection of candidates for vaginal birth in twin pregnancies, avoidance of vaginal birth in HOMPs and careful and prudent midwifery and obstetric care.

Postpartum hemorrhage due to uterine atonia is a problem that may be foreseen in multiple gestations given that this type of pregnancy, by definition, leads to an overdistended uterus. Active management of the third stage of labor with prophylactic administration of oxytocin, through various venues, utilization of other uterotonics, predelivery cross-matching of maternal blood and preparation of blood for transfusion, the collection and use of autologous blood lost during labor or prepared before labor, and prompt postpartum examination and evaluation of the parturient may reduce morbidity and mortality in these special circumstances. More detailed studies of prophylactic pharmacological management of the immediate postpartum period in multifetal pregnancies are needed. The management of this important issue is described in detail in Chapter 86.

## SUMMARY

Hemorrhage in pregnancy remains one of the most serious maternal and fetal complications, causing serious morbidity or even mortality to both gravida and conceptus. The incidence of antepartum and postpartum hemorrhage in multiple pregnancies is significantly higher than in singletons, although some specific etiologies may not be more common than previously thought.

We believe that multiple gestations, especially HOMPs, are at greater risk of hemorrhage, and therefore should be regarded as high-risk pregnancies in this aspect. Careful attention should be paid to the general and specific reasons for bleeding. Appropriate diagnostic and therapeutic measures may significantly reduce morbidity and mortality in these circumstances.

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# Management of Uteroplacental Bleeding Disorders

*L. Yeo and C. V. Ananth*

**84**



## INTRODUCTION

As is the case in singleton pregnancies, uteroplacental bleeding disorders can occur in twin gestations as well. Indeed, in certain clinical situations, it may occur more frequently. Uterine bleeding during the second and third trimesters is relatively common and occurs in approximately 6–8% of all pregnancies[1]. Regardless of etiology, bleeding is associated with an increased risk of preterm births and perinatal deaths[1]. Whereas up to 20% of bleeding episodes are attributed to placenta previa and 30% to abruptio placentae[2], at least half are of unknown etiology. In twin pregnancies, both placenta previa and placental abruption account for the majority of uteroplacental bleeding disorders. Other causes may include premature labor, genital tract trauma, carcinoma of the cervix or vagina, coagulation defects and hemorrhagic cystitis. The management of such bleeding disorders requires consideration of both maternal and fetal conditions, an understanding of the maternal pathophysiology and natural fetal outcomes and careful formation of a therapeutic plan. This chapter discusses placenta previa and abruption and the management of these disorders in twin gestations.

## PLACENTA PREVIA

Placenta previa is an obstetric complication whereby the placenta covers or comes in close proximity to the internal cervical os (Figure 84.1). It is a known cause of bleeding in the latter part of pregnancy (although it may be seen at any time), and has significant perinatal implications. Maternal complications associated with previa include hemorrhage requiring blood transfusion, disseminated intravascular coagulation (DIC) and hysterectomy. Previa occurs in 2–6 per 1000 pregnancies and has been implicated in up to 5% of all perinatal deaths[3]. Among surviving infants, previa results in increased rates of prematurity, low birth weight and associated morbidity[3]. In a recent population-based study of all live births in the United States, the rate of placenta previa was 40% higher among twins compared with singletons (3.9 vs. 2.8 per 1000 live births)[3]. As large placentas (secondary to twinning) occupy more surface area on the endometrium, they therefore tend to present a greater likelihood of encroaching the cervical os. Not all researchers find the occurrence of previa at delivery to differ between singleton and multiple gestations, however[4]. Other conditions thought to increase

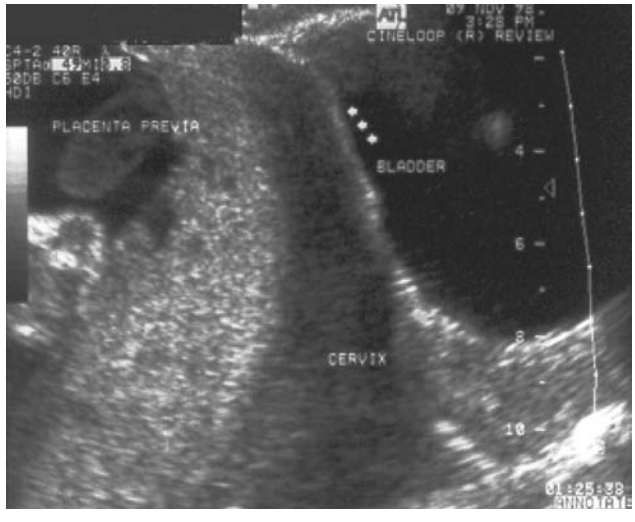


**Figure 84.1** Third-trimester sonogram depicting complete placenta previa overlying the cervix

the risk of previa include advanced maternal age, multiparity, prior cesarean delivery/abortion, smoking, cocaine use and a prior history of placenta previa[3]. Although expectant management of placenta previa improves outcome, preterm delivery because of maternal reasons remains a major cause of perinatal death. In addition, for any given fetal weight, perinatal mortality is likely to be somewhat greater with placenta previa than in the general population[5].

Bleeding from previa is usually painless and often happens without warning. Although the initial episode usually subsides spontaneously, bleeding tends to recur during pregnancy, and reappears at the onset of parturition because formation of the lower uterine segment with cervical dilatation inevitably leads to spontaneous placental separation. Hemorrhage occurs because blood vessels are disrupted via placental separation and the tearing of attachments. Bleeding increases further, secondary to the inability of the myometrium of the lower uterine segment to contract and constrict adequately around torn vessels.

## MANAGEMENT OF PLACENTA PREVIA

Placenta previa may be seen with some frequency in the second trimester of a twin gestation, but, as the uterus grows throughout the pregnancy, the placental site 'moves away' from the cervical os, and in most cases ends up being far from the cervix. As a result, the observed frequency of placenta previa decreases as gestation advances. Placental location can be monitored periodically throughout pregnancy (depending on the clinical situation) via ultrasonography (with transvaginal scanning if necessary). The accuracy of the sonographic diagnosis of previa is highest with transvaginal sonography, and may be as high as 93%[6]. Once an anterior placenta previa is diagnosed, especially in patients with a prior cesarean section scar, placenta accreta/increta/percreta should always be suspected, and there is a possibility of antenatal diagnosis of this condition sonographically[7]. This occurs when the placenta is unusually adherent to the implantation site, with scanty or absent decidua, so that the normal physiologic plane of cleavage through the decidual spongy layer is not present. The strongest recognized association of placenta accreta is with placenta previa and prior uterine surgery, such as cesarean delivery. The association with placenta previa is due to the presence of poorly developed decidua in the lower uterine segment. The presence of placental invasion predisposes to significant hemorrhage, with the potential for hysterectomy in the postpartum period.

Any pregnant patient with vaginal bleeding should be evaluated immediately. Intravenous access should be established, so that fluid and blood replacement can be given if necessary. A complete blood count, coagulation panel and type/cross-match of blood should be initiated. Both fetuses should be evaluated with electronic fetal heart rate monitoring (and ultrasound, if necessary, and when the condition permits) simultaneously as the mother is being evaluated. Digital cervical examinations should never be performed in patients with placenta previa, because they can incite massive hemorrhage. However, a careful speculum examination can be performed in stable patients to inspect the cervix visually for dilatation. In patients in whom significant hemorrhage occurs, delivery is usually mandatory, despite the presence of prematurity. In such instances, the benefits to the mother of undergoing iatrogenic preterm delivery far outweigh the risks of fetal immaturity. On the other hand, in the presence of placenta previa and prematurity, and in the absence of life-threatening bleeding, management should be expectant.

Over the years, maternal and perinatal mortality from previa has declined substantially owing to the more liberal use of cesarean section and the use of expectant management. On the other hand, when patients with previa have modest bleeding and are remote from term, the goal is stabilization, careful observation in the hospital and continuous assessment of maternal/fetal status. It is desirable to obtain the maximum maturation for the twin fetuses by utilizing an expectant approach, often assisted by nature in that the majority of bleeding episodes are self-limiting. Not only does a delay in delivery allow administration of a corticosteroid to obtain pulmonary maturity, but the gestational age of the twins may advance considerably. With expectant management, no sharp peak is seen in the incidence of deliveries at any given gestational week, but, rather, a steady rise as the pregnancy advances[8]. The probability that the pregnancy will be maintained for weeks is a function of the gestational age already attained. For example, a pregnancy at 32 weeks has an 80% chance of achieving 36 weeks, whereas a pregnancy at 36 weeks has only a 50% chance of gaining two additional weeks[8]. It should be noted, however, that these statistics have been described for singletons, and cannot be completely adopted for twin gestations. Patients may also be managed as outpatients in carefully selected instances where the initial bleeding episode subsides. However, management criteria must include being clinically stable with absence of bleeding, maintaining bed-rest at home, being reliable, having an adequate support system and being within a reasonable distance from the hospital.

Tocolysis is an option that may be safely undertaken if the maternal/fetal conditions do not mandate immediate delivery, if the gestation is less than

34 weeks and if bleeding is thought to be secondary to uterine contractions. However, it is important to remember that in twin gestations, tocolytics may cause complications such as pulmonary edema more frequently compared with singletons. In our experience, we generally use magnesium sulfate as the initial agent, with possible consideration of a terbutaline pump afterwards (depending on the clinical situation) once the course of magnesium sulfate is completed.

Several options exist with regard to the timing of delivery. An optimal method that allows preparation for both obstetricians and pediatricians is performing an amniocentesis at approximately 36 weeks of gestation on the twin that offers an accessible pocket of amniotic fluid. If the lungs are mature, then a scheduled cesarean section can be performed under non-emergent circumstances. Another option is to perform a scheduled cesarean section at 37 weeks' gestation. Of course, if life-threatening maternal hemorrhage occurs, or there is fetal distress of one or more fetuses at 24 weeks or beyond, then immediate delivery should be undertaken. A cesarean should be performed rather than starting tocolytic therapy in patients with placenta previa who are in preterm labor beyond 34 weeks. On occasion, tocolytics may be administered in a very premature pregnancy with non-viable twins and non-life-threatening bleeding. However, in the presence of life-threatening hemorrhage, delivery should take place with performance of a hysterotomy, if necessary.

Whereas cesarean delivery is necessary for complete previa, this need is less clear in situations in which the placenta is located 2–3 cm from the internal os at the time of anticipated delivery. In many instances, the fetal head may tamponade the lower margin of the placenta, and a vaginal delivery can be achieved without significant hemorrhage. However, the risk of intrapartum bleeding still remains significant, and if labor is allowed, one should still be prepared for an emergent operative delivery. The risk may be further compounded by the observation that vaginal delivery must be accomplished for both twins.

Several preparations should be made prior to delivery. The patient's blood should be typed and cross-matched, with blood available for transfusion, and the hemoglobin/hematocrit should be at least 10 g/dl and 30%, respectively. In addition, if a patient has been managed in the hospital owing to recurrent bleeding episodes, blood transfusions should be performed antepartum to keep the hemoglobin/hematocrit at the above-described values in anticipation of potential blood loss at delivery. The placental location should be examined sonographically prior to cesarean section, since an incision through the placenta can often create significant maternal as well as fetal blood loss. By 'mapping out' the location of the placenta(s), an appropriate uterine incision can be made, and blood loss can be minimized. For example, if there is an anterior previa, a very high vertical incision extending into the fundus can be performed, whereas with a posterior previa, an incision can be made in the anterior lower uterine segment.

A final note regarding consent is important. The patient should be consulted prior to the delivery regarding the possibility of accreta/percreta/increta, as well as the potential risk for cesarean hysterectomy and increased blood loss, necessitating blood transfusion. Accordingly, preparations should always be made in advance for possible hysterectomy, by having appropriate instruments, skilled operators and adequate anesthesia. Another option to minimize blood loss, which may also decrease the chances for hysterectomy, is pelvic artery embolization with catheterization being done in advance, prior to the surgery. This involves management/preparation with radiology and should be applied only to non-acute and non-emergent cases. After delivery of the placentas, blood loss may be difficult to control, as the lower uterine segment is only weakly contractile and may not be effective in occluding bleeding vessels. The placental bed can be sutured, and/or injection of methergine or 15-methyl prostaglandin $F_{2\alpha}$ into the bleeding area is mandatory. Packing of the area may be useful only as a temporary measure.

## PLACENTAL ABRUPTION

Placental abruption is defined as the complete or partial separation of a normally implanted placenta from its uterine site before the delivery of the fetus or fetuses. It complicates approximately 1% of all singleton pregnancies, and the incidence is at least doubled in twin gestations. A recent, population-based epidemiologic study in the United States found that abruption was recorded in 0.59% and 1.22% of singleton and twin births, respectively, and the twin to singleton relative risk was 2.1[9]. In addition, the risk of abruption among twin births was highest among multigravid (three or higher) women aged 35–49 years (relative risk 1.52, 95% confidence interval (CI) 1.19–1.94)[9]. Recently, the same authors confirmed that a birth-weight discordancy of 20% or more among same-sex twins (adjusted relative risk 1.2, 95% CI 1.1–1.4), and 40% or more among different-sex twins (relative risk 2.2, 95% CI 1.7–2.8), conferred an increased risk for abruption[10]. Moreover, relative risks of stillbirths and neonatal deaths among abruptions were significantly higher for each birth-weight discordancy group (for both same- and opposite-sex twins), compared with the

control group[10]. In contrast, in the non-abruption group the neonatal mortality rates were 24.9 and 19.0 per 1000 live births among same- and opposite-sex twins, respectively. These rates were approximately 3–4-fold higher among those infants born to women with abruption (91.1 and 81.9 per 1000 live births, respectively)[10]. The risk for delivering preterm was also increased, as more than two-thirds of twin pregnancies were delivered before 32 weeks among abruption births.

Despite numerous studies over decades, the exact etiology of placental abruption has yet to be precisely determined. Currently it is thought to be a disease of the decidua and uterine blood vessels. Medical and obstetric complications associated with an abruption risk in twins include eclampsia, preterm premature rupture of the membranes, maternal anemia, intrapartum fever, hydramnios, smoking and renal disease[9]. In contrast, neither chronic hypertension nor pregnancy-induced hypertension was associated with a risk for abruption in twins (but were risk factors in singleton pregnancies)[9].

A unique traumatic etiology of abruption in twins is the separation of the placenta which occurs after delivery of the first twin, with subsequent uterine decompression. In this scenario, there may be increased bleeding above normal, and/or an abnormal fetal heart rate tracing (including fetal distress) of the remaining twin. If this occurs, an expedited delivery by cesarean (unless vaginal delivery is imminent) should be performed, along with other supportive measures as necessary (units of blood available, crystalloids, etc.). Many possible fetal/neonatal complications arise from abruption, including fetal anoxia, prematurity, stillbirth and intrauterine growth restriction. The perinatal morbidity and mortality rate is as high as 20–40%[11], accounting for 15% of all perinatal deaths[12]. In one recent study among twins, fetal deaths were more common in the abruption group, and among surviving neonates, a greater proportion weighed less and delivered earlier in the abruption group compared with the non-abruption group[9].

Classically, abruption is described as occurring in the third trimester of pregnancy, but it can occur earlier in gestation as well. Abruption is suspected clinically when a patient presents with a sudden onset of vaginal bleeding, a tender uterus with increased resting tone and hypertonic or hyperactive uterine contractions. The occurrence of high-frequency, low-amplitude contractions is common. Abruption may also present as preterm labor that appears to be idiopathic[13]; indeed, as many as 10% of idiopathic preterm labor cases may be caused by concealed abruptio placentae. The diagnosis is confirmed at delivery when adherent clot(s), hematoma or hemorrhage to the placenta or membranes, with or without depression or disruption of the underlying placental tissue, is found.

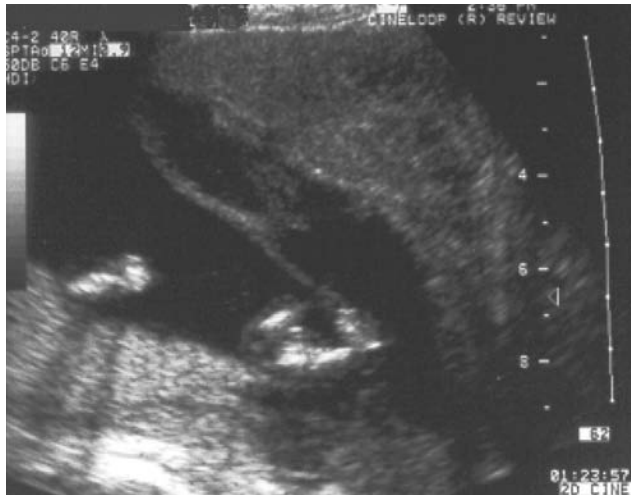


**Figure 84.2** Second-trimester ultrasound image showing a large sonolucent subchorionic abruption located anteriorly. The placenta parenchyma is located posteriorly

Because of the routine use of ultrasonography to assess bleeding early in pregnancy, an abruption is often diagnosed in the first, or early second trimester (Figure 84.2). Provided that the patient is hemodynamically stable, this can be monitored expectantly with serial sonograms. The size of abruption will either regress, remain the same or progress. Many pregnancies will subsequently progress normally and without complication. The size and location of the abruption may be important for prognosis. For example, retroplacental collections have a worse prognosis for fetal survival than subchorionic hemorrhages. Large retroplacental hemorrhages (more than 60 ml, or greater than 50% of placental involvement) are associated with a fetal mortality rate of 50% or more, whereas similar-sized subchorionic hemorrhages have a 10% fetal mortality rate[14]. Subchorionic hemorrhages may also increase the risk of miscarriage, stillbirth and preterm labor, with large abruptions carrying a worse prognosis than smaller ones. This information is important in managing and monitoring patients with suspected abruptio placentae.

In the past, the detection rate of placental abruption by sonography was reported to range anywhere from 2 to 50%[2,13,15]. However, since that time there have been great advances in sonographic resolution, imaging and interpretation, so that we find the sensitivity of sonographically detecting abruptions to be much higher. Recently we prospectively determined the diagnostic accuracy of targeted sonography in detecting abruptio placentae in patients with

vaginal bleeding and singleton gestations. The ultrasound examination targeted the following seven sonographic features of abruption: preplacental collection under the chorionic plate (between placenta and amniotic fluid), 'jello-like' movement of the chorionic plate with fetal activity, retroplacental collection (between placenta and myometrium), marginal collection (at the placental margin), subchorionic membranous collection (between the membranes and uterine wall), increased placental thickness or echogenicities (defined as greater than 4–5 cm perpendicular to the plane of the placenta throughout pregnancy) and intra-amniotic hematoma (collection within the amniotic fluid). In 73 patients with singleton gestations presenting with vaginal bleeding, the sensitivity, specificity, positive predictive value and negative predictive value of targeted ultrasound in detecting abruptio placentae (confirmed macroscopically) was 80%, 92%, 95% and 69%, respectively. Once an abruption is detected on ultrasound, close surveillance is indicated, as there may be an increased risk for preterm birth and perinatal compromise. Serial evaluations are useful in monitoring both abruption size and the growth/well-being of both fetuses.

Placental abruption can display a wide spectrum of clinical severity, in which 80% of patients manifest external bleeding, and the remainder have concealed hemorrhage and therefore delayed diagnosis. Most cases of severe hemorrhage occur before labor and have a concealed component, whereas milder cases tend to occur during labor with intermittent episodes of vaginal bleeding.

## MANAGEMENT OF PLACENTAL ABRUPTION

Once a placental abruption is diagnosed, the goal is to assure stability of the mother and her fetuses in a continuous, ongoing process, preferably in the hospital setting. Severe cases of abruption are associated with high maternal mortality and morbidity. The principal maternal complications include hemorrhagic shock, generalized coagulopathy occurring in 10% of cases (due to active consumption of clotting factors within the vascular tree and consequent secondary fibrinolysis) and ischemic necrosis of distant organs (such as the kidneys and pituitary gland).

Patients presenting with acute onset of bleeding should generally be admitted for complete assessment. Stability of maternal vital signs must be assured. When feasible, a careful speculum examination may be done to ensure that the bleeding is coming from the uterine cavity, rather than than the perineum, vagina or cervix. Continuous electronic fetal heart rate (of both twins) and uterine activity monitoring should be instituted as soon as possible, because although fetal heart rates can be normal initially, fetal distress develops in as many as 60% of patients presenting with a live fetus[12]. Indeed, fetal monitoring is helpful to assess the severity of abruption. Various abnormal tracings are characteristic for either or both twins, including tachycardia, loss of variability, sinusoidal pattern or late decelerations. Simultaneously, real-time ultrasonography is useful as a diagnostic aid in identifying the source of bleeding, and when unknown, determine gestational ages and estimated fetal weights. As the history and physical examination are being performed, a large-bore intravenous catheter should be placed, with consideration of a second line if heavy bleeding is present. In addition to carrying out laboratory studies, several units of blood should be made available. Anesthesia and neonatology departments, when applicable, should immediately be informed of the patient's status and potential for delivery. Because abruptions are often accompanied by concealed hemorrhage, the blood loss may be severely underestimated, and central invasive hemodynamic monitoring (Swan–Ganz catheter) may be considered if blood loss seems significant or concealed abruption is suspected. Foley placement allows accurate evaluation of urine output and provides information regarding kidney perfusion.

Maternal hypovolemia due to extensive blood loss is clinically manifest by a low or rapidly falling blood pressure, a rapid and weak pulse, generalized pallor with cold and clammy extremities, tachypnea and agitation or lassitude. Immediate treatment is replacement of the intravascular volume deficit as rapidly as possible and restoration of effective perfusion. This is accomplished via infusing crystalloid fluids until O-negative or crossmatched blood is available. Crystalloid therapy should initially involve volumes two to three times in excess of the actual amount of hemorrhage, since shock is often associated with major fluid shifts from the intravascular to the extravascular compartments.

The timing of delivery depends on the maternal/fetal condition, gestational age and cervical status. In the absence of life-threatening hemorrhage, some patients with abruption and normal fetal heart rate tracings could potentially be delivered vaginally. Oxytocin may even be used to augment contractions, although its use in abruption is very controversial in that it might theoretically enhance the escape of thromboplastin into the maternal circulation and therefore initiate or augment consumptive coagulopathy. In contrast, the abruption process may be so fulminating that brisk hemorrhage occurs, with complete detachment of the placenta and evidence of progressive uterine enlargement resulting from retroplacental accumulation of blood. In this situation, immediate delivery (almost invariably by

cesarean section) is indicated in order to preserve fetal lives (if possible) and stabilize the maternal condition. The fetal conditions deteriorate rapidly because of interference with the diffusion of oxygen in the intervillous area from the maternal to the fetal side. In the case of immature twins, or after intrauterine fetal death of both, attempts at vaginal delivery can be implemented; however, a deteriorating clinical situation with increasing blood loss or worsening coagulopathy may necessitate operative intervention for maternal reasons. During surgery, close attention should be paid to good hemostatic technique. A bruised Couvelaire uterus, by itself, is not a reason for hysterectomy. In this scenario, there is often fear of uterine hemorrhage secondary to atony. However, this is not usually the rule; in most cases, the uterus will still be able to contract sufficiently. The placenta or placentas of both fetuses should be sent for pathologic examination to evaluate the extent of the abruption. In some cases of abruption, bleeding may be so acute (or the blood may continuously leave the uterus) that there is no time for a blood/hemorrhagic collection to form on the placenta parenchyma/membranes.

Some patients with lesser degrees of abruption may be candidates for closely monitored ambulatory obstetric management. These patients are in a stable condition with a small resolving abruption, no increased uterine contractility and reassuring results of fetal surveillance[16]. Patients with preterm twin gestations who have a mild abruption and minimal bleeding may be managed expectantly with close observation. In certain patients, tocolysis may even be considered, if used cautiously. For example, in the setting of a stable mother/fetuses without distress or complications and with only mild bleeding associated with uterine contractions, tocolysis has been used by some clinicians. The theoretical benefit is that the pregnancy can be successfully prolonged, so corticosteroids can be administered to enhance fetal lung maturity[2]. Magnesium sulfate is the agent of choice, since beta-mimetics can have adverse hemodynamic effects on a bleeding patient by accentuating further signs of hypovolemia, such as hypotension and tachycardia. Of course, in the preterm twin gestation with persistent, heavy bleeding, tocolytics are contraindicated and delivery should be performed.

Clinical DIC presents as generalized bleeding from mucous membranes, intravenous sites or subcutaneous tissues, as profuse uterine hemorrhage or as uncontrolled bleeding at the time of surgery. If DIC occurs, its onset is usually within 8 h of abruption. The inciting event leading to DIC with placental abruption is thought to be the entrance of thromboplastic material from the site of placental injury into the maternal circulation. This causes widespread intravascular activation of the clotting cascade, producing a depletion of various clotting elements and a resultant hemorrhagic state. Levels of fibrinogen, prothrombin, clotting factors and platelets are decreased, and fibrin degradation products are formed. DIC is most commonly seen in severe cases of abruption associated with fetal death or massive hemorrhage. However, because approximately 50% of patients with abruption display laboratory evidence of a coagulopathy[17], the coagulation profile should be repeated every 2–4 h. Patient injury occurs because of the bleeding diathesis, and localized tissue necrosis in organs due to fibrin deposition in small vessels. The most effective and definitive therapy is delivery of the placenta and fetuses. Fortunately, most patients have a milder form of abruption and will exhibit no clinical problems with the clotting system.

Laboratory values should be obtained, including complete blood count with hemoglobin/hematocrit, electrolytes, renal function studies and a coagulation panel. As noted above, a specimen should be sent for type and cross-match. The Kleihauer–Betke and CA 125 tests are both of little clinical value in the work-up of patients with placental abruption[18,19]. The prothrombin time and partial thromboplastin time are also insensitive indicators of DIC, as more than 50% of clotting factors must be consumed before these test results become abnormal[20]. In contrast, fibrinogen levels are sensitive indicators of DIC on serial testing. In a pregnant patient, a concentration less than 200 mg/dl is abnormal[17]. The most sensitive test for diagnosing coagulopathy related to abruption is determination of fibrin–fibrinogen degradation products by a variety of techniques, including D-dimer assays. However, it should be noted that D-dimer concentrations have been found to be consistently and significantly higher in twins (vs. singletons and non-pregnant controls)[21].

In order to prevent renal ischemic damage as a complication of abruption, vigorous blood and fluid replacement therapy is essential to combat hypovolemic shock. The two major goals regarding fluid replacement are: first, re-establishment of hemodynamic stability; and second, correction of coagulopathy. Although replacement with fresh whole blood is ideal, this is not generally available, and patients managed with component therapy do well in most instances. In the presence of DIC, fibrinogen is the coagulation factor that most often needs to be replaced. A level less than 100 mg/dl may indicate the need for replacement with fresh frozen plasma, where one unit can be expected to raise the fibrinogen level by about 25 mg/dl. The effect of cryoprecipitate is not as predictable, but 4 or 5 units can be given, with the need for further therapy determined by laboratory testing. Urine output should be maintained at 30 ml/h or more and hematocrit at 30%.

**Table 84.1** Comparison of placenta previa and placental abruption in twin gestations

| | *Placenta previa* | *Placental abruption* |
|---|---|---|
| Rate | 3.9/1000 live births[3] | 12.2/1000 live births[7] |
| Diagnosis | ultrasonography (transvaginal, if necessary) | ultrasonography |
| Maternal complications | DIC<br>hemorrhage<br>hysterectomy | DIC<br>hemorrhage<br>ischemic necrosis distant organs |

DIC, disseminated intravascular coagulation

**Table 84.2** Management steps for placenta previa

| |
|---|
| Ultrasonography and serial scans |
| Evaluate bleeding episodes (IV access, laboratory tests including type and cross-match, FHR monitoring × 2, no digital examinations) |
| Expectant management or delivery |
| Certain cases may be managed as an out-patient |
| Anticipate recurrence of bleeding episodes |
| Tocolysis in certain cases, steroids for lung maturity |
| Suspect accreta/increta/percreta if anterior previa (especially in prior C/S) and be prepared |
| Type and cross-match, blood transfusion |
| Keep hemoglobin and hematocrit ≥ 10 g/dl and 30% |
| Amniocentesis for lung maturity vs. scheduled C/S |
| Consider pelvic artery embolization |
| C/S as delivery mode ('map' placentas ahead of time for appropriate uterine incision) |
| Anticipate DIC, hysterectomy, blood loss from LUS after placental delivery |

IV, intravenous; FHR, fetal heart rate; C/S, cesarean section; DIC, disseminated intravascular coagulation; LUS, lower uterine segment

**Table 84.3** Management steps for abruptio placentae

| |
|---|
| Ultrasonography and serial scans |
| Evaluate bleeding episodes (IV access, laboratory tests including type and cross-match, FHR monitoring × 2) |
| Expectant management or delivery |
| Certain cases may be managed as an out-patient |
| Tocolysis in certain cases, steroids for lung maturity |
| Type and cross-match |
| Laboratory studies (rule out disseminated intravascular coagulation, thrombophilias) |
| Blood/component therapy for transfusion, fluid replacement therapy |
| Vaginal delivery or cesarean section |
| Anticipate blood loss, disseminated intravascular coagulation |
| Send placenta for pathologic examination |

IV, intravenous; FHR, fetal heart rate

Post-delivery, strong consideration should be given to testing the patient for thrombophilia disorders, because of their association with abruption. Disorders that should be ruled out include hyperhomocysteinemia, protein-S and protein-C deficiencies, antithrombin III deficiency, resistance to activated protein C from factor V Leiden mutation and antiphospholipid antibody syndrome.

## CONCLUSIONS

Despite numerous advances in the field of obstetrics, both placenta previa and abruptio placentae in twin gestations remain among the most dangerous obstetric complications, with potentially serious implications for both mother and infant(s). Maternal and perinatal morbidity and mortality are determined by the severity of the condition, degree of prematurity, amount of blood lost and degree of difficulty encountered during the delivery process. Tables 84.1–84.3 compare some of the characteristics and review management steps for placenta previa and abruption in twin gestations. Despite knowledge of the various causes and pathophysiologic processes of these two conditions, both placenta previa and abruption continue to challenge even the most experienced clinicians.

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# Twin Pregnancy and Delivery: the Role of the Midwife in Sweden

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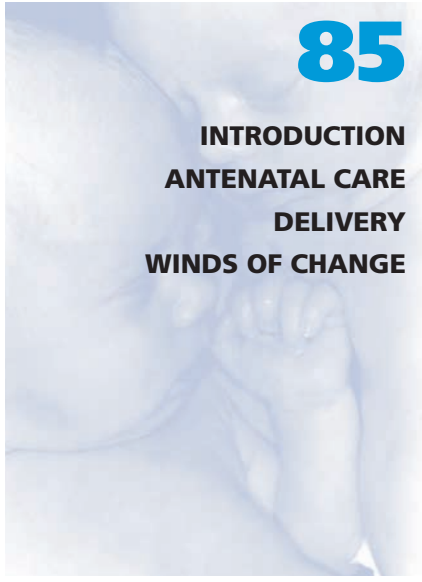


## INTRODUCTION

The Swedish Association for Obstetricians and Gynecologists (SFOG) and the Swedish Federation of Midwives (BF), in a document on common policy (1993)[1], stated that the doctor's and the midwife's professional knowledge complement each other in the appraisal of pregnancy risk. The document also stated that one category of professional cannot replace the other, and that the supervision of pregnancy should not be carried out by either doctors or midwives exclusively. The principles of this document were incorporated into the clinical guidelines for health-care in pregnancy published by the Swedish Board for Health and Welfare in 1996[2]. The mutual respect for each group's knowledge and competence is aimed at increasing safety for patients and achieving care at the appropriate level[3], as it is quite possible that the level of health-care offered to a county's population is governed by the number of care professionals available. This in turn becomes a question of priorities in education, which is a political concern. In Sweden in the year 2003, there were 1633 members of SFOG and about 7000 members of BF, who together are responsible for conducting about 100 000 deliveries.

## ANTENATAL CARE

The diagnosis of a multiple pregnancy may for some parents be a wonderful and welcome piece of news, whereas for others it may conjure up fear and apprehension. In general, obstetricians and midwives in Sweden strive to decrease apprehension by not treating the multiple pregnancy as something alarming. All large obstetric units in Sweden include a specialist antenatal clinic, which provides care for mothers-to-be with pre-existing medical conditions or a history of substance abuse. In many instances these clinics have assumed the care of multiple pregnancies as well. There is, however, a move away from this form of care in the case of uncomplicated twin pregnancy, in order to downplay parental apprehension and to assist in the dissemination of knowledge of multiple pregnancy amongst midwives. Parents-to-be are encouraged to attend their local antenatal clinic.

The basic premise for antenatal care of twin pregnancies is the same as for any pregnancy: the preservation of normalcy while maintaining vigilance for any of the expected or unexpected complications of pregnancy, for both singleton and especially multiple gestations. Because routine ultrasound screening after informed consent is carried out in Sweden at 17–18 weeks' gestation by specialist trained midwives, midwives most frequently confirm the presence of multiple pregnancy.

The goal of all antenatal care is to identify any barrier to the development of healthy fetuses and to identify any maternal illness or condition that may affect the pregnancy, fetal development or delivery[2]. The Swedish Board for Health and Welfare recommends a basic program of antenatal visits that is carried out for all pregnant women, whether or not any illness or other risk factor is known. One of the central ideas of the program is the evaluation during early pregnancy of an ongoing or newly found risk(s) to mother and fetus, followed by preparation of individual care plans. The number of antenatal visits in normal, uncomplicated pregnancy as recommended by the Swedish Board for Health and Welfare[2] is nine

**Table 85.1** Procedures during a normal twin pregnancy

| *Gestational age* (weeks) | *Care intervention* |
|---|---|
| 12 | booking visit at the antenatal clinic carried out by the midwife; 1 h for the taking of medical history, obstetric history, health risk behavior including smoking, drug abuse and alcohol consumption, worries and concerns of the parents-to-be; if there are no complications the obstetrician is not involved |
| 17–18 | ultrasound screening, after informed consent, by specialist midwife; the midwife discerns the thickness of the dividing membrane, whether the twin pregnancy is monochorionic (T sign) or dichorionic (λ sign), and these findings must be documented in the case notes |
| 21–23 | obstetrician and midwife together meet the parents-to-be in order to draw up guidelines for the monitoring of the rest of the pregnancy; obstetrician carries out new ultrasound examination in cases of monochorionicity |
| 24–term | the midwife monitors uncomplicated twin pregnancy at intervals of 2 weeks; cervical examination and cardiotocography are avoided as routine but carried out in cases where there is concern |

or ten. In an uncomplicated twin pregnancy the national recommendation for the number of visits is about 12, and the planned interventions shown in Table 85.1. The schedule is as follows. The father-to-be is always welcome to accompany his partner on her visits to the antenatal clinic. The couple are informed that a clinical psychologist is part of the care team. In the case that the partner is physically absent, another significant person is also welcome.

## Monochorionicity

In cases where the dividing membrane is thin (T sign), causing the midwife and obstetrician to suspect a monochorionic (MC) pregnancy, the mother is offered ultrasound checks at intervals of 2–3 weeks for the remainder of the pregnancy. The pregnancy continues to be monitored by the midwife as long as all remains well. For those with dichorionic pregnancy (λ sign), whether dizygotic or monozygotic, three ultrasound examinations are offered.

In the case that no dividing membrane is seen, a monochorionic, monoamniotic pregnancy is suspected, and the parents should be informed about the increased risks. In our view, these patients should be informed as early as possible that a cesarean section is the preferred mode of delivery, as early as in gestational week 33–35.

## Pelvimetry

At 37 weeks of gestation and more, if the midwife suspects that the first twin has breech presentation, she refers the mother-to-be for consultation with the obstetrician who then orders X-ray pelvimetry. X-ray examination of the pelvis is the preferred mode, a Swedish 'tradition' with very little support from evidence-based obstetrics. The lie of the second twin is academic at this point, and in line with evidence-based obstetrics. In Sweden, the lie of the second twin does not affect decisions regarding mode of delivery. Measurement of the fetus is not undertaken (see Chapter 78).

## In-patient care

In cases where the pregnancy becomes complicated before the 22nd week of gestation, the mother-to-be is admitted to a gynecologic ward where she is cared for by a team of doctors and nurses or, at most large units, midwives. After week 22, admissions are made to the perinatal ward where the team always comprises midwives and obstetricians.

## Preparation for twin parenthood

Giving parents-to-be realistic expectations of delivery and parenthood is possibly one of the most important tasks in midwifery care. Many units in Sweden make provision for the preparation of twin parenthood by sanctioning special prenatal groups for twin parents-to-be. Such groups are organized by a midwife, and in some cases a neonatal nurse who has a special interest in this area. They are considered complementary to the usual parentcraft classes and can provide preventive care, giving stimulus for psychological growth and maturity. One possible model includes three or four prenatal meetings and one postnatal meeting. Twin parents-to-be within a geographic district, all of whom are due to become parents within approximately 8 weeks of each other,

are usually invited to join in the discussion group. The basic idea of these groups is to provide a platform for the exchange of experiences to allow twin parents to become acquainted with others who have similar experiences and to strengthen competency in parenting twins. The perspective should be one of health psychology, focusing on inner resources and possibilities. The following are some aspects of the focus presented at these sessions:

(1) Many parents-to-be have been under considerable psychological strain for several years before the pregnancy, owing to existential issues arising from infertility problems. It is estimated that 25% of *in vitro* fertilizations result in twin pregnancy.

(2) To become parents of twins is something beyond the ordinary pregnancy experience. It is normal for these parents-to-be to show signs of a shock reaction to the news. Those who have been through years of childlessness may find the whole experience extremely paradoxical.

(3) The aches and pains of pregnancy are multiplied in multiple pregnancy. To be forewarned is to be forearmed. Mothers-to-be should be given realistic notions of what to expect and a good deal of information on self-care and management of these problems.

(4) The complications of multiple pregnancy and delivery cannot be ignored. While striving to avoid presenting a picture of alarm, the midwife gives information on the most common of these complications, what may be done to help minimize the risk of complication, what the health services can and cannot do in such circumstances and what may be possible outcomes.

(5) It is helpful to describe the physical appearance of infants who are born prematurely. A description of their special-care needs, including close physical contact with their parents (kangaroo parenting), preservation of body temperature, maintenance of effective airways and nutritional needs, is provided. Since many of these parents-to-be will spend time in the neonatal unit, it is of great help to explain the nature and culture of the neonatal ward. A visit to the ward is also beneficial.

(6) Modes of delivery, including cesarean section and ventouse/forceps, and methods for pain control used at the local obstetric unit are presented and discussed. The fact that twin delivery is always surrounded by many different members of the hospital staff (midwives, obstetricians, pediatricians, neonatal nurses, etc.) is also to be mentioned. The need for intravenous lines for the administration of oxytocin derivatives, and the presence of ultrasound and CTG/STAN (see below) machines, is presented.

(7) Breast-feeding is an increasingly important topic at parentcraft classes all over the industrialized world. Since twins are more often born preterm and are smaller for gestational age, it is vital that mothers be given every encouragement to breast-feed their twins. This encouragement starts in parentcraft classes where the father-to-be can also learn, as the partner's positive attitude to breast-feeding is of great value in the weeks following birth[4–6].

(8) Parents should be informed that after the birth, in cases of same-sexed twins where the dividing membrane is thick (λ sign), it is possible to determine whether the twins are mono- or dizygotic by analysis of blood from the umbilical cord. The parents pay for this test, which costs approximately $US150 (in 2003 currency). Not many parents choose this option.

## DELIVERY

### Vaginal delivery

Swedish midwives are trained to deliver breech presentations, and this enables them to deliver twins irrespective of fetal presentation. The attending obstetrician is informed of the presence in the delivery suite of the twin mother-to-be when a vaginal birth is planned. The pregnancy has reached 33 full gestational weeks (or is < 33 weeks in the case that the first twin is a vertex presentation). The midwife checks that all blood tests are up to date and establishes an intravenous route. She prepares an oxytocin drip and has quick-acting tocolytic drugs on hand[7]. As long as the labor is normal, the midwife reviews and judges the cardiotocography (CTG) and STAN tracings. ST analysis (STAN) of the fetal echocardiogram (ECG) is increasingly being used in Swedish delivery units at high-risk deliveries. The midwife and obstetrician work in close co-operation as labor progresses, making decisions about medical interventions together. Artificial rupture of the membranes is carried out only in the following circumstances:

(1) Where there is difficulty in monitoring both fetal heart rates simultaneously;

(2) Where there is concern about the CTG tracing;

(3) Where an overdistended uterus causes uterine inertia.

The twins are monitored by continuous CTG and/or STAN for the duration of labor. The obstetrician is summoned when the cervix is fully dilated. The mother-to-be is most often in the half-sitting lithotomy position, with the midwife sitting or standing between her legs. This enables the midwife to maintain good eye contact with the mother while conducting the delivery. The obstetrician is at the mother's side, checking the position of the twins by ultrasound and manipulating the lie of the second twin as necessary. The midwife gives the parents a calm and steady briefing about the progress of the first twin as it descends the pelvic channel and is born. Episiotomy is not routinely carried out, but used only when rapid extraction of the infant is deemed necessary or when the midwife perceives a risk for a large perineal tear. The infant is lifted into the waiting arms of the mother as its face is cleared of debris, and the midwife is assured of a favorable Apgar score. The pharynx is not routinely cleared of debris. The cord is then clamped and cut, and the 'maternal' side of the cord marked with a band to enable examination of the placenta and membranes after delivery. In many units, blood will be sampled from the cord for pH measurement. However, a number of units still argue that the Apgar score is the most appropriate way to evaluate the condition of the newborn baby. The baby is swathed in warm towels.

During this time, a second midwife stops the oxytocin drip if this has been in use, and the obstetrician checks the presentation by ultrasonic examination. The presenting part is now pressed down into the pelvic inlet by moderate manual pressure to the fundus (Figure 85.1). The mother's reaction to this maneuver must guide the care-givers as to how much pressure is used. At this stage it may be necessary to restart the oxytocin infusion. If intact, the membranes of the second twin are artificially ruptured during a contraction in order to minimize the risk of cord prolapse and cervical spasm. A scalp electrode is applied. While these measures are being carried out, the midwife keeps communication with the parents flowing, and the first twin remains under the watchful eye of the neonatal nurse. As long as the heart rate of the second twin is satisfactory, it is not necessary to force a rapid delivery of the second baby[7]. However, to be sure of correct monitoring of the second twin's heart rate, ultrasound is used as a complement to CTG tracing. If an episiotomy has been carried out, or if there has been any substantial perineal tear, it may be necessary for the midwife to apply digital pressure to any bleeding points until the presenting part of the second twin occludes the blood vessels. The mother may now feel exhausted, and the midwife has an important role to play in encouraging her to summon all her remaining energy to help her second baby into the world. The mother is helped by the midwife and the neonatal nurse to receive and embrace the second twin while the infant's face is cleaned and its condition is checked. The baby is swathed in warm towels. In cases of preterm birth, after a short meeting with their parents, the babies are placed together in an incubator at the mother's bedside with the neonatal nurse in attendance to monitor their progress.

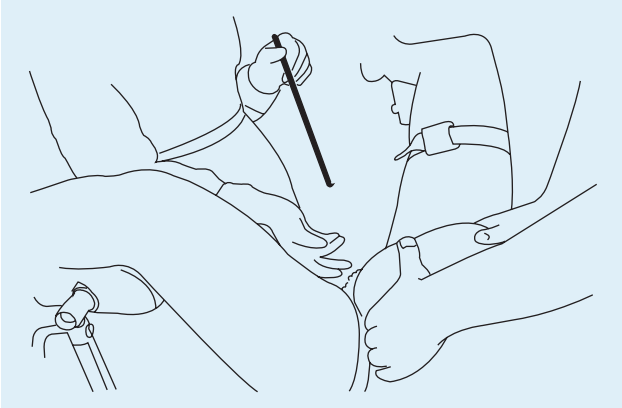

**Figure 85.1** The situation in a normal twin delivery. The midwife is standing between the legs of the mother, prepared to rupture the membranes for the second twin. Meanwhile the obstetrician is standing beside the parturient and manipulating the fetus into a longitudinal position. At signs of asphyxia and where a need emerges for extraction (with or without internal version) the obstetrician is always responsible for the appropriate actions. In the majority of Scandinavian units today, the majority of obstetricians will argue for an emergency cesarean section of the second twin. The evidence-based knowledge for this action is lacking

## Elective cesarean section

In Sweden the midwife is the first-line medical attendant for all laboring women, and twin labor is no exception. If the delivery is to be by elective cesarean section, the mother-to-be is admitted to the unit by the midwife who is responsible for all prebirth tests and preparation. It is her responsibility to check that all blood tests are up to date, that the patient is on the operating list, that the neonatal unit is informed, that the mode of anesthesia is confirmed and that CTG tracings are carried out. Apart from all these practical points, her presence as a calming, competent and empathetic professional is extremely important for the preoperative and postoperative well-being of the mother-to-be[8]. She accompanies the parents-to-be to the operating room, where she scrubs for surgery and assists until the birth of the first twin, which she then delivers into the gloved hands of the neonatal nurse before preparing to receive the second twin

from the operating obstetrician. If the infants have a satisfactory Apgar score and the mother is not under a general anesthetic, the babies are immediately placed on the bare breast of the mother and covered with warm towels. If the babies' condition is at all compromised, they will greet their mother momentarily before being examined by the pediatrician and, if necessary, transferred to an incubator. Should transference to the neonatal unit be necessary, the infants' father will most often accompany them. Mother–infant contact is maintained whenever possible, and if the condition of the twins improves they will be able to visit their mother on the postoperative unit, where breast-feeding will be initiated if the mother wishes and her condition allows.

### Emergency cesarean section

The midwife is the person in closest contact with the parents-to-be, even in cases where emergency cesarean section becomes necessary. It is the midwife who may alert the obstetrician to the fact that all is not well with a twin pregnancy. She is the parents' advocate, relaying to the doctor, in a correct and modulated way, the information she receives from them and from her own observations. Her calm professionalism can turn a potentially traumatic experience[9] into one of joy and thankfulness. The obstetrician may make the decision to operate over the telephone, and the midwife will then be the purveyor of this news to the parents-to-be. Quickly but without showing signs of personal stress she must inform the parents of the situation and carry out all the preparations for emergency surgery. While it is not possible to make any prediction about the outcome of emergency situations, the midwife should avoid seeming overly anxious, as this may adversely affect the mother-to-be and thereby affect the condition of the unborn babies[8].

## WINDS OF CHANGE

In 1985, Olofsson and Rydhström[7] wrote:

> 'We respect the hesitation and cautiousness of American obstetricians, dealing with a more litigious society than we are used to … Limited clinical experience of vaginal twin delivery is a growing problem. During the past decade the cesarean rate in twin gestations has more than doubled …'

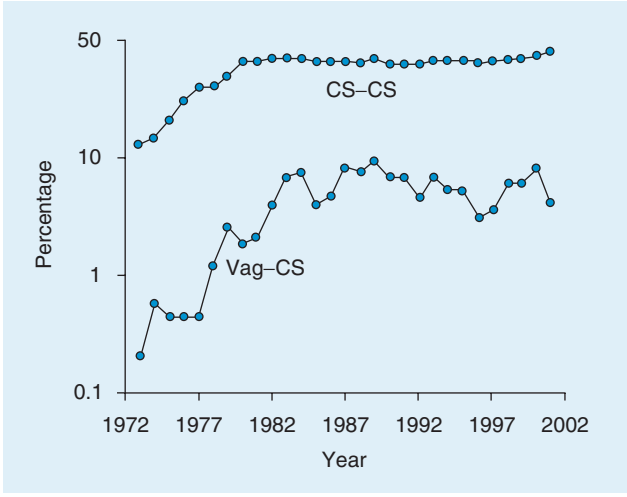


**Figure 85.2** The cesarean section (CS) rate for twins in Sweden between 1973 and 2001. Included in the overall cesarean section rate is approximately one-third elective and two-thirds emergency operations. A log-scale is used to make possible a direct comparison of a high cesarean–cesarean (CS–CS) and a rather low vaginal–cesarean (Vag–CS) rate

In Sweden, in the new millennium, about 50% of twin pregnancies are delivered by cesarean section, and another 2–6% of second twins are delivered by cesarean section after vaginal delivery of the first twin (Figure 85.2). There is also a growing 'problem' with litigation tendencies in Sweden. The problem of midwives and obstetricians gaining clinical experience of vaginal delivery of twins has accelerated. The debate arising from a Canadian study of breech delivery[10] has increased the risk of litigation, and this will spill over into the debate about clinical management of twin delivery. Our expertise in judging the quality of research and weighing the evidence must be constantly upgraded if we are to be able to offer the best possible evidence-based care in the special circumstances surrounding twin pregnancy and delivery.

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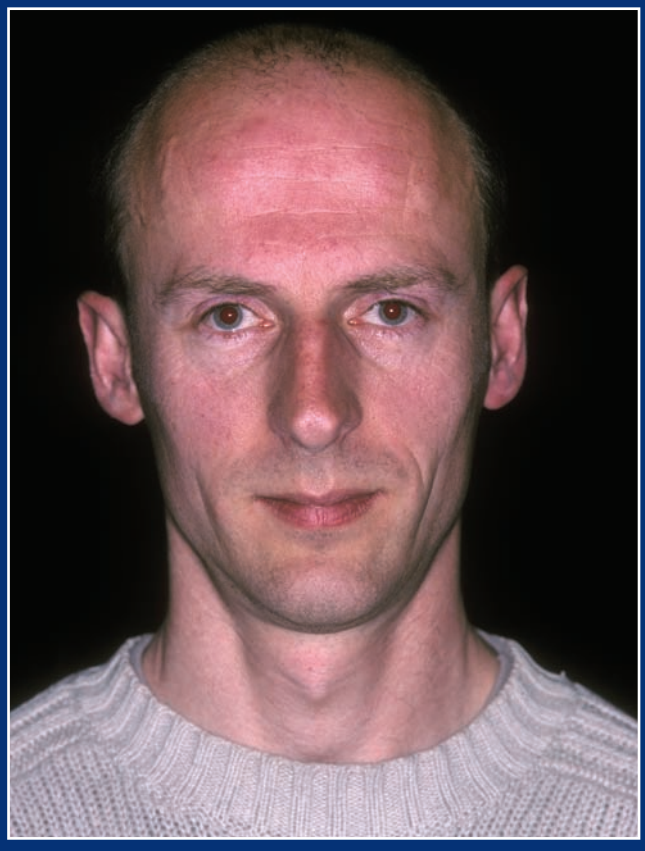
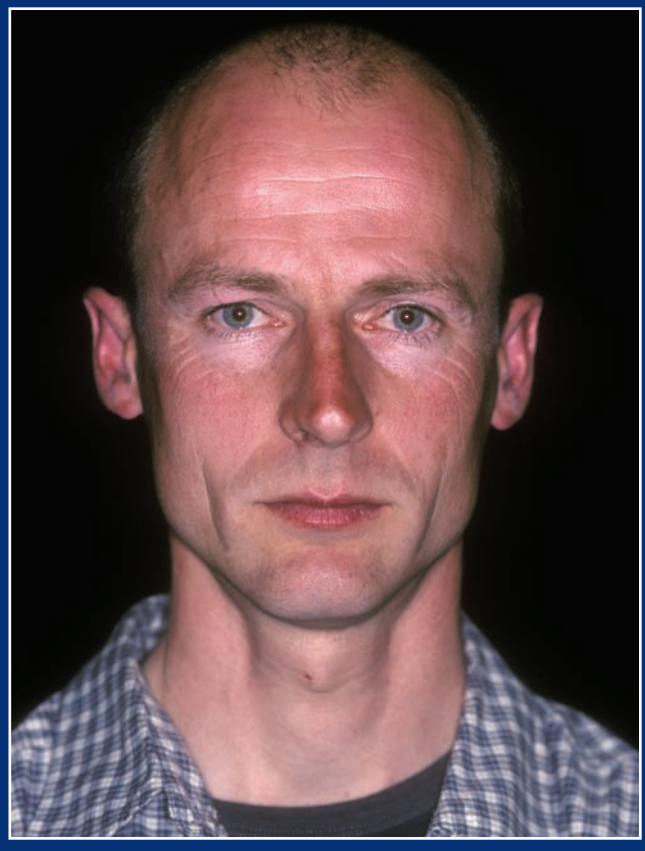
## SECTION VIII

# POSTPARTUM CONCERNS



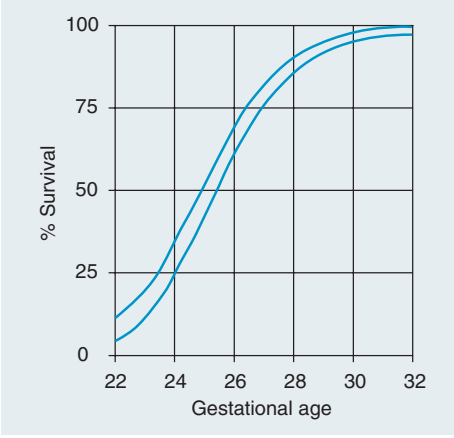


**36-year-old male monozygotic, dichorionic, mirror twins, Belgium, 2004.**

Participants since birth in the East Flanders Prospective Twin Study. Twin A left, Twin B right.

Plutarch (c. AD 45–125), in his treatise *Concerning Nature* (Book V, Chapter XVIII), detailed the views of the ancinet Greek scholars regarding the prognosis of preterm infants. One of the most interesting opinions was that of Polybus, the son-in-law of Hippocrates:

'*a hundred and eighty-two days and a half suffice for the bringing forth of a living child; that is, six months, in which space of time the sun moves from one tropic to the other; and this is called seven months, for the days which are over plus in the sixth are accounted to give the seventh month. Those children which are born in the eighth month cannot live, for, the infant then falling from the womb, the navel, which is the cause of nourishment, is thereby too much wrenched; and is the reason that the infant languishes and hath an atrophy.*'




A comparison of recent prognosis (survival rates) of extremely preterm infants (Figure)[1], with the 2000-year-old 'hundred and eighty-two day' (i.e. 26 weeks) and the 'eighth month' rules of Polybus, suggest two main differences. First, at present, infants delivered as early as 22 weeks survive, and, second, survival rates increase as a polynomial function of gestational age ($r^2 = 0.98$). Indeed, survival rates of extreme preterm infants represent one of the most significant achievements of modern neonatal care.

Neonatal outcome, in many aspects, signifies the end-point of all preceding events. Simply stated, the best clinical pregnancy rates following *in vitro* fertilization are meaningless if perinatal outcome is less than optimal. In the case of multiple pregnancies, the neonatal risks of preterm babies cannot be overemphasized. This section discusses various neonatal concerns.

*I.B. and L.G.K.*

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# Contents of Section VIII

# Puerperal Complications

*D. W. Skupski*

**86**



## INTRODUCTION

Despite the recent explosion in the number of multifetal pregnancies there remains a dearth of information about maternal complications accompanying these pregnancies, particularly in the postpartum period. Although any complication of the puerperium may occur after the delivery of multiples, this chapter focuses on the puerperal complications that occur with greater frequency. Some of the conditions cited below are increased consistently in many studies, whereas others merely carry a theoretical increase in rate based on biologic plausibility. The intent of this chapter is to provide practicing physicians with the knowledge and tools necessary to care for women with multifetal pregnancies and to be prepared for complications that arise in that important, but often neglected, time of the puerperium.

Table 86.1 lists the complications of the puerperium that are known or presumed to be increased in multifetal pregnancies. Immediate complications are defined as occurring within 24 h of delivery, and include important and familiar issues such as postpartum hemorrhage. Short-term complications are defined as occurring within 7 days of delivery, whereas delayed complications occur more than 7 days post-delivery. Undoubtedly there is some overlap in the timing of presentation. An example is peripartum cardiomyopathy, which can present antepartum or up to 5 months postpartum.

**Table 86.1** Puerperal complications of multifetal pregnancies

*Immediate*
Immediate postpartum hemorrhage
- uterine atony
- retained placenta/placental fragments
- birth canal lacerations
- coagulopathy secondary to pre-eclampsia or abruptio placenta

Need for blood transfusion
- blood-borne infection
- transfusion reactions
- subsequent isoimmunization
- graft versus host disease

Postpartum pulmonary edema
Intensive-care unit admission

*Short-term*
Puerperal infection
- febrile morbidity
- endomyometritis
- urinary tract infections
- wound infection/seroma/hematoma

Post-cesarean venous thrombosis
Postpartum pre-eclampsia/eclampsia
Anemia

*Delayed*
Delayed postpartum hemorrhage
- retained placenta/placental fragments
- placental site subinvolution

Peripartum cardiomyopathy
Postpartum psychologic dysfunction

## IMMEDIATE COMPLICATIONS

### Postpartum hemorrhage

Several lines of evidence suggest an increased rate of postpartum hemorrhage in multifetal pregnancies. These include an increased rate of antepartum hemorrhage, primarily due to abruptio placentae, and an increased rate of postpartum uterine atony due to the uterine overdistension that accompanies multifetal pregnancies[1]. Disseminated intravascular coagulation in the setting of abruptio placentae and the occurrence of retained placental fragments may also be causative factors. The largest study in the literature is a population-based study from South America with a population of over one million, which confirms a significantly increased rate of postpartum hemorrhage in multifetal pregnancies compared with singleton pregnancies (relative risk (RR) 2.0 (95% confidence interval (CI) 1.9–2.0))[2].

The intravascular blood volume in an average 60–70-kg pregnant woman is approximately 6 l. If she were to lose 15% of her blood volume or 1 l, there would be no change in vital signs[3]. On the other hand, if she were to lose 25% of her blood volume or 1.5 l, generally only a narrowing of pulse pressure and a delay in venous filling would be observed. It is not until 35% of blood volume (2 l) is lost that hypotension occurs. Profound shock does not occur until 40% of blood volume is lost (2.5 l). In contrast, a non-pregnant woman has a circulating blood volume of 4 l, and will be in severe shock when 1 l of blood is lost[3]. These figures presume that the mother is not anemic at the time of delivery and may not apply to women whose hemoglobin level is 10 g/dl or less at the time of delivery.

The classic description of average blood loss after vaginal delivery is approximately 500 ml, and after cesarean delivery is approximately 1000 ml, but more recent literature questions the factual bases upon which these figures were derived some 30 years ago. Combined with the fact that the visual estimate of blood loss is often grossly underestimated by a factor of at least two, this means that hemodynamic instability and hypovolemic shock can occur suddenly. If the estimated blood loss approaches or exceeds 1000 ml, immediate treatment with intravenous crystalloid fluids should occur and the patient should have type and crossmatch performed. If the estimated blood loss approaches or exceeds 1500 ml, rapid infusion of intravenous fluids should occur and transfusion of blood products should be considered. The estimation of blood loss is always problematic. Obstetricians are trained to recognize the amount of blood loss visually while attending to many other clinical factors and management decisions simultaneously. Because visual estimates are inexact, the best plan is to expect that any estimate is only one-third or one-half of the actual blood loss[3].

#### *Management*

Treatment begins with active management of the third stage of labor and, in rare instances, concludes with hysterectomy. In all instances, however, controlled cord traction and the use of uterotonic agents such as oxytocin may initially decrease the amount of time and blood loss following either vaginal or cesarean delivery[4].

Immediately after vaginal delivery, careful assessment of the perineum, vagina and cervix should identify lacerations that require repair. Before closure of the abdominal incision during cesarean delivery, careful inspection of the operative field for hemorrhage is mandatory to identify and ligate lacerated blood vessels. After either mode of delivery, careful inspection of the placentas is required to demonstrate the intact nature of the specimen. Delivery-room inspection should not only evaluate the placental mass for missing pieces, but carefully inspect the membranes for aberrant blood vessels that appear to be severed at the membrane's edge without reaching an area of placental substance. Placental shape and succenturiate lobe abnormalities may be increased in multifetal pregnancies and may predispose to retained fragments within the uterus. If the physician is suspicious of retained placental fragments on the basis of the immediate post-delivery placental evaluation, manual exploration of the uterus and/or uterine curettage should be contemplated. After cesarean delivery, manual exploration of the uterus with a free gloved hand (not encumbered by laparotomy pads) before uterine closure may also be able to identify retained placental fragments and avoid postpartum hemorrhage and its sequelae.

As blood loss after delivery is notoriously underestimated, peripheral intravenous access, typing and crossmatching of blood and careful monitoring of blood loss during the 24 h following delivery of multiple fetuses are required. Frequent assessment of vital signs to identify tachycardia and/or hypotension can alert the team to hemodynamic compromise, even when the amount of blood loss may have been underestimated. Continued use of uterotonic agents such as oxytocin, methergine and prostaglandin F2α during the first postpartum day may also improve uterine muscle tone and decrease the amount of bleeding.

As the first postpartum day continues, frequent assessment of the uterine tonus and amount of vaginal bleeding should be the rule. If an increase in vaginal

bleeding is noted, bimanual pelvic examination with fundal pressure to evacuate blood clots within the uterus may be necessary. If uterine tone remains good by palpation, but vaginal bleeding continues in amounts greater than expected despite the use of uterotonic agents, reexamination of the birth canal for lacerations may be necessary. If no lacerations are discovered, curettage may be necessary to remove retained placental fragments that can be the cause of hemorrhage. Ultrasound of the postpartum uterus can also be performed in an effort to identify retained products of conception for which curettage is required to decrease blood loss postpartum. However, experience is necessary in evaluating the ultrasound images of a postpartum uterus (Figure 86.1).

## Need for blood transfusion

The percentage of patients needing blood transfusion in all pregnancies is 1% or less[5]. With all cesarean deliveries, this ranges from 1 to 6%[6]. However, it may be necessary to resort to blood transfusion more often in multifetal pregnancies owing to the increased rate of postpartum hemorrhage and the increased rate of cesarean delivery.

If the patient is hemodynamically unstable, multiple large-bore peripheral intravenous lines with rapid infusion of both crystalloid and blood products is life-saving. If hemodynamically stable, however, slower transfusion may be chosen even if the hematocrit level is severely low. A general guide is to consider blood transfusion in two diverse settings: first, if the hematocrit is < 15% and the patient is asymptomatic, and second, if the hematocrit is < 25% in the presence of signs or symptoms. Symptoms of severe anemia that suggest tissue oxygenation is impaired and that blood transfusion may be of benefit include palpitations, headache, chest pain and dizziness or syncope during ambulation; signs include hypotension, persistent tachycardia, loss of consciousness, electrocardiographic changes consistent with cardiac ischemia and abnormalities of cardiac rhythm. Many physicians might choose to recommend blood transfusion at hematocrit values higher than the cut-offs listed above.

After massive hemorrhage, periodic hematocrit and platelet counts are necessary. Dilutional coagulopathy can occur if large amounts of packed red blood cells (RBC) are required. Serial assessment of prothrombin time (PT), partial thromboplastin time (PTT) and fibrin degradation products (FDP) are necessary in such circumstances.

The complications of blood transfusion include the transmission of blood-borne infections, acute transfusion reactions and delayed transfusion reactions. Blood-borne infections that may occur as a

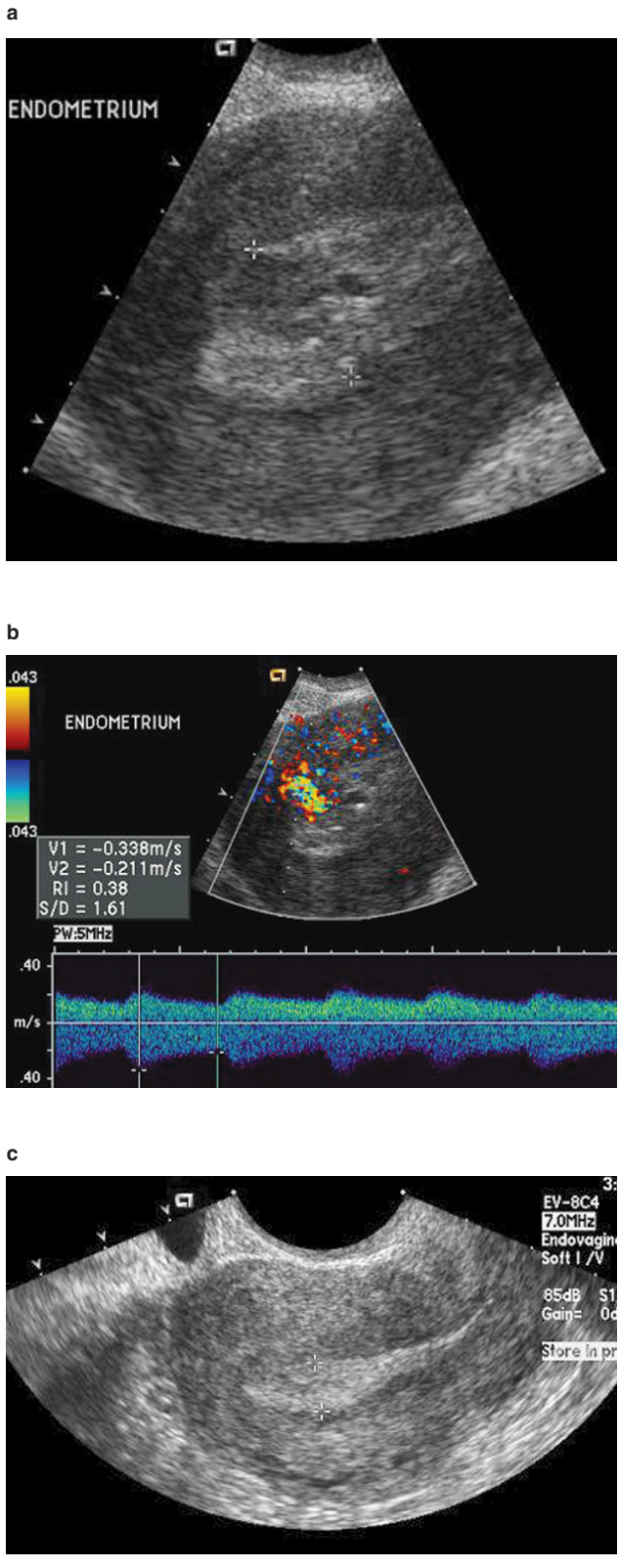


**Figure 86.1** (a) Postpartum sagittal view of the uterus showing retained placental fragments. (b) Pulsed Doppler analysis shows low-resistance peritrophoblastic blood flow that confirms retained placental fragments. (c) Postpartum sagittal view of the uterus showing normal findings and no evidence of placental fragments

result of blood transfusion include hepatitis B virus (HBV), hepatitis C virus (HCV), human T-cell lymphotropic virus (HTLV), human immunodeficiency virus (HIV), cytomegalovirus (CMV), herpes simplex virus (HSV), Epstein–Barr virus (EBV) and varicella zoster virus (VZV)[7]. Many of these viruses only produce clinical disease in patients with immunosuppression, but can be transmitted to anyone receiving a blood transfusion. However, blood bank practices include a host of preparation techniques that minimize the likelihood of transmission. Bacterial infections may also be transmitted, and preventive practices in the blood bank include limited handling, proper temperature control and limited storage intervals for components that are not frozen[8].

Acute transfusion reactions include fever, urticaria or rash, anaphylaxis, pulmonary edema and hemolysis. If any of these reactions occur, prompt involvement of a transfusion medicine specialist is prudent. Temperature should be monitored during blood transfusion and, if there is a rise of 1°C or more, the transfusion should be stopped, the unit should be checked to see if it is the intended or correct unit and the blood bank should be notified for help in management, including the performance of direct antiglobulin (Coomb's) test and free hemoglobin to diagnose acute hemolysis. The most likely cause of fever is a reaction between transfused leukocytes and antileukocyte antibodies (usually anti-human leukocyte antigen (HLA)) in previously pregnant or previously transfused individuals. The remainder of the transfused unit should be returned to the blood bank and acetaminophen should be used for control of the fever[9]. Urticaria or rash without hypotension is usually without serious sequelae and can be treated by slowing or temporarily stopping the transfusion and administering antihistamines. Anaphylaxis is caused by an anti-immunoglobulin A (IgA) reaction to IgA in the donor's blood components. Treatment with epinephrine and antihistamines may be necessary as a life-saving measure[9]. Pulmonary edema is very rare and detected by acute respiratory distress within 6 h of a transfusion. The treatment is to stop the transfusion and consult with critical-care medicine or maternal–fetal medicine specialists. Mechanical ventilation for 12–24 h may be necessary. Most patients reported are observed to resolve their symptoms within a few days[9].

Acute hemolytic reactions most commonly begin with fever and can have disastrous results if ignored[10]. Acute hemolytic reaction should be assumed when a fever appears during blood transfusion and appropriate treatment instituted, including stopping the transfusion, continuing intravenous hydration, maintaining adequate renal perfusion and treating hypotension if it develops. Critical-care medicine consultation may be necessary. The confirmation of an acute hemolytic reaction rests on the direct antiglobulin and serum-free hemoglobin tests for minor reactions, with the addition of total bilirubin and lactate dehydrogenase (LDH) values, which are elevated and peak 5–8 h post-transfusion, for more severe reactions[11]. The confirmation is difficult and does not rely on exact cut-off values of serum-free hemoglobin or enzymes. Consultation with transfusion medicine specialists is advisable.

Delayed transfusion reactions include post-transfusion purpura, RBC alloimmunization and graft versus host disease. Post-transfusion purpura is rare, due to antiplatelet antibodies, may not be preventable, is often self-limited and can be treated, if severe, with plasma exchange[9]. The process of crossmatching decreases the probability of subsequent RBC alloimmunization. The blood-bank practice of irradiation of units of blood for transfusion decreases the chance of graft versus host disease by inactivating the responsible lymphocytes[9].

## Postpartum pulmonary edema

Postpartum pulmonary edema is a common and life-threatening condition affecting women who undergo intravenous tocolysis[12]. Since women with multifetal pregnancies are more likely to undergo intravenous tocolysis, which sometimes fails, delivery may occur before the development of pulmonary edema. Postpartum pulmonary edema is not a rare event seen in women who have recently delivered multiple fetuses, although data on the exact rate are lacking. Multifetal pregnancy is a predisposing factor in the development of pulmonary edema *in pregnancy* in over 19% of cases[13]. Pulmonary edema occurs in the setting of either cardiac failure with increased hydrostatic pressure driving fluid out of the pulmonary vasculature, or increased pulmonary capillary permeability that allows fluid to leak out. Multifetal pregnancy, labor and tocolysis can together lead to a tripling of cardiac output over non-pregnant levels, causing cardiac failure, and is the combination of factors responsible for the increased hydrostatic pressure. Subclinical or overt infection or pre-eclampsia can be responsible for endothelial capillary damage that allows fluid to leak from capillaries. The risk factors for pulmonary edema include volume overload, tocolytic administration, multiple tocolytic agents, multifetal gestation, blood transfusion, infection (overt or subclinical, including prolonged preterm premature rupture of the membranes), steroid administration and pre-eclampsia. The single most important factor in the development of pulmonary edema is likely to be volume overload, but a combination of the above factors is probably necessary. When β-mimetic

tocolytic agents are used, they have potent mineralocorticoid (salt- and water-retaining) effects which exacerbate the effects of volume overload[13].

There is a clinical impression of a strong association of postpartum pulmonary edema with pre-eclampsia. In this setting, pulmonary edema tends to occur 1–3 days after delivery. This is probably due to the delayed mobilization of fluids from the extracellular space back into the vasculature that occurs with the resolution of pre-eclampsia at this time, and is heralded by the diuresis that is also seen.

The usual symptoms of pulmonary edema include shortness of breath, agitation and tachypnea, but they are not present in every case. Pulmonary edema is clinically diagnosed by the findings of auscultatory rales or characteristic findings on chest radiography.

#### *Management*

Prevention should be discussed first. Strict intake and output measurement should be standard practice for all women with multifetal pregnancy who are admitted, especially if they are thought to be in preterm labor or to have pre-eclampsia. The problem of volume overload is pernicious in such patients, and occurs in many instances because of the lack of hour-to-hour, shift-to-shift attention to provide the proper fluid requirements and avoid fluid overload. It is important to remember how these patients are educated prior to their arrival at the hospital. Despite a lack of evidence for the efficacy of oral hydration in prevention of preterm labor, many patients are instructed to have a hefty intake of oral fluids, and thus may be volume-overloaded before they begin hospitalized care. Even in the postpartum period, strict intake and output measurement should continue, and there should also be careful attention to vital signs such as respiratory rate and symptoms such as shortness of breath.

Treatment begins with furosemide for diuresis, upright positioning for comfort, oxygen administration and morphine sulfate intravenously. Morphine sulfate acts in two ways: increasing central venous capacitance and relieving anxiety and pain. Care should occur either in the labor and delivery suite or in an intensive-care unit. Serial monitoring of arterial blood gases, chest radiography and electrocardiogram are necessary. Consultation with internal medicine, pulmonary medicine, critical-care medicine and respiratory therapy staff may be necessary. Serum electrolytes should also be monitored and potassium or other salts replaced as necessary. Of course, fluid restriction is necessary. If the response to the initial therapeutic steps is not rapid, invasive hemodynamic monitoring (Swann–Ganz Catheter placement) may be necessary. Low urine output in the setting of pulmonary edema is of grave concern, suggesting pre-eclampsia, and should also warrant consideration of invasive hemodynamic monitoring.

It needs to be remembered that pulmonary edema may be the presenting sign of peripartum cardiomyopathy, which is discussed below.

### Intensive-care unit admission

In one recent French study conducted by eminent practitioners, multifetal pregnancy was an independent risk factor for admission to the intensive care unit (ICU) (odds ratio (OR) 2.3, 95% CI 1.2–4.5)[14]. In addition, the 1995 French national perinatal survey showed that women giving birth to twins had a significantly higher risk of transfer to an intensive-care unit than women having singletons (3.1% vs. 0.2%, $p < 0.0001$)[15]. Both studies are population-based, which makes it difficult to comment on the existence of truly severe disease. Senat and colleagues found that a very small percentage of patients were admitted to the ICU for postsurgical monitoring (20/435 or 4.6%); all other patients had life-threatening events[15]. Thus, these authors considered ICU admission a reasonably accurate indicator of severity of disease. Little specific information on the types of disease affecting patients with multifetal pregnancy was reported. Given the heightened risks to the mother discussed in this chapter, consideration should be made for delivery of multifetal pregnancies at institutions where intensive care is available. It may also be prudent to have the care and delivery of multifetal pregnancies occur in the hands of obstetricians experienced with their special needs.

## SHORT-TERM COMPLICATIONS

### Puerperal infection

It is not surprising that infectious complications are also seen at an increased rate because of the known increased rate of cesarean delivery in multifetal pregnancies[16,17].

Febrile morbidity after cesarean delivery is increased in incidence in multifetal pregnancies, with a rate as high as 84%[18]. The causes include true infections such as urinary tract infections, pneumonia and endomyometritis, but a large number are from atelectasis during the first day postpartum, and many are simply fevers without identifiable cause during the first postpartum day that resolve without further treatment. Urinary tract infections are seen at an increased rate in mothers who deliver multiple fetuses compared with a singleton fetus (RR 1.3, 95% CI 1.2–1.3)[2].

Controlled studies show an increased rate of endomyometritis after the delivery of multiple

fetuses compared with a single fetus. The rate of endomyometritis was increased nearly three-fold (13.1% vs. 4.7%) in one controlled study and two-fold in another (RR 1.8, 95% CI 1.7–1.9)[2,19].

The risk of wound infections in mothers delivering multiple fetuses compared with a single fetus is increased nearly two-fold (5.6% vs. 3.0%) in one study[19]. Problems of the wound, including infection, hematoma and seroma, with the likelihood of breakdown of the wound and healing by secondary intention, are common after cesarean delivery. Such patients must be monitored closely for signs or symptoms of infectious morbidity for several days postpartum. Any suspicion of deep-seated infection or abscess may require opening of the wound to allow drainage.

The diagnosis of infectious morbidity after the delivery of multiple fetuses depends on the same principles as are used after any delivery. Most importantly, temperature must be monitored regularly for several days postpartum. Examination for a productive cough, abdominal pain, chest pain, calf pain, dysuria or other symptoms should occur at least on a daily basis. In addition, careful inspection of the wound, auscultation of the lungs and palpation of the involuting uterus and of the lower extremities may allow a clinical suspicion of any one of a number of infections or other causes of fever.

### *Management*

The principles of the treatment of puerperal infection include the search for the source of fever, the culture of numerous likely sites of infection, the empiric administration of antibiotics that cover the likely infecting organisms, the careful and regular inspection of the wound and, if there is no response to antibiotic therapy within 24–48 h, a search for, and possible drainage of, abscesses. When fever is detected, cultures of sputum, urine, blood, endometrium and the wound may be necessary to guide antibiotic therapy. Whenever choosing antibiotics in the postpartum period, the issue of compatibility of antibiotics with breast-feeding must be considered. If a fever is persistent despite antibiotic therapy, a search should also occur for deep vein thrombosis, ovarian vein thrombosis and septic pelvic thrombophlebitis, and the diagnosis of antibiotic-associated fever should be entertained. Having said this, if fever persists and the patient comes from an area of the world where tuberculosis is endemic, this diagnosis must be ruled out and laparoscopy and sputum analysis may help in this regard.

## Post-cesarean venous thrombosis

The incidence of postoperative venous thrombosis is undoubtedly also increased because of the increased rate of cesarean delivery in multifetal pregnancies. The rate of venous thrombosis is five-fold higher after cesarean delivery[20]. The mechanism is thought to involve increased venous stasis on the basis of immobilization to a greater degree than with vaginal delivery, and the hormonal influences of pregnancy on the propensity to form thrombi. Physicians caring for women with multifetal pregnancies should have a low index of suspicion for deep venous thrombosis, pulmonary embolism and pelvic vein thrombosis.

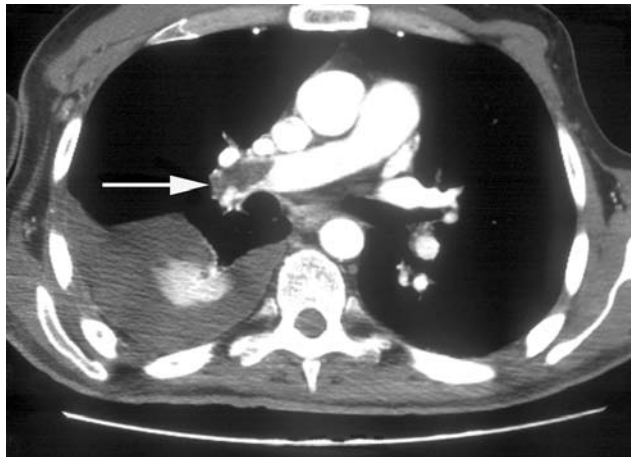

**Figure 86.2** Computed tomography scan of the chest showing a near-occlusive thrombus in the right main pulmonary artery (arrow)

Clinical presentation varies greatly. Classic signs and symptoms of lower-extremity venous thrombosis include an abrupt onset of pain and edema in one leg and thigh. However, signs can be as subtle as an isolated low-grade fever or isolated tachycardia.

The diagnosis begins with the low index of suspicion. The diagnostic work-up includes careful physical examination to describe the clinical suspicion of thrombosis, serum D-dimer measurement and lower-extremity Doppler ultrasound studies. If there is a high index of suspicion, anticoagulation should begin promptly, with diagnostic testing to follow. Studies that may be helpful in confirming the diagnosis include ventilation–perfusion lung scanning, computerized tomography and magnetic resonance imaging (Figure 86.2). Because of the variable clinical presentation and inaccuracy of the diagnostic tests, even when used in combination, an integrated diagnostic approach is probably best[21–24]. All practitioners should recognize that pulmonary embolism is frequently caused by isolated pelvic-vein thrombosis in the iliac veins without lower-extremity involvement.

### *Management*

Anticoagulation should begin when the diagnosis is first entertained owing to suspicious clinical signs or

symptoms. Prompt diagnostic testing is necessary. If the diagnosis is confirmed, anticoagulation and bed-rest are continued, and analgesia is provided. Anticoagulation can occur with unfractionated heparin, low-molecular-weight heparin or warfarin. In the puerperium, initial anticoagulation with heparin or a heparin derivative is necessary, followed shortly thereafter (1–2 days later) by a transition to warfarin. The American Academy of Pediatrics considers warfarin compatible with breast-feeding. For patients or physicians who do not desire a breast-fed infant to be exposed to warfarin, low-molecular-weight heparin given once or twice daily by subcutaneous injection is an acceptable alternative[25,26]. The length of anticoagulation is dependent on the type and severity of thrombosis (i.e. deep vein thrombosis vs. pulmonary embolism) and on the presence of co-morbidities. The usual duration of therapy is a total of 6 months' when venous thrombosis or pulmonary embolism is diagnosed, or until at least 6–12 weeks postpartum if the thromboembolism occurred during the antepartum period.

## Postpartum pre-eclampsia

The rate of pre-eclampsia is increased in multifetal pregnancies, but little information exists on the rate of pre-eclampsia developing in the puerperium[27]. It is not uncommon for physicians who care for multifetal pregnancies to encounter the first signs and symptoms of pre-eclampsia during the postpartum period.

The reason for the increase in pre-eclampsia in multifetal pregnancies is not completely clear, but the limitations of blood flow in the gravid uterus are thought to produce lower flow into each placenta of a multifetal pregnancy. Decreased uteroplacental blood flow is thought to be a predisposing factor in the development of pre-eclampsia[28]. In addition, if pre-eclampsia is produced in large part due to the presence of one or more serum factors produced in the placenta, it follows that a greater amount of any supposed serum factors would be produced by the larger volume of placenta present in a multifetal pregnancy. Although the cause of pre-eclampsia remains undetermined, the diagnostic criteria are fairly well established.

The diagnosis rests on the demonstration of persistently elevated blood pressures while at bed-rest, in combination with the appearance of proteinuria of more than 2+ on dipstick or more than 300 mg in a 24-h urine specimen. Atypical presentations are more common when pre-eclampsia presents in the postpartum period. The development of any of the signs or symptoms of severe pre-eclampsia should focus the attention of the physician on the possible diagnosis, including persistent headaches, visual changes, persistent vomiting, upper abdominal pain, excessive vaginal bleeding or oozing from a cesarean wound. Laboratory values need to be monitored for changes and abnormalities may be clues to the diagnosis, including elevations in partial thromboplastin time, elevations of liver function (aspartate aminotransferase, alanine aminotransferase), lowering of the platelet count, and decreasing hematocrit more severe than expected on the basis of estimated blood loss at the time of delivery. Also, the development of neurologic signs may indicate the appearance of intracranial hemorrhage as a sequela of pre-eclampsia or eclampsia.

### *Management*

The management of pre-eclampsia/eclampsia postpartum includes the standard measures of seizure prophylaxis with magnesium sulfate for at least a 24-h period, careful monitoring of intake and output, periodic auscultation of the lungs in order to allow early detection of pulmonary edema and careful monitoring of blood pressure. Antihypertensive therapy should be started when diastolic blood pressures are persistently elevated above 110 mmHg or mean arterial pressure is above 130 mmHg, in order to decrease the incidence of intracranial hemorrhage. Magnesium levels are not necessary as long as deep tendon reflexes are present; reflexes should be checked at least once every 8 h. Consideration should be given to invasive hemodynamic monitoring (Swan–Ganz catheter placement) if oliguria occurs (less than 100 ml urine production in a 4-h period). There are probably several physiologic variants of severe pre-eclampsia, and they may be distinguishable by invasive monitoring[29]. Invasive monitoring in this setting is thought to allow a management plan that is based on the relevant derangements in physiology and, hopefully, is more successful in preventing morbidity.

## Anemia

In pregnancies with multiple fetuses, the increased rates of postpartum hemorrhage and cesarean delivery are primarily responsible for a greater amount of blood loss and a greater incidence of anemia in the puerperium.

### *Management*

Many patients, even after a singleton delivery, may benefit from iron and vitamin supplementation, when the hemoglobin or hematocrit levels are demonstrated to be low. It has been our policy to use iron and vitamin supplementation routinely in women who have delivered multiple fetuses, and to emphasize their importance when the hematocrit level is

low (< 30%). In addition, those women who are breast-feeding multiple infants have substantial daily requirements for vitamins and trace minerals, and consideration should be made for vitamin and iron supplementation for the duration of breast-feeding.

## DELAYED COMPLICATIONS

### Delayed postpartum hemorrhage

There are few data available to conclude that late postpartum hemorrhage is increased in multifetal pregnancies, although this may be the case owing to the inherent characteristics of multifetal pregnancies. Late postpartum hemorrhage is generally thought to occur due to two mechanisms: placental site subinvolution and retained placental fragments. In multifetal pregnancies, the larger endometrial surface that acts as the placental site combined with a greater incidence of minor abnormalities of placental shape may well predispose to an increased rate of late postpartum hemorrhage. The rate of late postpartum hemorrhage in all pregnancies has been identified to be 0.7% (27/3822), with only one of the 27 women having retained placental tissue identified at curettage[30].

#### *Management*

The standard management of late postpartum hemorrhage in past years was uterine curettage in an effort to identify and remove retained placental fragments, but this therapeutic plan was challenged more than 20 years ago[31]. Current recommendations include avoiding routine curettage and using ultrasound imaging of the postpartum uterus to identify retained placental fragments, followed by curettage only for those cases where retained fragments are thought to be present. Experience in interpreting ultrasound images of the postpartum uterus is necessary because the presence of blood in the uterine cavity can be confused with retained placental fragments. For those instances where no placental fragments are identified within the uterus, management should include intravenous hydration, uterotonic agents such as methylergonovine, ergonovine, oxytocin and prostaglandins, and blood transfusion only if necessary. The management of life-threatening hemorrhage is detailed in the section on 'Immediate postpartum hemorrhage' above, and is well described in current texts devoted to obstetrics.

### Peripartum cardiomyopathy

There is a reported association of peripartum cardiomyopathy with multifetal pregnancy[32,33]. Peripartum cardiomyopathy is a rare, sometimes fatal, severe disease of unknown etiology that occurs with a currently accepted rate of incidence of 1 in 3000 to 1 in 4000 pregnancies; mortality can be as high as 56%[33,34]. The definition includes the development of cardiac failure during the last month of pregnancy or within 5 months postpartum in the absence of recognizable heart disease and without an identifiable cause[33]. Left ventricular dysfunction demonstrated by echocardiography should probably also be necessary for the diagnosis. Symptoms that are suspicious include paroxysmal nocturnal dyspnea, cough and chest pain. Suspicious signs include neck vein distension, pulmonary rales and new regurgitant-type murmurs.

#### *Management*

A multidisciplinary approach to the diagnosis and management of peripartum cardiomyopathy is necessary. This should include the input of obstetricians, maternal–fetal medicine specialists and cardiologists. Therapy should be instituted using standard heart-failure protocols[33]. Before delivery, patients diagnosed with heart failure require transfer to a high-risk perinatal center. After delivery, angiotensin-converting enzyme inhibitors are a mainstay of therapy. Subsequent pregnancies remain controversial, but should be managed at high-risk perinatal centers[35].

### Postpartum psychological disorders

The older literature suggests that postpartum psychologic disorders occur more frequently after the delivery of multiple fetuses[36]. The increased demands on the mother of managing more than one neonate may make it all the more important that 'postpartum blues' or depression is identified and treated promptly. Physicians should be aware of these disorders and empathetic when a new mother voices any concern, and should consider referral for evaluation or treatment whenever symptoms suggest mood disturbance during the first year after delivery of multiple fetuses, and especially during the first 3 months after delivery. These symptoms may include mood lability, crying, anxiety, insomnia, poor appetite, irritability and dysphoria.

## SUMMARY

The increased maternal risks seen during multifetal pregnancy continue into the puerperium. Physicians caring for women who have delivered multiple fetuses should be aware of these risks and institute prompt diagnostic and therapeutic measures so that morbidity and mortality can be prevented.

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# Incontinence and Pelvic Floor Dysfunction

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## INTRODUCTION

Female incontinence and pelvic floor disorders have gained increased recognition for their widespread prevalence and the substantial burden they impose upon post-reproductive women in medical, psychosocial and economic terms. Only recently have these conditions been evaluated among women who have undergone delivery of a multiple gestation. The Evanston Continence Center Mothers of Multiples (MOM) Study[1,2] investigated incontinence and pelvic floor symptoms, together with the risk factors associated with these symptoms, within a large cohort of mothers of multiples attending the National Organization of Mothers of Twins Clubs (NOMTC) annual meetings in 2001. An anonymous 77-item questionnaire included two validated quality of life measures: the Incontinence Impact Questionnaire, and Urogenital Distress Inventory[3]. From the target population of 769 women, 733 responded (95.3%). Of these, 94% were Caucasian, with a mean age 37 years (22–75 years), and parity 3.0 (2–12). The mean elapsed time since delivery was 7.6 years (standard deviation (SD) 9.5). The gestational order was twins among 93.4% of the respondents, triplets for 5.3%, and the remaining women reported higher-order births.

## PREVALENCE OF SYMPTOMS

A high prevalence of all pelvic floor symptoms was observed, including:

(1) Urinary incontinence (any type): 50%;

(2) Stress urinary incontinence: 46%;

(3) Urge incontinence: 27%;

(4) Mixed incontinence (stress and urge): 23%;

(5) Anal incontinence (any type): 25%;

(6) Fecal incontinence: 10%;

(7) Flatal incontinence: 25%;

(8) Fecal soiling: 10%.

The mean age at which symptoms reportedly began was: 35.2 years for stress incontinence, 37.0 for urge incontinence, 38.8 for flatal incontinence and 42.7 for fecal incontinence.

## EFFECTS ON QUALITY OF LIFE

Evaluation of both validated surveys, the Incontinence Impact Questionnaire (IIQ) and Urogenital Distress Inventory (UDI), revealed each pelvic floor symptom to be associated with strong and consistently negative effects on quality of life. Significantly higher mean UDI scores were reported by women with stress incontinence (12.3 vs. 4.7, $p=0.0001$), urge incontinence (14.9 vs. 5.7, $p=0.0001$) and mixed urinary incontinence (15.1 vs. 6.2, $p=0.0001$) compared with continent women. Similarly, higher mean IIQ scores were associated with stress incontinence (6.9 vs. 1.9, $p=0.0001$), urge incontinence (9.4 vs. 2.2, $p=0.0001$) and mixed urinary incontinence (9.3 vs. 2.7, $p=0.0001$), compared with continent women.

## IMPACT OF BIRTH MODE ON STRESS INCONTINENCE

Among women with a history of delivering multiples, the Evanston Continence Center MOM study

identified strong associations between birth mode and risk of subsequent incontinence. Women in the Evanston study cohort were more likely to report stress urinary incontinence than women who had delivered by 'cesarean only' (60.4 vs. 39.6%, $p=0.005$). Stress urinary incontinence was also associated with age ($p<0.0001$), higher parity ($p<0.0001$) and higher body mass index (BMI) ($p=0.001$) compared with asymptomatic women. Utilizing multivariate logistic regression to control for all potentially confounding variables including age, parity and BMI, vaginal birth mode was revealed as the most potent determinant of bladder function – conferring a nearly two-fold elevation in the risk of stress urinary incontinence (odds ratio (OR) 1.92, $p=0.002$). Weaker associations remained between stress urinary incontinence and age (OR 1.08, $p=0.001$) and BMI (OR 1.06, $p=0.002$).

## ONGOING RESEARCH

The Evanston Continence Center MOM study shows that urinary and/or fecal incontinence are common after multiple gestation and delivery, arising at a young age, and exerting a negative impact on quality of life. Among all major obstetric and demographic risk factors, vaginal birth appears to be most strongly predictive of subsequent stress urinary incontinence, whereas delivery by cesarean is associated with a protective effect. Beyond this new appreciation for the overall medical and public-health burden of incontinence among 'mothers of multiples', fundamental questions remain. Do these data reflect physical strains that are unique to multiple gestation and birth, or do they merely reflect the prevalence of symptoms that would be found among 'mothers of singletons' of equivalent age and parity? What is the most appropriate role for elective cesarean delivery for multifetal gestation, taking into consideration these maternal pelvic floor sequelae, and the demonstrated impact of birth route? Aside from cesarean delivery, which modifiable risk factors during labor and vaginal delivery may lessen the risk of pelvic floor injury? Although certain factors such as forceps delivery[4,5] and episiotomy[6–10] have been clearly associated with pelvic floor trauma, the potential effects of other obstetric techniques and strategies remain unexplored. Ongoing research will hopefully identify effective means for primary prevention of these disorders within this population. In the meantime, practitioners should bear in mind the prevalence and social burden of incontinence among mothers of multiples, and inform symptomatic women of their therapeutic options. It must be acknowledged, however, that the women who attend the NOMTC meetings are self-selected and may, therefore, constitute some degree of ascertainment bias.

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# Breast-feeding Multiples

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## INTRODUCTION

Human breast-milk is the best nutrition for human infants. Its unique composition is ideal for early growth and development. Many studies demonstrate the superiority of human milk for human infants over that of other species, as it contains leukocytes, specific antibodies and other antimicrobial factors that protect against common infections such as gastroenteritis, upper respiratory tract infection, sepsis, otitis media, urinary tract infection and meningitis[1]. Epidemiological studies document reduced incidences of chronic childhood diseases such as lymphoma, insulin-dependent diabetes mellitus, Crohn's disease, obesity and allergies among children who breast-fed[2–6]. Better neurodevelopmental outcome and many psychological and cognitive benefits accrue for breast-fed infants, compared with those who have not experienced this form of nutrition[7].

In principle, breast-feeding multiples is the same as breast-feeding a singleton, albeit accompanied by many potential difficulties that require a great deal of external support. Special attention should be given to the advantages of breast-milk for infants, as particular problems among premature newborns include feeding intolerance, increased risk for necrotizing enterocolitis (1–12% of very-low-birth-weight (VLBW) infants) and high susceptibility to infection (16–30% of VLBW infants)[8]. Such complications may predispose to suboptimal nutrition during the postnatal period that may be critical for later growth and development.

Specific advantages of breast-milk for premature infants include the following[9]:

(1) Immunological benefits: a specific source of protection for preterm infants is the enteromammary immune system, whereby antibodies in the milk that result from exposure of the mother to the nosocomial pathogens in the neonatal intensive-care unit environment are transferred to the infant via the breast-milk. Data suggest that preterm infants fed their own mother's milk had fewer episodes of necrotizing enterocolitis, diarrhea and urinary tract infection and needed less antibiotic treatment compared with formula-fed premature infants[9].

(2) Digestion and absorption: the predominance of whey in the protein content of human milk facilitates absorption, whereby a better balance of phenylalanine, tyrosine and methionine is achieved compared with commercial formula that is high in casein. Moreover, the high lactose content in human milk speeds gastric emptying, and the oligosacchrides contained therein are responsible for a softer stool consistency, non-pathogenic bacterial fecal flora and improved mineral absorption.

(3) Neurodevelopmental benefits: human milk contains the long-chain fatty acids docosahexaenoic acid (22:6, β-3) and arachidonic acid (20:4, β-6), which are associated with improved cognition, growth and retinal development and higher intelligence quotient[7]. Also, the antioxidant activity of compounds such as β-carotene, taurine and vitamin E may benefit visual function[7].

(4) Long-term effects: over the past decade, it has become increasingly clear that nutrition in the fetal and neonatal periods has a profound impact on health throughout adult life[2–7].

Evidence exists to support the concept of critical periods during fetal and neonatal life during which alterations in nutrient supply may result in lasting physiological changes, such as obesity, insulin-dependent diabetes mellitus, Crohn's disease, lymphoma and allergies[2–7].

## SPECIFIC ISSUES IN BREAST-FEEDING MULTIPLES

### How often do mothers succeed in breast-feeding multiples and for how long? What are the common reasons for stopping?

As mothers of multiples represent a unique group who often are not expected to breast-feed, few studies describe this process, in terms of either success or failure. Addy reported in 1975 a study of a select group of members of a 'mothers of twins' club in southern California among whom only 24% (41/173) breast-fed from birth[10]. Of these, 37% (15/41) breast-fed for less than a month, and only 20% (8/41) continued for 4–6 months. Reasons for the introduction of supplements were inadequate breast-milk in 28%, failure of the twins to thrive in 13%, local illness such as breast engorgement, retracted nipples or abscess in 15% and maternal illness in 7%. Interestingly, in only 2% of cases was an illness of the twins reported as the cause for stopping breast-feeding. On the other hand, the reasons for not starting were simply that the mother did not want to breast-feed in 36%, maternal or infant illness in 8 and 9%, respectively, physician advice in 9%, not enough milk in 8% and not enough time in 11%[10].

The evidence regarding breast-feeding rates among singletons and multiples shows no consensus. Data from a national survey of mothers in the USA in 1990 found no significant difference in initiation of breast-feeding between mothers of twins (48%) and singletons (51%). At 6 months, 13% of twins and 18% of singletons, respectively, were still breast-feeding[11]. Furthermore, Gromada and Spangler quoted Maureen Boyle of Mothers of Super Twins (MOST) who claimed that, during 1997, the breast-feeding initiation rate was close to 70% for 800 new mothers[12]. However, this higher rate may well represent that which can be achieved in a highly motivated select group. Regardless, no follow-up data concerning breast-feeding after discharge from the hospital are available in the literature.

As many multiples are born preterm, general assessments of the success of breast-feeding in multiples must focus on this high-risk group. Liang and co-workers compared singletons and twins among preterm infants of 29–36 weeks of gestation from a single center[13]. Multiples tended to start as partial breast-feeders and progressed later to exclusive breast-feeding. Overall, 93% of singletons and 89% of twins were being breast-fed at discharge from the hospital. In this hospital-based study, the rate of decline in singletons and twins was similar (68% at the age of 8–12 weeks and 49% at the age of 12–16 weeks)[13]. In contrast, Czeszynska and Kowalik in Poland studied preterm multiples of mean gestational age 35.6 weeks and found that, despite an intensive promotion program, only rarely were multiples discharged on exclusive breast-feeding, and most families reported using a combination of breast-milk with infant formula[14]. Factors associated with delaying early breast-feeding in this Polish cohort included respiratory distress in 22%, infections in 28%, cesarean section in 62% and maternal medications in 14%. Most of the infants started to breast-feed only 3–4 days after delivery[14].

Rozas and colleagues studied factors influencing the success of breast-feeding in mothers of twins in a Spanish-language community in Barcelona[15]. The main reason given for starting breast-feeding was the knowledge that it was 'better food' for the baby. Women with prior counseling started breast-feeding in greater numbers than those not counseled. Factors that did not influence breast-feeding in this study were maternal age, birth type, birth weight, maternal education, work and domestic situation and admission to the newborn unit. However, this was a small sample of relatively mature twins, and may not be representative of all multiples[15].

### To what extent is breast-milk nutritionally satisfactory in multiples?

A consistent finding in the media or on Internet sites dealing with multiples is the concern of mothers whether there is enough milk for more than one baby. This concern commonly results in a greater tendency to introduce early artificial feeding to twins. The simple answer to the question of sufficiency stems from the use of 'wet nurses' in the past. In foundling homes in France during the 17th century, each wet nurse fed 3–6 infants, who were often of differing ages and with different daily requirements[16]. Another historical source of evidence that women can provide enough milk for more than one infant comes from milk banks, first opened in Vienna in 1900 and 10 years later at the Massachusetts Infant Asylum. The milk provided to these banks was surplus milk from nursing mothers, which was made available to infants whose mothers were unable to provide adequate milk. These data clearly support the concept that certain, if not all, women are capable of expressing adequate volumes of milk for more than one infant given optimal circumstances, adequate nutrition, absence of illness and the desire to do so.

Over the course of lactation, the volume of human milk production is directly related to demand, irrespective of the number of infants[17]. Saint and coworkers studied the volume and composition of milk produced by mothers of singletons, twins and triplets, respectively[18]. The milk yield of mothers was determined by measuring the decrease in the mothers' weight, by beam balance, at each feed over a period of 24 h. Mothers of twins consistently produced twice the volume of milk as mothers of singletons[18]. Moreover, the mothers of triplets produced a remarkable volume of more than 3 l/day when the infants were aged 2.5 months. Whereas the concentrations of lactose, protein and mixed fat in the milk were variable, they were adequate in all mothers. The crux of this situation is informing the mother in the most supportive and reassuring terms that the more she nurses, the more adequate her milk supply will be. In order to achieve this goal, however, the mother must fulfill specific nutritional requirements.

## Maternal nutritional needs

### *Singletons (the general model)*

The mother's body prepares itself during pregnancy for subsequent lactation by developing breast tissue to produce milk and also by storing energy. The Subcommittee on Nutrition during Lactation of the Institute of Medicine recommends that the daily nutritional increase during a singleton pregnancy should include 300–500 kcal, 20–30 g of protein and 20% excess in all recommended daily allowances for vitamins and minerals. For each of these recommendations, the higher dose should be employed in women with poor pre-pregnancy nutritional status. Other specific situations are a double dose for folic acid and a 33% increase in calcium, phosphorus and magnesium[19,20].

### *Multiple pregnancy*

It is very important to prepare the mother during a multiple pregnancy for the task of feeding the coming newborns by giving the appropriate information and by closely following her weight gain. Weight gains of 35–45 lb are recommended, and gains as high as 60–100 lb have been reported[21]. Lactation requires energy that comes mainly from two sources: maternal storage of fat and protein during pregnancy and ongoing dietary intake during lactation[21,22].

### *Before delivery*

Nutritional factors influence the course and outcome of multiple pregnancy. The linear relationship between weight gain during pregnancy and birth weight is similar in both twin and singleton pregnancy. Consequently, as weight gain during pregnancy is a reliable, simple measure, many studies use it to evaluate nutritional status and pregnancy outcome. Maternal weight gain by the end of pregnancy of 20–24 kg is associated with birth weights of 2500–3000 g in twins[23]. Conversely, low weight gain, or even weight loss, during twin pregnancies is associated with preterm delivery[24].

Brown and Carlson calculated the theoretical caloric requirements for adequate weight gain during pregnancy. In order to achieve a weight gain of 5 kg above that of singletons, mothers of twins need an extra intake of 150 kcal per day[25]. Thus, suggested target weight gains for multiple pregnancies may be as follows:

(1) Twin pregnancy: the recommended overall weight gain is 35–45 lb, with an average of 1.5 lb per week during second and third trimesters of the pregnancy. The total weight gain in the first trimester should be of the order of 4–6 lb.

(2) Triplet pregnancy: data from a study of four triplet pregnancies suggest a weight gain of 50 lb with a steady increment of approximately 1.5 lb per week throughout pregnancy[26]. Another study by the same group of 194 triplet pregnancies showed that low maternal weight gain *before* 24 weeks of gestation was particularly correlated with poor fetal growth and lower birth weight[27]. In fact this was worse for pre-pregnant underweight and normal weight women than for overweight women.

(3) Little information is available on the nutritional requirements in quadruplet pregnancy. In a single case study, a 3000-kcal/day diet, with 100 g of protein, was associated with positive infant outcomes[28].

Women with multiple pregnancies require counseling regarding nutritional supplements. The National Academy of Sciences (USA) recommends supplements including 30 mg of iron, together with low to moderate doses of zinc, copper, calcium, vitamin $B_6$, folate, vitamin C and vitamin D after 12 weeks of multiple pregnancy[29]. Increased needs for other nutrients may best be met by increased consumption of nutrient-dense food. Adherence to these recommendations should ensure the energy stores needed later for breast-feeding.

### *After delivery*

Current recommendations for caloric supplementation during breast-feeding are 500–600 kcal per baby per day[29]. A mother nursing multiples will thus use a combination of reserves stored during pregnancy and increased intake during nursing.

The diet should be well balanced (protein 20% of total calories, carbohydrates 40% and fat 40%) and include vitamin supplements. Many mothers benefit from the help of an expert, such as a nurse, a lactation counselor, a physician or a dietitian.

Adverse maternal conditions influence the lactation as well as the volume of milk. Severe dehydration and malnutrition are prime examples. Stress is also believed to interfere with lactation performance via a number of potential mechanisms, including inhibition of oxytocin release, increased adrenocorticotropin-releasing hormone and activation of the peripheral sympathetic nervous system[30]. However, psychological studies have failed to show a consistent correlation between measures of stress and lactation performance. Despite this, stress-reducing interventions, such as skin-to-skin contact between the mother and the infant and relaxation therapy, improve lactation performance and prolong breast-feeding[30].

Breast-feeding multiples, in particular, with its attendant nutritional demands and lack of sleep, is a potentially stressful situation that may influence lactation performance. Mothers of twins may be aware of what they should be eating but may be unable to live up to such stringent demands. Thus, the importance of time management during lactation raises the issue of the different modes of breast-feeding.

## MANAGEMENT OF BREAST-FEEDING: TIME, SIDES AND POSITIONS

### Time

Twins may be breast-fed in any of three modes: simultaneously, separately on an individual demand schedule or separately on a modified demand schedule where one infant is fed on demand and then the other immediately afterwards. Simultaneous breast-feeding saves time and also provides a physiological advantage in that the more vigorous baby on one side may stimulate the let-down reflex for the other twin[31]. The most common practice is to start breast-feeding each baby individually, as it takes time for the mother to recover from the delivery. Both infants do not necessarily have the same sucking ability immediately postpartum, and the new situation is often quite overwhelming for the parents. Many mothers and infants adapt rapidly, and can soon choose their preferred schedule.

### Sides

Another issue is whether to alternate breasts between babies or to assign each baby to the same breast. In our opinion, it is preferable to alternate breasts when breast-feeding twins. This assures that each breast receives balanced stimulation from the different babies and assures that the milk yield for each baby will be the same, regardless of asymmetrical development or previous surgery in one breast.

**Figure 88.1** 'Double football'

### Positions for simultaneous breast-feeding

The three commonly used positions for simultaneous breastfeeding are as follows[31]:

(1) 'Double football': as shown in Figure 88.1, an infant's head is supported in each of the mother's hands (or on a pillow), with an infant's body lying under each of the mother's arms. Many mothers use this position initially until they gather more experience.

(2) 'Double cradle': in this position each infant is held like a singleton, in the cradle position. The two infants cross on the mother's abdomen (Figure 88.2). This position is often used when the mother is more experienced and the infants have better head control.

(3) 'Combination of cradle with football': one infant is held in the cradle position and the second in the football position (Figure 88.3).

Mothers of triplets or quadruplets who intend to provide their infants with some exposure to human milk may choose between the various possible combinations. Difficult as it may be for some mothers, even partial breast-feeding may offer potential advantages to high-order multiples.

### Obstacles to success

The mother of multiples is often faced with additional obstacles to success in lactation, as high percentages of multiples are delivered by cesarean section and many are preterm and suffer perinatal complications. Both factors have deleterious effects on breast-feeding. For example, infants delivered by

**Figure 88.2** 'Double cradle'

**Figure 88.3** 'Combination of cradle with football'

cesarean section start suckling later than those born by vaginal delivery[32], and preterm multiples are at particularly high risk for neonatal complications, congenital anomalies and mother–infant separation in the postpartum period that can also jeopardize the successful onset of breast-feeding.

### *Breast-feeding after cesarean section*

Epidural or spinal anesthesia is ideal in that it allows the mother to be awake and relatively pain-free in the immediate postoperative period, thus improving the chances for early initiation of breast-feeding. For some mothers, the best position for breast-feeding after surgery is the 'football position' (see above), as the babies will not lie on the mother's abdomen. Others put a cushion over the incision to reduce the pain. Mothers of multiples after cesarean section often report a delay in copious milk production, and thus much support and encouragement are required during the first few days after birth. Appropriate pain relief may aid during this period. It is important that the compatibility of all pain-relieving drugs with lactation should be carefully checked before prescription.

### *Prematurity*

Small, preterm multiples may benefit from expressed maternal breast-milk until they are capable of actively breast-feeding at around 30–34 weeks' gestational age. This process requires much support from a multidisciplinary team in the neonatal intensive-care unit. Caution is advisable for this fragile cohort of newborns, however, as exclusive feeding of unfortified human milk has been associated with poorer growth in the preterm population[33]. Growth and nutrient deficits can be corrected with the use of specific supplements such as human-milk fortifier. Commercial preparations contain protein, carbohydrate, calcium, phosphorus, magnesium, zinc, copper and vitamins, and these result in improved nutrient retention and better growth.

## 'In real life': does it work?

Leonard studied breast-feeding patterns in families with high-order multiples[34]. The parents who participated were a unique population and may not be representative of all families. Nonetheless, the information obtained provides a rare insight into their daily reality. The author conducted in-depth discussions with nine breast-feeding mothers and two fathers. The information was gathered by interviews via telephone, e-mail and mail. The study population included five primiparas and four families with another child at home. Gestational age was 26–35.5 weeks. All but one of the infants were healthy. Exclusive breast-feeding was achieved in five of the nine families, whereas the others breast-fed one or two and pumped between or after feeding, and gave a combination of breast-milk and formula.

The women talked about the ongoing struggles regarding the sheer intensity of the process of breast-feeding. A major factor in the decision of how much breast-feeding was given was the length of time required to feed each baby, as most infants needed 45 min per feed even at the age of 3–4 months. Overall breast-feeding demanded most of the mothers' awake time, as each session of nursing could last between 45 min and 2 h, every 3–4 h. During periods of accelerated growth, such as during the second month of life, nursing became almost continuous. After several weeks, most women became stressed by demand feeding, and changed to scheduled feeding. Night-time required special preparation and always more than one person. Regardless, the majority of the mothers preferred to feed their triplets consecutively

rather than simultaneously as they felt they could devote more attention to each infant. When asked about the effects of breast-feeding on their health and well-being, the women reported that they were considerably more thirsty and hungry. All were chronically tired and discussed the need to get away to seek adult company. The triplets put a special burden on the marriage and its intimate character, but parents in this small study managed mostly to handle the situation. The duration of breast-feeding was between 5 weeks and 6 months.

### Promoting breast-milk feeding

The decision to breast-feed is highly influenced by antenatal counseling[35]. Specifically, Friedman has shown that providing women with impending preterm delivery with a prenatal consultation that includes information on the importance of breast-milk markedly increases the initiation and duration of breast-milk feedings[37].

After delivery, hospital practices and the attitude of the medical team towards breast-feeding are crucial for promoting success. This includes preparation for early initiation of breast-feeding or expressing milk, continuous rooming-in (as soon as possible), demand feedings, avoidance of unnecessary formula supplementation, avoidance of artificial nipples, the availability of knowledgeable staff and instruction on correct breast-feeding technique. Mothers of preterm or sick infants in whom breast-feeding needs to be delayed should be instructed to pump their milk.

Many neonatal intensive-care units have task forces whose aim is to facilitate the above techniques. In our unit, a dramatic increase in breast-feeding rates in VLBW singletons and twins has been noted in recent years (Figure 88.4), due in no small part to such policies.

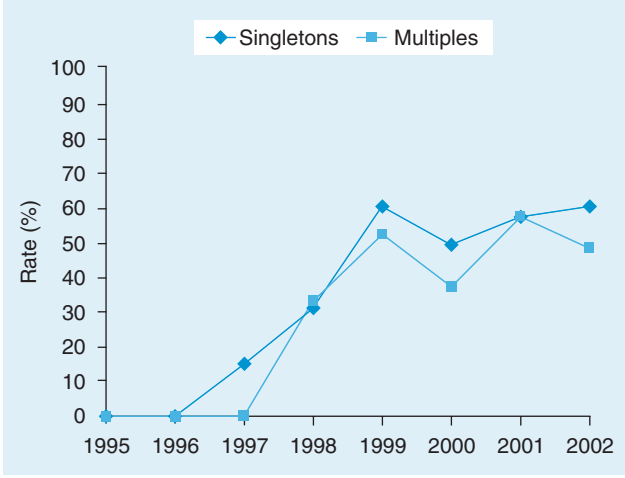


**Figure 88.4** Rates of breast-feeding in very-low-birth-weight singletons and multiples during 1995–2002

### Websites for the parents of multiples

Many websites focus on breast-feeding, multiple pregnancies or both, and should be of use to health-care providers as well as to parents of multiples. The following sites provide useful information on these two issues:

www.lalecheleague.org/bfmultiple.html
www.tripletconnection.org/bbfeed.html
www.dhs.vic.gov.au/phd/hce/hwu/breast/breast.htm
www.tqq.com/support_network.html

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## COMMENT

### The motif of breast-feeding twins in art

Breast-feeding as an artistic motif has been popular in diverse cultures since ancient times. The lactating mother symbolized nurturing, fertility and affluence, virtues that bypassed the male gender in artistic symbolization. Some scholars suggest that showing the naked female breast, usually in a posture not suitable for breast- feeding, also possesses some hidden erotic nuance. Regardless, the motif of a mother nursing twins probably had a more profound meaning, namely the idyllic superwoman capable of nurturing more than one infant at a time. Figure 1 shows the ancient Greek–Roman goddess Gaia (Gaea), or Mother Earth, usually depicted as a matronly woman, who emerged at the creation of the universe. In this Roman marble relief, Gaia holds twin infants in the nursing position, although her breasts are covered.

**Figure 1** Roman marble relief showing Gaia, goddess of the earth, holding twins in a nursing position

Twins were quite common in ancient Greek mythology (see Chapter 16). Greek mythology was spread around the Aegean sea by the Philistines, and twin mythology was imported into what is today called Israel by the ancient Canaanites, being used for religious as well as secular purposes. Figure 2 shows a mold-made clay statuette of the Ugaritic twins Shachar and Shalem, nursing from the breasts of the goddess Asherah. This figurine, uncovered near Revadim (Israel), is an excellent example of fertility figurines, which were very popular in the ancient Middle East.

Whereas the breast-feeding of twins, as shown in Figure 2, was assumed to take place *in utero*, other ancient artistic examples depict a more

**Figure 2** Canaanite clay fertility figurine showing the goddess Asherath nursing twins

realistic image of relatively large infants nursed by the large breasts of a huge mother. Notwithstanding the exaggeration of all involved motifs, the combination of these elements amplifies the grandeur of nursing twins. A good example is shown in the massive Sicilian sculpture of Mother Earth nursing large twins (Figure 3). Of interest is the accurate nursing position ('double cradle') of the twins, suggesting that this breast-feeding technique has been known since early times.

During the Renaissance, breast-feeding was a motif in religious paintings, but few depicted multiples. Of these, a prime example is Guido Reni's

**Figure 3** Statue of Mother Earth nursing twins in the 'double cradle' position

(1575–1642) painting showing a female (*Charity*) nursing triplets (Figure 4). This graceful portrait,

**Figure 4** *Charity* by Guido Reni (oil on canvas) showing a woman nursing triplets

symbolizing abundance, shows the three stages of breast-feeding: the hungry baby (left, eyeballing the mother and pointing to the breast), the sucking baby (right, in an attentive position) and the satiated baby enjoying a relaxing, postprandial, nap.

**Figure 5** Wooden statuette of a West African woman nursing twins

Finally, it appears that artistic representations of breast-feeding twins are also popular in African tribal art, where twins are known to be more frequent. Figure 5 shows a wooden statuette of a West African woman with a (postpartum?) pendulous abdomen sitting on a bench, nursing a pair of twins who are seated on each leg of the mother.

Isaac Blickstein

# Psychological Morbidity: Diagnosis and Treatment

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**89**



## INTRODUCTION

Factors specific to multiple gestations influence a mother's susceptibility to postpartum psychiatric complications. Beginning in the antepartum period, a woman can experience increased demands from pregnancy. The diagnosis of multiple gestations often entails an initial reaction characterized by a combination of ambivalence, anger, fear and shock[1,2]. As twin pregnancies are commonly considered to be 'double the joy', many patients are uncomfortable verbalizing their ambivalence.

As the risks of preterm labor and fetal demise are increased, the potential that either or both factors may become a reality holds separate risks for the psychological well-being of a pregnant woman. Not unexpectedly, the level of depressive symptoms in women with high-risk pregnancies is significantly greater during late gestation than is the case in non-high-risk controls[3,4]. Similarly, women placed on extended bedrest experience more anxiety, depression and somatic complaints[5]. Bedrest often disrupts family life and causes significant financial difficulties that impact on postpartum adjustment. Furthermore, in the antepartum period, mothers of multiples experience increased discomfort, weight gain and disrupted sleep in their pregnancies, all of which affect coping strategies and increase difficulties postpartum. Another common antenatal cause of stress relates to complications of fetal reduction. Although highly disturbing from a psychological point of view, this procedure is generally well tolerated and without significant psychological sequelae, at least in the long term[6]. In some cases, however, it may be associated with a bereavement reaction lasting less than 2 weeks[7].

## THE POSTPARTUM PERIOD

A number of biological, psychological and social stressors present themselves in the immediate postpartum period and often lead to an increased risk of anxiety and depression in mothers of multiples. There is an 8–13% incidence of postpartum depression in the general postpartum population[8]. No studies have systematically studied the incidence of depression and anxiety of mothers of multiples in this period; however, many factors suggest an increase exists. The incidence of child abuse is increased among parents of twins[9], and twins are nine times more likely to be abused than singletons[10]. Triplets are also affected, as evidenced by a 4-year follow-up study of mothers of triplets which revealed increased emotional distress and depression, with four of the 11 mothers interviewed expressing regret about having triplets[11].

Biologic factors appearing in the postpartum period accentuate the onset of psychiatric illness. Immediately postpartum, dramatic shifts occur in hormones, fluids and electrolytes. Progesterone and estrogen levels fall rapidly, with a rise in prolactin[12]. This latter change influences serotonin, norepinephrine and dopamine levels in the brain, and is believed to contribute to postpartum 'blues' and the unmasking of more serious mood disorders in vulnerable individuals. Yet another hypothesis for the etiology of postpartum blues is the role of oxytocin as a cause for emotional reactivity, believed originally to promote attachment behavior. Under conditions of high stress, this increase in emotionality may render a woman more susceptible to stress and contribute to the symptoms that occur in postpartum blues[13].

The risk of hypothyroidism is increased postpartum in all pregnancies, a further factor leading

to depression. Other factors, such as decreased ability to maintain sleep, nutrition and self-care, can also contribute biologically to psychiatric morbidity. Furthermore, genetic factors can increase the risk for postpartum mood disorders. A prior episode of a postpartum mood disorder, a history of a mood disorder and a family history of a mood disorder all can increase risk[8,14].

Psychologically, a parturition can precipitate a variety of maternal reactions. The shock of delivering undiagnosed twins or multiples, for example, can lead to acute stress and a challenge to the family's support structure. The postpartum role shift that is inevitable can cause psychological distress, as the abrupt change from the dual role of wife and worker to the triple demands of mother, wife and worker often calls for psychological strengths that some women may not possess. Moreover, the birth of multiples delays a mother's re-entry into the workforce, leading to fewer employment choices postpartum. At times mothers are unable to breast-feed their multiples, which can be an additional psychological blow and represent a loss. Furthermore, maternal–infant separation due to prematurity and the special-care nursery stays common in multiples not only increases anxiety but can delay the attachment process[15]. The death of an infant, although difficult for all mothers, can be more complex for mothers of multiples as often they experience the complex process of dealing with death and birth at the same time (see Chapters 95 and 103). Last, another psychological stressor that postpartum mothers of multiples commonly report is the fear of being unable to give equal care to all children and of favoring one child over another[1].

Mothers of multiples are also burdened by a variety of social factors that contribute to psychological morbidity. The increased financial burden of having multiples is alleviated by few, if any, government and private resources. A new mother must negotiate challenges in her family life and support system. Separation of multiples, whereby one multiple goes home sooner than the others (see Chapter 95), increases stress in the family unit. Mothers of multiples with young children at home report the highest level of stress in the family unit[16]. Finally, the withdrawal of former adult contact, as well as the strain on the relationship with her significant other, can lead to feelings of loss and isolation for one or both partners.

## TYPES OF DISORDERS IN PREGNANCY AND POSTPARTUM

### Hyperemesis gravidarum

Hyperemesis gravidarum, although not considered a psychiatric disorder, is a unique disorder that occurs in pregnancy and requires a biopsychosocial perspective. It is believed to have a primary endocrinologic etiology combined with the personality and life circumstances of the individual woman. A stressful home environment, the lack of social support and depressive symptoms are important contributing or exacerbating components, and should be carefully assessed and addressed.

### Antepartum depression

Depression during pregnancy is significant not only because it is a common disorder (prevalence 10–12%), but also because if untreated can lead to significant risks to mother and fetus. Antepartum depression increases the incidence of women neglecting prenatal care and self-care/nutrition, using tobacco, alcohol or cocaine and engaging in suicidal behavior[16]. Furthermore, untreated depression during pregnancy results in an increased rate of preterm delivery, decreased birth rates and smaller head circumference at delivery[17–19]. Although there is no reported increased prevalence of depression in mothers of multiples, this is especially risky in the multiple gestation population.

Antepartum depression often remains undiagnosed because the symptoms are similar to somatic complaints of pregnancy. The symptoms of insomnia, decreased energy, decreased concentration and appetite changes are common in both pregnancy and depression. A persistent depressed mood, feelings of hopelessness, frequent tearfulness, inability to enjoy previously enjoyable activities, social isolation and excessive guilt are symptoms of depression and do not occur in normal pregnancy. The Edinburgh Postnatal Depression Scale (Figure 89.1) is an evaluation that can be self-administered, and has proved to be highly sensitive to the diagnosis of depression both antepartum and postpartum[20]. Antenatal depressive symptoms are more common among adolescents, inner-city women and women with a past history of depression. Antepartum depression increases the risk of mood disorders postpartum. One half of pregnant depressed women will have postpartum depression[21].

### Attachment disorders

Disorders of mother–infant attachment range from ambivalent feelings towards the infant in the first few days postpartum to thoughts of harming the infant. Delayed attachment occurs in 10% of new mothers, and is hypothesized to be increased in mothers of twins[22]. A severe attachment disorder involves hostile thoughts about the baby, and occurs in 1% of new mothers[23]. A mother with an attachment disorder displays disinterest, neglect and a failure

***In the past 7 days.....***

**1. I have been able to laugh & see the funny side of things**

0) As much as I always could
1) Not quite as much now
2) Definitely not as much now
3) Not at all

**2. I have looked forward with enjoyment to things**

☐ As much as I ever did
☐ Rather less than I used to
☐ Definitely less than I used to
☐ Hardly at all

**3. * I have blamed myself unnecessarily when things went wrong**

☐ Yes, most of the time
☐ Yes, some of the time
☐ Not very often
☐ No, never

**4. I have been anxious and worried for not good reason**

☐ No, not at all
☐ Hardly ever
☐ Yes, sometimes
☐ Yes, very often

**5. * I have felt scared or panicky for no good reason**

☐ Yes, quite a lot
☐ Yes, sometimes
☐ No, not much
☐ No, not at all

**6. * Things have been getting on top of me**

☐ Yes, most of the time I haven't been able to cope
☐ Yes, sometimes I haven't been coping as well as usual
☐ No, most of the time I coped quite well
☐ No, I have been coping as well as ever

**7. * I have been unhappy that I have had difficulty sleeping**

☐ Yes, most of the time
☐ Yes, sometimes
☐ Not very often
☐ No,not at all

**8. * I have felt sad or miserable**

☐ Yes, most of the time
☐ Yes, quite often
☐ Not very often
☐ No, not at all

**9. * I have been so unhappy that I have been crying**

☐ Yes, most of the time
☐ Yes, quite often
☐ Only occasionally
☐ No, never

**10. * The thought of harming myself has occurred to me**

☐ Yes, quite often
☐ Sometimes
☐ Hardly ever
☐ Never

Response categories are scored 0, 1, 2, and 3 according to increased severity of the symptoms. Items marked with an asterisk are reverse scored (i.e. 3, 2, 1, and 0). The total score is calculated by adding together the scores for each of the ten items.

**Figure 89.1** Edinburgh Postnatal Depression Scale. Taken from reference 20

to protect, nurture or interact with her child. In mothers of multiples this can manifest by an inability to maintain contact with or ignoring one of the infants. Attachment disorders can occur as a primary psychiatric condition or can occur secondary to other psychiatric disorders, such as adjustment disorder, depression, mania, psychosis, anxiety, obsessive compulsive disorder (OCD) or personality disorders. Women at high risk for such disorders may have had inadequate or disrupted mothering themselves, be single teenage mothers, have infants with congenital defects or prematurity or have unwanted pregnancies[24].

Most attachment disorders resolve spontaneously, often within the first few days or weeks postpartum. If such exist, it is important to identify and treat the underlying psychiatric disorder first. Mothers may further benefit from practical advice and support concerning infant care (see Chapter 106), education about their disorder, psychotherapy and behavioral interventions to decrease anxiety when coping with the baby. In severe instances, in which the infant is deemed to be at serious risk for abuse or neglect, protective joint custody or enforced supervision may be necessary. Although delayed attachment or early temporary separation from the mother has not been shown to have significant long-term effects on the baby[25], ongoing lack of bonding may lead to failure to thrive, stunted emotional and cognitive development and difficulty developing peer relationships. Such children are also of increased risk of abuse, neglect and rejection.

## Postpartum blues

Postpartum blues are a common, benign, transitory condition generally occurring in the first 10 days postpartum and presenting in as many as 50–70% of all postpartum women. Typically beginning 3–4 days postpartum, symptoms peak on day 4–5, which coincides with milk let-down. Emotional lability, weeping and feeling low-spirited but not necessarily depressed characterize postpartum blues. Biological factors are most likely to be the cause, including rapid shifts in hormones and sleep deprivation. The percentage of women that go on to develop a major depressive episode is unknown. Suicidal ideations, thoughts of harm towards the infant and feelings of hopelessness or extreme helplessness are not seen in this disorder, and signify a more serious problem.

## Postpartum depression

Postpartum depression is a psychiatric disorder lasting more than 2 weeks, the severity of which meets *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn (DSM-IV) criteria for major depression (Table 89.1)[26]. The incidence is 8–13% in the general postpartum population[9]. The prevalence is estimated to be as high as 10–20% of women within 6 months of delivery[27]. It typically occurs within 1–6 months of delivery, and occasionally is simply a continuation and intensification of postpartum blues. Clinical presentation includes symptoms of depressed mood, sleep and appetite disturbance, decreased concentration, excessive guilt or hopelessness and thoughts of suicide. The symptoms of sleep disturbance are usually characterized by difficulty sleeping even when the infant is asleep or is being cared for by someone else. Some women may worry excessively about the health of the baby and feel they are inferior mothers. In severe cases, symptoms can include thoughts of suicide and thoughts of harming the infant. Harm to the infant rarely occurs in the absence of psychotic depression[13]. By contrast, stray intrusive thoughts in the absence of other psychiatric symptoms can be normal in the postpartum population. The Edinburgh Postnatal Depression Scale can be self-administered and has proved to be highly sensitive in postpartum depression. A score of 12 or more on this scale suggests depression, and indicates that the patient should be further evaluated and treated by competent psychiatric practitioners[20].

## Postpartum mania

Postpartum mania most commonly presents in the context of bipolar disorder, but may occur as a single episode postpartum. Bipolar disorder is a recurrent, episodic cyclic mood disorder characterized by one or more manic episodes. DSM-IV criteria for a manic episode include an abnormally elevated, expansive or irritable mood lasting at least 1 week with symptoms of inflated self-esteem or grandiose delusions, decreased need for sleep, increased rate of speech, increased level of activity, distractibility and the feeling that one's thoughts are racing. The incidence of postpartum mania is 1/300–1/1000 women. A recent study showed an incidence of postpartum psychosis of 260/1000 in women with untreated bipolar disorder[28].

**Table 89.1** *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. Criteria for major depressive episode (with postpartum onset)

Five of the following symptoms must be present during the same 2-week period:
- depressed mood
- markedly diminished interest or pleasure in activities
- significant change in appetite
- insomnia or hypersomnia
- psychomotor agitation or retardation
- fatigue or loss of energy
- feelings of worthlessness or excessive guilt
- diminished ability to think or concentrate
- recurrent thoughts of death

## Postpartum psychosis

Postpartum psychosis is a psychotic disorder arising after childbirth. The incidence is 1–2/1000 births. Primiparous women and those with a history of bipolar disorder are particularly vulnerable. Symptoms of postpartum psychosis occur abruptly, most commonly within 3 weeks of delivery, which is considered early onset. Late onset (after 3 weeks) is typically seen in women with chronic psychotic disorders such as schizophrenia or schizoaffective disorder[29–33].

Women experiencing psychosis present in a variety of manners. Prodromal symptoms include sleep disturbance, fatigue, depression, irritability, emotional lability and difficulty caring for the infant. The patient may appear perplexed, bewildered or dreamy, with memory complaints. Hallucinations or delusions, often persecutory in nature (i.e. that they are a bad mother or unworthy of their child), are not uncommon. Possible diagnoses include brief psychotic disorder, psychotic depression, manic psychosis, schizophreniform disorder or a psychotic disorder due to a general medical condition. It is important to rule out organic causes of a

psychotic presentation including infectious disorders, autoimmune disorders, endocrine disturbances or substance intoxication or withdrawal.

Postpartum psychosis is considered a psychiatric emergency and requires hospitalization, especially if the mother is in danger of harming herself or the child through neglect, abuse or acting on delusions or hallucinations.

### Anxiety disorders

Anxiety disorders with or without panic attacks may occur in the postpartum period, either as a new disorder or an exacerbation of a previous disorder. Symptoms of anxiety can include inability to control worry, hypervigilance, insomnia, difficulty concentrating, anticipating the worst and autonomic arousal symptoms including sweating, trembling or palpitations. OCD and obsessive compulsive symptoms also are possible in the postpartum period. Women with OCD can experience obsessions about cleanliness, germs or illnesses in the newborn. They may spend hours cleaning or sterilizing anything the infant comes in contact with. They also can experience unwanted and intrusive thoughts about harming their baby and may avoid situations in which they are at risk of acting on these thoughts, including bathing the infant or preparing food with sharp knives. Anxiety disorders of this type are often seen in women with co-morbid postpartum depression.

## TREATMENT

All antepartum and postpartum psychiatric disorders require a biopsychosocial treatment plan utilizing a multidisciplinary team approach. Initially, it is important to educate the patient about her illness, attempting to dispel women's fears of physical disease or inadequacy.

The clinician must be aware of the risks and benefits of various treatment modalities when choosing the appropriate psychiatric treatment for both antepartum and postpartum patients. Historic data confirm the adverse effects of maternal depression on infants and toddlers. Evidence shows that children of depressed mothers exhibit ineffective emotional regulation, greater anxiety, poor social interactions and delays in both cognitive and language development[34].

### Non-pharmacological treatment

Individual psychotherapy is an important component of treatment, and can be administered by psychiatrists, psychologists and social-workers. Four types of psychotherapy are effective. Interpersonal psychotherapy reduces depressive symptoms significantly and improves psychosocial functioning in antepartum depression. Cognitive or behavioral therapy or a combination of the two can be used for postpartum depression, panic symptoms and generalized anxiety aimed specifically at alleviating stress when caring for the baby. Cognitive behavior therapy is also effective in addressing obsessive compulsive symptoms. Psychodynamic therapy is effective in depression, attachment disorders, adjustment disorders and some anxiety disorders as it works towards resolving conflicts about the new maternal role, and understanding the relationship between this difficulty and past conflicts including the relationship with the patient's own mother. Finally, dynamic therapy can also address guilt over fertility treatment, inability to breast-feed, loss of a baby, feelings of alienation and identity shifts.

In addition, group psychotherapy, provided by postpartum support groups, can be helpful in the treatment of many postpartum disorders. Specifically, the benefits of multiples support groups are well known[35]. Numerous authors have recommended starting mothers of multiples prenatally in the support groups (see Chapters 85 and 106). Couples therapy may be useful if the predominant conflict involves a partner who is willing to undergo therapy. Couples therapy can also resolve conflicts, elicit support and ensure safety of the newborn if the mother has risk factors for harm to self or the infant.

Social intervention represents an essential element of the treatment plan. A skilled social-worker or mental-health counselor can provide practical advice and support regarding infant care and self-care. Such a person can facilitate environmental manipulation to obtain positive, gratifying child-care experience, available government resources including health insurance, shelter and food, a visiting psychiatric nurse and many more individualized interventions.

In-patient psychiatric hospitalization should be reserved for severe illness, specifically if there is a threat to the mother or the infant's safety. A mother–infant unit is ideal, and available in Europe, but few such units exist in the United States.

## PHARMACOLOGIC TREATMENT IN PREGNANCY AND LACTATION

The risk of postpartum mood disorders increases greatly if a mood disorder exists during the pregnancy. Thus, it is important to recognize and treat psychiatric disorders during the prenatal period. The best treatment is often a combination of medication and some form of psychotherapy. The use of psychiatric medication during pregnancy and

during lactation, however, is not without potential risks, including increased likelihood of spontaneous abortion, morphological teratogenicity, major or minor structural congenital abnormalities, fetal or neonatal side-effects, behavioral teratogenicity, fetal and neonatal withdrawal, premature labor and increased side-effects for the pregnant woman. The reproductive safety database regarding selective serotonin reuptake inhibitors (SSRIs) is among the most extensive studies of medications in pregnancy, and data continue to accumulate rapidly[36]. It remains, however, a methodologic challenge to determine whether any specific agent contributes to any of the above risk, as placebo-controlled trials are limited. As such, it is prudent to reserve pharmacologic treatment during pregnancy to symptoms that cannot be controlled with non-pharmacologic interventions.

Treatment of the postpartum woman often depends on her decision to breast-feed the infant. Postpartum patients ask their clinicians for advice regarding breast-feeding during psychiatric treatment. Once again, a careful look at the risks and benefits of breast-feeding versus the risks and benefits of psychotropic medication must take place with the patient and her family. Most antidepressant medications show equal efficacy in the treatment of postpartum psychiatric disorders. However, some agents have been studied more extensively than others in lactating women. Some psychotropics are excreted in breast-milk, although most antidepressants and their active metabolites are not detectable in nursing babies whose mothers are taking therapeutic doses of these medications. Concentration depends on drug solubility, protein binding, pH compared with plasma, neonatal absorption and neonatal metabolism[22,33]. Most evidence to date comes from case reports. However, collective findings indicate that infant SSRI exposure during lactation is considerably lower than transplacental exposure[36].

## Antidepressants

Antidepressants are used to treat major depression (with and without postpartum onset), panic disorder, OCD, dysthymic disorder, eating disorders, post-traumatic stress disorder and others.

The tricyclic antidepressants, although equally efficacious, are less specific and have more side-effects than newer antidepressants. These agents, including amitriptyline, nortriptyline, imipramine and doxepin, are still the most well-studied agents used in pregnancy. In the aggregate, none of the studies showed an increased likelihood of congenital anomalies after tricyclic exposure[33]. Furthermore, neurodevelopmental studies showed no difference up to age 7 years in exposed infants[37]. A few studies show anticholinergic side-effects in the newborn, but there are no reports to date of permanent damage or danger to the infant.

In lactation, there are no adverse effects noted other than one case of sedation with doxepin[38]. There are low/no detectable drugs or metabolites in breast-milk. Long-term effects are unknown.

In the non-lactating, non-pregnant patient, tricyclics would generally be considered only for treatment-refractory patients after the safer agents described below failed to provide an adequate response.

SSRIs remain the first line for treatment of anxiety and depression in the general population and in many pregnant and lactating women. These include fluoxetine, paroxetine, fluvoxamine, sertraline, citralopram and escitalopram, which have a relatively favorable safety profile in both pregnant and lactating women. Fluoxetine is the most studied SSRI in pregnancy. Studies show no increase in major congenital anomalies with SSRI exposure[33]. Children up to 7 years old show no increase in rate of neurodevelopmental difficulties with fluoxetine exposure[37]. However, several studies show 'neonatal toxicity' including restlessness, irritability, decreased birth weight and poor neonatal adaptation[36]. Some clinicians choose to taper the dose prior to delivery to decrease exposure and withdrawal in the infant.

The database of SSRIs represents the largest lactation database for any class of medications[36]. Overall, no significant adverse effects of SSRI or venlafaxine exposure during lactation have been reported. The SSRIs are detectable in the breast-fed infant at very low levels. No adverse outcomes have been reported with sertraline, paroxetine or fluvoxamine. There have been seven adverse events reported including colic, hyperactivity, diarrhea and emesis, and restlessness reported in infants exposed to fluoxetine during lactation[36,39,40]. A few case studies of buproprion show no metabolites found in breast-milk, but data are limited. Other common antidepressants, nefazodone and mirtazepine, have little or no lactation data, and generally should be avoided in pregnant and lactating women.

All antidepressants can take from 2 to 6 weeks to provide a clinical benefit. If after 6 weeks symptoms are not improved at a therapeutic dose, the clinician should consider changing agents. Clinically, when prescribing these agents it is important to monitor the patient's sleep, as SSRIs can cause further activation and insomnia initially. Also, the clinician should avoid agents that are too sedating, as mothers are often concerned that they will not be able to respond to their newborn.

### Anxiolytics

Benzodiazepines (clonazepam, lorazepam, alprazolam, diazepam, chlordiazepoxide) are effective in treating anxiety, including panic symptoms, generalized anxiety symptoms and insomnia. All agents are generally recommended for use on a short-term basis (several weeks to months) either as a scheduled agent or 'as needed' for acute symptoms. Caution should be used in the pregnant and lactating patient.

Benzodiazepines are considered weak teratogens in pregnancy, as they have been associated with oral cleft defects in the first trimester, and thus should be avoided if possible[33]. Neonatal toxicity has been documented, noted to be higher in women exposed to benzodiazepines in the late third trimester and during labor. Infants can develop 'floppy baby' syndrome consisting of lethargy, hypotonia, hyporeflexia, poor respiratory efforts and difficulty maintaining body temperature. If exposed to long-term use, withdrawal symptoms have been reported in the infant, including hypertonia, hyper-reflexia and tremor[33].

During lactation, these agents should be used with caution. Some benzodiazepines may accumulate in nursing infants, causing lethargy, jaundice and poor temperature regulation[41]. Long-term exposure can lead to withdrawal symptoms in infants upon weaning. Diazepam, owing to its long half-life, is not recommended. Lorazepam is preferred. When using these agents in pregnancy and during lactation, the clinician should prescribe the lowest possible doses for a limited time period. Such treatment may be beneficial for short-term relief of panic attacks or anxiety.

### Mood stabilizers

Mood stabilizers (lithium, valproic acid, carbemazepine, lamotrigine) are used primarily in the treatment of bipolar disorder, schizoaffective disorder and refractory depression. Caution must be taken in using these agents in pregnant or lactating women, however, as the use of antidepressants in women with symptoms of bipolar disorder can worsen the condition and induce mood cycling. All antidepressants should be discontinued if symptoms of mania are present in a postpartum patient.

Lithium carbonate is associated with Epstein's cardiac anomaly during first-trimester exposure. There is a four-fold increase in this anomaly, with a 0.05–0.1% incidence. No behavioral toxicity is noted in follow-up studies of *in utero* lithium exposure, but toxicity at birth has been reported, including poor suck, cyanosis, hypotonia and poor myocardial contractility[33]. Other potential complications include nephrogenic diabetes insipidus in the fetus, neonatal hypothyroidism and maternal toxicity. The American Academy of Pediatrics has recently changed lithium categorization from contraindicated in breast-feeding to 'should be given to nursing mothers with caution'[28].

Both valproic acid and carbemazepine are teratogenic, causing neural tube defects in 1–2% of exposed infants after first-trimester exposure. Both can deplete vitamin K-dependent clotting factors. Vitamin K should be administered to the neonate and the pregnant woman. Both are approved for breast-feeding by the Academy of Pediatrics, but cases of hepatic toxicity in the neonate have been reported[42].

### Antipsychotics

Antipsychotic agents are used to treat postpartum psychosis, chronic psychotic disorders and bipolar disorder. Typical antipsychotics have the greatest database for pregnancy and lactation, with high-potency agents showing relative safety in pregnancy. The drugs of choice are haloperidol and trifluoperazine. An increase in minor anomalies with chlorpromazine has also been shown[33]. Long-term behavioral teratogenicity studies show no effect on intelligence quotient. Withdrawal effects are rarely reported, including hypertonia, tremor and hyper-reflexia, all of which resolve without sequelae. Atypical antipsychotics (risperidone, olanzapine, quetiapine, clozapine, ziprasidone), which are preferred in the general population, have very limited data in pregnant and lactating women. Olanzapine has several reports in pregnant patients showing no adverse effects, with one study reporting gestational diabetes, excessive weight gain and toxemia[43].

Most data on high-potency, typical antipsychotic agents show relative safety in breast-feeding. Sedation was noted in one infant exposed to chlorpromazine. No reported lactation studies exist with the atypical agents.

## PREVENTION

The first step of prevention of psychological morbidity in multiple gestation pregnancies is to identify women at high risk. Risk factors for a postpartum psychiatric disorder besides multiple gestation include current mental illness, past history of psychosis or postpartum depression and bipolar illness (Table 89.2). Other risk factors include strong family history of affective illness and history of recurrent depression or anxiety disorders. Stressors associated with increased risk of depression include an unstable relationship with the father of baby, economic hardship and unplanned pregnancy. Marital status and level of available support correlate with poor maternal adjustment after birth[22].

**Table 89.2** Risk factors for postpartum depression

| |
|---|
| Mental illness during pregnancy |
| Past history of maternal depression or anxiety disorder |
| Past history of postpartum depression or anxiety disorder |
| Family history of mood disorders |
| Unstable relationship with father of baby |
| Unplanned pregnancy |
| Economic hardship |

It is important for clinicians working with mothers of multiples to consider prophylactic psychological, social and pharmacological intervention. The most vulnerable time for mothers of twins is the first 3 months after delivery. However, intervention should begin prenatally. Prenatal psychological screening of infertility candidates aids in identifying those at high risk and those currently suffering from mental illness, and can prevent further psychiatric sequelae of treatment (see Chapter 101). Counseling infertility patients on the risk factors associated with fertility treatments (multiple gestation, fetal reduction, increased perinatal morbidity and mortality) is an important factor in increasing awareness (see Chapter 102). Discussion of postpartum mood disorders during prenatal classes is likely to improve early detection and presentation for treatment. In a study of 15 women, Wisner and Wheeler[44] found that starting antidepressants in the first 24 h following birth can decrease the recurrence rate of postpartum depression. Postpartum prophylactic treatment of women with bipolar disorder maintained well-being longer than in those untreated[45].

## PROGNOSIS

Postpartum blues are benign and transitory, and resolve within 2 weeks without treatment. By contrast, postpartum depression usually lasts several months if not treated. Children of mothers with untreated postpartum depression may display behavioral, cognitive and social difficulties[46]. Women who suffer postpartum depression are more likely to experience future episodes of depression[47]. In postpartum psychosis, 95% of adequately treated women improve within 2–3 months.

New-onset anxiety disorders respond fairly quickly to treatment. Women with OCD or panic disorder in the presence of postpartum depression generally improve promptly with pharmacological intervention for depression. On the contrary, those with a chronic history of OCD with postpartum exacerbation are often treatment-resistant.

## CONCLUSIONS

Mothers of multiples have a higher incidence of psychiatric disorders, specifically in the postpartum period. A variety of biological, psychological and social factors specific to these women increase the psychological morbidity associated with the perinatal period. Untreated psychiatric illness in this population not only compromises the health of the mother, but can compromise the infant's physical, neurological and psychological development. A comprehensive approach that includes prevention, diagnosis and treatment should be in place for mothers of multiples. This treatment plan should involve a multidisciplinary team to provide a biopsychosocial model of intervention. This model includes an evidence-guided, individualized approach to prescribing psychiatric medication, psychotherapy and social intervention.

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# The Very- and Extremely-low-birth-weight Infant

*E. S. Shinwell and A. Nahum*

**90**



## PROLOGUE

A short one-act play

### Cast

Dr Senior (attending neonatologist)

Dr Worp (worn-out resident in pediatrics)

Mr and Mrs Potts (parents of twins or triplets)

### Scene 1 ('phone conversation)

Dr Worp: Hello, Dr Senior, I wonder if you could come to help here in the NICU?

Dr Senior: What's the problem?

Dr Worp [*with trepidation*]: The delivery room have just called to say that they have a 42-year-old woman after IVF with triplets in preterm labor at 28 weeks. They are planning a cesarean section within the hour.

Dr Senior: What!! Another one!! Oh, well, [*resignedly*] I'll be there soon. Meanwhile, start thinking about which babies can be moved out of intensive care to make space, and talk with the nurses about starting to get everything set up.

Dr Worp: Thanks ever so much. [*sarcastically, as a stage whisper*]

### Scene 2 (shortly thereafter, in the NICU)

Dr Senior: So, tell me, how are we going to make space for these triplets?

Dr Worp: Well, at the moment, we have 23 babies in 18 spaces. Of these, 12 are also multiples: two sets of triplets and three sets of twins, as usual. Also, there are a few nurses out on sick leave, so we are really stretched. And the most important news is that one of the obstetricians called to say that the mother of the triplets is having contractions and they want to start the cesarean section as soon as possible.

Dr Senior: OK, I'll deal with making the difficult decisions about moving out the least sick babies, while you can round up the troops. I want at least one physician and one nurse or midwife per triplet and at least one extra. Preferably there should be more than one neonatologist. Go to the operating room and start setting up all the equipment, and meanwhile, we'll get everything ready here. I just hope we'll be ready in time …

Dr Worp: Oh, I almost forgot. The obstetrician asked if you could talk with the parents before the delivery.

Dr Senior: Oh, thanks – I have nothing much better to do with my time at the moment.

**Scene 3 (in the delivery room)**

Dr Senior: Hello, I'm the neonatologist in charge this evening and I just wanted to let you know what is going to happen.

Mrs Potts: Thank you. Ouch! That one hurt!

Dr Senior: You are going to have three very small premature babies – probably each weighing around one kilo. We will have a lot of people at the birth so that each baby will get the best possible care. Afterwards, all being well, we'll take them to the NICU and then later we'll let you know how they are.

Mr Potts: Doctor, tell me the truth, what are their chances?

Dr Senior: They each have about a 90% chance of surviving. But, there are also complications of prematurity that can affect how healthy they will be in terms of their growth and their development.

Mrs Potts: Ouch! The contractions are getting closer!

[*At this point, the curtain falls, a cesarean section is performed and three new babies begin their long journey through the NICU*.]

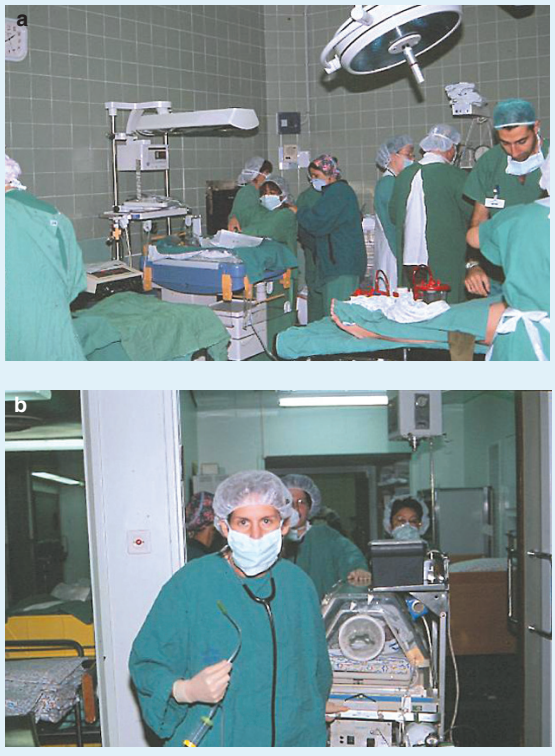


**Figure 1** (a) Crowd of nurses and physicians preparing for a cesarean birth of triplets; (b) the calm after the storm: a caravan of neonatal intensive-care unit (NICU) staff transferring the triplets from the operating theatre to the NICU

## INTRODUCTION

The ongoing epidemic of multiple pregnancies, resulting in a marked increase in the incidence of low- and very-low-birth-weight infants, serves as the basis for the current reality in neonatal intensive-care units (NICUs) around the world. Not only are many units overcrowded and understaffed, but up to half or more of the infants requiring intensive care are the products of multiple births. In the opinion of some, the resource expenditure for neonatal care represents a hidden cost of multiples and the iatrogenic epidemic, as it is borne by society as a whole[1].

This chapter provides information on the following issues: the extent of the epidemic of very-low-weight multiples, the demands of multiple births on NICUs, the major risks of extreme prematurity, the mean duration of singleton and multiple pregnancies and their attendant risks and, finally, carefully matched population-based studies of morbidity and/or mortality in multiples of similar birth weight and gestational age as compared with singletons.

## THE VERY-LOW-BIRTH-WEIGHT MULTIPLES EPIDEMIC

Several chapters in this book amply document the fact that the rate of twin and high multiple births in the USA rose consistently between 1980 and 1998, and that similar findings have been reported from Britain, Denmark, Canada and Israel[2–6] (see Chapters 1–7). In the USA, however, since 1998, despite the twin birth rate continuing to increase, the higher-order multiple birth rate has declined somewhat[2]. A somewhat parallel change is also reflected in the rate of births of very-low-birth-weight (VLBW) infants. Population-based data from the Israel National Very Low Birth Weight Infant Database documented a steady increase in the number of VLBW twins between 1995 and 2001 (up by 58%), accompanied by a parallel increase in the number of VLBW triplets until 2000 and followed by a decline commencing in 2001 (Figure 90.1)[6]. The emerging pattern from both the Israeli and US data suggests that either a tapering-off of the unbridled enthusiasm for assisted reproductive

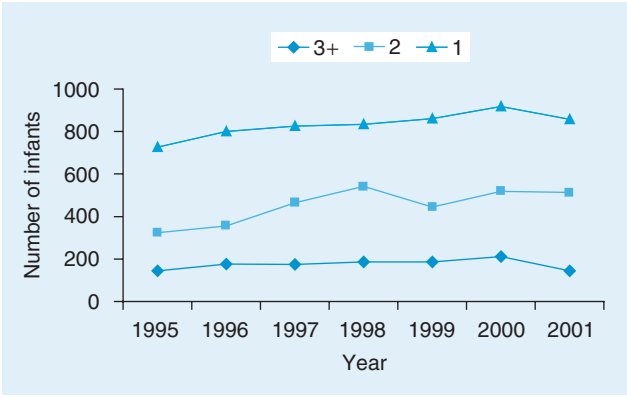


**Figure 90.1** Incidence of very-low-birth-weight (VLBW) singletons, twins and high multiples, 1995–2001, from the Israel National VLBW Infant Database. 1, singletons; 2, twins; 3+, high-order multiples

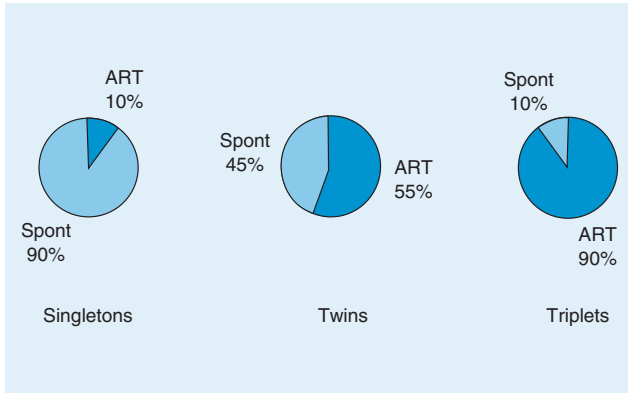


**Figure 90.2** Proportion of very-low-birth-weight (VLBW) infants conceived by assisted reproductive technologies (ART) among singletons, twins and triplets. Data from the Israel National VLBW Infant Database; Spont, spontaneous

technologies (ART) and/or an increased use of multifetal pregnancy reduction (MFPR) may be a cause for these changes (Figure 90.2).

Despite the general recognition that multiple pregnancies have higher rates of VLBW, it now appears that ART itself is an independent risk factor for having a VLBW infant[7]. Schieve and co-workers studied a large sample of more than 42 000 infants from the spontaneous and ART (SART) data in the USA. The relative risk for low birth weight in singletons conceived with the use of ART, compared with those conceived spontaneously, was 2.6 (95% confidence interval (CI) 2.4–2.7), and the risk for VLBW was 1.8 (95% CI 1.7–2.0), compared with spontaneously conceived infants. When the same analysis was applied for twins in this study, there was no increase in the risk for VLBW in twins conceived with the use of ART, compared with those conceived spontaneously. This may be related to the already higher risk in this population, and, thus, the added risk from ART is negligible.

## THE DEMANDS OF MULTIPLE BIRTHS ON NEONATAL INTENSIVE-CARE UNITS

The 'prologue' that begins this chapter provides a view of the day-to-day demands faced by NICU staff dealing with multiple births, particularly triplets and above. Table 90.1 offers a list of the most important requirements for receiving multiple births. This long list presents a unique organizational and managerial challenge in order to maintain calm efficiency in the middle of all the excitement that is often part of high-order multiple births.

## THE OUTLOOK FOR VERY-LOW-BIRTH-WEIGHT INFANTS (SINGLETONS AND MULTIPLES ALIKE)

VLBW infants are at high risk for mortality as well as short- and long-term morbidity in all body systems[8,9]. Breathing is the most common initial problem, and approximately 60% of VLBW infants suffer from respiratory distress syndrome in the first few days. Moreover, up to a quarter of these infants survive with chronic lung disease associated with prolonged oxygen dependency, recurrent respiratory infections, frequent hospitalizations and poor growth and development. Neurological morbidity includes severe intraventricular hemorrhage and periventricular leukomalacia, seen in about 10–15%, which are associated with risk for cerebral palsy and mental retardation. Other major morbidity includes nosocomial infection (25%), patent ductus arteriosus (30%), retinopathy of prematurity (20%) and necrotizing enterocolitis (5–10%). In the long term, adults who were born VLBW have more neurosensory impairments, lower intelligence quotient and lower academic achievement, invoking a huge financial and psychological burden on both families and care-providers[10].

## DURATION OF MULTIPLE PREGNANCIES AND THEIR ATTENDANT RISKS

Alexander and co-workers analyzed population-based data of US births and showed a clear inverse correlation between plurality and gestational age at birth[11]. Mean gestational age for singletons, twins and triplets was found to be 39, 35.8 and 32.5 weeks, respectively (see also Alexander and Salihu's Chapter 1 in this

**Table 90.1** Requirements in preparation for a high-order multiple birth

| | |
|---|---|
| *Delivery/operating room* | |
| Pediatricians | one per infant (preferably more), all trained in neonatal resuscitation |
| Supervising/back-up physician | at least one qualified neonatologist |
| Obstetricians | must be alert to importance of the pediatric team being fully prepared before beginning delivery/operation |
| Nurses/midwives | one per infant, all trained in neonatal resuscitation |
| Radiant warmer | one per infant, preferably with servo temperature control |
| Resuscitation equipment per infant | oxygen, ventilation bag, suction, laryngoscope, endotracheal tubes (various sizes), medications and other equipment; adequate space (often limited in operating rooms) |
| Temperature control | keep temperature at 24–26°C, to minimize ambient heat loss: this may be a little uncomfortable for the staff |
| Transport incubators | one per infant |
| *Neonatal intensive-care unit* | |
| Staff | as above, plus back-up for procedures, etc. |
| Radiant warmer/incubators | one per infant (not those from the delivery room) |
| Equipment | prepared in advance of delivery, for each infant: ventilators, monitors, sterile equipment for procedures (umbilical lines, etc.), intravenous fluids, etc. |

book). In addition, the relationship between preterm delivery and birth weight in multiples is complex, in that intrauterine growth in multiple pregnancies is similar to that seen in singletons up to the second trimester, when it begins to change. The divergence in fetal growth curves begins as early as 22 weeks and becomes much more marked at 28 weeks. Thus, infants from multiple pregnancies are more often both premature and smaller for gestational age than singletons.

Large population-based studies report the increased mortality risk for multiple pregnancies[12,13]. For example, national US data from 1999 showed the neonatal mortality rate per 1000 live births to be 6.6 for singletons, 32 for twins and as high as 71.8 for triplets. Although absolute numbers vary between reports, the relative risks are mostly consistent. Luke and Keith found the relative risk for VLBW to be 9.6 and 32.7 and for infant mortality to be 6.6 and 19.4, respectively, when comparing twins and triplets with singletons over a decade ago[13]. A more recent study of the Japanese vital statistics database showed the relative risk for perinatal mortality to be five-fold and 12-fold higher for twins and triplets, respectively, compared with singletons[14].

Evidence supports the impression that the gap in perinatal mortality rates between singletons, twins and high multiples is narrowing. In Japan, for example, the perinatal mortality rate for triplets was 11.1-fold higher in 1980 and 6.9-fold higher in 1998 than in singletons. This finding is probably related to general improvements in the care of low-birth-weight infants.

Although the relationship between plurality and mortality is primarily related to the incidence of premature birth, certain studies, such as that of Botting and colleagues suggest that the variation in mortality is not completely accounted for by shorter gestation but may be partly explained by the twinning process itself[15].

## EFFECTS OF PLURALITY IN VERY-LOW-BIRTH-WEIGHT INFANTS, WITH ADJUSTMENT FOR CASE MIX

Few studies have focused on the effect of plurality on morbidity and mortality in large, population-based samples with appropriate statistical methods to account for the marked differences in case mix between groups. One unique and ongoing study that does this is the Israeli very-low-birth-weight neonatal database that collects extensive perinatal and neonatal information on VLBW infants born in all of the country's 28 NICUs[16]. In this database, major adverse outcomes were compared between singletons, twins and triplets (the small numbers of quadruplets and quintuplets were excluded). In addition, marked differences were present between the groups in the incidence of important confounding perinatal variables. Multiple logistic regression analyses were performed to assess the independent contribution of plurality. The sample included 3717 singletons (66%), 1394 twins (25%) and 483 triplets (9%) born between 1995 and 1999, all of whom had a birth weight of less than 1500 g. ART use was found in 10% of singletons, 55% of twins and 90% of triplets (Figure 90.2). Mothers of twins and triplets were significantly more likely to begin antenatal care in the first trimester and to receive antenatal steroids. Delivery by cesarean section was more common in triplets (89%) than in twins (65%) or singletons (62%). A small inverse correlation was found between

gestational age (GA) and birth weight (BW; Table 90.2). Another important difference between the study groups was in the incidence of small-for-gestational-age (SGA) infants. Among singletons, 28.8% were SGA, compared with 15.5% and 16.4% of twins and triplets, respectively. This finding probably reflects the different etiologies for preterm labor in these groups: twins and triplets are born early primarily due to lack of space, whereas in singletons premature labor often reflects growth and development problems *in utero*.

Respiratory distress syndrome was significantly more common in twins (70%; odds ratio (OR) 1.58, 95% CI 1.32–1.89) and triplets (75%; OR 2.51, 95% CI 1.87–3.37), compared with singletons (60%), and this was in spite of higher exposure to antenatal steroids in these two groups (Table 90.3). It was previously suggested that there may be little beneficial effect of antenatal steroids in multiples, and that the effect is also influenced by race with the maximal effect seen in singleton, black infants[17]. These findings are as yet uncorroborated, and are the focus of further study of this database. The fact that the sample in the Israel Neonatal Network is primarily of Caucasian origin may partly explain this finding.

On univariate analysis, no significant differences were found between groups in incidence of the major adverse outcomes: chronic lung disease, adverse neurological findings (severe intraventricular hemorrhage, periventricular leukomalacia or ventricular dilatation) or death. However, multivariate logistic regression analysis, accounting for the relevant confounding variables, found triplets to be at significantly increased risk for mortality compared with twins and singletons (OR 1.54, 95% CI 1.13–2.11 (Table 90.3)). The risk for chronic lung disease and adverse neurological findings was similar in all groups.

In another large study, Donovan and co-workers compared the neonatal outcomes of singletons and twins from the Neonatal Research Network of the National Institute of Child Health and Development[18]. This network includes 12 prominent regional neonatal centers in the USA. In their study, twins constituted 19% of all VLBW infants admitted to these departments. As was the case in the Israeli study, marked differences were present between groups in the characteristics of both mothers and infants. Mothers of twins received more prenatal care and more antenatal steroids (29% in twins, 24% in singletons), and delivered more often by cesarean section (52% in twins and 46% in singletons). Although twins suffered from respiratory distress syndrome more often than their matched singletons (84% vs. 78%), no significant differences were found between groups in the incidence of mortality, chronic lung disease or intraventricular hemorrhage.

Studies that employed lesser degrees of matching of groups showed mixed results. For example, Buekens and Wilcox reported a very large population-based study of singletons and twins in Belgium from 1983 to 1984[19]. Birth weight-corrected mortality rates were higher for twins in each birth-weight category. Ericson and colleagues found similar results in Swedish infants from 1973 to 1988[20]. More recently, Jacquemyn and associates compared morbidity and mortality in singletons and twins from Flanders from 1998 to 1999[21]. Twins of 24–27 weeks had higher neonatal mortality rates than singletons. However, in other gestational age groups, no differences were found in morbidity or mortality. Indirect support for this last finding comes from the seminal study by Keily of perinatal mortality rates in New York in 1968–1986[22]. The perinatal mortality rate fell over this time period for both groups, but significantly more so for singletons.

Single-center studies such as those of Kaufman and colleagues[23], Ballabh and co-workers[24] and Maayan-Metzger and associates[25] report relatively small sample numbers. After correction for confounders,

**Table 90.2** Correlation between gestational age and birth weight in singletons, twins and triplets

| | *Gestational age* (weeks) | *Birth weight* (g) |
|---|---|---|
| Singletons | 28.9±2.6 | 1096±269 |
| Twins | 28.4±2.3 | 1062±271 |
| Triplets | 28.5±2.4 | 1049±259 |

**Table 90.3** Generalized logistic regression analyses for respiratory distress syndrome (RDS) and poor outcomes (chronic lung disease (CLD), adverse neurological findings (neuro) and death). Values are expressed as odds ratio (95% confidence interval)

| *Multiplicity* | *RDS* | *CLD* | *Adverse neuro* | *Death* |
|---|---|---|---|---|
| Singletons | 1.0 | 1.0 | 1.0 | 1.0 |
| Twins | 1.58 (1.32–1.89) | 0.96 (0.76–1.22) | 1.09 (0.88–1.33) | 1.12 (0.93–1.37) |
| Triplets | 2.51 (1.87–3.37) | 0.69 (0.46–1.02) | 1.29 (0.91–1.85) | 1.54 (1.13–2.11) |

however, no significant differences were found between singletons, twins and triplets in mortality and major morbidity. The comparative usefulness of these latter studies is compromised by their small size.

Finally, a recent study by Stewart and co-workers focused on abnormalities found on cranial ultrasound scan in VLBW singletons, twins and triplets[26]. After correction for relevant confounders, no significant differences were present between the groups, but a slightly lower incidence of intraventricular hemorrhage was noted in infants conceived by ART, compared with those conceived spontaneously.

## SUMMARY

The ART-associated epidemic of multiple pregnancies has produced a marked increase in VLBW infants who suffer a wide range of short-term morbidities in all body systems and, in a certain proportion, long-term neurological, developmental and other sequelae. Comparisons of outcome between singletons, twins and triplets are hampered by difficulties in collecting appropriately large samples and by marked differences in confounding variables between groups. A systematic review of the available data suggests that there are no differences in morbidity and mortality between VLBW singletons and twins in the same gestational-age group. In contrast, VLBW triplets appear to be at excess risk for neonatal mortality. It is important to remember, however, that infants from multiple pregnancies are significantly over-represented in the low- and very-low-birthweight groups, compared with their incidence in the general population.

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# Alternative Approaches to the Infant in the Neonatal Intensive-care Unit

*J. Gadzinowski and E. Gulczynska*

91



*Families expecting and rearing multiples need: access to information and guidance in optimal parenting practices regarding the unique developmental aspects of multiple birth children, including the processes of socialization, individualization and language acquisition.*

*Declaration of Rights and Statement of Needs of Twins and Higher Order Multiples* adopted by the Council of Multiple Birth Organizations of the International Society for Twins Studies, May 1995

## INTRODUCTION

The morbidity and mortality of newborns from multiple pregnancies are significantly higher than those of singletons. Major complications include: low birth weight, prematurity, and early and late sequelae of prematurity[1]. The incidence of these complications increases with plurality[2]. Approximately 60% of multiples deliver prior to 37 weeks of gestation, and numerous data indicate that almost 50% of twins and over 90% of higher-order multiples (≥ 3) have a low birth weight (< 2500 g)[1]. As a result of these circumstances, multiples more frequently require prolonged care in the neonatal intensive-care unit (NICU) compared with singletons. Some perinatal centers report the rate of admissions to the special-care baby unit as 30.5% for twins and 32.5% for triplets[3]. These infants also require prolonged hospitalization (9.8 vs. 25 days for singletons and multiples, respectively)[3].

Among multiples treated at the Research Institute of the Polish Mothers' Memorial Hospital in Lodz, the mean birth weight of triplets, quadruplets and quintuplets was 1656 g, 1166 g and 725 g, respectively. A decrease in the gestational age was also observed (32.4, 30 and 26.5 weeks, respectively). Ventilation support as well as hospitalization times were gradually extended (9.5, 22.2 and 57.5 days and 29.1, 64.1 and 79.6 days, respectively). One out of three triplet neonates required respiratory support (36.6%), whereas this figure reached 100% in quadruplets and quintuplets[4]. With rare exceptions, premature neonates demonstrate numerous medical problems arising from their immaturity. These difficulties are potentially aggravated by the intensive-care environment, which has a disadvantageous influence on neonatal development especially in terms of the brain, which is very susceptible to negative factors. Recently, the continual increase in the rate of survival of low-birth-weight neonates, as well as those born at the borderline of viability, has been balanced by the significant risk of cognitive and behavioral deficiency observed in follow-up care. These difficultiesn often remain beyond childhood. Among the most important negative factors are: prematurity and its complications (e.g. recurrent episodes of apnea and bradycardia, hypoglycemia, septicemia, intraventricular hemorrhage, periventricular leukomalacia, hyperbilirubinemia, neonatal hypothyroxinemia, nutritional deficiency and chronic lung disease), medications administered in neonatal intensive therapy such as glycocorticoids or methylxanthines and stress factors connected with prolonged hospitalization. With regard to stress, the high noise level, day and

night conditions of light and continual connection to monitoring devices and intravenous lines, which limit parent–child relations, all serve to play a major role in causing later problems[5].

Very-low-birth-weight (VLBW) neonates delivered prematurely belong to a high-risk population with negative developmental stimulation, in part due to the prolonged NICU stay and in part due to exposure to negative stimuli and improper newborn care, both of which could be harmful in this critical period of brain development. Lately, a tendency has emerged towards humanization of procedures in intensive-care units, encouraging parents to become involved in VLBW infant care, thereby supporting neonatal development and optimizing the preterm neurodevelopment outcome. Modification of the intensive-care unit environment includes reduction of noise intensity and the introduction of soft music, modulation of light exposure and intensification of infant–parent relations by implementation of the Newborn Individualized Developmental Care and Assessment Program (NIDCAP), 'kangaroo' care and co-bedding[5]. In many intensive-care units, one of the principal aims is to pay attention to individualizing premature care and mutual family relations. This also allows the development of parental trust of caregivers and modification of the initially traumatic experience of the NICU in the interest of the baby's developmental progress[6]. The increasing incidence of multiple births creates new problems, and also raises many questions concerning differences in the care of multiples versus singletons. Apart from difficulties resulting from complications of prematurity, the mutual relations initially formed in intrauterine life must also be taken into consideration.

## CO-BEDDING OF MULTIPLES

During intrauterine development, multiples share a small, dark and enclosed space in which their bodies touch and are jostled by each other. Each fetus is constantly interacting with its brother(s) or sister(s). During ultrasound examinations (between 14 and 36 weeks of gestational age), Piontelli and colleagues observed mutual interactions of fetuses, including facial and body explorations[7]. As a result of *in utero* tactile communication and the necessity of sharing the same environment, multiples often exhibit a synchrony in sleep and waking hours as well as a significant incidence of coincidental movements and heart rate accelerations. Because of physical separation at birth, neonates experience stress related not only to a change of environment but also to a breaking off of the mutual reactions previously created *in utero*[8]. Postnatal care differs in various parts of the world, and is often based on clinical and economic status as well as local tradition and culture. In developed countries, the presence of 'high-tech' medical equipment and standards of infection control usually lead to separation of multiples. In some low-resource countries, co-bedding is used partly due to equipment shortage and partly as a method of mutual thermoregulation. The medical staff providing care to neonates from multiple pregnancies have had an opportunity to confirm the beneficial influence of co-bedding on the behavior of multiples, their mutual snuggling and sleep synchronization[9]. As a result of these early observations, the idea of continuation of intrauterine experiences through multiple co-bedding was initiated. Continuous development of the co-bedding practice focuses on reconstruction of the unique prenatal environment and its ability to foster mutual interactions.

The neonatal-ward co-bedding tradition has a longer history in Europe, where this technique has been applied for over 10 years, than in North America. However, some hospitals in the USA have also begun to explore co-bedding. This method of care is usually offered to parents of twins born prior to 37 weeks of gestation and who do not require arterial lines and respiratory support[10]. In the mid-1990s, the first report regarding co-bedding was published describing the history of a set of twins (with birth weights 2 lb 3 oz and 2 lb, respectively) born at 28 weeks of gestation. Co-bedding led to better temperature regulation as well as respiratory and heart rate stabilization, and to a decrease in the supplemental oxygen requirement in the weaker sibling[11].

Table 91.1 lists inclusion and exclusion criteria for co-bedding. To date, few papers concerning this matter been published. In a small number of case reports, authors reported that co-bedded neonates displayed sleep–wake synchronicity and were less restless and irritable compared with twins who were single-bedded. In the study by Touch and colleagues, the number of central apnea episodes was higher in children receiving standard care than in co-bedded infants[12]. There were no statistically significant differences among other physiological parameters (bradycardia, periodic breathing) and the rate of adverse effects such as an increase in the supplemental oxygen requirement, temperature instability, pharmacotherapy changes and need for infection screening[12]. It is possible that diminution of the incidence of central apnea episodes was a result of changes in the sleep pattern caused by more frequent tactile stimulation between siblings. The same may be postulated regarding the regulation of breathing rhythm.

More recently, Byers and colleagues conducted a comparative study regarding the physiological stabilization and behavior of infants as well as their parents[13]. The sample population (37 infants and

**Table 91.1** Inclusion and exclusion criteria for co-bedding

| *Inclusion criteria for co-bedding* | *Reasons for multiples' separation* |
|---|---|
| Stable clinical state of neonates | necessity for respiratory support: NCPAP, mechanical ventilation |
| Lack of infection symptoms | infections |
| Comparable birth weights of infants | temperature instability |
| Absence of respiratory support (excluding oxygen cannula) | earlier weaning of one of the infants to the crib |
| Parents' agreement | combined body weight of infants too high for harmless co-bedding in one incubator |
| | multiples' incompatibility |

NCPAP, nasal continuous positive airway pressure

**Table 91.2** Advantages and disadvantages of co-bedding

| *Benefits* | *Risk factors* |
|---|---|
| *Physiological* | |
| Breathing rate normalization (highest-activity respiratory rates) | increased risk of SIDS (giving up the 'back to sleep' position recommended by AAP) |
| Stabilization of cardiac rhythm | increased risk of infection |
| Mutual tactile stimulation | |
| Thermal stabilization (lowered incubator temperature to maintain normal body temperature) | |
| Decrease in oxygen requirement of weaker siblings | |
| Rare stress reaction (behaviour), diminished anxiety | |
| Increase in ingestion | |
| Growth improvement | |
| Development improvement | |
| *Economic* | |
| Hospitalization time reduction | necessity of booking additional incubator in case of one child's clinical status deterioration |
| Lower hospitalization costs | |
| Decreased readmission rate | |
| Economy in medical devices (equipment) | |
| *Psychological* | *Medical errors* |
| Enhanced parent–children bonding | Unnecessary exposure to higher concentration of oxygen or phototherapy |
| Alleviation of parental suffering connected with their infants' NICU stay (parental satisfaction with NICU experiences, maternal attachment, decreased parental anxiety) | Medicine mistakenly administered to a wrong sibling |
| | Mistakes in other medical procedures (e.g. phototherapy, kinesiotherapy) |
| Improved communication between parents and medical staff (one nurse as a care-giver of multiples) | |
| Enhanced preparation for discharge and smoother transition home | |

SIDS, sudden infant death syndrome; AAP, American Academy of Pediatrics; NICU, neonatal intensive-care unit

their 19 parents) was divided into two groups: a co-bedded group and a single-bedded group (the control group). The authors found statistical differences concerning daily weight, feeding amount and highest-activity heart rate between co-bedders and controls. Sleep–wake synchronicity was higher in the co-bedded group (statistically significant only on day 1). Despite these differences, the study did not confirm a significant improvement in the clinical state of the co-bedded multiples or parental outcomes (parental state of anxiety, maternal attachment, parental satisfaction scores)[13].

Although the favorable effects are numerous, potential dangers also exist (Table 91.2). Among the

**Figure 91.1** Twins (Patricia 870 g and Olive 1170 g) delivered by cesarean section at 30 weeks of gestation. They started co-bedding in the third week of life

potential risks, there is a possibility of errors (infants mistaken or wrong drug administration). In such cases, the care-givers' intervention must differentiate children, equipment, connectors and lines easily. This could take the form of, for instance, different colored clothes, diapers, clipboards and name tags. Each multiple must have its own identity label, which could easily be switched to another location or another extremity during necessary procedures (e.g. when applying intravenous contacts). Differentiation of alarm sounds could also be very useful. Permanent assignment to one side of the incubator (twin A to the front, twin B to the back) or crib (left or right) may be another helpful solution[14].

Other potential problems could be cross-infections resulting from close contact. Infection control principles should be respected, and hand-washing before and after interventions for each infant is extremely important. In one prospective, comparative study of 16 co-bedded neonates, no adverse effects, medical errors or cross-infections were observed[13]. However, in a group of 25 sets of co-bedded twins, DellaPorta and colleagues described one case of smaller-infant hypothermia due to a wrong temperature in the

**Figure 91.2** Triplet girls (Agnes (T1) 2250 g, Dominige (T2) 1950 g, Ursula (T3) 2250 g) delivered by cesarean section at 35 weeks of gestational age. They started co-bedding on the fourth day of life

incubator, and one case of prolonged hospitalization caused by a mother's refusal to separate twins by taking one home[14]. One of the most serious of the potential dangers is sudden infant death syndrome (SIDS). The mutual encircling position of neonates used in co-bedding remains in opposition with the 'back to sleep' position, which is recommended for prevention of SIDS. The question of whether the 'face to face' or 'front to back' position, with simultaneous sibling tactile stimulation, is as safe still remains unanswered (Figures 91.1 and 91.2).

Regardless of a lack of scientific evidence concerning the benefits of co-bedding, this method is gaining more and more interest, and is widely applied in neonatal wards. Currently, special incubators adjusted for multiples' care are available (Isolette® Infant, Dräger Medical AG & Co., Lübeck, Germany). This equipment provides more space for the neonates, thus enabling nursing and simultaneous infant monitoring.

## NEWBORN INDIVIDUALIZED DEVELOPMENTAL CARE AND ASSESSMENT PROGRAM

Because neonates from multiple gestations usually require prolonged hospitalization in the NICU, more and more neonatal units are implementing new strategies of care, one of them being the NIDCAP. First described by Als and Lawhon and co-workers in 1986, this alternative therapeutic method aims to modify the neonatal environment in order to imitate the mother and provide adequate and positive infant stimulation[15]. In this sense, NIDCAP facilitates and promotes development of the immature neonatal brain by using a wide range of strategies that lead to minimization of negative

**Table 91.3** Beneficial outcomes of very-low-birth-weight infants' developmental care

| *Authors* | *Benefits* | *Statistical analysis* |
|---|---|---|
| Short *et al*., 1996[17] | higher score on the Morgan Neonatal Neurobehavioral Exam in the swaddled group (positioning with swaddling and hip roll) | mean difference 6.2, 95% CI 2.6–9.8 |
| Gaebler and Hanzlik, 1996[18] | shorter length of hospital stay in infants receiving tactile stimulation (stroking and perioral/intraoral stimulation protocol before feeding) | mean difference –3.9 days, 95% CI –7.1 to –0.7 |
| Gatts *et al*., 1994[19] | shorter hospitalization time in neonates receiving vestibular and auditory stimulation | not done |
| Kramer and Pierpont, 1976[20] | improvement of short-term growth outcome including weight gain and head circumference increment | mean difference 46.0 g, 95% CI 17.1–74.9 |
| Mann *et al*., 1986[21] | shorter feeding time, better weight gain and longer sleeping time in infants receiving auditory and visual stimulation | not done |
| Beckman, 1997[22] | shorter length of hospital stay in a group of nested infants | mean difference 8.1 days |
| White-Traut *et al*., 1993, 1997[23,24] | significant improvement in behavioral states of infant receiving vestibular, auditory, visual and tactile stimulation | not done |
| Fleisher *et al*.,1995[25] | effect in reducing ventilation days | mean difference –22.1 days, 95% CI –43.4 to –0.8 |

CI, confidence interval

NICU effects. These interventions include four groups of methods: positioning, clustering of nursery-care activities, modification of external stimuli (vestibular, auditory, visual, tactile) and individualized developmental care intervention.

In neonatal units where care is applied according to NIDCAP, special attention is paid to noise and light reduction, minimal handling and provision of longer rest periods. At the same time, behavioral observations and evaluation of physiologic, motoric and autonomic parameters as well as facial expressions are made[15,16]. Many authors report a beneficial outcome of VLBW infants' development after NIDCAP implementation (Table 91.3).

In 2002, Westrup and colleagues summarized the results of randomized control studies concerning NIDCAP effects conducted at the Karolinska Institute[26]. Among the newborns receiving care according to NIDCAP, a shorter ventilation time (2.8 vs. 4.8 days, $p$ not significant), shorter time of nasal continuous positive airway pressure support (26.1 vs. 43.9 days, $p = 0.45$) and earlier weaning from oxygen supplementation (33.0 vs. 38.1 weeks of post-conceptional age, $p = 0.007$), as well as decreased incidence of bronchopulmonary dysplasia symptoms, were noticed. In this group (NIDCAP care), better results of the Mental Development Index as well as the Psychomotor Developmental Index were observed in comparison with the control group; however, there were no statistically significant differences. The authors suggest several mechanisms which could explain the beneficial effect of NIDCAP: first, enhanced autonomic stability during the early neonatal period might reduce the incidence of severe brain lesions; second, NIDCAP provides the optimal environment for physiological development of the brain. Continual assessment of external stimuli, 'neither too much nor too little', by the medical staff has an advantageous effect on the processes of neuron multiplication and migration, and astrocyte and glial cell as well as normal cell differentiation by synaptogenesis and apoptosis[26,27].

NIDCAP leads to an increase in the sensibility of VLBW care-givers (parents, nurses, doctors) and their sensitivity to a child's needs. Mother–child interactions assessed according to the parent–child Early Relational Assessement Scale revealed three statistically significant differences: in child motor competence and quality, and parental physical and visual contact with the child[27,28]. To date, 31 randomized studies with a total of 2009 participants regarding the effects of NIDCAP have been carried out. A meta-analysis of these results was published in *The Cochrane Library*[16]. Although it was limited owing to a large variation of outcomes and a small number of randomized trials that included the same strategies, its results suggest the presence of some beneficial effects[25] (Table 91.4).

The economic aspects of this method should also be considered. Admittedly, both personnel training and time intended for NIDCAP care consume additional

**Table 91.4** Benefits of developmental care intervention (Newborn Individualized Developmental Care and Assessment Program, NIDCAP) in preterm infants[16]

There is evidence of some benefits of developmental care intervention overall (NIDCAP) in preterm infants:

improved short-term growth outcome
decreased respiratory support
decreased length and cost of hospital stay
improved outcomes to 24 months corrected age

and no major harmful effects

financial costs (according to Jacobs and colleagues, $2500–6000 per nurse[29]); an economic analysis carried out at the Karolinska Institute showed a reduction of hospitalization costs almost by $US10 000 per infant, primarily by diminution of ventilation time[29]. The meta-analysis of two randomized studies done in the USA[15,25] revealed reductions of total costs by $10 000 per infant, whereas the financial expenses of NIDCAP care amounted to $700 per infant plus $4000 per person for nurses' training[29].

## KANGAROO MOTHER-CARE

The kangaroo mother-care (KMC) method is defined as an early, prolonged and continual skin-to-skin contact between the mother and her VLBW child. This method of care is applied within the hospitalization period as well as after discharge to home, and it is usually continued until the 40th week of post-conceptional age. The KMC method was introduced in 1978 by Edgar Rey in Colombia at the Instituto Materno Infantile (Bogota) as an alternative method of VLBW neonatal care[30]. In some parts of the world it is a traditional method of care, but it is seldom used in developed countries, where newborn care (especially VLBW) is performed in a conventional manner. In the beginning, 'kangarooing' attracted attention in developing countries where resources to guarantee adequate VLBW infant care were lacking. Gradually, interest in this kind of care increased in countries with better resources.

The kangarooing program was initially based on the following principles:

(1) Warming the newborn through its placement under the mother's clothes and contact with the mother's skin;

(2) Exclusive breast-feeding;

(3) Prophylaxis of reflux and food aspiration by maintenance of the child's vertical position between the mother's breasts;

(4) Early discharge home to decrease risk of secondary infection.

Soon, however, the KMC program was supplemented by additional elements, including the mother's education and motivation to serve as a source of satisfaction of the child's needs and to increase the mother's competence to care for her premature child. Thus far, research, although usually not randomized, has focused on the following positive elements regarding the influence of skin-to-skin contact between mother and child:

(1) 'Return to the womb';

(2) Baby hears mother's heartbeat;

(3) Baby hears mother's voice;

(4) Baby feels swinging motion;

(5) Baby has good opportunity for suckling;

(6) Vertical position prevents regurgitation;

(7) Decreased risk of cross-infections;

(8) Possible synchronization of mother and child temperature.

Results of studies of KMC find it a very useful care strategy, enabling not only an increase in the early and late survival rate but also an improvement in VLBW neonates' well-being, especially those weighing 1200–2000 g[31]. Studies concerning skin-to-skin contact reveal a decrease in stressful behavior, an increased mutual regulation of respiration as well as heart rate and better thermal control, as well as an improvement of medical and developmental care outcome. Cattaneo and co-workers reported more frequent episodes of hypothermia and hyperthermia in a control group than in KMC infants. The same authors also showed a reduction of total costs by 50% for the KMC group[32]. Among kangarooing infants, Föhe and associates observed not only clinical and thermal stabilization but also a marked improvement of gas exchange parameters, which reached statistical significance[33]. The outcome of a meta-analysis published in *The Cochrane Library* revealed that KMC was associated with a reduced risk of: nosocomial infections at 41 weeks of post-conceptional age (relative risk (RR) 0.49, 95% confidence interval (CI) 0.25–0.93), severe illness (RR 0.3, 95% CI 0.14–0.67) and lower-respiratory tract disease at the 6-month follow-up[33]. KMC infants gained more weight per day prior to discharge than controls, and had a larger head circumference at 6 months corrected age. Although results of this meta-analysis suggest that KMC may be associated with a reduction in clinically important

adverse outcomes[34], there is currently no evidence to support the use of KMC in low-birth-weight infants as an alternative to standard care after the initial period of stabilization after conventional care.

Subsequent international randomized trials found that KMC was better accepted not only by mothers but also by medical staff[35]. Moreover, a considerably higher percentage of medical care-givers preferred KMC as a method of VLBW neonatal care, and more mothers desired to switch from the conventional study group to the kangarooing group.

In 1997 a questionnaire concerning KMC propagation was conducted among all neonatal departments in Germany[36]. KMC was used in 91% of neonatal units. All hospitals practicing KMC began to apply this mode of care between 1982 and 1996. According to the study, almost 43% of wards limited the time of KMC usage to 30–60 min, and a further 20% employed the method for over 60 min. The remaining wards did not limit the time of KMC usage, which was dependent only on the baby's physiologic condition. Approximately 49% of hospitals accepted the involvement of fathers in kangaroo care. The necessity for respiratory support did not contraindicate KMC in 76% of departments. In the same study, most respondents evaluated their experiences positively with ventilated children receiving KMC. During kangaroo care the possibility of the reduction of ventilation parameters as well as oxygen concentration in respiratory gases was often noticed. Some 63% of all neonatal departments described problems with a child's connection to a ventilator as rare (< 1%), whereas 29% of units did not notice any complications. However, 4% of the departments signaled frequent complications (> 10%); among these the most common were: desaturation (27%), bradycardia (17%), spontaneous extubation (11.3%), hypothermia (10.3%) and apnea episodes (9.3%)[36].

The majority of papers regarding KMC published so far refer to the care of singleton babies. In 2000, Dombrowski and colleagues described the usage of KMC in twins[37]. The authors introduced a new nomenclature related to different modes of kangarooing:

(1) Shared: one person holds both twins at the same time;

(2) Sequential: one person holds only one twin at a time;

(3) Separate: two people, each holds one twin at the same time.

A similar nomenclature is applied in higher-order multiples' care. In such cases, maternal and paternal versions of kangaroo care seem to be very useful. In 2000, Swinth and colleagues described a mother of four who delivered triplets at 35 weeks of gestation. Apart from typical anxiety related to a premature birth, the woman expressed fears associated with triplet care. These doubts quickly disappeared when she started KMC and held all three babies at the same time[38].

In 2003, Feldman and Eidelman published results of their studies regarding the KMC effect on autonomic functioning, state regulation and neurobehavioral status. Prematures in the study group (mean gestational age 30.28 weeks and mean body weight 1229.9 g) received KMC within 24.3 days, with an average amount of 29.7 h per child. In this group, the authors found an increase in vagal tone maturation and neurological development profiles, especially in behavior and orientation assessed by the Neonatal Behavioral Assessment Scale. They also observed an improvement in state organization related to longer quiet-sleep periods, alert wakefulness and shorter periods of active sleep[39].

## INFLUENCE OF ALTERNATIVE CARE METHODS ON PARENT–CHILD RELATIONS

A potential risk of abnormal psychosocial relationships exists among parents of multiples. The general problems are: frequent family separation and divorce, poor financial resources, mother's dejection as well as unrealistic visions concerning parenthood. Observations of mutual relations between mother and child prove that multiple birth can cause psychological stress. In general, these problems intensify at the moment of discharge from hospital. Arrangements for feeding multiples 6–8 bottles per child per day, including 1–2 feeds at night, as well as nursing and child transportation, are usually too much of a burden for a woman. The woman's reaction depends heavily on two factors: individual psychological conditions (some mothers display depression symptoms, whereas others develop defense mechanisms), and support received from relatives and/or friends. These situations refer particularly to mothers of higher-order multiples (≥ 3). Dejection behaviors concern approximately 30% of mothers delivering multiples; some of them have the feeling of being punished by the numerous offspring. Families of multiples (mother, father or both parents) often demand psychiatric care as well as more frequent psychotropic medical drugs administration[40].

In the study performed by DellaPorta and colleagues[14], beneficial effects of alternative methods of multiples' care were observed in many situations. These included avoidance of parents' negative reactions to prolonged hospitalization of their babies in the NICU, maintenance of their psychical stability and

an increase of guardians' satisfaction. DellaPorta and colleagues[14], using the State–Trait Inquiries and the Maternal Attachment Inventories, found increased anxiety and decreased maternal attachment in the control group receiving standard care, while inverse observations concerned the co-bedded group. In another paper concerning early implementation of KMC for premature twins (born at 32 weeks of gestation) by their adolescent parents (17-year-old mother and 16-year-old father), Dombrowski and associates noticed that implementation of early KMC contributed to the parents' willingness to assume responsibility for the care of their babies[41]. Feldman and co-workers showed a beneficial influence of mother–infant body contact practiced in KMC on parent–infant and triadic interactions. Both mother and father develop into more sensitive and less offensive persons, children show less negative behaviors and the family becomes more coherent[42].

Further research regarding potential physical, psychological and psychosocial advantages is required to provide better scientific evidence concerning the beneficial effects of all alternative methods discussed above.

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# Maturation and Neuromaturation of Multiples

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## INTRODUCTION

Intrauterine crowding accompanying multiple gestation frequently leads to intrauterine growth restriction (IUGR), preterm delivery or both. Either can have a profound effect on fetal and infant central nervous system (CNS) development. Preterm infants as well as infants with IUGR are vulnerable to a number of perinatal and neonatal complications. Additionally, they exhibit an increased incidence of neurodevelopmental disabilities, including the major disabilities (cerebral palsy and mental retardation) and more subtle disorders of CNS function (learning disability, language disorder, attention deficit, minor neuromotor dysfunction and behavior problems).

Immaturity increases the likelihood of death, perinatal and neonatal complications and neurodevelopmental disabilities (see Chapters 1, 34 and 97). Because of these considerations, acceleration of maturation therefore could be regarded as adaptive. As obstetricians closely monitor multiple pregnancies for fetal growth and well-being, two questions that inevitably arise regarding the optimal timing for delivery are: should multiple gestations be prolonged as long as possible so as to avoid the risks associated with prematurity? Should multiples be delivered as soon as there is evidence of a fall-off in fetal growth (or before this)? Any influence that multiple gestation has on rate of maturation may help to determine optimal timing for birth.

## AGE, SIZE AND MATURITY

Age, size and maturity are intimately related, but they are not one and the same, owing to individual variability in growth and development. Just as a 13-year-old can be tall or short, he or she may be relatively mature or immature for age. The same is true for the fetus or neonate, but the frequent interchangeable use of the terms fetal size, gestational age (GA) and maturity have been the basis of much confusion in the past. The current gold standard, for example, is early ultrasound determination of numerous fetal growth parameters, whereas before the 1960s, prematurity was simply defined in terms of birth weight (BW; i.e. below 2500 g). In a series of classic studies, Battaglia and Lubchenco and co-workers[1,2] demonstrated differential perinatal mortality and morbidity rates when neonates were differentiated into BW/GA groups on the basis of BW for GA (i.e. preterm and full-term small-, appropriate- and large-for-gestational-age (SGA, AGA and LGA) infants).

GA is traditionally calculated from the first day of the mother's last menstrual period (LMP), because the precise date of conception is generally not known[3]. Variability in time between LMP and conception (7–25 days) accounts for some of the inherent inaccuracy in dating pregnancies. Even with assisted reproductive technologies (ART), GA is calculated from 14 days before the known date of conception.

Interchanging measures of fetal size with GA is most legitimate in the first trimester, when there is little individual variability in fetal growth[3]. Measurement of crown–rump length before 12 weeks' gestation is most accurate for determining GA, whereas measurements of biparietal diameter of the fetal head, femur length and diameter of the chest and abdomen become less accurate as the pregnancy progresses. Detection of diverging fetal growth curves by race/ethnicity, gender and multiple gestation begins by the

late second/early third trimester[4–8]. IUGR detected in the second trimester is generally associated with major abnormalities (i.e. chromosomal disorders, congenital infections, major congenital anomalies). In contrast, IUGR due to deprivation of blood or nutritional supply becomes far more common with progression through the third trimester.

Because fetal maturity is difficult to measure directly, GA and fetal size are proxies for maturity[3]. Although duration of pregnancy and degree of intrauterine crowding influence timing of birth, the degree of fetal maturation ultimately determines survival and vulnerability to perinatal and neonatal complications. Finally, an as yet unknown indicator of fetal maturity may also be the primary trigger of the labor and delivery process.

## INTRAUTERINE GROWTH RESTRICTION

Fetuses confronted with deprivation of nutrient supply and/or gas exchange can compensate to some degree by preserving the nutrition and growth of certain organs at the expense of others[9]. Infants with asymmetric IUGR have decreased subcutaneous tissue and weight for their GA, but their head circumference and sometimes their length are closer to normal for GA. The mechanisms by which these compensations occur are not well understood. Adverse intrauterine circumstances can overwhelm these compensatory mechanisms, however, and lead to impaired CNS growth, signs of fetal distress, organ injury and, ultimately, fetal death *in utero*. The challenge for obstetricians has been, and will always be, to detect fetal distress before overwhelming intrauterine circumstances lead to fetal death.

IUGR or SGA infants are vulnerable to perinatal and neonatal complications, which in turn may contribute to a higher incidence of neurodevelopmental disability[10–13]. These infants are more likely to demonstrate fetal distress during labor, meconium aspiration and low Apgar scores. They also have a higher incidence of persistent pulmonary hypertension of the newborn, hypothermia, hypoglycemia, hypocalcemia and polycythemia.

Small prospective studies failed to demonstrate any increased incidence of major disability in full-term SGA children compared with AGA controls[10,11,14–22]. However, retrospective etiologic studies of large samples of children with major disability find a significantly higher proportion than expected of SGA children with cerebral palsy[23–26]. Multiple prospective studies find higher incidences of learning disability, language delays, visual–perceptual deficits, minor neuromotor dysfunction, attention deficit and behavior problems in IUGR children than in AGA controls[10,11,14,16,18,27–31]. These findings remain into adolescence and adulthood, with higher rates of school failure or drop-out, fewer professional or managerial jobs and lower income[21,28,29].

There is much interest in using evidence of abnormal uteroplacental flow to predict neurodevelopmental outcome of fetuses, especially when IUGR is detected. Gray and colleagues[32] found an association between placental markers of impaired uteroplacental blood flow and IUGR, but no association between these markers and the subsequent growth or development of the child at 1 year. In a study of 44 fetuses with abnormal Doppler velocity in the umbilical artery, Fouron and colleagues[33] found a higher incidence of neurodevelopmental deficits (defined as neurologic impairment, neurologic dysfunction or developmental quotient below 87) in children who had had abnormal flow through their aortic isthmus on fetal ultrasound. Half of 39 fetuses with net antegrade flow and all five fetuses with net retrograde flow developed neurodevelopmental deficits at 2–4 years of age. In a longitudinal study of high-risk pregnancies, Scherjon and co-workers[34,35] used Doppler pulsatility indices of umbilical and fetal middle cerebral artery flow (U/C) ratios to define fetal brain-sparing (>0.725). All infants were preterm (16–31 weeks' GA). More infants in the group with abnormally high U/C ratios than in the normal group were SGA (54% vs. 2%, $p < 0.0001$), had low BW ratios (actual BW divided by expected BW; 72% vs. 8%, $p < 0.0001$) and had intelligence quotient (IQ) scores below 85 at age 5 (54% vs. 20%, $p = 0.03$)[35–37].

Some degree of growth restriction undoubtedly begins to occur in multiple gestations during the third trimester (see Chapters 60 and 61). The more fetuses there are, the earlier the intrauterine crowding exerts an effect and the greater the degree of IUGR. As many as 36–37% of US twins and triplets are SGA, compared with only 9% of singletons[4]. Divergence in BW distribution for triplets, twins and singletons is generally apparent from 28–30 weeks' GA and progressively increases[4–8]. By 38–39 weeks' gestation, half of twins and 80% of triplets are SGA[4].

Careful examination of BW centile values from US infants born during 1991–95 reveals evidence of divergence as early as 22 weeks' gestation[4]. By 32 weeks' gestation, the difference between mean BW of twins and singletons was 300 g and between triplets and singletons was 450 g. By 38 weeks, mean BW differences increased to 500 g for twins and more than 1000 g for triplets. It is also of interest to note that BW at the 10th and 50th centiles decreased from 40 to 42 weeks' gestation in twins and from 37 to 40 weeks in triplets. This fall-off in weight gain parallels perinatal mortality rates, which are the lowest for twins born at 37–38 weeks' GA, whereas the

nadir for singletons is later, 39–40 weeks' GA[38,39]. Beyond 37 weeks' GA, perinatal and infant mortality rates are higher for twins than for singletons[38–41] (see Chapter 1).

## PREMATURITY

Multiple gestations account for 12–13% of preterm births and 16–19% of births of very-low-birth-weight infants (VLBW; with BW below 1500 g), but only 3% of all live births[42–45]. Half (48–54%) of all twins and 90% of triplets are delivered preterm, as compared with only 8–9% of singletons[5,38,44,46,47]. Mean GA decreases with each additional fetus: 39.0 weeks for singletons, 35.8 weeks for twins and 32.5 weeks for triplets[4,46]. Analysis of data from the March of Dimes Multicenter Prematurity and Prevention Study[44] found a higher rate of spontaneous preterm labor in twin compared with singleton births (54% vs. 44%, $p = 0.001$). Of the indicated preterm twin births, 44% were associated with maternal hypertension, 33% with fetal distress or IUGR, 9% with placental abruption and 7% with fetal death[44].

The rate of multiple births has risen dramatically in the United States over the past decade, owing to increasing maternal age and use of ART[42,45–49]. This has been accompanied by a concomitant increase in preterm multiple births, in part related to the use of intensive prenatal care and more decisions to institute an iatrogenic preterm delivery[45,50]. Such decisions are assisted by the fact that as preterm survival improved, obstetricians became more willing to deliver multiples prematurely[45,50–52]. For example, the rate of multiples' delivery at 35–36 weeks' GA increased by 50% in the past two decades in the USA. At the same time, Sweden noted an increase in cesarean section rate for VLBW twins[52]. Such trends have been associated with substantial reductions in twin stillbirth and infant mortality rates, not only in the USA but also in other countries[51].

Unfortunately, the dramatic decrease in neonatal mortality for preterm infants of all gestational ages and birth weights over the past few decades has not been accompanied by a concomitant fall in the rate of neurodevelopmental disability among preterm survivors[14,53,54]. Indeed, the recent focus of preterm outcome studies has been VLBW infants or infants born at the limit of viability, who have high rates of major disability (5–10% for VLBW infants and 50% for infants with GA below 25 weeks)[14,53–55]. Although the risk of cerebral palsy in more mature and larger preterm infants (with GA 32–36 weeks or BW 1500–2500 g) is ten times lower than in VLBW infants, it is also ten times greater than in full-term infants (i.e. 5–10% vs. 1% vs. 0.1–0.2%, respectively)[55]. Accordingly, moderately-low-birth-weight infants, or 'macropremies', constitute only 5–7% of the neonatal population, but as many as 18–37% of children with cerebral palsy and 7–12% with mental retardation[55].

The severity of adverse intrauterine circumstances tends to be greater in *preterm* SGA infants than in *full-term* SGA infants because their IUGR presents earlier, generally leading to their preterm delivery. However, whether the preterm SGA infant has an overall advantage or disadvantage over preterm AGA infants is controversial[10,11,14]. When controlling for GA, a few studies have found higher rates of death, neonatal complications or neurodevelopmental disabilities in preterm SGA children than preterm AGA children[18,56,57]. Others have found fewer neonatal complications in preterm SGA infants matched for GA with preterm AGA infants[58,59]. Very preterm infants born to mothers with hypertension during pregnancy (only 13% were SGA) had a higher incidence of respiratory distress syndrome (RDS; 54% vs. 39%, $p = 0.04$) but a lower incidence of intracranial hemorrhage (ICH; 2% vs. 10%, $p = 0.02$) and cerebral palsy (0 vs. 5%, $p = 0.04$), compared with very preterm infants born to mothers without hypertension[60]. Nonetheless, most studies find no differences in mortality, perinatal/neonatal complications or neurodevelopmental outcome between preterm SGA and preterm AGA infants, especially when controlling for GA[10,11,13,14,58,61]. The most striking feature of all of these contradictory studies is the high rate of neurodevelopmental disabilities in both preterm groups: major disability in 7–23% and learning disabilities in 36–50%.

## SURVIVAL, PERINATAL COMPLICATIONS AND DISABILITY IN MULTIPLES

Twins and higher-order multiples have five times higher infant mortality rates than singletons, and the vast majority of deaths occur in very preterm infants[40,41,48]. Multiple gestations also have higher rates of fetal death, and fetal death during labor (see Chapter 1)[44,62,63]. As many as 21 per 1000 triplet fetuses and 16 per 1000 twin fetuses die, in comparison with only four per 1000 singleton fetuses. Although twins constitute only 2% of live births in the USA, they have higher population-attributable risks for fetal mortality (10%), perinatal mortality (12%), neonatal mortality (11–15%), post-neonatal mortality (3%) and infant mortality (8%)[44,64].

There are few data to support the widespread belief among neonatal intensive-care unit (NICU) personnel that greater immaturity among preterm multiples makes them *more* vulnerable to death and neonatal complications than singletons of the same gestational age (GA). In an outcome study of infants

with BW below 800 g published over a decade ago, twins had a higher mortality rate (79% vs. 59%, $p = 0.03$) and incidence of major disability (67% vs. 13%, $p = 0.003$) than singletons[65]. All 12 of their male twins with BW below 750 g died in the neonatal period. A population study of US infants born in 1983 found higher relative odds of infant mortality for twins with BW below 750 g than for singletons (1.61 for Whites and 1.29 for African-Americans)[66]. In a study of infants with BW below 1000 g, Gardner and colleagues[44] found higher relative odds of neonatal mortality (1.6) in twins than in singletons matched for GA at 26–28 weeks, but no differences after 29 weeks' GA. Other studies have found no differences in neonatal mortality in preterm or VLBW multiples compared with singleton controls[43,48,67,68].

Preterm multiples do not have higher rates of most complications of prematurity (i.e. low Apgar scores, chronic lung disease, severe ICH, necrotizing enterocolitis or retinopathy of prematurity) than preterm singletons, but it is controversial whether they have a higher incidence of RDS[43,44,67–69]. In a large study of VLBW twins and twins born below 28 weeks' GA matched to preterm singletons, twins were more likely to develop RDS and to receive surfactant[43]. Mothers of twins in this study were also more likely to have labor, cesarean delivery and antenatal steroid exposure.

We compared survival and perinatal and neonatal complications in a cohort of 1040 preterm infants with GA below 33 weeks born during 1987–92 at the Johns Hopkins Hospital[67]. The 223 preterm multiples had a higher incidence of breech presentation, cesarean section, RDS (52% vs. 41%, $p < 0.05$) and polycythemia (1.8% vs. 0.2%, $p < 0.05$) than the 817 preterm singletons. The increase in RDS persisted when we controlled for race and gender. There were no differences in BW, GA or neonatal mortality, but more singleton mothers had hemorrhage, illicit drug use and chorioamnionitis.

Friedman and colleagues[68] matched 112 sets of preterm (24–34 weeks' GA) twins for GA, race, gender and mode of delivery to preterm singletons, and specifically excluded all infants with fetal anomalies or a history of twin–twin transfusion, premature rupture of the membranes, pre-eclampsia or other maternal medical disease. These investigators found only that the preterm twins were more likely to have antenatal steroid exposure (58% vs. 49%, $p = 0.03$), lower BW (1609 vs. 1787 g, $p < 0.001$) and NICU admission (88% vs. 72%, $p < 0.001$). Their finding of no differences in mortality or any preterm complications (even when also matched for antenatal steroid exposure) suggests no disadvantage in *non-stressed* twin gestations.

Three follow-up studies found no differences in neurologic, cognitive or sensory abnormalities between preterm twins and matched singletons assessed at term, 1 year and/or school age[70–72]. One study of preterm infants with BW below 1251 g found that preterm multiples had a lower incidence of ICH (19% vs. 34%, $p < 0.05$), but a slightly higher GA (by Dubowitz examination) and no differences in 1-year or school-age outcomes compared with preterm singletons[71].

The strong impression of greater vulnerability of extremely preterm multiples may be a matter of perception. Parents of extremely preterm multiples have a much higher likelihood of having at least one of their babies die or develop severe complications or disability than do parents who have only one extremely preterm infant[67]. As the number of fetuses within a multiple gestation increases, so do the odds of one of them developing a disability.

Mortality rate is clearly higher in full-term multiples than in full-term singletons, and it remains unclear whether mortality in extremely preterm infants is influenced by multiple gestation[38–41,43,44,48,62,63,65–68]. In contrast, there is strong evidence that larger multiples (i.e. with BW 1250–2500 g) born later in the third trimester, actually have *lower* neonatal mortality rates than those of singletons with similar BW[19,39,41,44,48,66,73]. This is the time period during gestation when there is increasing fetal growth restriction in multiple gestations (see Chapters 60 and 61)[4–8]. A large study of five population cohorts in the USA and Australia found that twins with BW below 2500 g had lower BW, neonatal mortality and cerebral palsy rate than singletons with BW below 2500 g[35]. These data raise questions as to whether it is IUGR (and its resulting stress) that improves preterm survival. Lower mortality rates for multiple gestations (compared with singletons) during the second half of the third trimester and high rates of fetal death *in utero* as multiples approach term raise questions about optimal timing for delivery of multiple gestations[35,44,51,62–64,74]. Further elucidation of how and why survival advantage is conferred upon multiples during the second half of the third trimester may well include measures of fetal maturation.

## PULMONARY MATURITY

In 1971, Gluck and colleagues[75] published a method of determining fetal lung maturity by measuring amniotic fluid lecithin/sphingomyelin (L/S) ratio. These investigators found a correlation between L/S ratios less than 2 and acute RDS in preterm infants, with no RDS when L/S ratios were greater than 2[75–77]. Since then, the amniotic fluid L/S ratio has

been widely adopted as a measure of degree of pulmonary maturity.

In later investigations, Gluck and co-workers[77,78] further noted that L/S ratios matured earlier in pregnancies with complications (e.g. maternal hypertension, chronic abruption) and when BW was below the 50th centile for GA. It was hypothesized that stress in pregnancy accelerates pulmonary maturation, perhaps through endogenous corticosteroids[77–79]. It is now widely appreciated that corticosteroids (betamethasone) improve survival and reduce the risks of RDS and ICH in preterm infants when mothers are treated prior to delivery[80]. Larger doses of corticosteroids lead to decreased ventilator and oxygen requirements when given to preterm infants with lung disease, which supports the idea that they accelerate pulmonary maturity (although they increase the likelihood of cerebral palsy)[81].

It is possible that the stress of multiple gestations in the third trimester, as fetuses outgrow their uteroplacental supply and develop fetal growth restriction (relative to singleton fetuses), also increases rate of fetal pulmonary maturation. In a study that graded maturation of placentas in infants born during the third trimester, Ohel and associates[82] found that placentas of multiple gestations matured earlier than placentas of singleton gestations. Accelerated pulmonary maturation might account for lower neonatal mortality in preterm multiples born during the third trimester[19,41,48,66]. Leveno and colleagues[83] also found, using amniotic fluid ratios, that twin gestations (GA 31–35 weeks) achieved fetal lung maturation several weeks earlier than uncomplicated singleton gestations. However, a more recent study by Winn and colleagues[84] found no differences in L/S ratios between twin and singleton gestations or among twins. This study was limited to pregnancies complicated only by preterm labor or premature rupture of the membranes. It may be that pulmonary acceleration is only seen in pregnancies with chronic stress, and it is only the stressed multiple gestations that trigger accelerated maturation.

## NEUROMATURATION OF MULTIPLES AND INTRAUTERINE GROWTH-RESTRICTED INFANTS

The complexity of CNS development and its normal individual variation present difficulties in detecting changes in neuromaturation of the fetus and preterm infant. Nevertheless, normal fetal and preterm neurologic development proceeds in an orderly manner according to GA or postmenstrual age (PMA; i.e. GA plus chronologic age)[85–94]. Timing of the evolution of extremity flexor tone, axial (neck and trunk) tone, behavioral and sensory responses, postural control and deep tendon, pathologic (e.g. Babinski) and primitive (e.g. Moro) reflexes have been well described in non-viable aborted fetuses[93,94], in preterm infants born during the third trimester[89–91,93,94] and in very preterm infants[85–88] with normal motor outcome. A number of assessment tools use these measures clinically to assess the degree of neuromaturation of neonates. Several studies using these measures have noted associations between rate of neuromaturation and chronic stress in pregnancy, including IUGR and multiple gestations.

Gould and colleagues[77] used the neurologic subscores of the Dubowitz GA assessment[95] to screen 51 neonates born after high-risk pregnancies, who had known GA and no RDS (74% had amniotic fluid L/S ratios greater than 2.0). Using a definition of neurologic age in advance of GA by 3 weeks or more, eight (16%) had accelerated neuromaturation. Another 25 preterm infants with GA below 32 weeks had unusually mature amniotic fluid L/S ratios (i.e. above 2.0). All 25 infants demonstrated Dubowitz neurologic GA scores that were 3–8 weeks (mean 4.5 weeks) in advance of their GA. Others have not focused on advanced maturation, but have noted the imprecision of the Dubowitz GA assessment by 1–2 weeks in preterm infants and as much as 4 weeks in extremely preterm infants[96–98]. Spinnato and colleagues[99] noted that the greatest degree of error was in the Dubowitz neurologic items, which measure only passive tone, and in the group of infants born to mothers with hypertension during pregnancy.

Amiel-Tison pioneered a neurologic GA assessment that consists of items that measure active as well as passive extremity flexor and axial tone[89–92]. She reported 16 infants from 13 pregnancies with GA 28–33 weeks whose neurologic examination age was 4–7 weeks in advance of their GA[100]. In a review 11 years later[101], she reported another 16 infants with neurologic examination age 2–3 weeks in advance of their GA. All were born after complicated pregnancies, often with maternal hypertension (i.e. chronic and/or pregnancy-induced hypertension). Many were multiple gestations; the smallest within a set was generally more advanced neurologically than the larger co-multiple(s), although the larger multiples tended to be advanced beyond expected for GA. Most infants with advanced neuromaturation (94%) had BW below the 50th centile for their GA; three-quarters had BW below the 25th centile and one-third had BW below the 10th centile for GA (SGA). All AGA infants had stressed, complicated pregnancies. These findings suggest that factors in stressed pregnancies that lead to fetal growth restriction also advance neuromaturation (at least in some infants). The advanced maturation seen in growth-restricted preterm infants is not an 'all or nothing' response, but a 'progressive response by a variable degree'[101].

Amiel-Tison and associates[98] evaluated neurologic maturity in a cohort of 101 multiples born at 32–37 weeks' GA during 1991–93. All had precise dates with early prenatal ultrasound scans to confirm obstetric GA. Neurologic maturity could be accurately determined in 69 (68%, i.e. each had concordance in at least six of nine responses). Three-quarters of these multiples with accurate determination of neurologic maturity (52 of 69) demonstrated neurologic advance of 3 weeks or greater over GA. Using physical characteristics to score maturity[102] in 96 of 101 multiples, physical advancement was observed in 78 of 96 (81%).

We developed a method of assessing neuromaturation in preterm infants in a NICU that involves serial comprehensive neonatal neurodevelopmental examinations and summing the measures that describe evolution of flexor posture, flexor extremity and axial tone, deep tendon reflexes, pathologic reflexes, primitive reflexes, behavioral responses and postural control[85–88,103]. By performing serial examinations while the infant was in the NICU, we were able to measure their rate of neuromaturation in the NICU and evaluate contributing perinatal and neonatal factors. We studied rate of neuromaturation in a sample of 435 preterm infants with BW below 1500 g born at or transferred to the Johns Hopkins Hospital in Baltimore, MD, during 1994–2000[67,104]. Using Student's *t* test, we found no differences between preterm multiples and singletons in rate of neuromaturation or in degree of maturity at 34 weeks' PMA. Even when we used multiple linear regression models to control for confounders (i.e. BW, GA, IUGR, maternal age, cesarean rate, chronic lung disease and socioeconomic status), multiple gestation did not influence our measures of neuromaturation. It is certainly possible that many of the multiples in our sample were still too immature at birth (mean GA was 28.8 weeks) to have had the 'benefit' of accelerated maturation. Alternatively, compensatory mechanisms may have been overwhelmed, leading to fetal compromise or organ injury, signs of fetal distress with subsequent emergent delivery despite their young GA. Most of the data supporting accelerated pulmonary and neurologic maturation are in larger preterm multiples born closer to term. Our data raise a caution that obstetricians should not assume that multiples below 32–34 weeks' gestation have accelerated neuromaturation.

In addition to clinical neurologic measures, advanced neuromaturation has been documented in IUGR infants using electrophysiology. Conduction time between waves I and V of brainstem auditory evoked responses (BAERs) decrease rapidly in preterm infants between 27 and 40 weeks' GA[105,106]. Pettigrew and co-workers[107] found significantly lower mean conduction times in 25 preterm SGA infants compared with 76 preterm AGA infants. The preterm infants were born at 26–34 weeks' GA and studied between 32 and 40 weeks' PMA. Preterm SGA infants had significantly shorter conduction times than AGA infants, although the distribution of conduction times for the SGA group overlapped those for the AGA group. Henderson-Smart and colleagues[108] found lower BAER conduction times for interval I–V (i.e. more advanced) during the entire preterm period in SGA infants born to mothers with hypertensive disease of pregnancy. The mean brainstem conduction times for AGA infants born to hypertensive mothers were in between mean conduction times for SGA infants and AGA infants born to mothers without hypertension. These findings provide further support for a progressive acceleration of neuromaturation in response to adverse intrauterine circumstances[101].

Acceleration of neuromaturation has been observed only in the CNS, and not in peripheral nerves. The latency of wave I on BAERs, which is felt to represent conduction through the auditory nerve, is not different during preterm development in SGA and AGA infants[101,107]. Peripheral motor nerve conduction times decrease (i.e. conduction velocities improve) during the last trimester of pregnancy and in preterm SGA and AGA infants[109,110]. Even preterm SGA infants with lower brainstem conduction times have normal peripheral nerve conduction velocities (i.e. the same as preterm AGA controls)[110].

Scherjon and co-workers[35–37,111] found similar results using visual evoked potentials (VEPs). They identified 28 fetuses with evidence of 'fetal brain-sparing' on Doppler flow studies of the umbilical artery and middle cerebral artery (i.e. U/C ratio). They followed these 28 infants longitudinally along with 45 control infants who had documented normal U/C ratios. The group with high U/C ratios had shorter (i.e. more mature) VEP latency times at 6 months, but did not demonstrate a further decrease between 6 and 12 months and were similar to controls at 12 months.

Most physicians assume that advanced neuromaturation is beneficial in that it improves the infant's ability to cope with extrauterine life. However, the lesson learned with postnatal steroids that decrease a preterm infant's chances of RDS but increase the likelihood of cerebral palsy may be relevant here[112]. Although Scherjon and co-workers[36,37] found no differences between groups on neurodevelopmental assessment at 3 years, more children who had evidence of 'fetal brain-sparing' were cognitively delayed compared with controls when assessed at 5 years. Mean IQ was lower than that of controls.

A linear regression model demonstrated that both U/C ratio group status and VEP latency significantly contributed to the variance for IQ. This suggests that the price that a growth-restricted fetus pays for advanced neuromaturation is suboptimal neurodevelopment.

## CONCLUSION

The question remains, 'do factors involved in multiple gestations increase or decrease organ maturation of multiples?' Clearly, many factors potentially influence fetal organ development in multiple gestations. The most vulnerable organ is the CNS. CNS development requires many complex and interrelated developmental processes during intrauterine and early extrauterine life. We do not fully understand how neuronal migration, dendritic arborization, synaptogenesis, myelination and neuronal support are organized and supported by the fetal–placental unit. Nor do we understand how maternal, genetic and environmental factors interact to influence structural and functional CNS development.

Despite our best efforts in NICUs, we are not knowledgeable enough to provide the type and extent of support needed for optimal development of a preterm infant in comparison with a normally functioning mother and placenta. Twins and higher-order multiple gestations result in some degree of intrauterine stress as the pregnancy progresses. Often this stress is not shared equally among the fetuses. As a result of adverse intrauterine circumstances, extremely preterm multiples may be more vulnerable to some complications of prematurity (e.g. RDS). In these cases, adverse intrauterine conditions must be severe, since they present so early in pregnancy, precipitating delivery even before the beginning of the third trimester.

Most multiples, when compared with singletons, demonstrate a degree of intrauterine growth restriction. As the third trimester progresses, the forces that lead to growth restriction also can accelerate pulmonary and/or CNS maturation. This does not occur in every multiple gestation. It is 'a progressive response to a variable degree' and not an 'all or none phenomenon'[101]. This acceleration of neuromaturation appears to occur in the CNS but not in peripheral nerves. However, this adaptive response, which aids the fetus in adapting to earlier extrauterine life, comes at a price: that is, curtailing 'normal' growth and development of the CNS, with some resulting functional impairment. Just as the adaptive response is on a continuum, its timing and degree of its shaping of the CNS influence the type and degree of the child's functional impairment.

What can these data tell us about fetal growth, development and optimal time for delivery of multiple gestations? Obstetricians, neonatologists and parents will continue to grapple with this issue. Knowing the complications and consequences of preterm birth and IUGR will aid in making this decision, but it is clear that each decision about timing of delivery must be individualized. Until we know enough to be able to reverse adverse intrauterine circumstances or fully support the extrauterine growth and development of preterm infants, obstetricians must continue to monitor high-risk pregnancies as closely as possible. The optimal time of delivery is the point at which the adverse consequences of preterm birth no longer outweigh adverse intrauterine circumstances. The challenge is to identify when this occurs during multiple gestation.

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# Multiple Pregnancies at the Extremes of Maternal Age

*H. M. Salihu*

93



## INTRODUCTION

Pregnancy at the extremes of maternal age is not just a subject for the curious mind but is of importance owing to concerns that both mother and fetus are at risk of heightened morbidity and mortality. The definition of the 'lower' maternal age is much clearer than 'upper', for which controversies exist as to the cut-off point beyond which adverse birth outcomes become more frequent. Most, if not all, clinicians and researchers agree that low maternal age (generally below 20 years) represents a distinct obstetric entity in terms of risk thresholds[1–5]. For the upper limit, however, no agreement is present concerning what constitutes the cut-off. In the 1980s and most of the 1990s, women who were 35 years or over were considered to be of advanced age and representing a special high-risk obstetric entity that warranted intense monitoring. As the cohort of women undergoing assisted reproduction procedures increased, however, more women over 35 became pregnant, and what had been uncommon became common. At the same time, intensive antenatal-care monitoring improved, as did the survival rate of infants born to these mothers. Thus, the cut-off point for advanced maternal age has now shifted to around 40 years, on average. Some authors use the term 'older mothers' or 'advanced maternal age' to describe pregnancies among women beyond 50 years of age[6,7], but this is not what is commonly understood by the term 'older'. The latter cases reflect the dynamics of improved obstetric care and the continuous success of medical technology to reverse the course of dwindling reproductive function even beyond the menopause.

This chapter defines the lower extreme of maternal age as below 20 years of age, since virtually all studies of multiple pregnancy and low maternal age apply this definition. For the upper limit (advanced maternal age), all studies that use the cut-off points of 35 years or 40 years are included. Pregnancies beyond 50 years are excluded, as they are still a rare phenomenon with a probability of 1 in 25 000 births[6].

## LOW MATERNAL AGE AND MULTIPLE BIRTH

Few studies have been conducted among multiples born to teenage mothers, although recent reports suggest that the epidemic of multiples in the United States is not only confined to older mothers but also involves younger women, albeit far less dramatically[8]. The incidence of twin pregnancy among live births to US teen mothers is 1.5%[5]. The frequency of twinning among teenagers in the United States has increased in the past 20 years along with the global increase of multiples (Table 93.1). Approximately 76% of teen twin deliveries are to the major ethnic groups (white (54.9%) and black (45.1%) mothers), whereas the remaining 24% occur in other racial and ethnic minorities. The likelihood of twinning is 41% higher among black as compared to white teen mothers (odds ratio (OR) 1.41, confidence interval (CI) 1.37–1.46). In addition, the proportion of young adolescent mothers (< 15 years) with twin gestation is about three-fold higher in Blacks than in Whites[5]. Compared with more mature mothers (20–29 years old), teen mothers with twin pregnancy are more likely to be unmarried (77.0% vs. 35.6%)[9], and tend to be disadvantaged in terms of the

**Table 93.1** Frequency of twin and higher-order gestations among United States teens over the past two decades

| | Year | | |
|---|---|---|---|
| | *1980* | *1990* | *2000* |
| Total number of live births among teenagers (*n*) | 562 330 | 533 483 | 477 944 |
| Total number of multiples (*n*) | 7295 | 7690 | 7688 |
| Twins (*n*) | 7212 | 7605 | 7577 |
| Higher-order multiples (*n*) | 83 | 85 | 111 |
| Multiple birth rate* (%) | 1.3 | 1.4 | 1.6 |
| twin birth rate* (%) | 1.3 | 1.4 | 1.6 |
| higher-order birth rate† (per $10^4$) | 1.5 | 1.6 | 2.3 |

*$p < 0.0001$, †$p = 0.002$ for trend

adequacy of received prenatal care because they are less endowed economically compared with their mature counterparts[9].

To understand better the influence of low maternal age on birth outcomes among twins, we examined a total of 218 896 individual twins born to teenage and young mature (20–29 years of age) mothers from the period 1995 through 1998 using the matched multiple birth files compiled by the National Center for Health Statistics (NCHS)[10]. These individuals had complete information regarding birth weight and gestational age, and the delivery occurred at or after 20 weeks of gestation. Significant differences in gestational age and birth weight were observed between infants of teen and those of young mature mothers. Twin neonates of teenagers were born about 6 days earlier (mean ± standard deviation (SD), 34.5 ± 5.0 weeks) than those of young mature gravidas (mean ± standard deviation (SD), 35.3 ± 4.0 weeks). They also weighed, on average, 223 g less (mean ± SD, 2094.3 ± 725 vs. 2317 ± 681 g).

### Triplets

We recently analyzed 23 004 matched triplets delivered to 7668 mothers from 1995 through 1998 using the matched multiple dataset for the period[11]. Of these, 354 triplets were born to teenage mothers (1.5%) and 6858 to young mature mothers (20–29 years) (~ 30%). The two age cohorts differed significantly in terms of a number of selected sociodemographic characteristics, just as was the case with twins. Specifically, teenage mothers were more likely to be black, unmarried and nulliparous, and to have received inadequate prenatal care.

There was significant divergence in mean gestational age and birth weight between triplets of the two maternal age groups. Triplets of adolescent mothers were born an average of 10 days earlier than those of mature young mothers (29.9 vs. 31.3 weeks, $p < 0.0001$). They also weighed 286 g less (1284g vs. 1570g, $p < 0.0001$)[11].

After adjustment, the risk for stillbirth was three times as high among triplets of teenage pregnancies as compared with those of young mature mothers; the likelihood for neonatal death was twice as high, and infant mortality over 1.5 times as high[11].

Finally, and in order to have a comprehensive picture of the association between low maternal age and birth outcomes across plurality subtypes, we combined data for singletons, twins and triplets in an array pattern. Figure 93.1 summarizes results of the association between teen birth and mortality for singletons, twins and triplets after adjusting for confounding characteristics. For each additional fetus, there was a corresponding widening of the risk disparity between the two maternal age cohorts for both intrauterine and extrauterine demise ($p < 0.0001$ for trend in all cases). Among both singletons and twins, the widest gap was observed for neonatal mortality, whereas for triplets, the disparity was most pronounced for intrauterine demise. The adjusted excess mortality burden associated with teenage pregnancy as a function of uterine fetal number is presented in Figure 93.2. Again, the dose-dependent pattern for each of the mortality indices is very apparent.

## OLDER MATERNAL AGE AND MULTIPLE BIRTH

Although the increase in multiple births occurred in all maternal age groups across the past two decades, the increases in multiple birth ratios varied by maternal age with a peak among older gravidas[8]. From 1980 to 1999, multiple birth ratios increased more than 27% for women aged 20–24, 42% for those 25–29 years old and more than 62% among

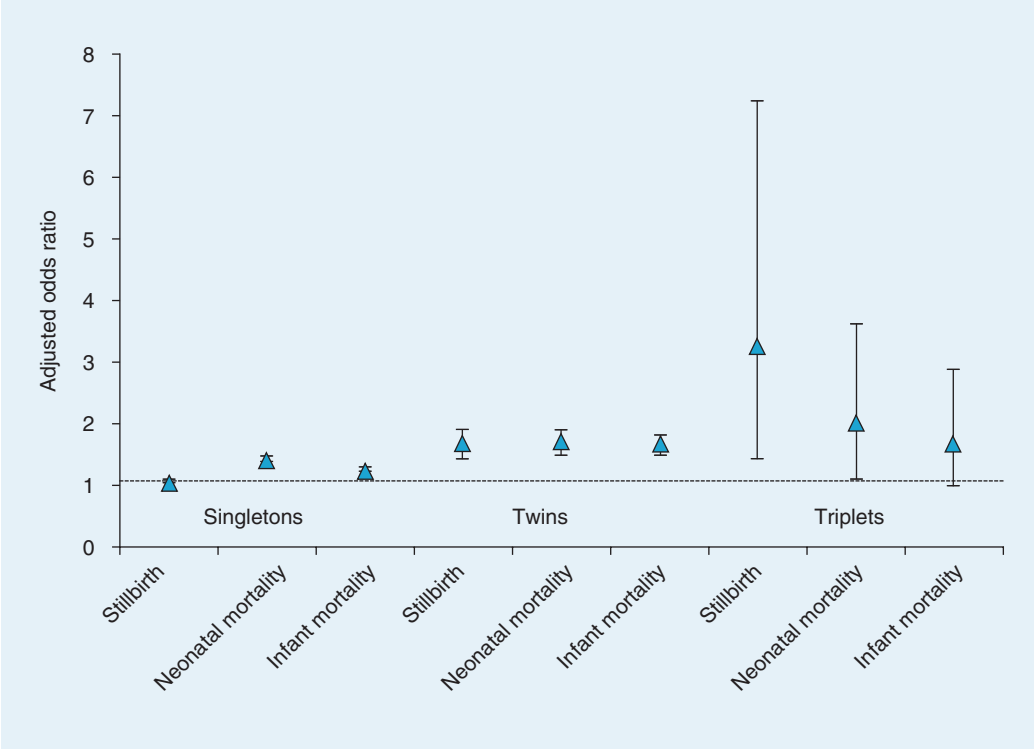


**Figure 93.1** Adjusted odds ratios for death among infants of adolescent mothers by plurality subtype. Adjusted estimates were obtained by including the following variables in the model for the generalized estimating equation: race, parity, marital status, maternal smoking during pregnancy and adequacy of prenatal care. 20–29-year mothers are the referent category. The I bars represent 95% confidence intervals. $p < 0.0001$ for trend

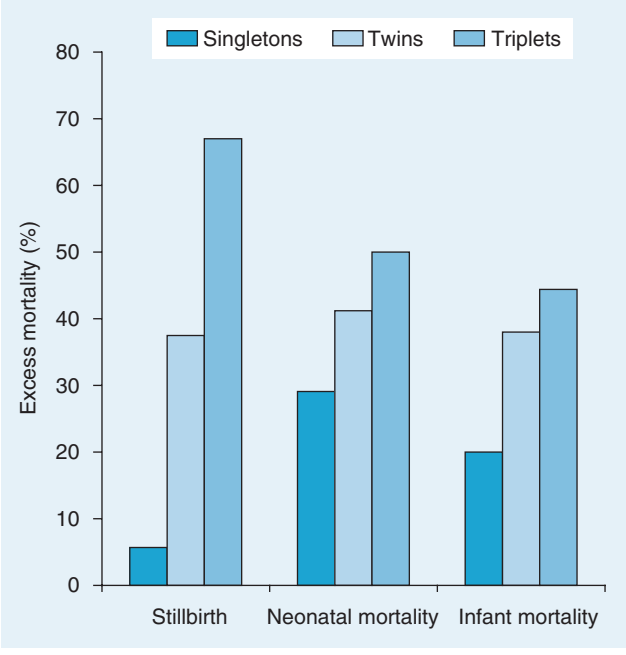


**Figure 93.2** Level of excess death associated with low maternal age across plurality subtypes. Excess deaths were computed using the formula: $[(OR-1)/OR] \times 100$, where OR is adjusted odds ratio

women in their early thirties (30–34 years old). In the same years, the increase in multiple birth ratio was more than 81% for those aged 35–39 and more than 110% for the 40–44 age category. The increases for higher-order multiples were more dramatic (265% for 25–29 year olds; 518% for those in the 30–34 age group; 777% for 35–39-year-olds; and 1683% for women aged 40 years and beyond)[8].

In an analysis of 155 777 twin and 5630 triplet pregnancies, Zhang and colleagues[12] examined the impact of advanced maternal age (defined in that study as women older than 35 years) on birth outcomes, specifically, very preterm very low birth weight, and perinatal and infant death. Among singletons, the authors observed significantly elevated risk in gravidas older than 35 years, while the risk estimates were comparable for twins. The interesting finding in the study was that among triplet births, women older than 35 years showed lower risk for these same birth outcomes. Unfortunately, the study did not examine small for gestational age.

We extended the work of Zhang and colleagues[12] by refining the definition of older mothers using the cut-off of 40 years and older to evaluate risk for infant morbidity (including small for gestational age)

**Table 93.2** Comparisons of neonatal morbidity among twins and triplets by maternal age (in years)

| | *20–29* | *30–39* | *40+* |
|---|---|---|---|
| | (*n* = 4929) | (*n* = 10 128) | (*n* = 738) |
| Mean birth weight in grams (± SE)*** | 1572.8 ± 8.7 | 1730.0 ± 6.0 | 1813.9 ± 21.2 |
| Low birth weight*** | 95.1% | 92.1% | 90.4% |
| Very low birth weight*** | 41.6% | 32.1% | 27.4% |
| Mean gestational age in weeks (± SE)*** | 32.1 ± 0.1 | 33.4 ± 0.1 | 34.4 ± 0.4 |
| Preterm*** | 94.7% | 93.2% | 85.9% |
| Very preterm*** | 53.5% | 41.8% | 34.5% |
| Small for gestational age (SGA) | 11.6% | 11.5% | 10.3% |
| Low Apgar score*** | 11.4% | 7.3% | 6.0% |

***$p < 0.0001$ for trend

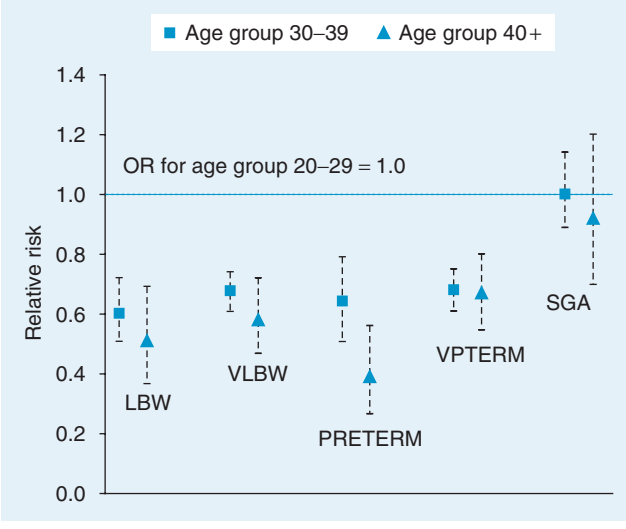


**Figure 93.3** Adjusted odds ratio (OR) for fetal growth inhibition for maternal age groups 30–39 and 40+. LBW, low birth weight; VLBW, very low birth weight; VPTERM, very preterm; SGA, small for gestational age

and mortality among triplets[13]. Table 93.2 illustrates the rates for specific neonatal morbidities by maternal age groups. Mean birth weight and gestational age at delivery correlated with maternal age in a dose-dependent manner ($p < 0.0001$ for trend). The inclusion of low birth weight and preterm birth in the table is only for comparative analysis, since triplets are almost by rule of low birth weight and preterm. The overall rates for low and very low birth weight were 93% and 34.8%, respectively. For both conditions, babies born to younger mothers demonstrated higher risk as compared with those of older mothers in a monotonic pattern. Similar gradation of risk was discerned for preterm and very preterm births, as well as for the likelihood of poor Apgar scores. The adjusted estimates were confirmatory (Figure 93.3). Interestingly, the risks of small for gestational age (a proxy for intrauterine growth restriction) among triplet babies were comparable across the maternal age categories.

In the same study[13], we observed a total of 774 stillbirths among the 15 795 triplet babies, yielding an overall crude stillbirth rate of 49 per 1000. The crude stillbirth rate by maternal age category was 30 per 1000, 63 per 1000 and 16 per 1000 for young (20–29 years old), mature (30–39 years old) and older mothers (≥ 40 years old), respectively. Table 93.3 shows the adjusted estimates for stillbirths and neonatal, perinatal and infant mortality. After taking into account the effects of confounding characteristics, the risk for stillbirth was higher among mature and older mothers, although the confidence interval included unity. Mature and older mothers had a 35% and 40% higher likelihood of experiencing a stillbirth delivery, respectively, in comparison with younger mothers. Paradoxically, the opposite effect was observed for neonatal, perinatal and infant mortality. On the other hand, triplets born to mature and older mothers were less likely to die during the perinatal, neonatal and infancy periods in comparison with those of younger mothers, and this finding was statistically significant. The results remain essentially the same after controlling for gestational age (Table 93.3; bottom half).

The paradoxical association between advanced maternal age and birth outcomes among triplets as illustrated may also be present among higher-order multiples (e.g. quadruplets and quintuplets). To that effect, we performed a similar analysis of 1448 quadruplets and 180 quintuplets delivered in the United States between 1995 and 1997[14]. Infants of older mothers (≥ 35 years old) were compared with those of younger ones (< 35 years old) in terms of early mortality indices, and adjusted mortality probabilities were computed by yearly intervals of maternal

**Table 93.3** Mortality estimates by maternal age using the generalized estimating equation (GEE) framework

| | *Age* (years) | | | |
|---|---|---|---|---|
| | *30–39* | | *40+* | |
| *Mortality type* | *AOR*[*] | *95% Confidence interval* | *AOR*[*] | *95% Confidence interval* |
| Stillbirth | 1.35 | 0.94–2.0 | 1.40 | 0.61–3.14 |
| Neonatal mortality | 0.47 | 0.38–0.60 | 0.36 | 0.19–0.67 |
| Perinatal mortality | 0.66 | 0.54–0.82 | 0.53 | 0.32–0.89 |
| Infant mortality | 0.50 | 0.41–0.62 | 0.37 | 0.20–0.67 |
| *Adjusted for gestational age*[†] | | | | |
| Stillbirth | 1.56 | 1.06–2.28 | 1.42 | 0.62–3.26 |
| Neonatal mortality | 0.67 | 0.57–0.79 | 0.59 | 0.37–0.93 |
| Perinatal mortality | 0.81 | 0.70–0.93 | 0.69 | 0.47–0.99 |
| Infant mortality | 0.69 | 0.58–0.84 | 0.59 | 0.34–0.98 |

[*]AOR, adjusted odds ratio. Adjusted estimates were generated by taking into account the confounding effects of race, level of education, parity, level of prenatal care utilization, smoking and drinking habits during pregnancy. The 20–29 age category is the referent group

[†]Also adjusted for race, level of education, parity, level of prenatal care utilization, smoking and drinking habits during pregnancy, in addition to gestational age

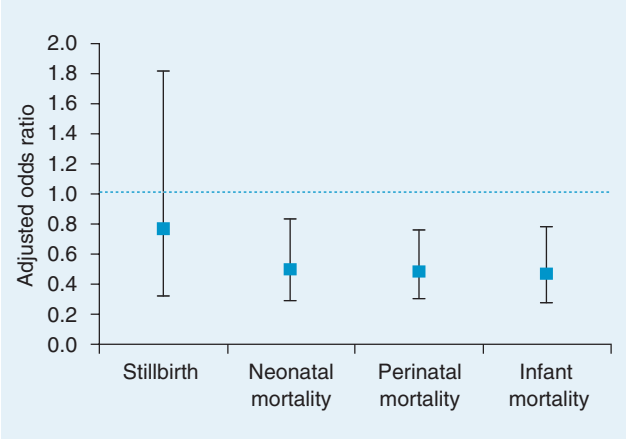


**Figure 93.4** Adjusted odds ratios (AOR) for stillbirths and neonatal, perinatal and infant mortality among quadruplets and quintuplets in the United States, 1995–97 (babies of mothers <35 years are the referent category). The I bars represent 95% confidence intervals. Adjusted estimates were generated by taking into account the confounding effects of race, level of education, parity, level of prenatal care utilization, smoking and drinking habits during pregnancy

age. The likelihood for stillbirths was 23% lower among younger mothers in comparison with older ones, although the difference was statistically not significant (Figure 93.4). The risk for neonatal, perinatal and infant mortality was significantly lower among older mothers. Mothers younger than 35 years of age and carrying a quadruplet or a quintuplet pregnancy had about a two-fold increased likelihood for neonatal, perinatal and infant mortality. For each unit decrease in age of the mother with either a quadruplet or a quintuplet pregnancy, the odds of stillbirth and neonatal, perinatal and infant demise went up by 9%, 12%, 13% and 12%, respectively, in a dose-dependent manner ($p < 0.0001$ for trend). When risk thresholds for these mortality events were compared across the spectrum of maternal age stratified by 5-year maternal age quintiles, we found that with every 5-year decrease in maternal age, the probability for stillbirth and neonatal, perinatal and infant mortality increased by a factor of 57%, 78%, 82% and 75%, respectively (Table 93.4). Older-age mothers of quadruplets and quintuplets appear to parallel their counterparts who have twins and triplets[15].

**Table 93.4** Maternal age-specific model-based probability estimates for early mortality (%) of quadruplets and quintuplets in the United States, 1995–97

| *Maternal age* (years) | *Stillbirth* | *Neonatal mortality* | *Perinatal mortality* | *Infant mortality* |
|---|---|---|---|---|
| 20 | 14.1 | 9.0 | 8.3 | 9.7 |
| 21 | 13.1 | 8.1 | 7.4 | 8.8 |
| 22 | 12.1 | 7.3 | 6.7 | 7.9 |
| 23 | 11.1 | 6.6 | 6.0 | 7.1 |
| 24 | 10.3 | 5.9 | 5.3 | 6.4 |
| 25 | 9.5 | 5.3 | 4.7 | 5.8 |
| 26 | 8.7 | 4.7 | 4.2 | 5.2 |
| 27 | 8.1 | 4.2 | 3.8 | 4.7 |
| 28 | 7.4 | 3.8 | 3.4 | 4.2 |
| 29 | 6.8 | 3.4 | 3.0 | 3.8 |
| 30 | 6.3 | 3.0 | 2.7 | 3.4 |
| 31 | 5.8 | 2.7 | 2.4 | 3.0 |
| 32 | 5.3 | 2.4 | 2.1 | 2.7 |
| 33 | 4.8 | 2.2 | 1.9 | 2.5 |
| 34 | 4.4 | 1.9 | 1.7 | 2.2 |
| 35 | 4.1 | 1.7 | 1.5 | 2.0 |
| 36 | 3.7 | 1.5 | 1.3 | 1.8 |
| 37 | 3.4 | 1.4 | 1.2 | 1.6 |
| 38 | 3.1 | 1.2 | 1.0 | 1.4 |
| 39 | 2.9 | 1.1 | 0.9 | 1.3 |
| 40 | 2.6 | 1.0 | 0.8 | 1.1 |
| 41 | 2.4 | 0.9 | 0.7 | 1.0 |
| 42 | 2.2 | 0.8 | 0.6 | 0.9 |
| 43 | 2.0 | 0.7 | 0.6 | 0.8 |
| 44 | 1.9 | 0.6 | 0.5 | 0.7 |
| 45 | 1.7 | 0.6 | 0.4 | 0.7 |
| 46 | 1.6 | 0.5 | 0.4 | 0.6 |
| 47 | 1.4 | 0.4 | 0.4 | 0.5 |
| 48 | 1.3 | 0.4 | 0.3 | 0.5 |
| 49 | 1.2 | 0.3 | 0.3 | 0.4 |
| 50 | 1.1 | 0.3 | 0.3 | 0.4 |

## COMMENT

The greater risks for fetal birth outcomes in multiple births are well described in the other chapters of this book. Nevertheless, a positive aspect of the current epidemic of multiples in the United States is that it has provided us with a unique opportunity to examine, in a more comprehensive way, the interaction between maternal age and fetal birth outcomes. Thanks to the preponderance of multiples, we now have epidemiologic results that have challenged previously held notions regarding the effects of maternal age based on singleton gestations alone.

For multiple pregnancies at the lower end of maternal age, it is now crystal clear that teenagers are consistently at higher risk for adverse fetal birth outcomes. What is new and more interesting, however, is the hitherto unknown relationship between fetal number and birth outcomes in this age group. For the first time, we have evidence demonstrating that the association between low maternal age and pregnancy outcome is dose-dependent. In other words, the risks for stillbirth and neonatal and infant mortality among teen mothers increase directly with the number of fetuses. Regarding this finding, one may speculate that the average risk threshold elevation associated with increase in fetal number (multiple gestations) differentially impacts upon fetuses of teenagers more than on those of mature women. It is possible that normal pregnancy-associated physiologic and biochemical changes are more negatively altered at lower than at higher maternal age in a monotonic fashion as uterine overcrowding progresses. This will suggest a strong biologic interaction linking maternal reproductive maturation processes, fetal number and intrauterine and extrauterine environmental factors of feto-infant survival. As fascinating as this may sound, however, we have no data to date to support this argument, and further research is required to uncover the underlying mechanisms of the relationship.

It is also interesting to note that the association between older maternal age and fetal number is opposite to that of low maternal age with respect to fetal outcomes. Whereas, among singletons, older maternal age elevates the risk for fetal outcomes, the risk is obliterated among twins, and actually lowered among triplets and higher-order multiples. Hence, a reverse dose–response pattern characterizes the influence of advanced maternal age on fetal outcomes as fetal number rises. One reason offered for this finding is the intense surveillance among older women, since multiples in this age group are more likely to be assisted reproductive technologies (ART)-induced when compared with younger women[12]. The same authors also suggest that multiple gestations among older women are more likely to be dizygotic (because they are ART-induced), and this could explain the improved fetal outcomes. However, the recent finding that improved fetal outcomes among older women are also observed for quadruplets and quintuplets[14] weakens these two arguments, since almost all quadruplets and quintuplets in the United States are induced[16], a fact that eliminates the differential occurrence of dizygosity or preferential monitoring. This underlines the complexity of the relationship among maternal age, fetal number and outcomes, and highlights the need for more in-depth research in this domain.

## ACKNOWLEDGMENT

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# Postpartum Zygosity Determination

*L. G. Keith and M. Karoshi*

**94**



## INTRODUCTION

Twins are currently classified into two main types, monozygotic (MZ) and dizygotic (DZ). A more complex classification was proposed some years ago by Keith and Oleszczuk to recognize some of the problems that may attach to the simplistic MZ–DZ paradigm (see below for details). DZ twins occur when two oocytes are fertilized by two spermatozoon. MZ twins occur when one oocyte is fertilized by one spermatozoon and at some later time divides to form two embryos. The causes of this split are uncertain. Familial MZ twinning is rare, but does occur. Similarly, many families appear to be 'twin' prone, but controversy exists on the exact cause of this phenomenon. MZ twins occur at approximately two to three times the normal rate in pregnancies resulting from assisted reproductive technologies (ART)[1,2], be they *in vitro* fertilization (IVF) or ovulation induction.

## WHY ZYGOSITY TESTING?

In the antenatal period, the issue of zygosity is usually not considered and is less important than chorionicity (although chorionicity may provide some clues to zygosity) (see Chapter 39). This is because chorionicity and external genital sex are the only means by which zygosity can be assessed at this early stage of pregnancy. Unfortunately both methods (chorionicity and confirmation of external genital sex) are imperfect means of assessing zygosity.

When unlike-sex twins are born, no question exists regarding their zygosity. They are, by definition, DZ. On the other hand, when like-sexed twins are born, the issue of zygosity becomes paramount. Unless chorionicity has been demonstrated accurately and correctly interpreted in the delivery room (and/or by the pathology department) (see Chapters 25 and 26), parents are at risk for the most common mistake in zygosity assignment based on placentation and membranes – that is, the assumption that their (like-sexed) twins are DZ because they are determined to be dichorionic (DC) at birth. The genesis of this error is the widespread lack of recognition that like-sexed DC twins (with fused or separate placental disks) may be DZ or MZ (approximately 25% are MZ). The perpetuation of this error is assured when parents report this misinformation to their children. Indeed, twins often proceed through life wondering why, having been told that they are DZ, they look so much alike but are not perfectly 'identical'.

The term 'identical' is commonly used as a shortcut for MZ, but as shown below, in this chapter and other chapters (24 and 28) of this monograph and on the section dividers of this volume (courtesy of Dr David Teplica), this too is a serious misnomer. Rarely if ever are MZ twins 'identical' in their phenotypic appearance, even if they carry the same genetic patrimony at the time of the original zygotic split. Having provided this disclaimer, important medical and social reasons underlie the need for twins to know their zygosity. From a medical point of view, the allegedly identical genes of an MZ twin pair will usually (but not always) exhibit concordance in many major and chronic disorders, such as diabetes, asthma, Alzheimer's disease, depression, cancer, etc. Similarly, matched genetic complement is of paramount importance when one member of a twin pair requires organ transplantation. In suitable circumstances, the co-twin is an ideal donor, with no

need for anti-rejection therapy[3]. Moreover, should one MZ twin develop cancer, the other could be considered at similar risk, and careful assessment on an ongoing, preventive basis is necessary. Finally, from a social point of view, one could argue that the twins themselves have a unique right to this information and that to withhold it is to deny their birthright. Just as it is unethical forcibly to separate twins (or other multiples) for adoption, it is unethical to deny twins knowledge of a fundamental biologic fact because of its supposed frivolity or presumed cost.

## WHEN TO TEST?

The optimal time to determine zygosity is at delivery. This assessment is most easily and efficiently achieved by the obstetrician, alone or in consultation with the pathologist (see Chapters 25 and 26). The benefits of such assessments include: first, the ability to state to the parents with certainty, and in writing, that their monochorionic (MC) twins are MZ, and second, institution of formal zygosity testing, using placental tissue, in all like-sexed DC twins, recognizing that about 25% of these twins are MZ and the remainder, DZ. If these opportunities are lost, twins' families may draw false conclusions and/or will of necessity be forced to resort to other methods of zygosity testing later in life.

## AVAILABLE METHODS

### Historical background (Weinberg methodology)

In 1874, the French mathematician Bertillon assumed that the sex of each zygote of a pair of DZ twins would be determined independently. He then postulated that the number of DZ pairs was equal to twice the number of unlike-sexed pairs, with the remainder of the like-sexed pairs presumably MZ. This concept was restated in 1902 by Weinberg, and subsequently became entrenched in the literature as 'Weinberg's rule'. It was criticized, however, almost from its inception, and is still subject to intense negative interpretation (see Chapter 36). Its usefulness is purely confined to statistical samples, and it cannot be applied to the zygosity determination of a given pair of multiples.

### Assessment of physical characteristics

Any comprehensive review of the use of physical characteristics for zygosity determination must recognize the extraordinary contribution of the late Luigi Gedda, then Director of the Gregor Mendal Institute, Rome, in his monumental volume, *Twins in History and Science*[4]. Among the characteristics studied and reviewed by Gedda were biometric parameters, skeletal structures, skin, hair and dermatoglyphics, ocular and orbital anatomy, nasal and dental characteristics and specularity (mirrored or reversed asymmetry). Unfortunately, many such physical structures or characteristics are poorly developed in newborns, if present at all. Moreover, later in life, comparisons of various physical characteristics are often not sufficiently robust to determine a definitive diagnosis of zygosity. Among the characteristics used in such analyses, albeit with varying degrees of efficacy, are: ear forms, patterns of ridging on the tongue and dental eruption patterns, as well as tooth morphology[4]. Fingerprints obtained from MZ twins, which one might intuitively suppose would be identical or nearly so, are never completely identical. Moreover, the fingerprint system first proposed by Bertillon was for exact identification of criminals rather than diagnosis of zygosity. The same may be said for the use of iris identification, the most recent advance in commercial and governmental security applications. The probability of two different irises agreeing by chance in more than 70% of their phase sequence is about one in 7 billion[5].

According to the older literature (see Gedda), the ideal test for zygosity was concomitant intertwin acceptance of skin grafts. Not only is this intervention invasive in nature, costly and fraught with potential for morbid consequences, it is currently considered unethical in view of the many other methods that exist. Indeed, it is the use of more precise methods of zygosity determination that has furthered the ability of MZ twins to undergo organ transplantation without rejection.

## CURRENTLY APPLICABLE METHODS OF ZYGOSITY DETERMINATION

### Blood groups

A commonly used and relatively inexpensive method of zygosity determination is the use of blood groups and human leukocyte antigens (HLA). A complete discussion is provided by Bryan[6]. Zygosity can be determined from blood by studying common population variants known as polymorphisms. These include the common blood groups, HLA types, serum proteins, enzyme polymorphisms and, most recently, DNA polymorphisms. In the case of ABO blood groups, for example, if the father of twins is blood group AB and the mother is group O, the offspring may be either group A or group B. If one twin is group A and the other is group B, the pair is clearly DZ. If both are A or B, however, zygosity

**Table 94.1** An example of the determination of chances of dizygosity in a pair of twins alike or all blood group and biochemical markers and of the most common phenotype of all loci. From reference 6

| *Marker system** | *Phenotype* | *Relative chance of dizygosity for a particular system* | *Relative chance of monozygosity for a particular system* |
|---|---|---|---|
| Initial odds | | 0.7000 | 0.3 |
| Sex | Female | 0.5000 | 1.0 |
| ABO | A | 0.6945 | 1.0 |
| MNSs | MS | 0.5161 | 1.0 |
| Rh | $R_1r$ | 0.5400 | 1.0 |
| Kell | K- | 0.9548 | 1.0 |
| Secretor | Sec | 0.8681 | 1.0 |
| Duffy | Fy(a+) | 0.8099 | 1.0 |
| Kldd | Jk(a+) | 0.8616 | 1.0 |
| Dombrock | Do(a+) | 0.8094 | 1.0 |
| Xg | Xg(a+) | 0.9573 | 1.0 |
| Pl | I | 0.7006 | 1.0 |
| $PGM_3$ | I | 0.7569 | 1.0 |
| $ACP_1$ | I | 0.6320 | 1.0 |
| ADA | I | 0.9409 | 1.0 |
| ES-D | I | 0.9054 | 1.0 |
| GPT | 2–1 | 0.6250 | 1.0 |
| Gc | I | 0.7569 | 1.0 |
| Pi | I | 0.9555 | 1.0 |
| Combined test after testing<br>Chance of dizygosity = 0.00560/0.3056 = 0.0183 | | 0.00056 | 0.3 |

*P, YI and Hp have not been used as they are not fully developed in the newborn, and Lu, $PGM_1$ and AK because they are linked to Sec, Rh and ABO, respectively

**Table 94.2** Efficiencies of eight common blood group systems. Adapted from references 7 and 8 by permission of the authors and W. B. Saunders Co. Ltd

| | *Secretor* (Le) | *Kell* (K) | *Duffy* (Fy) | *ABO* | *$A_1A_2BO$* | *MNSs* | *Rh* |
|---|---|---|---|---|---|---|---|
| Number of alleles | 2 | 2 | 2 | 3 | 4 | 4 | 8 |
| Minimum *p* (concordance\|DZ) | 0.5937 | 0.5937 | 0.5937 | 0.4630 | 0.4023 | 0.4023 | 0.3198 |
| *p* (concordance\|DZ) | 0.5947 | 0.9050 | 0.5938 | 0.5933 | 0.5651 | 0.4351 | 0.4647 |
| Efficiency | 0.9977 | 0.2337 | 0.9997 | 0.7572 | 0.7277 | 0.9451 | 0.7870 |

is unproven. There is a one in two chance that these same patients will produce a group A zygote that goes on to produce MZ twins. The chance of producing two DZ group A zygotes is a half of one in two, or one in four. In clinical calculations this number is usually shown as the relative chance (or odds) of DZ : MZ, which in this case would be 1/4 : 1/2, or 0.25 : 0.5. This process can be repeated for many other sets of polymorphisms, with the intent of establishing differences (diagnostic of DZ) or, alternatively, a high statistical probability of MZ on the basis of failing to detect any differences. It is important to note that the higher is the statistical probability desired, the more difficult it is to achieve (see Table 94.1).

Table 94.2 clearly shows that the more complex, multiple allele systems are not necessarily more efficient for determining zygosity, at least in this data set. For example, the rhesus (Rh) system is less efficient than several simple blood group systems. Also, nothing is gained by differentiating between the $A_1$ and $A_2$ antigens in the ABO system.

### DNA

The most sophisticated form of zygosity detection from blood is commonly characterized as 'DNA fingerprinting'[9–11]. Whereas many writers describe this analysis as being most accurate, it is not always the case, for reasons stated below. DNA testing analyzes the genes directly rather than their protein products. In this type of analysis, several genetic loci are tested at the same time, and a pattern unique to each individual is quickly assembled. Using this technology, MZ twins share identical genomic patterns in some studies, whereas the probability that a DZ pair would also exhibit superimposable patterns may be as low as $3 \times 10^{-14}$. At first glance, calculations such as these suggest that technology is the most accurate available for zygosity testing. However, like many emerging technologies, DNA fingerprinting is not perfect, and is associated with disadvantages as well as advantages. Advantages include that only small amounts of DNA (from blood, placenta, etc.) need to be obtained. Additionally, dried biologic specimens such as semen and hair can be used. Indeed, because of the stability of DNA, the zygosity of stillborn fetuses can be established in cases where proteins have already disaggregated; in other instances, archival histologic tissue blocks can be treated to yield high-quality DNA from any pair of twins. The major disadvantages of DNA testing include its alleged high cost and its relative unavailability in comparison with more standard laboratory methods. In reality, however, DNA fingerprinting is not more expensive compared with extensive and full blood group analysis. Moreover, batched sampling and analysis can further reduce cost per test. Commercial kits that look for severely limited numbers of specific DNA polymorphisms are now available. Whereas these are convenient because DNA can be extracted in sufficient quantity from mouthwashes or buccal brushings, for example, the risk of insufficient statistical power to exclude dizygosity is high (see below). With further refinements and a standardization of loci, DNA kits might possibly become more robust, thus making them fully acceptable and avoiding the need to obtain blood samples. This would be particularly attractive to the parents of young children if archival placental tissue is not available. Whether and how soon this might happen is unknown.

The major problem in DNA analysis for the determination of zygosity relates to the existence of small-scale mutations, the process by which DNA is mutated in specific zones, e.g. point mutations, deletions and insertions, trinucleotide repeat sequences (such as are found in X-linked mental retardation and Huntington's disease) and tandem repeat sequences. When Derom and colleagues[9] reported their initial DNA finding in 1985, they examined six different polymorphic sites using four restriction enzymes and six DNA probes in a sample of 22 pairs with known zygosity determined by placentation. Their sample was placental DNA. Within the 12 MZ pairs, concordance was complete, and only one of the ten DZ pairs was not demonstrably different. In the same year, Hill and Jeffreys[10] reported the use of similar technology on umbilical cord blood samples collected at delivery, or peripheral blood samples (0.5–1.0 ml) obtained from each baby the day after birth. Their sample consisted of five twin pairs and two sets of triplets. Their conclusion was, 'minisatellite DNA probes provide a single genetic test that should allow positive determination of zygosity in all cases of multiple pregnancy'. The discussion on the appropriateness of using this technology continues, however, and standardization of the number of microsatellite probes, also called variable number of tandem repeat markers (VNTR), or their specific nature for the purpose of zygosity determination has yet to be accomplished.

In an effort to avoid the complexities and costs of DNA evaluation of blood or placental tissues, some laboratories turn their attention to 'mouthwash' kits because of their ease of use. Such kits, often popularized in the lay media or advertised to the public, may be used at home or in field studies and then analyzed later at a remote location. Although we have not performed a survey and/or analysis of existing kits of this type, Dr Geoffrey Machin (personal communication, 2002) suggests that their general application should be viewed with caution for at least two reasons: first, the lay press reports of such kits fail to state the number of genetic probes used, and second, the accuracy of these tests, which clearly is related to the number of probes, is often unknown to the public. According to Machin, who used the best available mouthwash polymerase chain reaction (PCR) kit in Edmonton, Canada to test 50 pairs of twins who were known to be DZ by VNTR Southern blot, the kit failed to find genetic differences between one of these DZ pairs, thus yielding a false MZ result.

## INCREASING POSTNATAL DISCORDANCE

This specific phenomenon underlies the fact that MZ twins are not truly 'identical'. It is currently unclear how many mutations occur, under what circumstances they occur and to what degree they continue to occur. The senior author (L.K.) has observed more than 20000 sets of twins over the years at the Twins Day Festival in Ohio, most all of whom exhibited variations in body phenotype under close scrutiny. Only one pair stands out as being indistinguishable

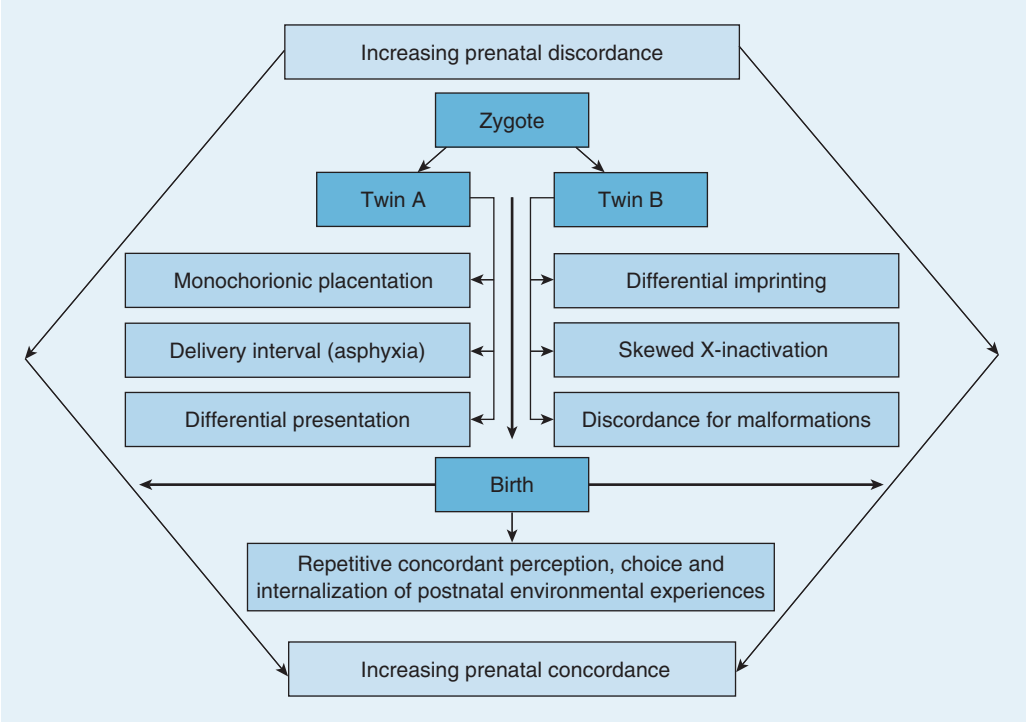


**Figure 94.1** Acquisition of discordance in twins from conception to mature extrauterine existence. Adapted from reference 12

on an individual basis. These elderly gentlemen invariably puzzled the most sophisticated and experienced judges of the twin contest. It is not possible to say whether the phenomenon of post-zygotic mutational change affecting phenotype was not operational in this pair. It is also not known whether DNA tests were ever obtained from these individuals. Figure 94.1 is a composite describing various phenomena affecting post-zygotic discordancy.

Keeping this in mind, Figure 94.2 is the absorption spectrum obtained from a mouthwash sample of one of the authors (L.K.) and his co-twin, Donald Keith. A difference was found in one DNA zone where multiple repeat sequences were present, whereas the other zones gave identical results. Despite this, the Keith twins were later confirmed to be MZ using restriction fragment length polymorphism (RFLP) technology in two different reference laboratories (Figure 94.3). The clinical paradox occasioned by the different interpretation derived from Figures 94.2 and 94.3 is explained by the fact that RFLP methodology examines segments of DNA at 'lesser magnification', as it were. It therefore provides a 'broad brush-stroke' diagnosis of monozygosity by failing to pick up the inevitable, smaller, post-zygotic mutational differences that are now thought to be present in most, if not all, MZ twin pairs. RFLP technology is the type that is generally used for forensic purposes, paternity testing, etc. In contrast, the tandem repeat

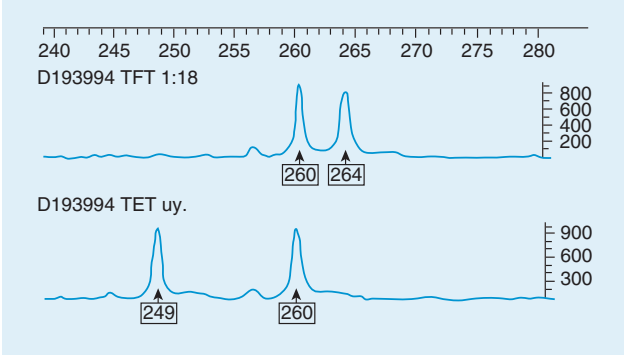


**Figure 94.2** Absorption spectra of genetic material from Louis Keith and his twin brother, Donald, showing a difference in one area (all others identical). Courtesy of Dr Andreas Busjahn, Max Delbruck Center for Molecular Medicine and the Franz Volhard Clinic of Humboldt University, Berlin

sequences could be considered too sensitive for use in zygosity testing, although the fact that they can be obtained from a mouthwash sample versus blood is an advantage. Figures 94.4–94.7 show Louis and Donald Keith at ages 4, 7, 32 and 67. Close inspection of these figures show subtle changes in facial phenotypic features that increase with age. Whether these relate to post-zygotic changes or the effects of the environment, lifestyle and diet is not known. Possibly some changes relate to the phenomenon of

**Figure 94.3** DNA fingerprints of the Keith twins, courtesy of Dr Fiona Bamforth, University of Alberta, Edmonton, Alberta, Canada

post-zygotic changes, with the exception of the nasal difference, as Donald incurred a broken nose in childhood. At present, neither Louis nor Donald is able to identify himself in the pictures obtained at age 4 and 7. It is precisely the difference in technology and the lack of standardization of the number and types of markers that stands in the way of DNA fingerprinting becoming a more useful tool for clinical zygosity determination. In summary, no DNA gold standard currently exists and it is not clear when one will be developed.

Because of the uncertainties just described, the use of combinations of tests has been proposed. One author[13] recorded global impressions of zygosity obtained by two objective (based upon physical resemblance questionnaire; dermatoglyphic analysis) and two subjective procedures (parental impressions and physician's impressions), which were then compared with blood typing of 53 twin pairs. The judgments of the investigator furnished the most accurate indication of zygosity (94–96% accuracy). Laboratory tests were repeated for five pairs when the results proved incompatible with the investigator's ratings. In all five instances, the investigator's judgments were confirmed, indicating that a laboratory error had occurred. It appears that the opinion of a skilled observer of twins can provide a convenient and highly effective alternative to blood typing or even DNA analysis.

The repeated observations that zygosity tests are not error-free has prompted some investigators to develop self- or parental-administered questionnaires

**Figure 94.4** Louis and Donald Keith at age 4. Photo by Myron Keith

to assess zygosity, most often with results that are considered more than 90% reliable. In one of the most recent studies, Ooki and Asaka[14] examined zygosity in 224 twin pairs identified by genetic markers including DNA samples, of childhood age, by simple questionnaire administered to twin mothers and to the twins themselves. The questionnaire items included twin similarity of physical features, degree of similarity and frequency of being mistaken (confusion of identity) when twins were about 1 year of age. The twins themselves responded to three questionnaire items dealing with only confusion of identity items. The results were calculated with logistic regression analysis, which showed that the total accuracy of mothers' questionnaires was 91.5% when using only the items dealing with confusion of identity. This accuracy was slightly lower than that obtained by twins' self-reports answered by both twins separately, with 93.3% accuracy. The total accuracy of mothers' questionnaire responses rose to 95.1% when the authors used all 19 items. This study concluded, 'twin zygosity can be estimated by the use

**Figure 94.5** Louis and Donald Keith at age 7. Photo by Harry Johnson

**Figure 94.6** Louis and Donald Keith at age 32. Photo by Myron Keith

of the mother's simple questionnaire with sufficient accuracy even in young twins about 1 year of age'.

## IMPLICATIONS FOR CLINICAL PRACTICE

The following implications for practice derive from recognition of the complex nature of zygosity testing, its long and continuing evolution and recent advances in ultrasound and molecular genetics:

(1) All MC twins are MZ, but they may be discordant for genetic disease, malformations, etc., and also some DNA tests of zygosity if sufficiently detailed and exhaustive tests are used.

(2) Unlike-sexed twins are DZ.

(3) Not all like-sexed DC twins are DZ. In fact, about 25% in the Caucasian twin population resident in the United States and Europe are MZ.

**Figure 94.7** Louis and Donald Keith at age 67. Close inspection of Figures 94.4–94.7 shows subtle changes in facial phenotypic features that increase with age. Photo courtesy of Marc Hauser, Chicago. © 2003

(4) Not all like-sexed twins conceived using ART are DZ.

(5) Not all twins who are discordant for genetic disease, chromosome constitution or a major malformation are DZ. If a major malformation is present in MZ twins, it may affect only one of the pair or may be phenotypically less severe in the other member of the pair.

(6) Selective termination in discordant twins and higher-order multiples must be approached with caution and only after great efforts to establish chorionicity definitively. Because the presence of fetal vascular anastomoses may lead to the death of both twins if traditional means are used, selective termination can be achieved only by umbilical vessel occlusion in MC–MZ twins discordant for lethal malformations or chromosomal abnormalities (see Chapter 64).

(7) All like-sexed DZ twins have the right to know their zygosity, and this should become the standard practice in perinatal medicine. Likewise, all parents of MC twins should be informed in writing that their twins are MZ. The ultimate responsibility for this endeavor might be assumed by the department of obstetrics, pathology or neonatology so that parents of all surviving MC twins would receive a letter declaring the twins to be MZ rather than identical. A copy of this

letter would be retained in both the maternal and pediatric hospital records.

(8) Correct terminology, monozygotic/dizygotic, should always be used rather than misleading and inaccurate lay-terms such as identical/fraternal. Parents are able to understand and accept these terms. For parents of MZ twins, it is a relief to understand that MZ twins are seldom, if ever, absolutely identical. This settles the issue of zygosity for them.

## A LOOK TOWARDS THE FUTURE

In the context of zygosity, future nomenclature should include qualifying descriptions of those characteristics which are phenotypically and or genetically discordant, in order to provide a more precise diagnosis of zygosity. Whereas it may be sufficiently accurate to characterize a pair of twins as DZ, it may be imprecise to characterize a pair as MZ with no further qualification, especially when such qualifications would clearly explain phenotypic or other types of discordance. For example, a pair of twins might be more accurately characterized as MZ-discordant for schizophrenia, MZ-discordant for breast cancer or MZ-discordant for Duchenne muscular dystrophy. In this regard, based upon analysis of childhood sleep patterns, it has already been postulated that there are three clinical types of MZ twins: those who are identical in every sense of the word, those who are opposite in every sense of the word and the remainder who share some, but not all similarities and dissimilarities[15].

## SPECIAL CONSIDERATIONS

Josef Mengele, also known as Auschwitz's 'Angel of Death', held a fascination with twins. As Auschwitz's senior 'physician', he conducted so-called and never-published 'genetic experiments' on nearly 1500 sets of twins between 1943 and 1944. For this purpose, he selected twin sets from the lines of prisoners coming off the cattle cars. With the blessing and support of his senior mentor, Baron Otmar Von Verscher at the Kaiser Wilhelm Institute in Berlin, Mengele tested various genetic theories with the aim of illuminating Hitler's racial dogmas. Twins were considered particularly useful, because so-called identical twins were thought to be an identical gene pool and their responses to mutual treatments could be monitored with this in mind.

## ACKNOWLEDGMENT

This chapter is based in part on two prior publications of the senior author (L.K.):

1. Keith LG, Gandhi S, Machin GM, *et al*. Zygosity determination: an evolving technology. Invited paper presentation at the *First Annual St Valentine's Day Symposium of TSI*, Royal Society of Medicine, London, UK, February 14, 1997
2. Oleszczuk JJ, Machin GA, Keith DM, Keith LG. Zygosity of twins: is it time for a new terminology? *Ginekol Pol* 2000;71:1307–16

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3. Tilney NL. Renal transplantation between identical twins: a review. *World J Surg* 1986;10:381–8
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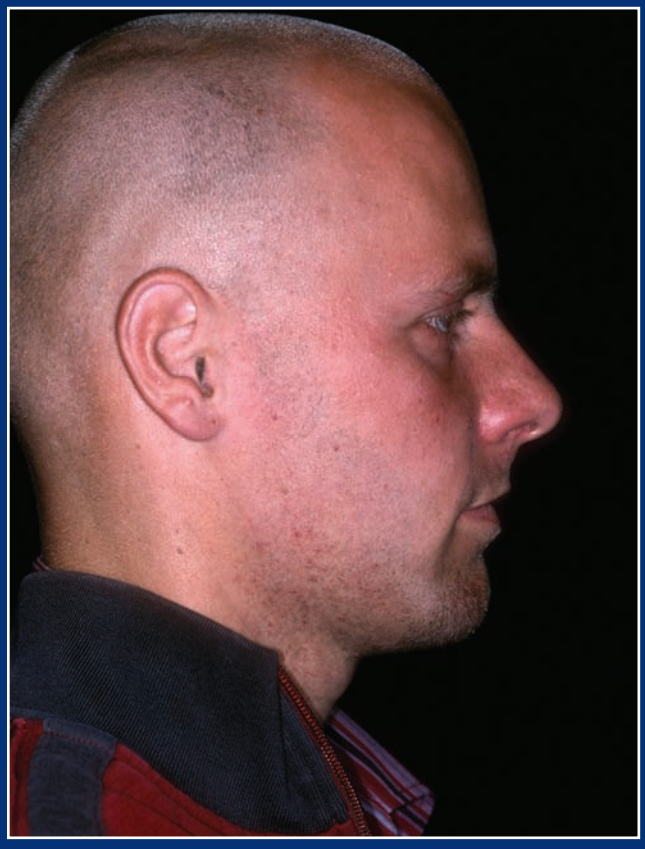
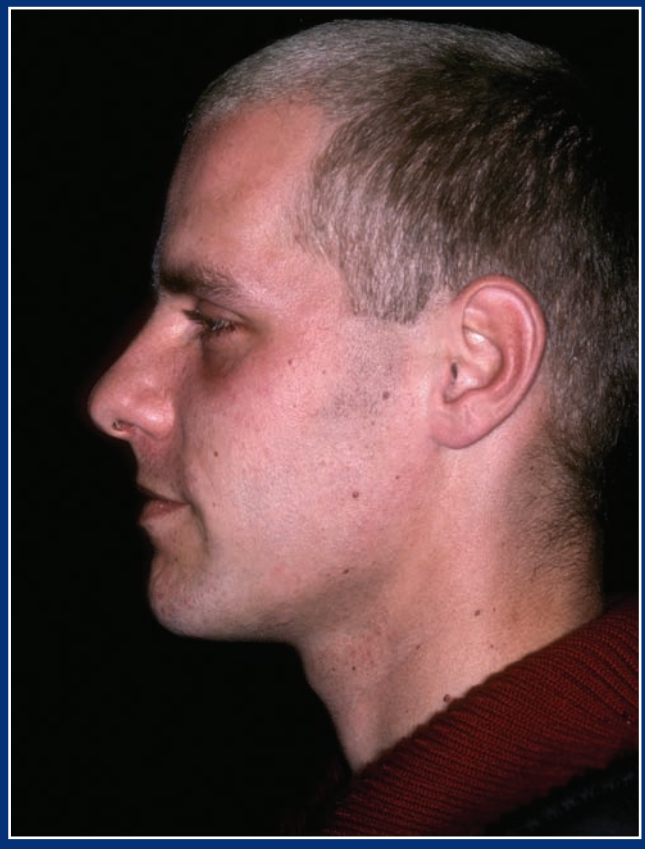
# SECTION IX
# CHILDHOOD CONCERNS





**25-year-old male monozygotic, monochorionic, mirror twins, Belgium, 2004.**

Participants since birth in the
East Flanders Prospective Twin Study.
Twin A left, Twin B right.

Romulus and Remus nursed by the she-wolf. Pallazio Del Conservatori, Rome, Italy

In the legend of Romulus and Remus, King Amulius ordered his slave to throw the twin brothers born to Rhea Silvia (his niece) and Mars (the god of war) into the Tiber River. Disobeying him and risking his life, the slave left them in their cradle and sent it floating down the river where they were subsequently found and nursed by a she-wolf (Figure). Despite their shared childhood as twins, they aggressively expressed their individuality during adulthood. The dispute over whether a city should be built on the Palatine or on the Capitoline Hill led, among other things, to a fight. At the end, Romulus killed Remus, and became King of the new city, which was named Rome in his honor.

This mythological narration of the founding of Rome, is but one example of the importance attributed to childhood issues of twins in establishing their future as adults. Some of the most important are discussed in this section. Our slightly amended Ten Commandments about 'Twindividuality', as proposed by Pamela P. Fierro serves as a prelude to this section (http://multiples.about.com/cs/familyissues/a/twinidentity.htm).

1. Because twins and multiples share their parents, time spent on a one-on-one basis with each child increases his/her individuality.
2. Whenever possible, avoid labeling the children as 'the twins' or 'the triplets'; call each child by his/her name.
3. Rewards or punishment should be individualized.
4. Encourage the multiples to have individual activities and interests.
5. Despite the fact that multiples are each other's best friends, this relationship should not be exclusive. Individual and separate friendships should be encouraged.
6. Avoid unfair comparisons between sibs, and adjust standards and expectations for each child.
7. Each child should have a chance to share the spotlight. The identification of good, but different, characteristics, builds self-esteem.
8. Celebrate individual achievements despite the possibility of jealousy.
9. Each of the multiples should have his/her own child's memories, such as a set of pictures and baby book.
10. Each multiple should have something recognized as his/her own. It is not necessary to share everything. Later, during adulthood, this will lead to respecting individual privacy and property.

*I.B. and L.G.K.*

# Contents of Section IX

# Childhood Issues

*E. Bryan*

**95**



## INTRODUCTION

Many women dream of becoming the mother of twins. Those who have them often find that the reality is very different from their expectations. The challenge of looking after and responding to two babies can be difficult under any circumstances, but is particularly so as one or both of the twins is likely to be more vulnerable than its singleton counterpart. This situation is compounded by the common perception of the public – and not uncommonly of the professionals too – that twins are accompanied by unqualified joy from conception onwards. This misperception often makes it hard for parents to admit their difficulties and obtain professional help when they need it. Physical, emotional and financial strains in the postpartum period may lead to serious difficulties in relations between the parents.

Quite often, parents who conceive twins as a result of infertility treatment feel under extra pressure to cope, as their many years of childlessness may have created unrealistically high expectations of parenthood. Some misguidedly believe that they brought the problems they are now experiencing upon themselves, and may be especially reluctant to admit to them, partly because they expect a less sympathetic response than that given to women who have conceived their babies spontaneously[1]. Women who have been successful in demanding careers find the transition to motherhood (let alone 'multiple motherhood') particularly difficult.

This chapter examines these situations as they relate to the childhood experiences of the twins.

## FAMILY RELATIONSHIPS

### Maternal concerns

For many mothers, relating to *one* baby is a full-time occupation, both emotionally and physically. The complexity of relating simultaneously to two babies, in addition to the extra physical effort involved, can be stressful. Some mothers initially find it hard to tell their babies apart, and are distressed by the confusion, believing that such a deficiency is indicative of inadequate maternal instincts and parenting skills. These difficulties are compounded when one or both infants are ill and therefore separated from her.

It is much more common for mothers of twins to have to cope with the acute emotional crisis caused by the birth of a premature baby. If one baby is notably more ill than the other, mothers are more likely to relate to the healthier infant[2]. The situation is particularly difficult if one baby is thriving and the other is critically ill. Size and appearance typically influence maternal feelings, especially in the early days, The larger baby may be favored and the smaller baby viewed as imperfect[3]. On the other hand, this smallness or weakness may inspire an urge to provide special care and protection. Several studies show the latter to be a more common reaction during at least the first year[4,5]. Whereas it is not unusual for one twin to be ready to go home before the other, most units nowadays try to discharge both together, not least because the baby left behind may suffer in its relationship with its mother. Furthermore, earlier

discharge from hospital is the most significant factor influencing the later self-esteem of a school-age twin[6], whereas birth weight and birth order are also significant. On the other hand, if discharge of the babies together from hospital is not practicable, one baby needing a very much longer stay, parents should be encouraged and assisted to visit the remaining baby with facilities being provided for the healthy baby to come with the parents.

Although mothers generally aim to give both babies the same amount of attention and to love them equally, this is not always what happens (Figure 95.1). One baby may demand, and indeed require, more attention than the other. Mothers often notice marked differences in the personalities of their babies within a few days of birth, shown, for example by different feeding patterns or visual responsiveness. Where one baby is more demanding, the mother may feel guilty and resentful that she has to attend so much more to the difficult baby at the expense of the more responsive one.

The long-term effects of different patterns of the early mother–twin relationship have yet to be clearly established. It is known, however, that mothers of preterm twins tend to show fewer initiatives towards their babies than mothers of preterm singletons[7]. They also tend to be less responsive to crying as well as to positive signals, have less physical contact and talk with their twins less. At 18 months, the cognitive development of the twins is less advanced than that of the singleborn controls, and maternal behavior in the newborn period is predictive of the level of development of the children at 18 months[7].

Early preference for one twin influences the way in which a mother later talks about or responds to each child[8]. However, a mother may actually make a conscious effort to compensate the less favored twin by spending more time with him. The traditional transcultural image of motherhood portrays dedication to one baby at a time. Mothers of multiples may understandably feel deprived of this experience, and frustrated by the sheer impossibility of giving undivided attention to either child. This is exacerbated if parents are reluctant to separate their twins even for short periods, so that they might spend quality time with each one. Others find that even short separations are hard to organize for practical reasons. Still others believe that by letting someone else, even a relative, look after one of the babies, their 'special' status as a parent of twins may be diminished or their competence questioned.

## Paternal concerns

The importance of the father caring for twins cannot be overestimated, but is often overlooked in the literature. The same may be said for his need for adequate antenatal preparation and ongoing support. Inevitably, he has to be more heavily involved with the care of twins than he would have been with a single-born baby. Under these circumstances, the earlier he can be encouraged to recognize his role and participate, the better. As even the most willing and supportive father may be apprehensive about handling a small preterm baby, his confidence should be deliberately augmented by involving him in the care of the twins while still in hospital.

**Figure 95.1** Sharing maternal attention between young monozygotic (MZ) twins. With permission of the mother

The main problem generally affecting fathers involves the emotional and financial pressures inherent in twins, which represent a barrier to effective sharing of time and energy between work and family. Increased living costs may mean working harder or longer hours, circumstances which promote guilt if the family feels neglected. As if this were not enough, exhaustion can also affect fathers, and cause friction between the partners. If the babies are often noisily awake at night, many fathers find it especially hard to function effectively the next day.

Although twins tend to have less contact with both parents compared with singletons, the relative amount of time spent with their father tends to be greater. One study found more 2-year-old boy twins than singleton boys choosing their father as their primary figure of attachment[9], an observation that supports the importance of fathers establishing strong one-to-one relationships with each child. This may amount to nothing more than taking one child out while the mother spends time with the other, but it is highly beneficial for both parents as well as their twins.

## Sibling needs

However good their intentions, parents with new babies inevitably have less time to spend with their

older child, especially in the early months. The arrival of multiples often disturbs other children, particularly the single toddler who had been the center of the family until suddenly displaced by an attention-attracting pair. Not surprisingly, the effect of the arrival of twins on the older sibling is significantly greater than if the arrival were a singleton, and behavior problems in the older child are more common[10], often taking the form of attention-seeking infantile behavior or of strenuous efforts to win parental approval by being unnaturally good. On the other hand, sometimes the older child may just become withdrawn.

A single child may feel especially isolated by the arrival of twins, in that he sees both parents and the babies as pairs, whereas he has no partner. An uncle, aunt, godparent or even a responsible teenager can make all the difference by giving special and continuing attention to the older child. It can significantly improve their morale and their consequent behavior.

When twins are expected, the sibling needs to develop a confident relationship with an adult other than their father who can be responsible for their care if the mother has prolonged hospitalization. After the twins are born this relationship remains a useful safeguard, and may continue to be important for years.

There are ways to help the older child relate to each baby individually. These include the choosing and giving of separate presents to be prominently displayed on each cot (crib). Later, when the twins become toddlers, older siblings often feel daunted or even excluded by the power of the twin unit. He/she should be encouraged to develop a rewarding relationship with each of the twin children by spending time at home or going on outings with just one.

### Grandparents

Many grandparents thoroughly enjoy their twin grandchildren, as well as the reflected prestige that twins appear to bestow. They often develop rewarding and individual relationships with the children and, where they can actively support the mother in coping, may get to know their twin grandchildren better than they might have done a singleton. In addition, grandparents often provide continuing and consistent attention and care which could otherwise be lacking in a multiple-birth family.

Occasionally, proud grandparents add to the workload in the early days by bringing too many visitors to see the new babies, and expecting the mother to entertain them. Others, however, particularly those faced with triplets or more, may feel overwhelmed by the enormity of the task and distance themselves from the family, even to the point of moving away[1]. Because twins and triplets are used to relating to several care-givers, they may not develop such an intimate relationship with their grandparents, and the latter sometimes find the relationship with multiple-birth children less rewarding than with their singleton grandchildren. It is essential that grandparents understand the vital importance of relating to the children individually, and hence of quickly learning to distinguish between them. They should habitually refer to each child by his/her name and be encouraged to give identifiably individual presents or cards.

Professionals would be unwise to assume, however, that even the best-intentioned grandparents will be able to provide a given family with appropriate or sufficient help. Indeed, new parents often find that the amount of help dwindles very rapidly after a few weeks, and can be disconcertingly unpredictable.

## THE EARLY MONTHS

It is well established that most new mothers – and many fathers – of twins suffer from lack of sleep[11] and consequent chronic fatigue[12]. Exhaustion is the most common complaint from mothers of twins, and this is likely to be a major factor contributing to the depression and anxiety that characterize this group. Unfortunately, depression may persist for some years beyond the period of acute fatigue[13], but many other factors contribute to it. One of the most prominent is that many women feel guilty that they are able to give so little attention to their partner, and also, in the houseproud, that they cannot maintain previously high domestic standards. Many such couples choose to paint a deceptively rosy picture of their domestic situation, and it is only on a home visit that the full stress is revealed, even if not acknowledged.

Too often, parents of multiples strive to live up to the 'happy family' image that they feel society, including health-care professionals, expects of them. Professionals are sometimes no better at understanding the reality. Parents who have confessed to their feelings of exhaustion, inadequacy and a need for help may be met by reassuring platitudes that they are coping perfectly well, a reaction that may well amplify their concealed distress.

Lack of social contact adds to feelings of depression. Mothers of very young twins tend to leave the house much less often than those with single babies[14], and social isolation becomes an increasing problem for many. Many do not have access to a car during the day, or at all. Travel by public transport is very difficult with two babies, and when there is a toddler sibling it may well be impossible.

## FAMILY SLEEP PATTERNS

Getting the babies into a satisfactory sleep pattern is a common problem. Many parents blame themselves

later for unnecessarily allowing troublesome sleep patterns to take hold.

Not only can two wakeful babies take turns disrupting the household, but the crying of one may disturb the other and establish an endless cycle of distress. Twins may be slower to find a satisfactory routine owing to prematurity, the need for frequent feeds and their past experience of constant attention and broken sleep on the neonatal unit. Unfortunately, mothers often reinforce bad sleeping habits by responding immediately to the cries of one baby to prevent the other being disturbed, and children quickly learn to take advantage of this easily won attention.

### Co-bedding

Based on recent evidence, parents often now choose to co-bed their twins in the neonatal period and early months. Preliminary studies suggest that such babies may have more settled sleep and more synchronous waking[15]. In preterm twins, more rapid weight gain and earlier discharge from hospital have also been reported[16]. Interestingly, there is no significant increase in core temperature or lowering of oxygen saturation in co-bedded infants (Ball and colleagues, personal communication), no evidence of an increase in sudden infant death syndrome (SIDS) and anecdotal evidence that such physical contact reduces the frequency of apneic episodes in preterm pairs. Babies sharing one cot also bring the advantage of being easier to remain in the parents' bedroom for a longer period of time – an important factor in the prevention of SIDS (see Chapter 91).

**Figure 95.2** Co-operation between monozygotic (MZ) twins. With permission of the mother

**Figure 95.3** Conflict between twins. With permission of the mother

## THE INTRAPAIR RELATIONSHIP

From the start, the emotional environment of a twin baby differs markedly from that of a singleton, because he must develop two strong emotional ties simultaneously: to the mother and to the co-twin (or vice versa). The age at which twins become distinctly aware of each other varies greatly. Some ignore each other for up to 8 months, while others appear sensitive to each other from the start. Regardless, the sleeping, feeding and even the breathing patterns of one twin baby may be influenced by those of the other from a very early age[15].

The relationship between twins is unique in that it is shared by both partners throughout their lives unless they are separated by life circumstances or death (Figures 95.2 and 95.3). The intensity of this relationship varies greatly. For many pairs, the companionship, help, stimulation, comfort and reassurance is of inestimable benefit. For others, the negative aspects such as dependency, conflict and rivalry are serious handicaps. Some pairs come to overdepend on their twinship and lack confidence on their own, finding it hard to establish an individual identity except as a part of the twin pair. In the aggregate, however, the positive influences of twinship appear to outweigh the negative, at least as judged by social adjustment in adolescence[17].

### Personality and identity

Personality differences may appear at a very early age, even in monozygotic (MZ) twins, although these tend to be more similar in their behavior than dizygotic (DZ) pairs[18]. In the early years the differences between the children tend to manifest themselves more in temperament, whereas later a variance in the degree of sociability is more common.

Twins are usually very conscious of which of them was born first. In most cultures (but not for example among the Yoruba of Nigeria) the first-born is regarded as the senior. Birth order is one of the

factors that later determines a twin's self esteem[6], possibly leading to the first-born having traits characteristic of the eldest child in a family[19], including leadership skills and aggression. This phenomenon is probably due to the disproportionate interest in birth order so frequently shown by other people.

In the past, twin children were more likely to be treated as a single unit, dressed alike, rarely separated from each other and frequently given twin-sounding names. Unfortunately, this still occurs in some families. Even having the same initial can be a serious nuisance to a teenager, especially in relation to schoolwork and personal correspondence. Dressing infants and children the same makes it more difficult for people to tell them apart, use their correct names and treat them as individuals. Whereas many parents now appreciate the importance of the two children developing their own identities, external pressures (not least from grandparents) may make it difficult for them to carry out their intentions of, for example, dressing twins differently. Identical outfits are seen as cute, even though they are the enemy of personal identity. Photography can reinforce the tendency to treat twins as a unit, especially if the twins are photogenic, and the twins are often portrayed together without even clearly naming them. Inevitably, in later years, parents as well as the twins have difficulty in identifying each MZ twin from such photos. This can be disconcerting for the family.

It is helpful for parents to be introduced to the concepts of identity and individuality during the pregnancy, not least to allow them to educate grandparents and friends who may otherwise shower the family with pairs of identical outfits. Unfortunately, some MZ twins become so obsessed by their apparent sameness that they remain almost pathologically tied to each other for decades, even into old age.

### Behavior

From infancy onwards a twin child is different from a single-born in that he/she may never spend time alone, or experience the solitude and silence which normally gives children the chance to pursue their own fantasies, learn about self-awareness and how to be comfortable alone with themselves.

Twin children tend to be more easily distracted, have more difficulty in concentrating and be more prone to attention deficit hyperactivity disorder[20]. This may well result from constant distraction by the co-twin throughout the early years, or parents who reinforce this tendency by shifting attention from one child to the other when the twins are together or trying to compensate for their perceived neglect by overstimulation when they spend time alone with only one child. Indeed, 'quality time' need not be intense or active, but it clearly should represent something special for parents and their children.

The close relationship between twins often empowers the pair to defy parental discipline or present a daunting front to other children. The combined force of determined and well-practiced twins can be extremely difficult to manage. Collusion between the pair can exclude all other members of the family, especially if they, not uncommonly, develop their own secret language. The effects can be devastating when their combined ingenuity is compounded by growing physical strength, as many kitchens clearly show. Moreover, twins often encourage each other and persevere with their mischief-making for much longer than would a single child. In a child psychiatric clinic, Simonoff[21] found no overall increase in psychiatric problems in twins, but conduct disorders were significantly more common.

Parents of twins need to contrive special opportunities for praising good behavior and developing a stronger relationship, one to one, with each child. They need to avoid inflicting punishments that affect both children if only one twin has misbehaved. Reprimands and punishment should be administered to the guilty child alone and in private.

## ILLNESS AND DISABILITY

### Acute illness

If twins are born preterm, they will be vulnerable to infection, especially during the early months. Apart from this, however, twins are in general no more prone to most physical illnesses than single-born children. If, on the other hand, one child has an infectious illness, it is much more likely that the twin will contract it also.

If one twin has to go into hospital during the early years, the effect on both children may be profound, especially if they have never previously been apart or the admission is unexpected. Both twins lose their closest companion and, unlike a singleton, the hospitalized twin suffers the trauma of separation simultaneously from the co-twin and the mother. In this situation, regrettably, many hospitals do not allow co-admission of the healthy twin baby. If both infants are still being breast-fed, the mother do suffer additional strain because of the logistical problems of maintaining this routine. Hospitals should make every effort to ensure that both twins can maintain close contact with their mother and each other.

### Accidents

No precise data are available on the accident rate in twins, but it would be surprising if it were not

relatively high, as it is plainly more difficult to keep an eye on two active toddlers simultaneously. Furthermore, the combination in twins of mutual encouragement and physical co-operation is likely to lead not only to much more reckless activity but to the accomplishment of many feats of danger or destruction at an earlier age than a single child on its own would achieve. Whereas some parents develop a remarkable ability to keep an eye on several children at the same time, relatives and other carers usually find it difficult. An added danger exists for MZ twins if they are dressed alike because, at a distance, they may be indistinguishable to the parents, let alone teachers and others, who therefore are unable to shout an individual warning in an emergency.

Serious injury which leads to long-term disability and/or disfigurement also gives rise to a special problem. For an affected MZ twin, the constant reminder of what his/her appearance and abilities should have been like may increasingly induce frustration and anger with time. Meanwhile, the unaffected twin may feel guilty that it is growing up unscathed. For the very same reason, if the father or mother were directly responsible for such an accident, the contrast between the children exacerbates feelings of remorse and grief and may adversely affect the parents' relationship with each other.

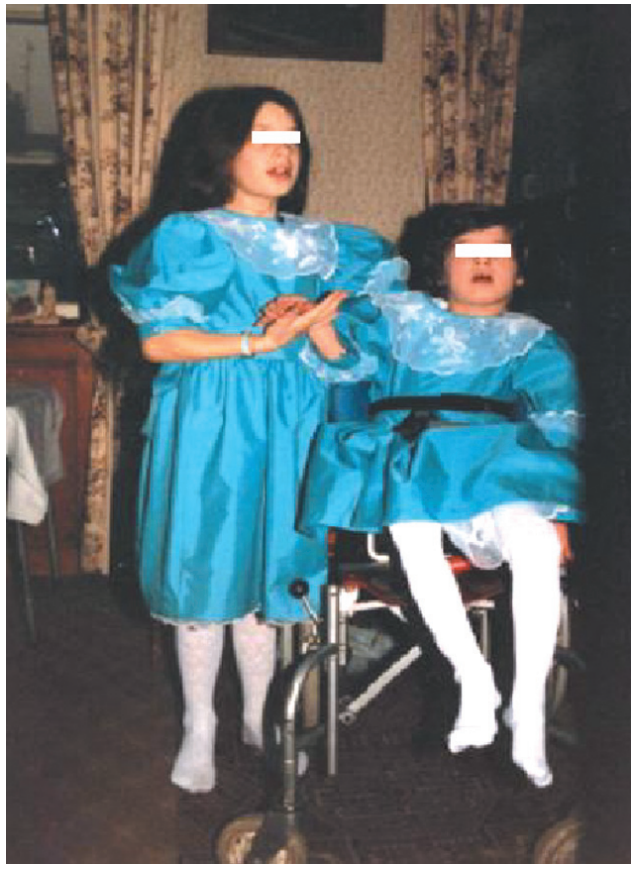


**Figure 95.4** 8-year-old dizygotic (DZ) twins dressed alike, one with cerebral palsy and intellectual impairment following birth asphyxia

## CHRONIC ILLNESS AND DISABILITY

The care of a twin child with special needs invariably poses challenges for parents who are faced with the difficulty of caring simultaneously for another child (or children) of the same age, but with very different needs[22]. As a result of the extreme needs of one child, the very special needs of the unaffected child are often inadequately recognized.

The disabilities experienced by multiple-birth children are of course, in themselves, the same as those suffered by singletons. However, the origin of the impairment may be unique to twins (e.g. the twin–twin transfusion syndrome, or the effect of a monochorionic intrauterine death on the surviving twin). Disabilities may also occur with greater frequency (e.g. cerebral palsy or intellectual impairment), mainly due to long-term complications of a preterm birth (Figures 95.4 and 95.5).

In many cases the diagnosis will be made prenatally or at birth. In others, however, parents may become increasingly anxious about their child's physical or mental development during the early months and years, so much so that some become unnecessarily alarmed by the slightest discrepancy in development between the twins. In DZ twins, this discrepancy may result from different rates of normal development. In any event, parental concerns should always be taken seriously and never dismissed on the grounds that the delay is 'just because they're twins',

**Figure 95.5** 14-month monozygotic (MZ) triplets, one with spastic diplegia (right). With permission of the parents and the Multiple Births Foundation

an explanation all too often offered by health-care professionals. Any disparity in the physical or mental development between MZ twins, particularly if this is increasing, is always a cause for investigation.

### The twin with special needs

The child with a disability will find it difficult to understand why, in some respects at least, it does not have the same abilities as its twin. Many are keen to understand their disability, and an explanation may provide comfort. If, for example, the cause of an impairment was severe neonatal illness, a child may develop a sense of triumph that it survived against the odds. It is inevitably painful, however, for the disabled child to watch their co-twin doing things that he/she may never be able to do. In particular, MZ twins are faced with the constant image of how they might have been, or even appeared. Later, the disabled child may resent the co-twin's ability to become more independent. In these circumstances, jealousy, anger and depression are not uncommon.

There are, however, some positive aspects of being a twin with special needs rather than the equivalent single-born child. The unaffected child can be a constant source of companionship and stimulation, bringing friends who are able to provide opportunities to relate to healthy children of a similar age.

Even if the two children are at very different levels of physical and mental development, parents may find it hard to stop treating them in exactly the same way. This artificial imposition of 'twinness' can become an added burden for one or both children. To dress a child in a wheelchair in the same outfit as a healthy co-twin may be unkind to both children.

### The unaffected twin

It is not unusual for a healthy sibling of a child with a disability to present with signs of psychological stress. In twins, however, additional difficulties present themselves. The care of the unaffected child tends often to be delegated to friends and relations from an early age, and the mother's apparent favoritism towards the affected twin may be sorely resented. The constant friendly attention of the many health-care workers towards the disabled child may add to feelings of rejection on the part of the healthy twin, who often turns to attention-seeking behavior, welcomes or exaggerates an illness, contrives accidents or exhibits outright regression in imitation of the twin. In all such instances, an obvious if often neglected remedy is to ensure that *both* twins acquire and keep some of their own special adult friends, whether an extra aunt, neighbor or honorary grandparent.

The healthy twin's personal activities and social life may be curtailed by the limitations of the disabled twin, which in turn can restrict the activities of the entire family. In addition, he/she may feel embarrassed or reluctant to invite friends to the house. Later, complex emotions including jealousy, guilt and a deeply felt burden of responsibility are not uncommon. The well twin may spend an undue amount of time caring for the affected sibling, often at the expense of personal activities. Parents can help the unaffected child from an early age to understand the difficulties faced by the co-twin, the reasons for them and the implications for the family. Reassurance, where appropriate, should be given that they are not going to be similarly affected and that he/she is in no way responsible for the co-twin's problems.

## CHILD ABUSE

Child abuse in twins, but it appears to be significantly higher in multiple-birth families[23], and any singleton sibling may be at as great a risk as the twin children[24] (see Chapter 101). In general it is more common for only one of the twin pair to be abused. When this is the case, the affected child tends to be disadvantaged in some way, usually by disability or neonatal complications. A disparity in development or responsiveness is a key factor in these cases[23]. When both children are abused, it is more likely that the mother is suffering from severe psychosocial problems[23].

If only one of the twins has been abused and it is thought necessary to remove this child from the parents, a dilemma arises as to whether both children should be placed in care. There is no easy answer to this question, but whatever happens, the children should be allowed to keep in touch with each other and the new carers should be made aware of the importance of the twin relationship.

## ADOPTION

The critical factor of twinship must be considered when, for any reason, placement of a twin for adoption becomes an issue[25]. In the past, twins who were being adopted were often separated, causing much distress and much unresolved searching[26]. Most adoption agencies would now agree that healthy twins should be placed together. In contrast, there is less agreement where one is ill or has special needs. In such cases, the choice of placements will inevitably be reduced, and the adoption of the healthy child may therefore be delayed. Some would also question whether the healthy child should be burdened with a disabled twin sibling when this situation could be avoided by separate placement.

It is essential that potential adoptive parents are first given information about twins in general, and a realistic picture of the emotional and physical demands they bring with them. Like all couples expecting twins, potential twin parents will also benefit from an introduction to the local twins club, as well as relevant literature. Finally, but most important, potential adoptive parents need to clarify their own motives for adopting two babies/children at once.

Any child given up for adoption may feel that he has been rejected by his biological parents. However, when one of the twins is placed for adoption, as may be the case when the biological parents decide they want only one child or where only one of the twins is abused (see above), the adopted child has the added burden of feeling that a twin sibling has been chosen in preference to him. Such a child will not only be deprived of a twin relationship, but feel an even greater degree of rejection than would exist if the parents had given both babies away, or had been thought incapable of caring for any child at all.

## DEATH

### The single surviving twin

A twin has a greater risk of death all the way from conception right through the first 10 years of life[27]. Many more parents of twins are likely to experience bereavement at some time than those with single-born children, and so are twins themselves. As this chapter is concerned with childhood issues, the focus is on the young, single, surviving twin. The perinatal loss of both twins is considered in Chapter 103.

The more common situation is the death of one twin (or triplet). The number of single surviving twin children is difficult to determine, especially if loss in early pregnancy is included, but numbers of twin children whose twin was stillborn or died in childhood is estimated as between 5 and 15% of all twin pairs[28].

In many respects, the death of a twin child has the same effect on the family as that of a single-born child. There are, however, some aspects of the bereavement that are different.

### Perinatal death

Parents who lose one twin commonly find that their loss is underestimated, even by professionals who are liable to say that at least they have the live twin as solace. Furthermore, many parents feel a double bereavement in that they lose not only a precious child, but also their special status as parents of twins, as having twins may be the most special event a couple ever experiences. The surviving twin thus suffers not only from a personal sense of loss but also from the effects of being brought up by grieving parents who may idolize the child who has died. A number of adult twin survivors believe that their parents blamed them for the intrauterine death of their twin, or that they would have preferred the other child to have survived, particularly where it was of the opposite sex[29].

The child whose co-twin died in the perinatal period may later feel distress, anxiety or even just curiosity, but often are reluctant to express these feelings for fear of upsetting the parents. The survivor may also have more complex reactions to the death. Many feel angry: angry with their twin for deserting them; for causing such unhappiness in the family; for making them feel guilty as the survivor. Survivors may also be angry with their parents for 'allowing' the twin to die. Still others feel guilty that they have survived, particularly if at the expense of their twin as, for example, in the twin–twin transfusion syndrome.

The surviving twin child may be bewildered as to why special events, such as birthdays and starting school, both of which are happy occasions for most families, make his parents sad. Many surviving twins feel relief when they finally talk about their twin, sometimes not until many years later.

In the past, many surviving twins of a perinatal twin death did not discover they were a twin until adulthood. Most professionals now would agree that both parents and children are likely to cope better with their bereavement if the dead baby is freely discussed from the start, and the survivor can participate in sharing mementoes of their brother or sister, including photographs of the two babies together. If one does not exist, two photographs can be merged, or an artist can prepare an attractive sketch based on separate original photographs, a process which is particularly helpful if the dead baby is disfigured. The same may be said for naming a stillborn baby, to make it easier for the child to refer to his twin in later life.

Too often, when a twin child dies early in life, it is never mentioned. Teachers and even nursery staff who do not know of the twin miss the chance of giving comfort and explanation to a bereaved child. This is important, because a young child often finds it easier to explore and express feelings through drawing and painting than through words (Figure 95.6).

Parents who delay telling the survivor often find it increasingly difficult to break the news, risking that the child discovers the truth from other sources and is puzzled or shocked that such an important aspect of life should have been hidden. Reactions of children who are only later told that they were born a twin vary from indifference, distress or confusion to elation, pride and curiosity. Many who have not

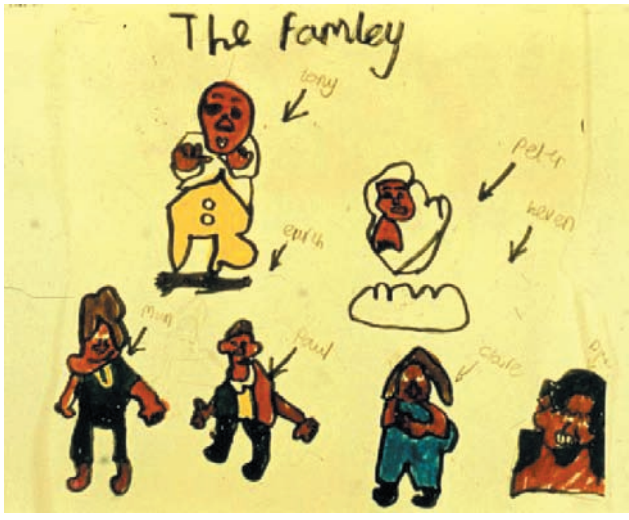



**Figure 95.6** Drawings by a 9-year-old boy whose twin, Peter, died aged 6 weeks. Reproduced with permission of the artist, Tony

discovered their twinship until adulthood have said that the revelation explained a long-held inner feeling of loneliness.

Parents may need help in breaking the news if the survivor is not aware of being a twin, although, in general, the earlier this is done the easier it is likely to be. In some instances, they should be reassured that a further short delay is wise, so that they can then emotionally prepare themselves for the child's possibly complex reactions. The child can also be prepared, perhaps through bedtime stories, to understand the concept of twins (or higher multiple births) and of prematurity. A child can be told in simple terms about low birth weight and the sad fact that small or preterm babies sometimes die. Teachers and close friends should know that the child is to be told about his twin so that they can be prepared for comments and questions.

After the child is informed, parents may offer to show places associated with the twin, such as the hospital where they were born and the baby's grave if one exists. They may also find it helpful to introduce the child to an adult or older child whose own twin has died in infancy. Most countries now have organizations for bereaved twins such as the Lone Twin Network in the UK. The contact details of these are available on the website of the International Society for Twin Studies (www.ists.qimr.edu.au).

### Twin death in childhood

Whenever a twin dies in childhood, whether from accident, chronic illness or acute infection, the effects on the survivor are devastating, as the surviving twin will never have known life without a constant partner of the same age. This problem is likely to be accentuated when the twins have had little experience of being separated or where the one who died was the 'leader'.

A twin can only be prepared for life without a constant partner if that child is as closely involved with his brother or sister's illness and death as the level of understanding allows. Parents may need help in deciding when to tell the child that the twin is going to die, how the illness is likely to progress and what form the death is likely to take. The child understandably may have fears, unspoken or acknowledged, of developing the same illness, or indeed, dying in the future. The dying child (and the twin) may have outstanding business to settle before the death, such as deciding to whom special possessions should go.

Many surviving children resent the premature sorting or discarding by parents and teachers of their twin's belongings after death, often without consultation. Parents may, probably mistakenly, want to turn away from such painful reminders, but, for many children, the harboring of mementoes can be a necessary part of coming to terms with the death, and the sorting usually needs to be done gradually.

A surviving twin may well feel guilty, after the death, to have been the one chosen to live. This guilt, of course, is compounded if the survivor assumes direct or indirect responsibility for the twin's death. Guilt is also compounded if the parents seemed to have preferred the other child, or placed undue store on being 'parents of twins', and betray this aspect of their grief.

Many parents, while still grieving, find the survivor's disturbed behavior extremely stressful. In MZ twins this is often reinforced by the constant reminder of the dead child provided by the survivor – not only in appearance but also in behavior and mannerisms. The parents often forget the trespasses of the dead twin, and idealize this child to the detriment of the survivor. Even when parents have been open and sensitive to the surviving child's needs, it may be extremely hard to come to terms with becoming the sole focus of his parental (and others') attention. This is particularly likely when death follows a long illness during which the 'healthy' twin has inevitably remained in the background.

## SUPPORT FOR FAMILIES

Families with multiple births need informed advice and support from their professional care-givers, and most will need a lot of extra practical and often some financial help. Even more important, however, is the advice and emotional support provided by other experienced parents of twins. Many countries now

have a national twins association which will provide useful information and advice, as well as being an umbrella for a network of local parents-of-twins clubs which provide mutual support for parents. Telephone helplines can also provide an invaluable service to both parents and professionals.

The Multiple Births Foundation (MBF) was established in the UK in 1988 as the first organization to offer professional support to families with twins, triplets and more, as well as information, advice and training to the many medical, educational and social-work staff concerned with their care. It has also produced a series of five sets of comprehensive guidelines for the professional care-givers of multiples, which provide guidance from before conception through childhood to adolescence[30].

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# Risk and Early Development: Findings from the Louisville Twin Study

*M. L. Riese*

96



## INTRODUCTION

The nature of twinning often places twins at risk for developmental and behavioral problems. The long-term research programs of the Louisville Twin Study have contributed significantly to the investigation of risk factors in the early years. The Louisville Twin Study is a research project in the Department of Pediatrics at the University of Louisville. It began in the mid-1950s as one of the international studies of child development, with an emphasis on the longitudinal study of how genetic and environmental factors influence physical growth and mental development. In 1976 the main focus of the program became the assessment of temperament in infant twins, with personality, language and behavior also studied. Twins, triplets, quadruplets, siblings of twins and parents of twins were assessed, and procedures included hospital observations, laboratory observations, physical measures, questionnaires, interviews and parental reports.

Central to the study of risk for twins is the assessment of whether risk is short-lived or permanent, and determination of relevant variables and conditions. The current presentation focuses on temperament and mental development, with consideration of how variables such as gestational age, size for gestational age, weight discordance between co-twins and gender may be related to risk in those areas.

## TEMPERAMENT

### The neonate

Much of the study of temperament began by evaluating the twins in the neonatal period, allowing for an assessment of behavior before familial and environmental socializing factors could influence the behaviors of interest. The assessment included spontaneous activities of the infant in different behavioral states, as well as the infant's responses to external stimulation. The behaviors of interest were determined to have a constitutional basis and a relation to the integrity of the nervous system[1–3].

Neonates were assessed during a period from one stated nursery-scheduled feeding time to the next nursery-scheduled feeding time (3 or 4 h, depending on the size of the infant). Comprehensive details of the assessment items and administration, rating scales and scoring are available elsewhere[1–3], and summarized briefly here. Infants were observed:

(1) Before, during and after the feeding for spontaneous behaviors, responsiveness to the care-giver and feeding abilities;

(2) During the first active sleep state following the feeding for spontaneous behaviors;

(3) While awake for the evaluation of maturational level, sensorimotor status and orienting behaviors, including visual and auditory responses, reflexive responses, alertness, activity and interactive behaviors;

(4) Responsivity to a mildly noxious stimulus consisting of a cold object placed on the infant's thigh;

(5) Both spontaneous and responsive irritability and soothability throughout the assessment, and including a standardized series of soothing procedures before a scheduled feeding[1].

The scores from the entire assessment battery were combined into six categories of behavior: irritability,

**Table 96.1** Comparison of newborn twins' temperament ratings by birth gestational age. Adapted from references 3 and 4

| *Variable* | *Age group* | *Comparison* | *Age group* | *Age group* |
|---|---|---|---|---|
| Irritability | 38–41 weeks | more than | 35–37 weeks | 29–34 weeks |
| Resistance to soothing | 38–41 weeks | more than | | 29–34 weeks |
| | 35–37 weeks | more than | | 29–34 weeks |
| Reactivity | 38–41 weeks | more than | 35–37 weeks | 29–34 weeks |
| Activity asleep | 38–41 weeks | less than | | 29–34 weeks |
| Activity awake | 35–37 weeks | less than | | 29–34 weeks |
| Reinforcement value | | no differences | | |

resistance to soothing (soothability), reactivity, reinforcement value (of the infant's behavior to the examiner), activity level while awake and activity level during sleep. Inter-rater reliabilities for exact agreement on scores ranged from 0.85 to 0.97[1].

### *Prematurity*

The preterm infant is clearly at risk for various developmental disabilities, ranging from 'hard' neurological abnormalities, including severe cognitive deficits, to 'soft' neurological signs, such as fine motor impairment (for review, see reference 3). Although early research typically evaluated mental and motor performance to examine the developmental integrity of preterm infants, the evidence linking temperament to a relationship between the nervous system and behavior called for an evaluation of potential detriments in temperament development for preterm infants. Because a large proportion of twins are born prematurely, temperament for 120 full-term and 160 preterm twins was compared to determine whether being premature, as well as degree of prematurity, affected temperament scores during the neonatal period, as well as temperament and other areas of development in the first few years of life.

The full-term twins were assessed in the first few days of life[3]. The preterm twins were assessed when they were medically stable, shortly before discharge from the hospital, between 2 and 53 days of age. Analyses were conducted to determine whether there were differences in average ratings in the neonatal scores between full-term twins of 38–41 weeks' gestation, preterm twins born between 35 and 37 weeks' gestation and preterm twins born between 29 and 34 weeks' gestation[3,4]. The full-term infants were found more irritable than both groups of preterm infants, more difficult to soothe than the earlier-born preterm infants (29–34 weeks), more reactive to auditory and visual stimuli than both groups of preterm infants and less active during sleep than the earlier-born preterm infants (Table 96.1). As such, these findings defined levels of performance on these temperament variables among healthier, better-integrated infants compared with infants at risk due to prematurity. More mature infants were those who were more irritable, more difficult to soothe, more reactive to auditory and visual stimuli and less active during sleep than less mature infants. Although the direction of some scores for lower-risk infants might be counter-intuitive (e.g. lower-risk infants were more irritable and more difficult to soothe than higher-risk infants), the obtained average ratings were not in the extreme ranges that might suggest abnormally high scores for any of the behaviors assessed, but rather the average ratings included normal ranges of behavior.

Differences were also observed between the two groups of preterm infants. Specifically, later-born preterm twins (35–37 weeks) were more difficult to soothe and less active while awake than the earlier-born preterm infants (29–34 weeks, Table 96.1). Degree of prematurity was related to ease of soothing and activity while awake, thereby demonstrating increased risk in certain behavioral areas with increasing prematurity for the twins. No differences were present between the groups in ratings received for reinforcement value of the infant's behavior for the examiner.

These results suggest potential difficulties for parents in their interactions with their preterm twins. Although lower levels of irritability might make parenting easier, particularly for parents of twins who typically face greater demands in caregiving than parents of singletons, neonatal crying expresses various needs and demands. Furthermore, alert and responsive neonates have mothers who are more responsive and stimulating with their infants[3,4]. The preterm twin does not elicit as much interactional behavior as the full-term twin, and opportunities for interaction and stimulation between

parent and child are reduced. It may be helpful, then, to counsel parents of preterm twins in order to encourage increased opportunities for interaction, because the infants' behavior patterns would not be as likely to elicit appropriate responses from the parent(s).

### *Size for gestational age*

Size for gestational age is also related to risk in development. In addition to demonstrated delays in infancy, small-for-gestational-age (SGA) children have more learning difficulties at school, a higher incidence of neurological and behavioral abnormalities and poor scores on developmental tests, compared with appropriate-for-gestational-age (AGA) children (for review, see reference 5). Therefore, to determine whether small size for gestational age was a risk factor for twins' early temperament, neonatal ratings were compared for same-sex twins within pairs in which one twin was AGA and the other twin was SGA[5]. Separate evaluations were made for same-sex full-term and preterm twin pairs, because behavioral deviance was demonstrated for preterm twins in these areas when compared with full-term twins.

The sample consisted of 17 female and 12 male full-term pairs, and eight female and seven male preterm pairs born between 31 and 37 weeks' gestational age. For the full-term twins, a significant difference was found for irritability ratings, with AGA twins being rated as more irritable than their SGA co-twins. No behavioral differences were noted between the AGA and SGA preterm co-twins. Because normal levels of both spontaneous and responsive irritability elicit parent–infant interaction, these findings suggested, similar to those for full-term and preterm differences, that the full-term SGA twin may present fewer opportunities for interaction than the full-term AGA twin. In contrast, the preterm SGA twin did not display different behavioral patterns from those of his or her AGA co-twin, indicating no increased risk beyond the prematurity itself.

### *Weight discordance*

An additional means to evaluate the relationship between size at birth and behavioral risk is to assess twins who are discordant for weight. Co-twins typically have different weights at birth. According to the published literature, a difference of 10% between co-twins was considered to be the norm, and 15 or 20% or more to be abnormal, thereby defining discordance for weight for these studies. (See Chapter 60 for a current discussion on the definition of weight discordance in co-twins.) A comparison of co-twins was conducted with full-term twins who were discordant in birth weight to determine whether the slower intrauterine growth of one twin was reflected in early behavioral differences between the co-twins[6].

A review of previous studies conducted with discordant pairs[6] indicated contrasting results in that the lighter twin performed more poorly, at a higher level or at the same level as the heavier twin on tests of cognitive development from 3 months to 17 years of age. Other studies reported more problem behaviors for the lighter twin when measured between infancy and 8 years of age, less easy-going and self-assured behaviors for lighter teenage twins and higher attention and more easily soothed behaviors for 1-year corrected-age preterm lighter twins, compared with their heavier co-twins[6]. The potential limitations of previous studies, however, included the combining of full-term and preterm twins, as well as defining premature to include SGA infants; wide-ranging ages for testing in a single study; varying definitions of discordance across studies; and the interaction of environmental variables with the birth-weight differences potentially influencing the findings.

Our study examined the significance of relative birth weight on neonatal behavior for a sample of 70 full-term twin pairs who were at least 15% discordant for birth weight[6]. Percentage difference in birth weight was defined as [(birth weight of larger twin – birth weight of smaller twin)/birth weight of larger twin] × 100. For this sample, percentage discordance ranged from 15 to 47%, with a mean of 23%.

A comparison of the discordant co-twins on the neonatal temperament variables indicated that the larger twin was more irritable, more difficult to soothe, more active while awake, more active during sleep, less reactive to visual and auditory stimuli and less reinforcing to the examiner (Table 96.2). Because of the wide range of weight discordance, additional analyses were conducted to determine whether degree of birth-weight discordance between twins influenced neonatal behavioral differences between the co-twins. The lower and upper quartiles of percentage of birth-weight discordance (15–17%, and 29–47%) were designated as the extreme groups. For co-twins in the upper quartile, the larger twin was more irritable, more active while awake, less reactive to visual and auditory stimuli and less reinforcing to the examiner than the smaller co-twin. For co-twins in the lower quartile, the larger twin was rated as more irritable than the smaller twin. Co-twins with greater birth-weight discordance were more likely to display differences in neonatal temperament scores than co-twins with less discordance. These findings may have clinical significance by suggesting that the twins in the upper extreme group are more compromised than other twins in the sample.

**Table 96.2** Comparison of full-term newborn twins' temperament ratings by weight discordance (larger or smaller co-twin). Adapted from reference 6

| *Variable* | *Size group* | *Comparison* | *Size group* | *Total or extreme group* |
|---|---|---|---|---|
| Irritability | larger | more than | smaller | total<br>most discordant<br>least discordant |
| Resistance to soothing | larger | more than | smaller | total |
| Reactivity | larger | less than | smaller | total<br>most discordant |
| Activity asleep | larger | more than | smaller | total |
| Activity awake | larger | more than | smaller | total<br>most discordant |
| Reinforcement value | larger | less than | smaller | total<br>most discordant |

The differences obtained for irritability ratings, activity while awake and reinforcement value were similar to those observed previously for other high-risk groups. These similarities suggest that the smaller twin in the discordant group demonstrates behavioral deviance, compared with the larger co-twin. On the other hand, however, the larger, presumably lower-risk twin, had lower reactivity scores than the smaller, presumably higher-risk twin, similar to the performance of preterm infants compared with full-term infants.

The discrepant findings may be related to intrauterine factors. The lighter twin is typically considered to be deprived *in utero* in terms of nutrition and/or blood supply. The heavier twin may also be at a disadvantage, however, as in the case of anastomoses in monozygotic twins in which the larger fetus has a significantly increased blood volume. Brain development in dizygotic co-twins could also be affected differentially by other placentation variables, similar to the effect on physical growth rate for weight discordance. In summary, it appears that co-twins who are more discordant in birth weight may be more compromised in early behaviors than co-twins who are less discordant in birth weight.

### *Prematurity and weight discordance*

An additional study was conducted to determine whether gestational maturity at birth influenced behavioral differences between discordant co-twins[7]. Neonatal temperament ratings for 66 preterm discordant twin pairs were compared for the lighter and heavier co-twins. Percentage discordance ranged from 15 to 48%, with a mean of 24%. In contrast to the findings for the full-term discordant co-twins, no significant differences were noted between the larger and smaller preterm co-twins on any of the temperament variables. The lack of differences in ratings for the preterm group suggests that continued exposure to the intrauterine environment until full-term status for twin pairs who are discordant for weight may be a risk period for early behavioral development, especially as the difference between the co-twins becomes larger. Thus, brain development and subsequent neonatal behavioral development may be affected by the same prenatal environment that resulted in the large weight differences for the extremely discordant twins.

### *Gender*

Sex differences are of interest not only for their social implications, but also because they may describe differences in risk during development. The origins of sex differences in development are speculative, so that an evaluation of such differences in the neonatal period could address the question of environmental or biological influences on behavior. For twin pairs, sex differences observed in unlike-sex pairs could have implications for interaction patterns with parents and other care-givers.

Earlier research typically found few sex differences in behavior during the neonatal period, specifically in activity level, crying, visual tracking of moving objects, auditory receptivity and soothability. An exception is the consistent finding that female neonates are more sensitive to both tactile and oral stimuli than are male neonates (for review, see reference 8). Somewhat later research reported higher orienting scores for girls than for boys, higher levels of low-intensity motor activity for males than for females, higher activity during quiet sleep and while awake and more crying for males than for females, and more facial movements for females than for males. That early research typically examined only a

few features of behavior during a relatively short period of time. Our later evaluation of sex differences in ratings on the more comprehensive neonatal assessment for unlike-sex twins provided more robust and reliable descriptors of behavior, and, by inclusion of co-twins, controlled for maternal familial and social variables that could differentially influence neonatal behavior[8].

Thirty pairs of full-term, unlike-sex twins were included for this evaluation. Female twins were more irritable and more difficult to soothe than their male co-twins. The previous results comparing full-term and preterm twins, and AGA and SGA co-twins, indicated that the lower-risk twins were more irritable and more difficult to soothe than the higher-risk twins. These findings for unlike-sex twins indicated, therefore, that in these two areas of behavior, the neonate male twins resemble the previous high-risk populations, and that male twins are at higher risk than their female co-twins. These behavioral differences may reflect transient maturational gender differences, or may have long-term implications for infant–care-giver interactions, as has been discussed in relation to other groups. Other research had demonstrated that mothers' responsive behaviors, such as talking and holding, are different for irritable girls and boys (for review, see reference 8). For twins, the higher irritability of girls may continue to influence interaction, so that more opportunities are presented for the care-giver to talk to girls than to boys.

## SLEEP BEHAVIORS

### Small-for-gestational age neonates

Another means to evaluate integrity for possible early identification of infants at risk for developmental problems is by observation of neonatal sleep behaviors and behavioral state cycling, as the organization of states has been related to central nervous system (CNS) functioning (for review, see reference 9). These variables are predictive of later developmental problems observed from 8 months to 12 years of age, such as poor organization of behavioral states, medical or behavioral dysfunction, poor regulation of attentional patterns and lower intelligence quotient (IQ) scores, and are also considered to be good indicators for detecting normal and abnormal CNS development (for review, see reference 9). For these reasons, the frequency of occurrence of specific behaviors during active sleep, as well as sleep cycling, were compared for 20 pairs of same-sex (ten female, ten male), full-term AGA and SGA co-twin neonates[9].

For this assessment, infants were observed for 10 min during the first active sleep period following the nursery-scheduled feeding, beginning 2 min after active sleep was confirmed. Time-sampling recordings, consisting of alternating 15-s observation and recording periods, were made of the occurrence of the following spontaneous behaviors: the number of limbs moved (0–4) and vigor of limb movement (slight, moderate or large); body movements consisting of startles, stretches and head movements; movements of hands to face; and mouth movements consisting of smiles, grimaces, sucks and other general mouth movements. The length of the first sleep cycle was determined, including the length of the first active sleep period and the first quiet sleep period. Inter-rater reliabilities for sleep behaviors and behavioral states ranged from 0.85 to 1.00. These specific sleep behaviors are those which are described as spontaneous behaviors observed in specific states in the neonatal period, which define the specific neonatal states, and which have been found to differentiate full-term infants from preterm infants (for review, see reference 9).

AGA twins had more vigorous movements, more right hand-to-mouth movements and fewer spontaneous smiles than their SGA co-twins. Several trends suggested that AGA twins had more small limb movements, fewer startles and more left hand-to-face movements than their SGA co-twins. Using a composite of these variables strengthened the differentiation between AGA and SGA twins, while at the same time eliminating the potential redundancy of related variables. Because the frequency of neonatal complications was not different for the two groups, these behavioral differences were most likely related to intrauterine factors associated with growth restriction. Furthermore, these specific behaviors have previously been found to be markers of risk, having differentiated other risk populations from healthy neonates.

No differences were observed between the AGA and SGA twins in time spent in first active sleep or first quiet sleep, nor in the length of the first sleep cycle. Contrary to the findings that indicated differences in these variables for preterm and full-term infants, or for infants exposed to *in utero* drugs and alcohol, measures of neonatal state cycling did not differentiate between AGA and SGA co-twins.

## LONGITUDINAL STUDIES

### Prematurity

The knowledge that preterm infants are delayed in several areas of development, as well as finding differences between full-term and preterm infants in temperament ratings in the neonatal period, indicates that temperament should be included as an

area of risk for the later development of the preterm infant. Associations between temperament variables, poor behavioral adjustment and intellectual achievement have been described (for review, see reference 10). Because those behavioral areas are also areas of risk for preterm infants, understanding temperament development for these infants helps to determine whether temperament is associated with other developmental disabilities encountered by preterm infants.

Many of the twins assessed in the neonatal period were also evaluated in the first few years of life, using a laboratory assessment of temperament designed to provide all infants with the same sequence of age-related events[11,12]. During a visit to the laboratory, one twin was left alone for a solo episode with the staff for the temperament assessment, while the co-twin was taken for mental testing. The laboratory assessment consisted of a series of age-appropriate vignettes in which the twin interacted with the staff during a structured series of play activities. The activities were videotaped, and the twin's behavior was rated later for successive 2-min periods on four scales: emotional tone, attentiveness, activity and social orientation to staff. The ratings for all 2-min periods were summed to yield an aggregate score for each rating scale. In addition, measures of period-to-period change in emotional tone and activity were obtained. Inter-rater reliabilities ranged from 0.72 to 0.91.

### *Neonate to 24 months*

The longitudinal association between temperament assessed in the neonatal period and temperament assessed at 24 months of age was compared for full-term and preterm twins[10]. For 67 full-term twins, significant, although modest, relationships between the neonatal period and 24 months of age were observed[13]. Neonatal irritability was related to 24-month emotional tone, attentiveness, social orientation to staff and activity variability. Irritable neonates were rated at 24 months of age as more distressed, less attentive to stimuli, less positive to the staff and more variable in activity level across situations. Significant predictive relationships between neonatal activity while awake and 24-month activity variability, and between neonatal activity during sleep and 24-month emotional tone variability, demonstrated that neonate twins who were more active while awake were more variable in activity level across the laboratory vignettes at 24 months, and those neonates who were more active during sleep were more variable in emotional tone across the vignettes at 24 months of age (Table 96.3)[13].

Although there were several variables that related the neonatal and 24-month periods, the principal variable providing a consistent link between the two ages was emotionality at each age. In the main, for the full-term twin, continuity of behavior was maintained through a period of dramatic transitions in development[13].

**Table 96.3** Longitudinal predictions from neonatal temperament to 24-month laboratory temperament for full-term and preterm twins. Adapted from references 10 and 13

| *Neonate* | *24-month-old* |
|---|---|
| *Full-term* | |
| More irritable | more distressed<br>less attentive to stimuli<br>less positive to staff<br>more variable in activity level |
| More active while awake | more variable in activity level |
| More active during sleep | more variable in emotional tone |
| *Preterm* | |
| More active during sleep | more variable in emotional tone |

The results for 63 preterm twins were compared with those for the full-term sample[10]. A comparison of ratings at 24 months indicated that, in contrast to the findings in the neonatal period, no significant differences were observed between the full-term and preterm groups on any of the variables. Correlational analyses between the neonatal and 24-month temperament variables indicated that the longitudinal relationships observed for the full-term sample, particularly as related to emotionality, were not obtained for the preterm twins. The only significant longitudinal relationship obtained was between neonatal activity during sleep and 24-month emotional tone variability. Similar to the finding for the full-term twins, preterm twins who were more active during sleep in the lying-in period were likely to be more variable in emotional tone at 24 months. Length of hospitalization and size for gestational age were not relevant to the longitudinal correlations. Additional analyses indicated that there was stronger consistency in temperament ratings from the neonatal period to 24 months of age for the full-term infants than for the preterm infants[10].

These findings suggested that complications associated with prematurity may inhibit the full expression of temperament by reducing the arousal level of the infant, particularly as related to measures of irritability/emotionality. Temperament development and stability are areas of risk for preterm twins. The developmental function of the underlying processes

in the neonatal measures appears to be different for full-term and preterm twins.

### *Stability over ages*

To examine the issue of constitutional influences on temperament development, and relation to risk, the stability of temperament measures over successive ages of 6, 9, 12, 18 and 24 months was compared for full-term and preterm twins[14]. The sample size ranged from 81 to 109 full-term twins and 63 to 81 preterm twins in the different age groups, with the sample size decreasing with increasing age for each group.

Separate correlations were computed across ages for the full-term and preterm twins. For full-term twins, significant stability was present across all ages (6–9 months, 9–12 months, 12–18 months and 18–24 months) for all temperament variables, with the exception of social orientation to staff between 18 and 24 months. Temperament stability was observed from 6 months on, and the age-to-age stabilities became stronger with increasing age for emotional tone, attentiveness and social orientation to staff. A similar increase was not noted for activity, however, as the age-to-age relations began at a higher correlation from 6 months onward than for the other variables.

A similar pattern of temperament stability over ages was not obtained for the preterm twins. A significant relationship was obtained for only one variable between 6 and 9 months, social orientation to staff. This stability was not maintained consistently across later age periods, and, in fact, disappeared between 12 and 18 months. Stability across ages was not obtained for emotional tone until the 9–12-month period, remaining stable across ages from that point. For attentiveness, stability across ages was not obtained until 12–18 months. For activity, stability across ages was sporadic, being observed between 9 and 12 months, and between 18 and 24 months.

In summary, stability of temperament was not observed as early, or as consistently, for preterm twins as for full-term twins. Prematurity appeared to depress longitudinal stability during early development, although some temperament patterns were observed to be more stable with increasing age. The differences in longitudinal stability between the groups may be related to differences in rates of maturation within the groups. If temperament is influenced by constitutional factors as suggested, and constitutional factors interact with maturation and experience, then maturational phases influence the degree of stability of temperament in the first 2 years of life. Rates of maturation may also affect the way infants experience events in the environment. In general, it is more difficult to predict certain behavioral patterns for preterm twins than for full-term twins.

## Size for gestational age

To address the question of appropriate longitudinal development for SGA twins, predictive relations between the assessment of reactivity in the neonatal period and laboratory-assessed temperament at 12, 18 and 24 months of age were examined[15]. This measure of reactivity is a component of temperament that reflects responsivity to environmental stimuli, and is a measure of individual differences. Furthermore, auditory and visual abilities are important for processing environmental stimuli.

The sample included 22 pairs of same-sex (eight male and 14 female) AGA/SGA co-twins. The visual and auditory orienting items consisted of responses to a bull's-eye, rattle, bell, voice and face plus voice combined. The scores across trials for each stimulus were combined to create the composite score, reactivity.

Predictive correlations indicated that AGA neonate twins with higher reactivity scores were likely to be rated as more negative in emotional tone at 12 and 18 months of age, less active at 12, 18 and 24 months of age, less attentive at 12 and 18 months of age and less approachful and positive to the staff at 18 months of age, compared with neonate twins with lower reactivity scores (Table 96.4). Several components of temperament at 12 and 18 months of age, and one component of temperament at 24 months of age, were predicted by neonatal reactivity. The results indicated the presence of an underlying process in neonatal reactivity that is meaningful for later infant temperament.

For the SGA twins, there were no significant relationships between neonatal reactivity scores and 12-month temperament ratings. Predictive relations were observed at the later ages, however. Higher neonatal reactivity scores were predictive of more negative emotional tone ratings at 18 and 24 months of age, lower activity ratings at 18 and 24 months of age and lower ratings on approach and orientation to staff at 18 and 24 months of age, compared with lower reactivity scores. No predictive relations were present between neonatal reactivity and later attentiveness for the SGA twins, as had been found for the AGA twins. Neonatal reactivity and alertness were meaningful for later temperament for the SGA twins, but the same pattern of predictive associations between the neonatal period and the later ages was not found for the SGA twins. Intrauterine growth restriction may have depressed the longitudinal associations at the early age for the SGA twins. These findings confirmed previous suggestions that differences in rates of maturation associated with constitutional variables play an important role in temperament development.

**Table 96.4** Longitudinal predictions from neonatal reactivity to 12-, 18- and 24- month laboratory temperament for appropriate-for-gestational-age (AGA) and small-for-gestational-age (SGA) twins. Adapted from reference 15

| *Neonate* | *12-month-old* | *18-month-old* | *24-month-old* |
|---|---|---|---|
| *AGA* | | | |
| More reactive | more distressed<br>less active<br>less attentive | more distressed<br>less active<br>less attentive<br>less positive to staff | less active |
| *SGA* | | | |
| More reactive | | more distressed<br>less active<br>less positive to staff | more distressed<br>less active<br>less positive to staff |

Differences exist between AGA and SGA twins in CNS integrity as related to these behaviors. In this study, the association between higher neonatal reactivity scores and negative temperament ratings in later infancy indicated that the well-integrated twin is likely to express a certain amount of autonomy by displaying more negative emotional tone and more shifting attention when placed in a strange play setting. Furthermore, the better-integrated twin with higher neonatal reactivity scores will be less active at later ages. The SGA twin did not exhibit the same behavioral association as early in development, or as consistently, as the AGA twin.

### Questionnaire ratings for appropriate- or small-for-gestational-age co-twins

Mothers were asked to complete standardized temperament questionnaires for their twins during early development. They completed the Infant Temperament Questionnaire[16] when the twins were 6 and 9 months of age, and the Toddler Temperament Scale[17] when the twins were 12, 18, 24 and 30 months of age. The questionnaires included 95 and 97 items, respectively, rated on six-point scales. Ratings were combined to yield nine scores representing the temperament categories activity, rhythmicity, approach/withdrawal, adaptability, intensity of reaction, mood, attention/persistence, distractibility and threshold of responsiveness. Additionally, during the visit to the laboratory, the Bayley Scales of Infant Development[18] were used to assess each twin while laboratory temperament assessment of the co-twin was carried out.

A sample of 22 pairs of same-sex (eight male, 14 female) AGA/SGA twins was tested at 6, 9, 12, 18, 24 and 30 months of age. Correlational analyses were computed between the neonatal temperament ratings and both the questionnaire ratings and the mental development scores at each age[19]. Separate correlations were computed for the AGA and the SGA twins.

Patterns of significant predictive relations were observed between the neonatal ratings and the questionnaire ratings for the AGA twins (see reference 19 for the specific significant correlations at each age). Individual differences detected for AGA twins during the neonatal period were related to mothers' ratings of their twins' temperament between 6 and 30 months of age. Similar predictive patterns were not observed for the SGA co-twins. For most of the developmental ages, a pattern of predictive relations was present from the neonatal period for the AGA twins. In contrast, no similar pattern, no similar single predictors or very few predictive relations were obtained for the SGA twins. It was noteworthy that a pattern of predictive relations was observed between an objective assessment of neonatal behaviors and maternal ratings of temperament up to 30 months of age for twins who were appropriate for gestational age at birth.

For mental development, correlations between the neonatal assessment and Bayley scores from 6 to 30 months of age yielded a few significant predictive relations up to 30 months for the AGA twins, but no significant predictive relations for the SGA twins. For the AGA twins, then, neonatal ratings of soothability, activity during sleep, reactivity and reinforcement value were meaningful for later mental developmental status.

### Weight discordance

Finding temperament differences between full-term discordant co-twins in the absence of comparable differences for preterm discordant co-twins suggested an evaluation of whether the discordant intrauterine growth of the twins is meaningful for the behavioral development of one or both

twins[20]. To determine whether there were long-term consequences of birth-weight discordance, the laboratory ratings of temperament and mothers' ratings on the temperament questionnaires, at 6, 9, 12, 18, 24 and 30 months of age, were compared for a subset of 30 pairs of full-term discordant twins and 17 pairs of preterm discordant co-twins.

Physical measures were compared first. Differences in weight present at birth were maintained to 30 months of age for both groups. For height, full-term larger twins were taller than smaller twins to 30 months of age, but for the preterm twins, significant differences in height were not observed past the neonatal period. For head circumference, differences were not observed past the neonatal period for either group.

For the laboratory measures of temperament, no significant differences were noted between the co-twins on any of the laboratory measures at any age between 6 and 30 months, either for the full-term or for the preterm co-twins. Thus, the full-term discordant twins overcame the adverse *in utero* influences on early behavioral development that had been observed in the neonatal period.

For the mothers' ratings of temperament, a few differences were present between the discordant co-twins. For the full-term twins, the larger twin was rated as more negative in mood than the smaller co-twin at 9 and 24 months of age. For the preterm twins, the smaller co-twin was more easily distracted than the larger co-twin at 6 months of age. Because of the small number of significant differences, it is possible that they represent chance findings. Prior research demonstrated a predictive relationship between neonatal and 9-month laboratory ratings of emotionality and between neonatal and 24-month laboratory ratings of emotionality, however, suggesting the significance of the 9- and 24-month age periods for the expression of emotionality. The longitudinal discordant co-twin differences, therefore, may reflect true differences in mood between the larger and smaller co-twins as seen by the mother at ages when emotionality is probably expressed more powerfully. The direction of the ratings, both for irritability and for mood, suggests that measures of emotionality might provide a measure of risk for the smaller full-term discordant twin.

In contrast, the single significant difference found for the preterm twins in the questionnaire ratings probably represents a chance finding, as there is no statistical trend or theoretical frame to support it. For full-term twins, therefore, intrauterine variables associated with discordant birth weight may be meaningful for early emotionality development. For other areas of temperament, however, risk based on relative birth weight does not appear to be a predictor of future temperament differences for discordant twins.

## MENTAL AND MOTOR DEVELOPMENT

The mental and motor development of twins is an issue at the forefront of discussion for parents as well as for professionals who follow the development of twins. The Louisville Twin Study began to look at these developmental areas under the direction of the late Ronald S. Wilson. The initial study examined the performance of a twin sample on the Bayley Scales of Infant Development[18] at 6, 12 and 18 months, and compared the scores with singleton norms[21]. Twins scored significantly lower than singletons on the Mental Scale at 6, 12 and 18 months, and on the Motor Scale at 6 and 18 months of age. Correlations between birth weight and the twins' scores on both scales indicated decreasing correlations with increasing age. That is, at 6 months the correlations were between 0.30 and 0.40; at 9 and 12 months they were 0.20 and by 18 and 24 months, they fell to zero. These findings demonstrated the strong retarding effect of twins' low birth weight on early mental and motor developmental scores, with decreasing influence with increasing age in infancy. It also was found that the family's socioeconomic status (SES) did not affect the twins' mental and motor development.

Measures of twins' mental development were extended to 6 years of age[22], with the Stanford–Binet Form L-M administered at 3 years[23], and the Wechsler Preschool and Primary Scale of Intelligence at ages 4, 5 and 6 years[24]. Twins' scores were significantly lower than the singleton norms beginning at 18 and 24 months of age, were comparable to those of singletons at 3 years, were lower again at 4 and 5 years but then equaled scores for singletons at 6 years of age. (The deviation at 3 years was noted to be related to the unusual method of standardization of the Form L-M, resulting in scores that were abnormally high at that age.) At 4 and 5 years of age, scores on Verbal IQ were significantly lower than scores on Performance IQ, reaching a similar level at 6 years of age. Thus, with the exception of 3 years of age, the trend for the twins' mental development showed a linear increase to age 6 years. Sex differences were found, with girls scoring higher than boys until 6 years of age, when the scores for girls and boys tended to equalize. Parental education and SES were modestly related to the twins' IQ scores at 6 years.

Additional analyses indicated that the deficit was larger for the preterm group, with a significant lowering of scores in the first year, and a recovery during the second year. Full-term twins had scores

that were more comparable to the singleton norms in these periods, although a slight decline was noted in the second year[25]. Examination of scores in the lowest (first) centile indicated that a larger proportion of twins than singletons were defined as developmentally retarded, particularly during infancy[25]. Moreover, twins weighing less than 1750 g were more likely to be below average in IQ at 6 years of age (68% of that sample). Eighty per cent of pairs in which both twins were of low birth weight had IQ scores below the norm of 100. Further analyses[26] indicated that twins with birth weight less than 1750 g and whose families were defined as upper SES were likely to achieve the singleton norms at 6 years of age, whereas those whose families were of lower SES were not (mean IQ scores of 101.1 and 86.5, respectively).

The above studies demonstrated that much of the lag in early mental and motor development observed for twins can be accounted for by risk variables that are also related to the early development of singleton children, specifically prematurity, low birth weight and low SES. Because the incidence of prematurity and low birth weight is notably higher for twins than for singletons, a higher proportion of twin infants than singleton infants will be born at risk.

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# Cerebral Palsy and Multiple Births

*P. O. D. Pharoah*

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## INTRODUCTION

The earliest clinical description of cerebral palsy (CP) is attributed to the orthopedic surgeon, Little, who in 1862 entitled his paper: 'On the incidence of abnormal parturition, difficult labour, premature birth and asphyxia neonatorum on the mental and physical condition of the child, especially in relation to deformities'[1]. Subsequently, notable contributions were made by Freud[2] and Osler[3]. Freud classified cerebral palsy in terms of clinical neurological syndromes. Osler focused on the different clinical syndromes that constitute cerebral palsy and described pathological abnormalities found at autopsy. It is presently understood that cerebral palsy is not a single nosological entity but a collection of motor disorders due to cerebral impairment that have occurred during either fetal or early child development.

The complexity of what constitutes cerebral palsy is underlined by its numerous definitions and the variety of its classification systems. In an early attempt to devise a universally acceptable definition, members of the Little Club in London proposed that 'cerebral palsy is a persistent but not unchanging disorder of movement and posture, appearing in the early years of life and due to a non-progressive disorder of the brain, the result of interference during its development'[4]. Since then, numerous other definitions have been suggested[5–7], including a consensus definition that CP 'is an umbrella term covering a group of non-progressive, but often changing, motor impairment syndromes secondary to lesions or anomalies of the brain arising in the early stages of its development'[8].

The classification of cerebral palsy is as contentious as its definition. As long ago as 1952, Perlstein noted that classification may use a variety of criteria depending on the emphasis or viewpoint desired[9]. Table 97.1 summarizes the classifications of CP that have been used.

The difficulties in adopting a universally acceptable definition and classification underline the great variety of clinical abnormalities observed, and suggest that several pathogenic mechanisms may be responsible for the syndrome.

## EPIDEMIOLOGY OF CEREBRAL PALSY

Cerebral palsy is the most common of the many severe physical disabilities that affect children. In spite of the magnitude of the problem worldwide,

**Table 97.1** Classifications of cerebral palsy

| | |
|---|---|
| Anatomical site of brain lesion | cerebral cortex, pyramidal tract, extrapyramidal tract or cerebellum and its connections |
| Clinical symptoms and signs | spasticity, dyskinesia or ataxia |
| Topographical involvement of extremities | quadriplegia, diplegia, double hemiplegia |
| Degree of muscle tone | isotonic, hypotonic or hypertonic |
| Timing of the presumed insult | prenatal, intrapartal, postnatal |

routine data sources are notoriously poor in terms of the epidemiology of this condition. Several population-based surveys[10] have addressed the question: 'How common is CP?' In addition, the high risk of CP among low-birth-weight infants, improving survival rates and the lack of routine data on cerebral palsy prevalence have all encouraged the development of population-based registers[11–17], the prime objectives of which are to monitor trends in prevalence and to put forward hypotheses of pathogenesis.

Crucial to describing the epidemiology of any condition is the use of a universally accepted definition (see above) and a population-based denominator that enables incidence and prevalence to be examined. Because CP is not a single entity, several pathogenic mechanisms may operate. The timing of the insult may be prenatal, perinatal or postnatal. Postnatal cerebral impairment is judged to have occurred when a normally developing infant suffers an infection such as encephalitis or meningitis, physical injury to the brain or a period of severe anoxia following which the clinical abnormalities of CP become manifest. Such postnatally acquired impairment has been termed 'late-impairment' to distinguish it from 'early-impairment' CP that is acquired pre- or peripartum[18]. Late-impairment CP has no specific association with multiple births and is not considered further. In contrast, multiple compared with singleton births are at significantly increased risk of early-impairment CP[19].

Before focusing on the specific association of multiple births and CP, it is relevant to consider birth-weight-specific trends in prevalence. Early data from population-based registers showed conflicting trends in the prevalence of CP, not only in the overall trend but also in that of low-birth-weight-specific groups[11,15,20,21]. Subsequent data, however, have shown a significant increase in the prevalence among very-low-birth-weight infants[22–24].

Whether dealing with singleton or multiple births, crucial to interpreting trends in prevalence and in determining etiological mechanisms is the recognition that what is being measured is prevalence and not incidence. The relationship between prevalence and incidence is: prevalence $\propto$ incidence $\times$ duration. If the incidence and the mean duration of the disease are constant, then: prevalence = incidence $\times$ duration.

Thus, prevalence is determined by both the incidence and the duration of the disease. If the pathogenesis is pre- or peripartum, as it is for the majority of cases of CP, then counting the number of cases sometime after birth can determine only prevalence. It is invalid to refer to incidence because it is not possible to determine how many were early or late fetal deaths. This applies not only to CP but also to all congenital anomalies. Therefore, the increasing prevalence of CP in low-birth-weight infants may be the result of an increase in incidence or the improved survival of infants with prepartum-sustained cerebral impairment. This distinction is of medicolegal importance to both obstetricians and neonatal pediatricians. In years past, when CP was often attributed to birth injury, it was generally held that improvements in obstetric care would lead to a reduction in prevalence, but this has not occurred. It must be emphasized that if the cerebral impairment is sustained prepartum, improvements in obstetric and neonatal care will increase the prevalence of CP because prenatally damaged infants will be kept alive, thereby increasing the duration of the disease. Only if the cerebral impairment occurs peri- or postpartum will there be a decrease in prevalence with improving obstetric and neonatal care[25].

Any consideration of the association of CP with multiple gestation must take place against the background that cerebral palsy is not a single nosological entity, a fact that is highlighted by the lack of consensus in the definition of the syndrome. Furthermore, all data sets, whether they be case series or population-based registers, can only examine prevalence rates. When considering etiology, it is knowledge of the incidence of the syndrome that is of crucial importance. Taking these caveats into account, the relationship between CP and multiple gestation may be viewed from two perspectives. One is the role of multiple gestation in the pathogenesis of cerebral palsy, and the other is the consideration of cerebral palsy within the wider spectrum of mortality and morbidity attributable to multiple gestation.

## MULTIPLE GESTATION AND CEREBRAL PALSY

Twinning as a risk factor for CP was recognized by Freud over a century ago[2]. Since then, numerous case series have found twins to have a 5–10-fold increased risk[26–34], and a recent study based on five populations from Australia and the USA found a four-fold increased risk of CP in twins compared with singletons[35].

Although the crude prevalence of CP is higher in multiple compared with singleton births, birth weight is an important confounding factor. Table 97.2 shows the crude and birth-weight-specific prevalence of CP in singleton and multiple births. The trend of increasing prevalence with decreasing birth weight is clear in both singleton and multiple births. A further striking feature of the table is the highly significant increased risk of cerebral palsy in twins compared with singletons of birth weight $\geq$ 2500 g. The five-fold difference in crude prevalence is of the same order of magnitude as that found in most studies. Clearly, the higher risk of CP in multiple births is

**Table 97.2** Cerebral palsy birth-weight-specific prevalence per 1000 infant survivors in singletons, twins and triplets. Combined data from Western Australia[36], North East Thames Region, UK[37] and Mersey Region, UK[38] population registers

| *Birth-weight group* | *Singletons* | *Twins* | *Triplets* | *Twin–singleton relative risk (95% CI); p value* |
|---|---|---|---|---|
| < 1500 g | 56.1 | 61.3 | 82.5 | 1.09 (0.84–1.42); NS |
| 1500–2499 g | 9.7 | 9.4 | 22.5 | 0.97 (0.74–1.28); NS |
| ≥ 2500 g | 1.3 | 4.6 | 0 | 3.44 (2.47–4.80); $p < 0.0001$ |
| All birth weights* | 2.0 | 10.5 | 36.2 | 5.16 (4.39–6.06); $p < 0.0001$ |

*All birth weights, Mantel–Haenszel weighted relative risk (twin vs. singleton) 1.26 (1.07–1.48); $p < 0.01$; CI, confidence interval; NS, not significant

attributable to both an increased risk of preterm delivery and a high risk in twins compared with singletons delivered at term.

Among twins, the surviving twin of a co-twin fetal death is specifically at high risk of serious morbidity. Numerous reports of individual cases have drawn attention to this, and, in the majority of cases, monochorionicity appears to be a crucial factor[39–50]. This high risk is confirmed in studies from population-based registers. In two such studies, 4/33 and 6/63 twin survivors of a co-twin fetal death, respectively, had CP, so the risk in a twin whose co-twin died *in utero* was about 1 : 10[38,51].

An analysis of the combined data from three national surveys of birth and death registrations of twins and a regional cerebral palsy population-based register examined the birth-weight-specific prevalence of cerebral palsy when both twins were live-born and both survived infancy, and in the surviving twin whose co-twin died *in utero* or was a live birth but died in infancy[52–55]. Ideally, mono- and dizygotic twins should be analyzed separately; however, zygosity is not registered at the time of birth, and a partial, although less than adequate, surrogate for zygosity is to compare like- with unlike-sex twins. Unlike-sex twins must be dizygotic, but like-sex twins comprise both di- and monozygotic twins. Table 97.3 compares birth-weight-specific like- and unlike-sex CP prevalence rates in three groups: when both twins survive infancy; the co-twin survivor of a fetal death; the co-twin survivor of an infant death. The table presents several salient observations. Primarily, like- compared with unlike-sex twins are at increased risk of CP in both birth-weight groups in each of the three independent components (panels a, b and c) of Table 97.3. A Mantel–Haenszel weighted relative risk for like- compared with unlike-sex using six strata (two birth-weight groups × three component groups) is 1.74 (95% confidence interval (CI) 1.27–2.36); $p < 0.001$ (panel d). It is unfortunate that only like- and unlike-sex can be compared. If Weinberg's rule were to be applied to the data to estimate the birth-weight-specific cerebral palsy prevalence in mono- and dizygotic twins, the relative risk would be 2.27.

Second, the high risk of CP in the surviving twin of a co-twin fetal death that was observed in population-based CP registers is confirmed (Table 97.3a).

Third, an extremely high risk of cerebral palsy is also observed in the surviving twin if both are live births but one dies in infancy, and is particularly notable in infants of birth weight < 1500 g (Table 97.3b). The cerebral impairment in many of these low-birth-weight cases may be attributable to peripartum hypoxic–ischemic episodes leading to periventricular leukomalacia and intraventricular hemorrhage associated with severe prematurity. In this low-birth-weight group, not only is the CP prevalence higher, but also the infant mortality is higher in like- than in unlike-sex twins. The probable interpretation is that the like-sex twin survivors sustained prepartum cerebral impairment, which, in addition to the extreme prematurity, prejudiced their survival to a greater extent than in unlike-sex twins, thereby accounting for their higher infant mortality.

In Table 97.3d, the prevalence of CP in like- and unlike-sex twins combined is 11.8/1000 infant survivors and is similar to the prevalence of 10.5/1000 noted from population-based cerebral palsy registers in Table 97.2. In contrast, the CP prevalence in all infant survivors, irrespective of birth weight or plurality, is about 2–2.5/1000 infant survivors[21,56,57].

## PATHOGENIC MECHANISMS OF CEREBRAL PALSY IN MULTIPLE BIRTHS

Undoubtedly, some of the excess risk of cerebral palsy in multiple compared with singleton births is attributable to immaturity, irrespective of zygosity. Problems of maintaining normality in several

**Table 97.3** Birth-weight-specific cerebral palsy prevalence in twins[52–55]

| | *Like sex* | | *Unlike sex* | |
|---|---|---|---|---|
| *Birth weight* | *Cerebral palsy/number responders* | *Cerebral palsy prevalence/1000 infant survivors* | *Cerebral palsy/number responders* | *Cerebral palsy prevalence/1000 infant survivors* |
| *a: Cerebral palsy in surviving twin of co-twin fetal death** | | | | |
| < 1500 g | 15/91 | 164.8 | 3/29 | 103.4 |
| ≥ 1500 g | 20/246 | 81.3 | 2/104 | 19.2 |
| All | 35/337 | 103.9 | 5/133 | 37.6 |
| *b: Cerebral palsy in surviving twin of co-twin infant death†* | | | | |
| < 1500 g | 44/207 | 212.6 | 12/87 | 137.9 |
| ≥ 1500 g | 8/187 | 42.8 | 0/75 | 0 |
| All | 52/394 | 132.0 | 12/162 | 74.1 |
| *c: Cerebral palsy: both twins survive infancy‡* | | | | |
| < 1500 g | 52/984 | 52.8 | 17/393 | 43.3 |
| ≥ 1500 g | 54/12037 | 4.5 | 13/5841 | 2.2 |
| All | 106/13021 | 8.1 | 30/6234 | 4.8 |
| *d: a + b + c: Combined cerebral palsy birth-weight-specific prevalence§* | | | | |
| < 1500 g | 111/1282 | 86.6 | 32/509 | 62.9 |
| ≥ 1500 g | 82/12470 | 4.5 | 15/6020 | 2.5 |
| All | 193/13752 | 14.0 | 47/6529 | 7.2 |

Like vs. unlike sex, Mantel–Haenszel weighted relative risk* 2.60 (95% confidence interval (CI) 1.06–6.39); †1.77 (95% CI 1.01–3.25); ‡1.29 (95% CI 0.71–2.21); §1.76 (95% CI 1.29–2.41)

physiological variables in a very immature infant predispose to a risk of hypoxic–ischemic brain damage. However, in multiple births, an additional risk is associated with the zygosity of the conception. The greater risk of cerebral palsy in monozygotic compared with dizygotic twins as suggested in Table 97.3 is compounded by two factors. First, the lower is the birth weight of twins, the greater is the probability that they will be monozygotic. In a national England and Wales data set, an estimated 24% of twins in the birth-weight group ≥ 3500 g were monozygotic compared with 51% in the birth-weight group < 500 g, with a highly significant trend between these extremes[55]. Thus, part of the higher risk of cerebral palsy in monozygotic twins is attributable to their greater propensity for being born prematurely. A second factor affecting cerebral impairment in a fetus from a monochorionic conception relates to feto-fetal transfusion problems.

Various pathogenic mechanisms that have been proposed to explain the cerebral damage leading to CP in monochorionic multiple conceptuses are illustrated in Figure 97.1. The debate about the mechanism has focused primarily on those cases of cerebral palsy in the surviving twin of a co-twin fetal death. Over 40 years ago, Benirschke[58] reported cerebral, splenic and renal cortical necrosis in a newborn infant with a macerated twin. He proposed that embolization with thromboplastin-rich material from the dead twin to its live co-twin led to disseminated intravascular coagulation and produced vascular occlusion in the surviving co-twin (Figure 97.1a). Other proponents of this mechanism of fetal damage have described microcephaly, porencephalic cysts, intestinal atresia, aplasia cutis and limb amputation in the surviving twin[59–62]. A variant of this hypothesis is that arterial occlusion by an embolus from the dead fetus may be the cause of a variety of pathological

abnormalities[43]. However, in the majority of cases, neither emboli nor intravascular coagulation has been demonstrated in the surviving twin. An alternative and more correct hypothesis is that acute hemodynamic and ischemic changes result from acute twin–twin transfusion at the time of intrauterine death, with exsanguination of the live twin into the hemodynamically low resistance of the dead fetus[47,63,64] (Figure 97.1b). Both mechanisms illustrated by Figure 97.1a and b presuppose that *in utero* death of one twin is essential for the brain of the co-twin to be impaired. However, even when both twins are live births and one dies in infancy, the survivors in like- compared with unlike-sex twins are at increased risk of cerebral palsy, and *in utero* death is not essential to the phenomenon (Table 97.3b). An alternative hypothesis is that monochorionic placentation *per se* and not a dead fetus may be responsible for the white-matter brain lesions due to bidirectional shunting of blood as a result of hemodynamic instability[65–68] (Figure 97.1c). If this hypothesis is correct, the demise of one fetus and the cerebral impairment in its co-twin are both the result of the bidirectional shunting of blood.

Whereas monochorionic placentation, with its potential for feto-fetal hemodynamic transfusion abnormalities, may explain many cases of cerebral palsy, it fails to explain those cases occurring in unlike-sex twins. It has been suggested that anastomoses may occur in dichorionic placentas early in gestation that subsequently disappear, or, albeit rarely, may even be found in term placentas[69,70].

An extremely important anomaly that can affect the determination of plurality and zygosity of birth is the non-registration of fetal deaths. The World Health Organization definition of fetal death is 'death prior to the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of the pregnancy'. In the USA, not all fetal deaths are required to be registered. The 1992 Revision of the Model State Vital Statistics Act and Regulations recommends reporting of fetal deaths of 350 g or more, or if the weight is unknown, of 20 completed weeks' gestation or more. Generally, fetal deaths are registered in the USA if gestation is at least 20 weeks; however, there are variations in registration depending on geographic area. Some use birth weight as the primary determinant, others use gestational age and still others require all fetal deaths to be reported. Problems arise in the registration of those fetal deaths weighing less than 350 g or of less than 20 weeks' gestational age. These early fetal deaths are usually manifest as a fetus papyraceous. Such variation in whether or not a fetal death may be registered is a feature of most countries subscribing to the World Health Organization definition. As shown in Table 97.3a, fetal death of one twin poses a high risk of cerebral palsy in the surviving co-twin. If such a fetal death is not registered and the co-twin suffers from cerebral palsy, then the erroneous assumption made is that the surviving twin is a singleton. In one series, six of 18 cases of cerebral palsy with clinically recorded fetal death of the co-twin, only a singleton survivor was registered[71]. Similarly, only twins may be registered following the non-reporting of a fetal death in a triplet or higher-order multiple pregnancy. When this occurs, twins of unlike sex are not necessarily both from a dizygotic conception.

The advent of ultrasonographic assessment early in pregnancy as an aid to subsequent management has been an important technical advance in obstetrics. Among its many benefits, the use of ultrasonography leads to the earlier recognition of multiplicity of pregnancy. The phenomenon of multiplicity of pregnancy in early gestation with very early loss of one conceptus is now clearly described as the 'vanishing' twin along with the subsequent delivery of a singleton infant. If two sacs are identified by ultrasonography in early gestation, loss of one conceptus can be expected in about 40% of spontaneous conceptions. The rate of loss of one conceptus appears to increase, the earlier in gestation that the ultrasonography is carried out[72]. As fetal death in a monochorionic twin in the second or third trimester is recognized as a risk for cerebral palsy in the surviving co-twin, it has been hypothesized that first-trimester loss of a twin as a 'vanishing' twin may be the cause of the majority of cases of prenatally acquired cerebral palsy in apparently singleton infants[73].

## ASSISTED REPRODUCTIVE TECHNOLOGIES AND CEREBRAL PALSY

There has been a rapid increase over the past three decades in the number of multiple gestations as a result of developments in the treatment of infertility[74,75]. This has given rise to concern over the possible increase in morbidity, particularly CP, which may be attributable to these therapies, because the higher is the plurality of a pregnancy, the greater is the risk of CP when compared with singletons (Table 97.2). When assessing the potential effect of assisted reproductive technologies (ART) on the prevalence of CP, two factors must be considered: the greater probability of preterm delivery and the chorionicity of the multiple pregnancy.

To reduce the probability of preterm delivery, there has been a trend in selective reduction of multifetal pregnancies. Success in increasing the gestational age at delivery will reduce the prevalence of CP in ART pregnancies. Against this must be

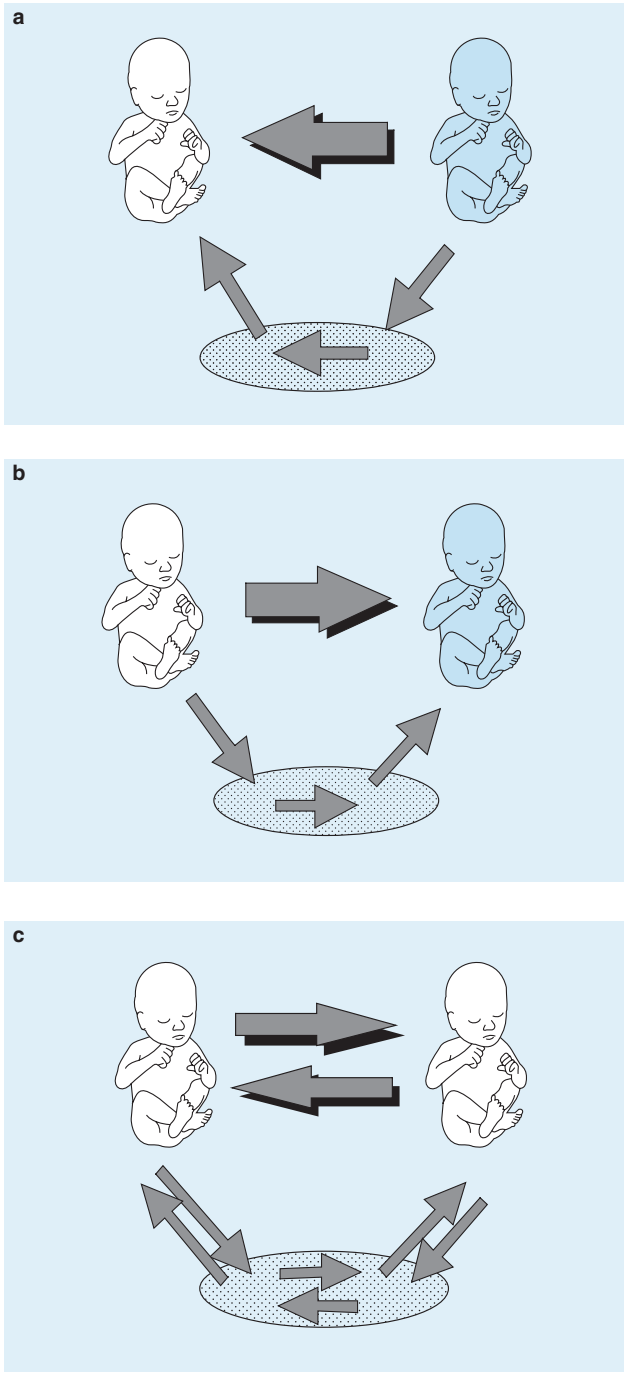


**Figure 97.1** Proposed mechanisms of cerebral damage leading to cerebral palsy in monochorionic multiple conceptuses. (a) Embolic theory: thromboplastin-like material or emboli are transferred through an open placental anastomosis to the survivor. (b) Ischemic theory: blood is shunted into the low-resistance circulation of the dead fetus. (c) Hemodynamic instability theory: bidirectional shunting leads to ischemic damage affecting either or both fetuses

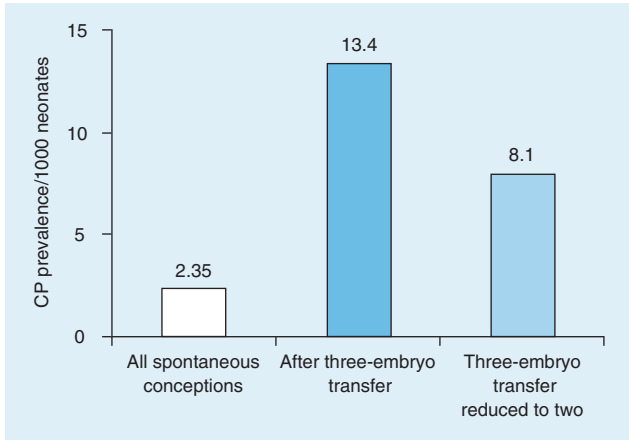


**Figure 97.2** Estimated risk of cerebral palsy (CP) following three-embryo transfer

balanced the knowledge that spontaneous fetal demise in a multifetal pregnancy is associated with a significantly increased risk of CP in the survivor[38,51,52]. Therapeutic fetal reduction needs to take this into consideration. However, an important component of risk of CP following spontaneous fetal loss in multiple pregnancy is monochorionicity, and ART results predominantly in dizygotic and, therefore, dichorionic conceptuses, and should not be liable to this risk. Nevertheless, it has been estimated that there may be about an 8% increase in the prevalence in CP in the USA between 1990 and 1997 due solely to the rise in multiple births from ART[76]. For the reason just given, this is probably an overestimate. A caveat needs to be added. Monozygotic twins are more frequent in ART than in spontaneous conceptions[77,78], occurring in about one in 200–300 spontaneous conceptions and one in 10–15 assisted conceptions[79]. It has been estimated that 15% of ART twins are monozygotic[80]. Attempts at fetal reduction in spontaneous monochorionic twin pregnancies invariably lead to the loss of both fetuses, and this is likely to be so also in ART pregnancies that have undergone monozygotic division.

An estimate comparing the rates of CP after spontaneous and assisted conception has been made by applying population-based CP rates in singletons, twins and triplets to assisted conceptions in which two or three embryos were transferred[81]. It suggests that CP rates in spontaneous conceptions are significantly lower than after embryo transfer, and that CP rates after three-embryo transfer are greater than when three transferred embryos are reduced to two (Figure 97.2).

## CEREBRAL PALSY IN MULTIPLE GESTATIONS

Consideration is given above to the role of multiple births in the pathogenesis of cerebral palsy, and to

**Table 97.4** Possible combinations of severity of fetal damage in twins

| *Twin 1* | *Twin 2* | *Comment* |
|---|---|---|
| Early fetal death | normal live birth | singleton with 'vanishing' twin |
| Early fetal death | live birth with cerebral palsy | cerebral palsy in apparently singleton infant |
| Late fetal death | late fetal death | mono- compared with dizygotic twins; highly significant relative risk of 11 |
| Late fetal death | live birth with cerebral palsy | case reports and cerebral palsy register data indicate monochorionicity is dominant feature |
| Live birth with cerebral palsy | live birth with cerebral palsy | large preponderance of monozygotic twins |
| Live birth with cerebral palsy | normal live birth | more common in like- compared with unlike-sex twins |

the possible mechanisms that may account for the higher risk of cerebral palsy in multiple compared with singleton births. Current evidence suggests that, in many cases, prenatally sustained cerebral impairment, presenting clinically as cerebral palsy, is attributable to ischemic damage due to hemodynamic instability in monochorionic twins. On theoretical grounds, it is unlikely that such ischemic damage is confined to a single organ, the brain. The possible spectrum of effects that could accrue from ischemic damage in the fetus can be examined within three dimensions: the degree or severity of damage; the spatial dimension of whatever organ or part of an organ may be damaged; and the timing of the damage such as the first, second or third trimester.

The severity of damage in a fetus may result in early fetal loss (spontaneous abortion), late fetal loss (stillbirth), a live birth dying in infancy, a live birth with clinical morbidity or a clinically normal live birth. In multiple births, this range of severity options may occur in each conceptus so that several combinations are possible, some of which are outlined for twins in Table 97.4. Thus, cerebral palsy in an apparently singleton infant or in one or both twins is part of the spectrum of cerebral impairment resulting from hemodynamic instability in monochorionic twins during fetal development. Even within the panorama that is characterized clinically as cerebral palsy, the severity of clinical abnormality may vary from minimal motor disability to global abnormality with severe cognitive, motor and sensory disabilities.

The spatial dimension may also be highly relevant. The brain is not the only organ at risk of ischemic damage during fetal development. Several congenital anomalies of the heart, intestine, kidneys and skin are consonant with an ischemic pathology, and have been described in the surviving twin after the fetal death of a monochorionic co-twin[82]. Furthermore, many such congenital anomalies are more common in twins than in singletons, and within like-sex twins there is low concordance suggesting that a simple gene-segregation process is unlikely to account for the anomaly[83]. An acardiac fetus is known to occur only in a monochorionic twin set, and may represent the severe end of the spectrum of congenital cardiac disease. Other candidates for an ischemic etiology attributable to monochorionic twinning are the valve atresias and coarctation of the aorta. Similarly, esophageal atresia with or without tracheoesophageal fistula, other intestinal atresias and renal agenesis (uni- or bilateral) have all been described in survivors of a monochorionic co-twin fetal death. Examples of these congenital anomalies in apparently singleton infants may be attributable to early loss of one conceptus.

The timing of ischemic impairment may also be pertinent to the pathology that is observed. A large variety of neurological abnormalities have been reported when there has been fetal death of one twin. These include holoprosencephaly, hydranencephaly, polymicrogyria and multicystic encephalopathy. It has been proposed that early fetal demise of one twin is associated with neuronal migrational abnormality in the co-twin, in contrast to the multicystic encephalomalacia observed when the demise occurred at or near term[84]. Whether timing of ischemic damage is a relevant factor leading to differences in the type of anomaly seen in other organs is a matter for conjecture.

## SUMMARY

(1) Multiple compared with singleton gestations have a 5–10-fold increased risk of CP.

(2) Some of the increased risk is attributable to an increased risk of preterm delivery of multiple gestations. In these cases, the CP may be attributed to peripartum periventricular hemorrhage or

leukomalacia, and the increase in risk will apply to both mono- and dizygotic conceptions.

(3) An additional risk is associated with monochorionic multiple gestations and feto-fetal hemodynamic transfusion instability leading to cerebral ischemia. In twins, the lower is the gestational age at delivery, the greater is the probability that they are monozygotic. Thus, monozygotic conceptions have a dual risk of cerebral impairment, from prematurity and from monozygosity.

(4) The pathogenic mechanism of cerebral impairment in monochorionic conceptuses is probably ischemic, from hemodynamic instability in feto-fetal transfusion. Fetal death of one conceptus is not essential for cerebral impairment in the co-twin as both twins may be live-born. Thromboemboli, or the liberation of thromboplastin from the fetus that died, or the shunting of blood from the live fetus to the low-resistance circulation of the dead fetus cannot explain CP in either or both twins when both are live-born.

(5) CP in an apparently singleton infant may be associated with fetal demise of a twin that has not been recognized or recorded. It has been postulated that the ultrasonographic recognition of twins with early loss of one as a 'vanishing' twin may account for a significant proportion of singleton children with CP.

(6) ART conceptions are at greater risk of CP than spontaneous conceptions predominantly because of the greater risk of preterm delivery. A reduction in the number of fetuses in a multifetal ART conception is unlikely to affect the CP prevalence, because the majority of ART conceptions are dizygotic.

(7) CP may be part of a wider spectrum of congenital cardiac, intestinal, renal and other anomalies in multiple gestations that are attributable to ischemic damage during fetal development. Some of these anomalies in apparently singleton infants may also be associated with the unrecognized or unrecorded loss of a co-twin.

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# Preterm Labor, Infection and Cerebral Palsy

*J. S. Park and E. R. Norwitz*

**98**



## INTRODUCTION

Cerebral palsy refers to a group of chronic conditions characterized by abnormal control of movement or posture, having in common the fact that they are all cerebral in origin, arise early in life, are non-progressive, and are frequently accompanied by seizure disorders, sensory impairment and/or cognitive limitation[1–3]. The term 'cerebral palsy' is attributed to Sir William Osler who, in 1889, associated the condition with asphyxia of the newborn following complicated deliveries[4]. Cerebral palsy is heterogeneous in both its clinical manifestations and its causation. Whether by ignorance or convenience, and despite substantial epidemiologic evidence demonstrating that no more than 10% of all cases of cerebral palsy occur as a result of peripartum hypoxia[1–6], intrapartum mismanagement and resultant hypoxic–ischemic encephalopathy remains uppermost in the minds of non-obstetric care providers as the major cause of cerebral palsy. This review briefly summarizes our current understanding of the prevalence and etiology of cerebral palsy before focusing on multiple pregnancies and two specific risk factors: preterm birth and intrauterine infection.

## DIAGNOSIS AND DEFINITIONS

The diagnosis of cerebral palsy is typically made at age 2–3 years, although few studies are willing to wait this length of time for a definitive diagnosis. For this reason, many investigators choose to focus on surrogate end-points, including neonatal encephalopathy, hypoxic–ischemic encephalopathy (HIE) or pathologic antecedents such as intraventricular hemorrhage (IVH), hydrocephalus, periventricular leukomalacia or sonographic echolucency (Figure 98.1).

*Neonatal encephalopathy* refers to 'a clinical phenomena of compromised neurological function in the term or near-term infant, [which] manifests during the first few days after birth'[7]. Compromised neurologic features may include seizures, coma, abnormal tone and reflexes, and respiratory and/or feeding difficulties, but it is important to recognize that many cases of neonatal encephalopathy do not result in cerebral palsy[2,3,5,7,8].

*Hypoxic–ischemic encephalopathy* refers to a subset of the much broader category of neonatal encephalopathy in which the etiology is felt to be intrapartum hypoxic–ischemic injury. Before peripartum hypoxic acidemia can be considered as the cause of neurologic injury, a set of specific criteria defined by several recent national and international consensus panels – including, among others, the International Cerebral Palsy Task Force[2], the American College of Obstetricians and Gynecologists (ACOG)[8] and the American Academy of Pediatrics[9] – must all be met. These are summarized in Table 98.1.

Several forms of cerebral palsy are described based on the clinical presentation, including spastic diplegia (34%), spastic hemiplegia (30%), spastic quadriplegia (20%) and dyskinetic cerebral palsy (16%). Although cerebral palsy has existed throughout history, it was not described in the medical literature until 1844 when W. J. Little, an orthopedic surgeon who specialized in childhood contractures, outlined a sequence beginning with difficult labor

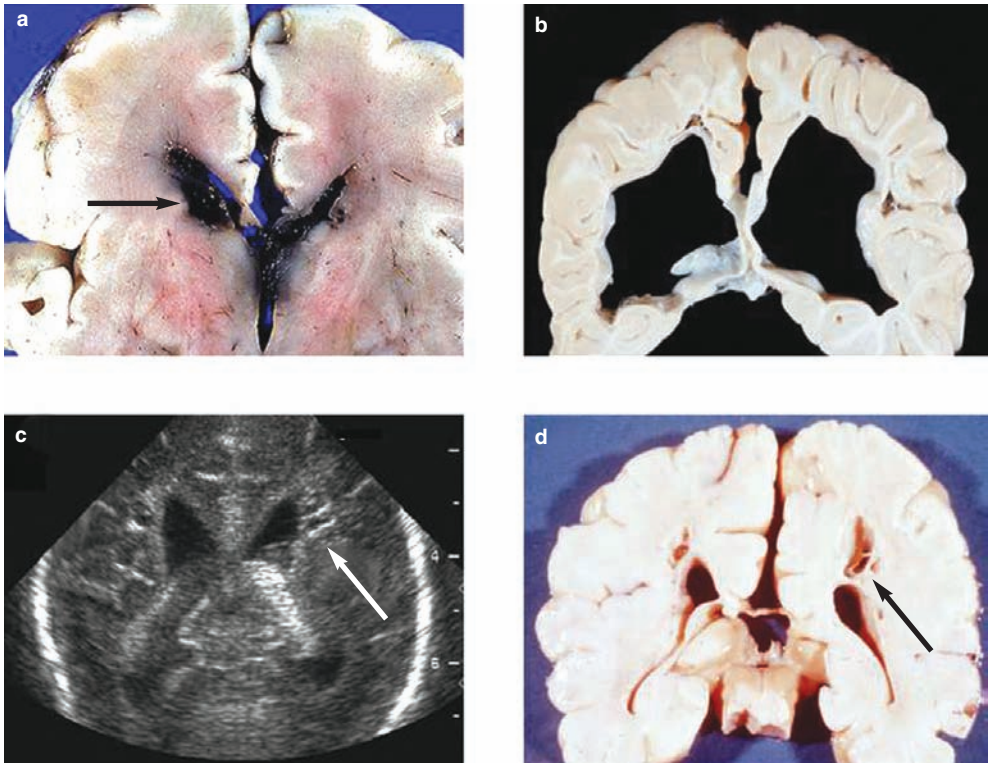


**Figure 98.1** Pathologic antecedents to cerebral palsy. (a) Intraventricular hemorrhage (designated by an arrow). (b) Hydrocephalus as seen on a pathologic specimen. (c) Sonographic diagnosis of periventricular echolucency (designated by an arrow). (d) Periventricular leukomalacia (designated by an arrow) as seen on a pathologic specimen

**Table 98.1** Criteria to define a peripartum hypoxic–ischemic event. Data from references 2, 8 and 9

| |
|---|
| Profound metabolic or mixed acidemia (pH < 7.00) in an umbilical cord arterial blood sample, if obtained |
| Persistent Apgar score of 0–3 for longer than 5 min |
| Evidence of neonatal neurologic sequelae (seizures, coma or hypotonia) |
| Neonatal multiorgan system dysfunction |

('asphyxia neonatorum') followed by neonatal seizures and, eventually, spastic motor paralysis[10]. Interestingly, Little's disease – spastic diplegia – is no longer believed to result from intrapartum events[11]. The only two forms of cerebral palsy that have been associated with hypoxic–ischemic encephalopathy are spastic quadriplegia and dyskinetic cerebral palsy[1,7,12,13], although the bulk of evidence indicates that, even for these conditions, intrapartum hypoxic– ischemic encephalopathy is an infrequent cause[1–3,5,6].

## PREVALENCE

Cerebral palsy is the most serious handicap of infancy, and is the major cause of medicolegal disputes in obstetrics[14]. Cerebral palsy is the most common developmental disability in the United States, affecting approximately half a million individuals. According to the statistics of the Centers for Disease Control and Prevention of the United States (1991–94), the average annual prevalence rate is 2.8 per 1000 children aged 3–10[15]. Annually, at least 8000 new cases are diagnosed in infants in the United States alone, and a further 1500 are identified in children of preschool age[16].

In 1986, Nelson and Ellenberg[17] observed that '… despite earlier optimism that cerebral palsy was likely to disappear with the advent of improvements in obstetrical and neonatal care, there has apparently been no consistent decrease in its frequency in the past decade or two'. This statement is true even today, and has been confirmed by other investigators (Figure 98.2)[18–20]. These observations probably reflect that the causes of newborn encephalopathy and cerebral palsy are heterogeneous, and many causal pathways are likely to start early in pregnancy.

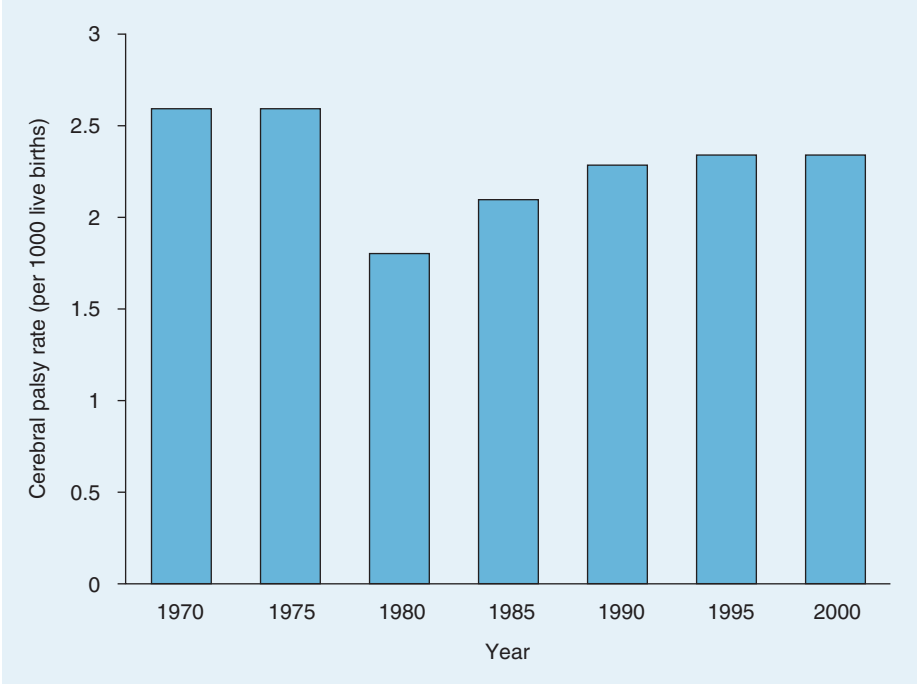


**Figure 98.2** Cerebral palsy rates per 1000 live births, 1970–2000. Data from reference 20

**Table 98.2** Risk factors for newborn encephalopathy. Data from references 18, 19, 23 and 24

| *Preconceptional factors* | *Antepartum factors* | *Intrapartum factors* |
|---|---|---|
| Increased maternal age | Male fetus | Intrapartum fever |
| Primiparity | Maternal thyroid disease | Prolonged rupture of membranes |
| Unemployed, unskilled laborer or housewife | Severe pre-eclampsia/eclampsia | Thick meconium |
| | Bleeding in pregnancy | Malpresentation and malposition |
| No private health insurance | Viral illness during pregnancy | Intrapartum hypoxia |
| Infertility treatment | Prematurity | Acute intrapartum events (including cord prolapse, abruptio placentae, uterine rupture, maternal seizures) |
| Family history of seizures | Post-term pregnancy | |
| Family history of neurologic disorders | Placental abnormalities | Forceps delivery |
| | Intrauterine growth restriction in the fetus | Emergency cesarean delivery |
| | Structural anomalies in the fetus | |
| | Twin pregnancy | |

## ETIOLOGY

New insights into the origins of cerebral palsy have recently transformed the opinion that most cases of cerebral palsy begin in labor. Many causes are implicated, including developmental abnormalities, metabolic abnormalities, autoimmune and coagulation disorders, trauma, infection, genetic disorders, and antepartum or intrapartum hypoxia in the fetus or newborn[1–3,6,8,15,16,18–22]. In a given clinical scenario, however, it may be difficult to assess which features are causally related to the cerebral injury. In many instances, the etiology remains unknown. Known risk factors for newborn encephalopathy are summarized in Table 98.2 and Figures 98.3 and 98.4. Many cases do not result in cerebral palsy[2,3,5,7,8], and the data on risk factors for cerebral palsy are more limited. Despite this limitation, several risk factors appear to be consistently associated with cerebral palsy (Table 98.3). Interestingly, after adjustment for confounding variables, pre-eclampsia appears to be independently protective against neurologic injury

and possibly against the development of cerebral palsy[37,38], although the exact mechanism by which pre-eclampsia exerts its protective effect is not known. A discussion of all of these factors is beyond the scope of this chapter and they have been reviewed in detail elsewhere[18,19,21–24,37,38]. The remaining sections focus on three specific risk factors: twins, prematurity and intrauterine infection.

## TWINS AND CEREBRAL PALSY

After controlling for confounding factors, multiple pregnancy is an independent risk factor for adverse neurologic outcome in the fetus[28,29,39]. The prevalence of cerebral palsy is exponentially related to the number of fetuses[40]: 1.6 vs. 7.3 vs. 28 per 1000 infants surviving to 1 year of age born from singleton, twin and triplet pregnancies, respectively[29] and 2.3 vs. 12.6 vs. 44.8 per 1000 infants surviving to 3 years of age born from singleton, twin and triplet pregnancies, respectively[39]. The increased risk of cerebral palsy in multiple pregnancies appears to result in large part from an increased risk of low birth weight and preterm birth. However, even when controlling for birth weight, prevalence rates of cerebral palsy in twins weighing >2500 g is greater than that of singletons of comparable birth weight[28,39]. Interestingly, this disparity is not apparent for very-low-birth-weight infants (<1500 g)[28,39] or for premature infants[41]. It is likely, therefore, at least in infants delivered at term, that the causes of cerebral palsy are different between infants born from singleton and multiple pregnancies[40,41].

Aside from low birth weight and premature delivery, multiple pregnancies are also at risk of other complications that may lead to fetal neurologic injury. Such complications are typically more common with monochorionic placentation. For example, neurologic injury can occur in the surviving co-twin of a monochorionic twin pregnancy complicated by intrauterine fetal demise. As surviving co-twins are also at increased risk of other pathologic lesions (multicystic encephalomalacia, renal cortical necrosis),

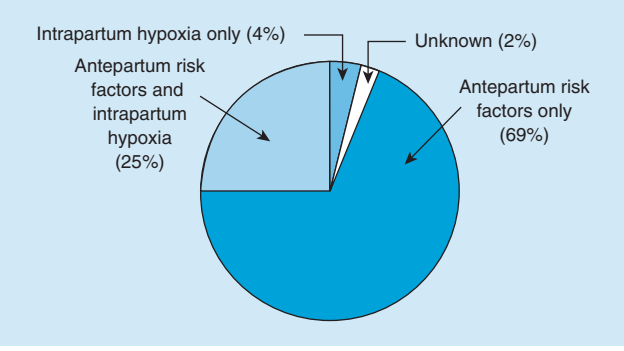


**Figure 98.3** Distribution of risk factors for newborn encephalopathy. Data from references 18 and 19

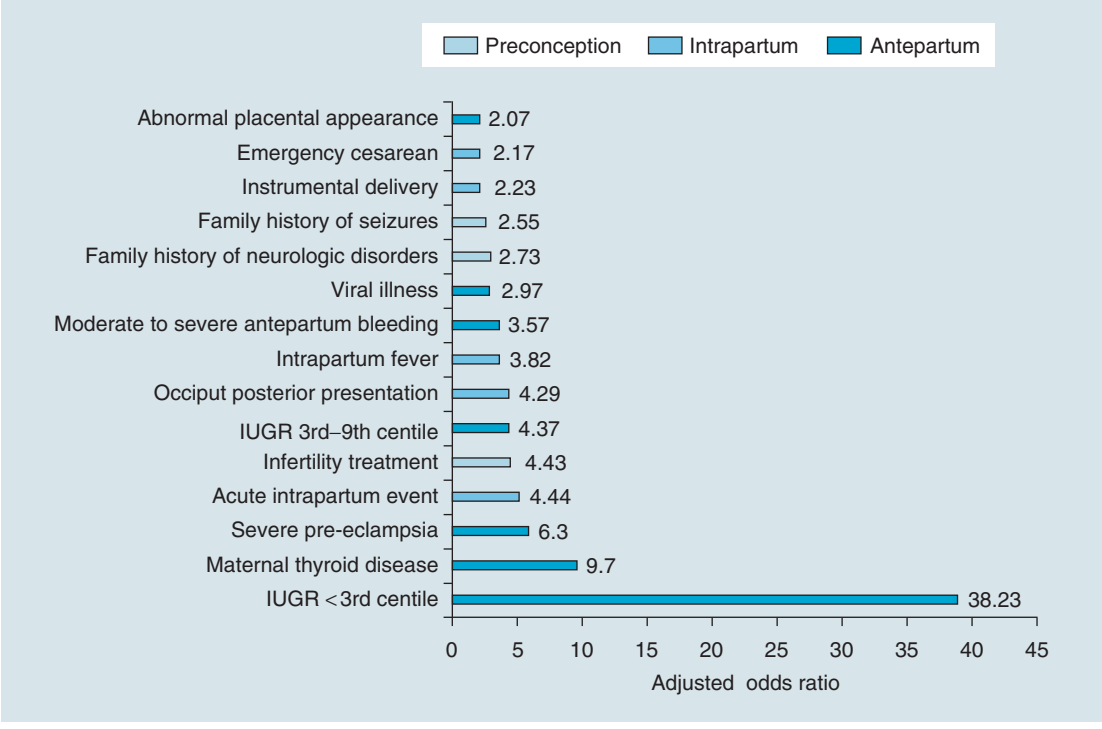


**Figure 98.4** Risk factors for newborn encephalopathy. Data from reference 19. IUGR, intrauterine growth restriction

**Table 98.3** Risk factors for cerebral palsy

| *Risk factors* | *References* |
|---|---|
| Prematurity | Nelson and Broman[25], 1977<br>Nelson and Ellenberg[26], 1985<br>Naulty *et al.*[27], 1994 |
| Low birth weight | Nelson and Ellenberg[17], 1986<br>Naulty *et al.*[27], 1994 |
| Multiple pregnancy | Grether *et al.*[28], 1993<br>Petterson *et al.*[29], 1993 |
| Pathologic antecedents | |
| intraventricular hemorrhage | de Vries *et al.*[30], 1998<br>Finnstrom *et al.*[31], 1998<br>Spinillo *et al.*[32], 1998 |
| periventricular leukomalacia | Perlman *et al.*[33], 1996 |
| Infection | Nelson and Ellenberg[26], 1985<br>Murphy *et al.*[34], 1995<br>Alexander *et al.*[35], 1998<br>Grether *et al.*[36], 1996 |

it is likely that the lesions result from a common pathologic process related to the presence of placental vascular connections. Initial suggestions that such injuries may be due to the passage of thromboplastin from the dead to the surviving twin[42] are not supported by subsequent literature[43,44]. More recent reports suggest that the inciting event is immediate and profound hypotension in the surviving co-twin due to loss of blood into the dead twin, resulting from a loss of vascular tone. Unfortunately, immediate cesarean delivery does not appear to protect the surviving twin from neurologic injury[45], and ultrasound and fetal testing may not be able to identify fetuses with multicystic encephalopathy[46]. Although the precise incidence is not known, it is estimated that the risk of neurologic injury in the surviving co-twin in a monochorionic pregnancy complicated by intrauterine fetal demise is in the order of 20%[47]. Even in the absence of fetal demise, fetuses born of monochorionic twin pregnancies complicated by twin-to-twin transfusion syndrome are at increased risk of neurologic injury[48,49]. Interestingly, cerebral palsy is more common in the non-presenting twin[50]. The reason for this is not clear. Table 98.4 summarizes the data on cerebral palsy and multiple pregnancy[40].

## PREMATURITY AND CEREBRAL PALSY

Epidemiologic studies show an association between premature birth (defined as delivery before 37 weeks' gestation) and cerebral palsy. For example, Williams and colleagues[41] found a cerebral palsy frequency of 3.2% among live births < 29 weeks' gestation, 2.8% at 29–32 weeks, 0.3% at 33–36 weeks and 0.07% at ≥ 37 weeks. Similarly, using birth weight as a proxy for prematurity, the risk of cerebral palsy increases with decreasing birth weight, with an incidence of 15 per 1000 live births in low-birth-weight infants (< 2500 g) and 13–90 per 1000 live births in very-low-birth-weight infants (< 1500 g)[41,51]. Paradoxically, similar statistics from developing countries often appear more favorable, because premature infants in such countries frequently fail to survive long enough to manifest signs of cerebral palsy. In developed countries, however, improvements in neonatal care have led to vastly improved survival rates at the expense of an increased incidence of long-term neurologic injury. Even so, low-birth-weight infants account for only around one-third of all cases of cerebral palsy[41,51].

Exactly why premature infants are at increased risk for neurologic injury is not clear, but several possibilities exist. First, premature infants are more likely to develop intraventricular hemorrhage, which may lead to long-term neurologic sequelae[30–32]. Second, such infants are more likely to result from multiple pregnancies[28,29] and from pregnancies complicated by infection[26,34–36], both of which are known to be independently associated with cerebral palsy. For example, a significant proportion of women with spontaneous preterm labor have subclinical intrauterine infection and this risk appears to be inversely related to gestational age. In one series, the risk of subclinical intrauterine infection (as evidenced by a positive amniotic fluid culture) was 45% (9/20) at 23–26 weeks, 17% (4/24) at 27–30 weeks and 11% (7/61) at 31–34 weeks[52]. Even in the absence of a positive amniotic fluid culture, women

**Table 98.4** Associations between cerebral palsy and multiple pregnancy. Data from reference 40

| *Accepted associations* | *Proposed but unclear associations* |
|---|---|
| Rates of cerebral palsy ↑ with increasing numbers of fetuses | In the absence of structural anomalies or twin-to-twin transfusion syndrome, monozygotic twins are *not* at ↑ risk of cerebral palsy |
| Rates of cerebral palsy ↑ in low-birth-weight infants (< 2500 g) | In the absence of structural anomalies or twin-to-twin transfusion syndrome, monochorionic twins are *not* at ↑ risk of cerebral palsy |
| Multiple pregnancies are at ↑ risk of preterm delivery and rates of cerebral palsy are ↑ in premature infants | Even without fetal demise, the presence of twin-to-twin transfusion syndrome may ↑ the risk of cerebral palsy |
| Of all infants with birth weight > 2500 g, those born from multiple pregnancies have an ↑ risk of cerebral palsy compared with singletons | Risk of cerebral palsy is likely not ↑ in the setting of birth weight discordance > 25% |
| Of all infants born at term, those born from multiple pregnancies have an ↑ risk of cerebral palsy compared with singletons | Risk of cerebral palsy is likely ↑ in multiple pregnancies complicated by growth restriction |
| Rates of cerebral palsy ↑ in surviving co-twins of monochorionic twin pregnancies complicated by intrauterine fetal demise | Elective cesarean delivery for low birth weight and of birth weight discordance > 25% does not appear to protect against cerebral palsy |
| Elective cesarean delivery before labor protects against cerebral palsy | Loss of a co-twin early in pregnancy may be associated with ↑ risk of cerebral palsy in the survivor |

with spontaneous preterm labor are more likely to have elevated non-specific markers of infection, such as proinflammatory cytokines, prostaglandins and serum C-reactive protein[53,54].

## INTRAUTERINE INFECTION AND CEREBRAL PALSY

A diagnosis of intrauterine infection (chorioamnionitis) during pregnancy is associated with an increased risk of cerebral palsy in infants with a birth weight ≥ 2500 g[21,55–58]. In very premature infants, the association between infection and cerebral palsy has been less consistent and, when present, less strong[3,21,59]. Intrauterine exposure to infections other than toxoplasmosis, rubella, cytomegalovirus and herpes simplex virus (TORCH) is believed to account for approximately 12% of cases of otherwise unexplained spastic cerebral palsy in non-malformed singleton infants of normal birth weight[55,60]. For example, in a case–control study of 155 636 singleton infants born in the San Francisco area (1983–86) with a birth weight of > 2500 g who survived to age 3 years, 192 infants were identified with moderate to severe cerebral palsy[55]. Independent risk factors for moderate to severe cerebral palsy included clinical chorioamnionitis (odds ratio (OR) 9.3, 95% confidence interval (CI) 2.7–31), intrapartum fever > 38 °C (OR 9.3, 95% CI 2.7–31) and histologic chorioamnionitis (OR 8.9, 95% CI 1.9–40).

Although the 'gold standard' for the diagnosis is often reported as a positive amniotic fluid culture, chorioamnionitis remains primarily a clinical diagnosis. Unfortunately, the clinical definition is imprecise and there is often disagreement between the histologic indicators and the clinical diagnosis[61]. Epidural analgesia in labor, for example, is associated with an increased risk of intrapartum fever[62–64] resulting in more antibiotics being administered and more infants being evaluated for sepsis, but this does not appear to translate into higher rates of postpartum infection or neonatal infectious morbidity[65,66].

Epidemiologic data show an association between intrauterine infection and neonatal neurologic injury, but cannot prove causality. Experimental evidence from animal data, however, suggest that infection does indeed cause the neurologic injury[67–70]. In a rabbit model, for example, Yoon and colleagues[68] demonstrated that intrauterine infection leads to white-matter lesions in the fetal brain that resemble the lesions of infection-associated cerebral palsy seen in the human infant. Neurologic injury may be mediated either directly by fetal infection, indirectly through inflammatory cytokines or both[71–77]. The precise mechanisms of fetal brain injury are not clear, but likely involve such factors as cytokines,

nitric oxide, free oxygen radicals and possibly hyperthermia. Such factors may also lead to preterm labor, in an attempt to deliver the fetus from a hostile intrauterine environment.

Not all fetuses exposed to intrauterine infection are at equal risk for neurologic injury. The nature and location of the infection appears to be important. For example, the strongest correlate with cerebral palsy is histologic evidence of funisitis (infection of the umbilical cord) and/or placental vasculitis[77–79]. The nature of the fetal inflammatory response may also be important in determining the extent of the fetal injury, including the genetic predisposition of the fetus (such as specific cytokine polymorphisms). Cytokines appear to be involved in causing neurologic injury. In many patients with intrauterine infection, elevated levels of lipoxygenase and cyclooxygenase pathway products are demonstrable in maternal serum, fetal serum and amniotic fluid[72,74]. There are also increased concentrations of cytokines (including interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α)) in the serum and amniotic fluid of such women[72,74,75], which may predate the development of clinical chorioamnionitis by weeks or even months[76]. Higher levels of proinflammatory cytokines (TNF-α and IL-6) have also been documented within the periventricular leukomalacia (PVL) lesions themselves[80,81] as well as in the amniotic fluid and serum of neonates who later developed cerebral palsy[82–84].

Does the neurologic injury arise from acute or chronic infection? Data from Yoon and colleagues[85], for example, suggest that levels of inflammatory cytokines in amniotic fluid collected from women undergoing routine mid-trimester genetic amniocentesis are elevated in pregnancies destined to deliver preterm. Whether this is true also of pregnancies resulting in an infant who later develops cerebral palsy is not known. In pregnancies complicated by preterm premature rupture of the membranes, McElrath and associates[86] showed that, as expected, the latency period correlated directly with the risk of clinical as well as histologic chorioamnionitis. However, prolonged latency was not associated with an increased risk of fetal neurologic injury (echolucency, PVL or hydrocephalus), which would be expected if the acute infection were the causative factor. Taken together, these data suggest that adverse pregnancy outcome (such as preterm labor or neurologic injury in the infant) may result from low-grade, chronic inflammation.

## CAN WE PREVENT CEREBRAL PALSY?

Despite the clinical and socioeconomic significance, no effective clinical strategies have yet been developed to prevent or counteract this condition[3,22]. However, a few approaches are worthy of further comment:

(1) *Antenatal corticosteroids* protect against the development of IVH and possibly against other long-term neurologic injury in preterm infants[87], and should be administered to pregnancies threatening to deliver prior to 34 weeks' gestation.

(2) Recent data suggest that *antepartum magnesium sulfate* administration may be associated with a decreased incidence of cerebral palsy[38,88–91]. This association was initially noted by Kuban and colleagues[37] in very-low-birth-weight infants born to mothers who were given magnesium for seizure prophylaxis in the setting of pre-eclampsia, but has more recently been confirmed in a number of other retrospective analyses[38,88–90] with a reported crude odds ratio of 0.11 (95% CI 0.02–0.81)[90]. This effect appears to be independent of steroid therapy[90,91]. Moreover, the effect is also observed in infants born from pregnancies not complicated by pre-eclampsia[88]. The proposed mechanism of action is speculative, but magnesium may act to increase the threshold and decrease excitability in membranes of neurons and muscle cells. Some investigators suggest that magnesium may reduce the prevalence of cerebral palsy simply by increasing the death rate among susceptible fetuses and infants. Indeed, during the Magnesium and Neurologic Endpoints Trial (MagNET), a large randomized clinical trial designed to test the neuroprotective effect of magnesium sulfate in the setting of preterm labor (not pre-eclampsia), the occurrence of excessive total pediatric mortality in the children exposed to magnesium (ten of 75 fetuses randomized to magnesium or saline control versus one of 75 infants randomized to 'other' tocolytics or saline control; $p = 0.02$) led to early termination of the trial[91,92]. The authors concluded that, despite the alarming findings in MagNET, it is conceivable that exposures to doses of magnesium sulfate less than those used for aggressive tocolysis might be neuroprotective without being lethal[92]. This conclusion is potentially supported by the recently published MagPie Trial[93], a clinical study of 10 141 women with pre-eclampsia randomized in 33 countries to receive either magnesium sulfate or placebo for seizure prophylaxis. This study showed no substantive short-term harmful effects of magnesium sulfate on the fetus. Because of the ongoing controversy, it is not currently standard of care to administer antenatal magnesium sulfate to women threatening to deliver extremely premature infants to protect against neurologic injury.

(3) There is evidence to suggest that perinatal brain injury may evolve over a period of hours or days, thereby providing a possible window of opportunity for early postnatal intervention. Preliminary studies of the use of *neonatal hypothermia treatment* suggest that such an approach may provide some neuroprotective effect[94,95]. Until further studies are available, however, such treatment should be regarded as investigational.

(4) *Elective cesarean delivery* prior to labor is protective against the development of cerebral palsy[18,23]. However, cesarean delivery after the onset of labor likely mitigates against this protective effect. At this time, it is not reasonable to offer elective (prophylactic) cesarean delivery routinely prior to labor to prevent cerebral palsy.

(5) If infection is causally related to brain injury, can *antibiotic therapy* prevent the development of cerebral palsy? Existing randomized trials of the use of antibiotics during pregnancy were designed primarily to investigate short-term perinatal outcome measures and have not been large enough or willing to follow the children long enough to examine whether such therapy can reduce the risk of cerebral palsy. Because of the possibility of harmful consequences of the widespread administration of antibiotics during pregnancy, an evaluation of the safety and efficacy of such medications in pregnancy should require randomized clinical trials that include the evaluation of long-term neurologic outcomes. Such studies are still awaited.

## CONCLUSIONS

Cerebral palsy is a syndrome since the etiologies are varied. Considerable evidence suggests that no more than 10% of all cases of cerebral palsy occur as a result of an intrapartum event. There are as yet no effective strategies available for the prevention and/or treatment of fetuses and newborns at risk for cerebral palsy. A better understanding of the pathophysiologic mechanisms responsible for fetal and infant brain injury will further our knowledge about disorders of neurologic development, including cerebral palsy.

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# Coping with the Special Needs Child

*D. A. Hay*

**99**

**WHICH SPECIAL NEEDS ARE MORE LIKELY IN MULTIPLES?**

**HOW FAMILIES ADAPT TO DIAGNOSIS OF SPECIAL NEEDS**

**IMPACT ON THE NON-DISABLED MULTIPLE-BIRTH CHILDREN**

**INFORMING EXPECTANT COUPLES ABOUT RISKS TO MULTIPLES**

**LONG-TERM EFFECT OF MULTIPLES WITH SPECIAL NEEDS**

## INTRODUCTION

It is almost 50 years since Shere observed, 'This study appears to suggest that the condition of cerebral palsy can be more harmful to the social and emotional development of the non-cerebral-palsied child than it is to his cerebral-palsied twin'[1]. Even so, it is entirely appropriate to begin this chapter with this comment for two reasons. First, despite the growing recognition of the high incidence of morbidity and mortality in multiples, Shere's[1] study remains one of the very few to adopt a quantitative approach to psychological effects of a specific disorder on the co-twin, let alone the entire family. Although this statement may appear confrontational and/or debatable to some readers, it clearly emphasizes the need to consider disability and the twin family, rather than just the twin with the disability. Second, the questions then arise, what can be done about this problem and how can help for the twin or higher-order multiple with a disability be linked with help for the entire family and especially the non-disabled co-twin?

Today's practitioner is confronted not only with more multiples but with more significant morbidity[2–5]. Improved medical management of high-risk pregnancies and births contributes enormously to an increase in surviving multiples with significant morbidity. For example, Bryan[2] discusses the much higher incidence of pervasive developmental disorder among multiples of < 800 g birth weight than among singletons (67% vs. 13%). Such children would not have survived but a few years ago. Multiples are grossly overrepresented in this low-birth-weight group, being 1 in 8 among those < 800 g vs. 1 in 90 in the general population. In parallel to this, Western Australian data[4] demonstrate that prior to 1970, 5.3% of all cerebral palsy was in multiple births, but this number rose in the period 1980–90 to 10.3%.

To date, the extensive epidemiologic work on mortality and morbidity in multiples (see Chapters 1 and 4) has not been complemented by thorough studies of the psychological impact of either on families and especially co-twins. Thorpe and colleagues[6] found that depression 5 years after the birth was more common both when one twin had died at birth and when moderate to severe disability was present in the child(ren). In a large study of Japanese women who conceived multiples spontaneously or after infertility treatment, Yokoyama[7] found that the infertility group had lower rates of anxiety about managing the multiples than did those who conceived spontaneously. However, this author reported higher rates of depressive symptoms in the infertility group after the birth, despite these women having more support from family members. The main predictor of their depressive symptoms was disability in the multiples. Having at least one child with a 'disability' (including cerebral palsy, sensory disorders, intellectual disability or limb malformations) was associated with a two-fold increased risk for depressive symptoms. This pattern was not present in mothers who conceived spontaneously, suggesting that the greater expectations around finally having children were associated with more of a let-down when a significant disability was present in one or more of the children. Unlike Thorpe who used a population database, Yokoyama's mothers were volunteers, and this trend may be an underestimate, as those mothers most depressed or most upset after the diagnosis of a disability were least likely to participate in the postnatal phase of the study.

Interestingly, although Yokoyama[7] argued strongly for the provision of specific support for mothers of disabled multiples, the question remains whether appropriate behavioral interventions can identify and reduce the secondary psychopathology associated with mortality and morbidity in multiples, and help the family to cope better with the stresses associated with the child who has problems.

## WHICH SPECIAL NEEDS ARE MORE LIKELY IN MULTIPLES?

Other chapters in this book address issues such as perinatal mortality (Chapters 1 and 77), congenital anomalies (Chapter 33), cerebral palsy (Chapter 97) and postnatal psychopathology (Chapter 96). Bereavement in multiples is addressed in Chapter 103 and is not covered here. The key areas of medical risk for the multiple-birth family where there is evidence for negative psychological impact on the family include those mentioned below.

### Intellectual or physical disability (especially cerebral palsy)

In the population-based Western Australia data, the incidence of cerebral palsy per 1000 live births is 1.6 for singletons, 7.4 for twins and 26.7 for triplets[4]. As discussed by Bryan[2] and Petterson and colleagues[4], cerebral palsy is often associated with the death of the co-twin, placing additional pressures on the entire family. The rate of intellectual disability in multiples is uncertain, partly because of bias in ascertainment[2] but also because of a developmental issue with some equivocal evidence, summarized by Allen (see reference 8) that twins catch up in performance on measures of intelligence. Bryan[2] reports that at 12 months, 12.8% of twins scored below 70 on the Bayley Scales, but this number declined to only 5.4% when intelligence quotient (IQ) was measured at age 36 months. Bryan[2] attributed this difference in part to selective mortality of the least able. A further complication is the association between dizygotic twinning and fragile-X syndrome[9], one of the most common genetic causes of learning and intellectual disability and one which, by its very nature, causes particular problems for the family in supporting the disabled child. The mother, who is usually the genetic carrier, may herself have learning problems and some psychopathology (more so than other mothers of similarly disabled children).

### Correlates of very preterm birth or growth restriction

At present in Australia, twins are born on average at about 37 weeks and weigh 2500 g, but triplets are born at only about 33 weeks. However, as one examines data for very-low-birth-weight children, a vast excess of multiples is found. Tresmontant and colleagues[10] showed that whereas French authorities calculated 360 neonatal intensive-care unit (NICU) days needed for every 1000 singletons, this number increased to over 4100 NICU days per 1000 twin deliveries. Data from our national study of twins in Australia show that almost 50% of twins would be classified as growth-restricted and under the singleton 10th centile for weight/gestational age. This finding has behavioral consequences in terms of speech, reading and attentional problems[11], with growth-restricted twin boys being at a 'triple disadvantage', having three compounding risk factors contributing to their much higher incidence of problems.

Recent developments in neonatal medicine and the improved survival rates of extremely-low-birth-weight (ELBW) babies mean that more children may survive with significant disability. The study by Anderson and co-workers[12] of a cohort of ELBW children born in the 1990s indicated that some 55% had significant 'neurobehavioral impairment'. This global term covered children with sensory, intellectual, educational and behavioral difficulties, and probably provides a better idea of the global impact of ELBW than results of the specific measures of cognitive performance and behavior. However, some caution is required regarding the behavioral assessments, which were made by parents and teachers using the Behavioral Assessment Schedule for Children (BASC). Knowing that the child was born so small may have influenced perceptions and reporting of the child's behavior.

Our own work in the prospective study in Victoria discussed below[13] shows that parental preoccupations can have major effects not only on their own mental health but also on their ability to cope pre- and postnatally. This is consistent with the growing emphasis on family-focused interventions for preterm infants[14,15]. Although such programs are designed to address the recognized problems of attachment to a preterm baby, additional problems with multiples in terms of differential attachment also appear[16].

### Behavioral problems, especially attention deficit hyperactivity disorder in one/both twins

In the 1980s, we demonstrated[17] that the well-known problems in language development in multiples were also associated with later literacy problems. Analyzing data from a national and very representative sample of 10- and 13-year-olds indicated that the chief problems for twins lay in the area of attention. Subsequently we developed the nationwide ATAP study (Australian Twin ADHD Project) demonstrating

that attention deficit hyperactivity disorder (ADHD) is more common in twins than in their siblings[18]. Although ADHD is more common in boys than in girls, the twin–singleton differences are consistent across the genders. No other behavioral problems are any more common in twins than in singletons. Our current thinking is that distractibility and impulsivity arising mainly in the unique postnatal environment of multiples underlie a whole range of twin problems, one of which is childhood accidents, where the only data to date are anecdotal[2]. A study in the UK of families attending a child psychiatry clinic[19] indicated an excess of twins being referred for externalizing behavioral problems. Not all studies have found an excess of attentional problems in multiples, however. Pulkkinen and colleagues[20] provide a comprehensive review of this topic and highlight some of the methodological issues. Although they interpret their own results as suggesting that twinness may be adaptive and multiples have fewer problems, their data derive from a fairly unique approach, namely rating by classmates. Although twins may be popular (and in Finland they are almost always in the same class), the ability of 12-year-olds to rate psychopathology makes the generalizability of this study difficult to assess.

Evidence for an excess of multiples in other behavioral disorders remains equivocal. With obstetric complications being so common, it is reasonable to expect more multiples with schizophrenia, a disorder where such complications are one of the more frequently observed environmental risk factors. Yet, even from large-scale population-based twin registers[21], the data on schizophrenia in multiples remain equivocal. Another area needing additional study is that of the connection of autism and twinning. In one of the large autism family studies of 166 affected sib pairs, 30 of these were twin pairs[22]. The authors went to great lengths to exclude ascertainment bias and pervasive developmental disorder as explanations, but were left with the unsatisfactory conclusion that 'twinness was a risk factor for autism'. It was not clear whether this meant abnormal fetal development or postnatal factors possibly associated with the language delays common in multiples. Given the impact of autism on the child and family, an effect of this magnitude needs further study.

## HOW FAMILIES ADAPT TO THE DIAGNOSIS OF A MULTIPLE-BIRTH CHILD WITH SPECIAL NEEDS

Diagnosis may be easier for the multiple-birth family for two reasons. First, as part of antenatal education they may have been made aware of the fact that things can go wrong. At the same time, neonatal and pediatric staff may be more alert to potential problems. Second, the ease of comparison of two or more babies of the same age facilitates identification of differences in motor or language development or attention. However, as our earlier work emphasized the ease of stereotyping differences between multiples, one may be identified as the 'slow developer' while in fact one is following the usual growth norms and the other is advanced.

At the same time, diagnosis may be more difficult because of the lack of good norms for physical or behavioral development in multiples who were preterm or small for gestational age[11]. This may be compounded by widespread acceptance that multiples are slower in areas such as speech and language development. Comments such as, 'this is typical of twins', or, 'he [or she] will grow out of it', may be accurate or may be a misguided means of trying to alleviate parental concerns. The point of the article by Anderson and co-workers[12] is a real concern, therefore. Although there may be older data on the developmental catch-up of multiples, it is reasonable to ask how relevant this is to the more recent cohort of multiples, a significant proportion of whom may not have survived.

### Psychosocial impact of special needs on the multiple-birth family

Despite the fact that these examples clearly illustrate the range of stressors that the multiple-birth family is likely to experience, each has been approached in a different way. At present, there is no means of identifying common themes and strategies for intervention that may be more broadly applicable as the family adapts to the diagnosis of disability. In the final analysis, adaptation is dependent on the family resources, their appraisal of the situation and their ability to cope with the stressor. All issues are explored more formally in Chapter 101. At the same time, the effects on the family may not be directly associated with the apparent effects. Among the examples discussed earlier, ADHD may seem much less of a burden than cerebral palsy, but there is growing evidence of the negative impact of ADHD on the family[23]. In the case of monozygotic twins, for example, the concordance for ADHD is well over 80%; the family is likely to have not just one but two ADHD children, and this impact on parents as well as other children needs to be considered. A study from our group (Roisin Reed, unpublished data) has shown that ADHD is associated not only with as much parental stress and psychopathology as having a child with cerebral palsy but also with more stress around child-rearing issues. The reasons for the latter are unclear. It may be that cerebral palsy is more visible and support from the community is

more forthcoming, or it may relate to the more ambiguous etiology[24] and diagnosis of ADHD, with parents blaming themselves for the disorder or questioning whether there is any 'real' problem with their child. This latter problem is more likely if the twins are the only family progeny and no siblings are available for comparison.

### Differences from the singleton family with special needs

The issue is much more than the frequency of specific disabilities in multiple-birth children. The common association between increasing maternal age and assisted reproductive technologies (ART) influences parental perception of disability, on the one hand because of the extensive period of longing for and expectation of a healthy child or children, and on the other hand because of the extra challenges that older parents may have in meeting the demands of two or more children of the same age, one or more of whom may have a disability. The issue of expectations of two or more healthy babies after years of infertility treatment and what happens if this is not achieved is discussed elsewhere[7].

### Higher-order multiples

The practicality of caring for three or more children of the same age may itself be a major stressor. The population-based study of all triplets, quads and higher multiples born in Britain over a 10-year period[5], as well as a contemporary review of higher-order multiples, indicates the range of health, social, educational and medical problems experienced by these families[25]. The problem with the UK study is the qualitative nature of many of the measures and the difficulty of estimating the extent of formal psychopathology in the parents. Common sense and impressions of the data in the UK study clearly suggest that the psychological impact of triplets is much more than might be explained by the medical morbidity alone (rates of cerebral palsy, retinolental fibroplasia, etc.), but it is not possible to determine this precisely from the data obtained. One clear indicator of the increased vulnerability of these families and especially the mothers, however, was the emphasis on an external locus of control, attributing everything negative to forces outside themselves, whether this be the higher-order multiple children or even, in the case of assisted reproduction, the agencies involved.

### Identifying the family that copes better with special needs

Although the concept of resilience in coping with a child who has special needs is well established, it has never been formally applied to the multiple-birth situation. In particular, it is not clear what coping mechanisms are required to deal with one child who is fine and another who has special needs. Equally debatable is how parents, the extended family and the broader community interpret this situation. Crucial to answering these questions is how the family interprets the diagnosis of special needs. Here, the best source of information probably comes from the family where one twin dies[26,27]. To be sure, this is a very unfortunate example, but the need to celebrate the arrival of one or more healthy multiples, while at the same time acknowledging those disabled (or dead), is the most significant dilemma for most families. One constantly hears of the ambivalence among acquaintances and work colleagues about coming to terms with this situation. Simply stated, do you congratulate or sympathize, or in many cases, do you best say nothing at all?

Because problems do not end with the realization that one or more of the multiples has a special need, three (largely unanswered) questions arise for long-term planning:

(1) Is there a key time in development when stressors/resources have most impact? This is the case, for example, with an intellectually disabled child, for whom there are three identified times of stress: at diagnosis, at the start of school and at the move out of school[28].

(2) Is it possible to identify which problems may be developmental and increase or diminish with time?

(3) Are there robust indicators of families at especially high risk over the course of caring for the special needs child?

## IMPACT ON THE NON-DISABLED MULTIPLE-BIRTH CHILDREN AND POSSIBLE INTERVENTIONS

In terms of developmental impact of the disability, not enough attention has been paid to the multiples without disability. The study by Shere[1] of the effect of cerebral palsy on the co-twin used multiple behavioral measures which were sophisticated for their time and demonstrated an unambiguous negative effect of the disability. Today, two concerns about this article are clear. First, she did not attempt to identify the mechanism by which these effects came about. Was it simply lack of attention, while the focus was on the twin with cerebral palsy, or was it pressure to compensate for the more limited achievements of the disabled twin? Second, although the effects were very significant, they may not occur almost 50 years

later with a much more enlightened approach to cerebral palsy and the integration of these children into the wider community. Given the strong association of cerebral palsy with multiple births, there is an urgent need to determine what the current situation is for the non-disabled co-twins.

Despite a complete lack of studies of the effects of an intellectually disabled twin on the co-twin, a growing body of relevant literature is available on siblings[29,30]. The ability to predict a sibling's adaptation and psychological well-being has serious practical and clinical implications for intervention and the prevention of behavioral and psychological problems. As the presence of a child with intellectual disability is a source of familial stress, it would be expected that siblings might have greater adjustment problems. Indeed, several studies indicate that siblings are at increased risk of developing emotional and behavioral problems as a result of growing up alongside a sib with intellectual disability[31]. Nevertheless, other studies report conflicting findings, indicating that in addition to being well[32], siblings may also benefit from the experience of living with a child with intellectual disability[33].

One of the key issues with siblings of children with special needs in general and multiples in particular is to develop more openness. Anecdotal information from siblings groups highlights their concern about having to contribute to the care of such individuals when the parents are no longer capable. This may be present in siblings as young as 8–9 years, and in the absence of any discussion with the parents. Although it has never been studied, it is easy to see how such concern would be heightened in multiples compared with other children in the family, with the premise that they alone would be most responsible for 'their' twin. In such situations young people need to talk, especially to others in the same situation. A program being developed at Curtin University by Monique Nesa called 'Sibs and US' supports teenagers with an intellectually disabled sibling by such strategies as:

(1) Sharing their experiences;

(2) Developing a better understanding of the disability;

(3) Creating strategies to enhance relationships with their sibling;

(4) Working on coping skills to handle the challenges of such a sibling;

(5) Developing their skills at explaining the sibling's disability to others.

Such work needs an experienced facilitator, as none of it is complex, the main message for siblings in general and for multiples in particular being to talk. It is unclear how frequently such discussions take place in families with a disabled multiple, or whether the impact on the non-disabled multiple's life is even mentioned. Equally unclear is whether the effect of disability differs between monozytic and dizygotic twins, as suggested by Segal[34], who argued that the loss of a twin is more significant in evolutionary terms for monozygotic twins. In a highly selected sample relying on volunteers, Woodward[27], in her study of 200 adults, demonstrated that the sequelae of twin loss were still evident many years later, with such gestures as naming their first child after the dead twin. Lewis and Bryan[35] summarized many of the dilemmas unique to the loss of a multiple compared with a singleton child, including 'blame' on the survivor and the need to 'compensate' for the achievements that the dead child would not make. It is easy to see how this translates to disability rather than death.

## INFORMING EXPECTANT COUPLES ABOUT RISKS TO MULTIPLES

Essentially all psychoeducational models for prospective families with multiples are based around their capacity to seek information. As already indicated, there is growing evidence[6,36] that not all families are coping well, and Fisher and Stocky[37] provide a good review of perinatal mental health in mothers of multiples.

Two fundamental problems exist in trying to determine the coping ability of families, both before and after the arrival of multiples. First, those who are depressed are unlikely to become engaged in any such activity, and second, it is important to consider the mental health of both partners, with the growing recognition of the contribution of psychopathology around the time of birth in fathers as well as mothers[38]. Psychopathology in the father may work negatively, both as an additional stressor on the mother and through the inability to provide support[38].

Data on frequency of occurrence of psychological problems in mothers and fathers of multiples, both before and after birth, are scant indeed. The nature of anxiety and depression is such that parents in this situation may either not enroll in research studies or may drop out, which makes our own study particularly useful. This program, 'Having twins: how does the family cope?', was a longitudinal study of 200 women expecting twins in Victoria, from the time of diagnosis until the children were 6 months old[13]. Particular emphasis was placed on finding a representative sample of the population, with a focus on rural areas, on areas of low socioeconomic status

**Table 99.1** Classification of groups by self-reported psychopathology (total number of parents 152)

| *Group* | *Classification definition* | *Parents n (%)* | |
|---|---|---|---|
| 1 | *no problems* either before or after birth | mothers | 22 (28) |
| | | fathers | 31 (42) |
| 2 | one or both parents report *distress before* not after birth | mothers | 10 (13) |
| | | fathers | 8 (11) |
| 3 | one or both parents report *distress after* not before birth | mothers | 12 (15) |
| | | fathers | 19 (25) |
| 4 | those where *distress* is present both *before and after* | mothers | 34 (44) |
| | | fathers | 16 (22) |

and with no emphasis on marital status. Families had monthly interviews by trained mothers of twins, with back-up from midwives when more complex queries arose. Some indication of the representativeness of the sample is given by the fact that well over 50% of all multiple-birth families in the state (Victoria, Australia) in the study period agreed to participate. As this was not a population-based study, this number is likely to be the majority of those who were informed of the study. Only two families dropped out: one during a difficult divorce and one through moving overseas. As recruitment progressed, it became apparent that families thought they were benefiting just from participating in the study. It was not uncommon for the interviewers after a few visits to arrive to find both parents at home during the working day with a list of issues they wished to discuss. Thus, the study had to change to involve three groups, one from the time of diagnosis, one from birth until 6 months and one with just a single visit 6 months after the birth. A comparison of psychopathology in these three groups is in preparation. Only the data from the group seen since diagnosis are considered here.

The data in Table 99.1 are based just on the group seen from the time of diagnosis. Given the amount of support these families received and the fact that those who experienced a death or significant morbidity were excluded, this makes the results of even more concern.

The measure of distress is based on the appropriate clinical cut-off scores of the General Health Questionnaire (GHQ), widely used as a general screen for anxiety, depression, psychosomatic and sleep problems in both the UK and Australia. Because we used lay interviewers, no more rigorous form of assessment of psychopathology was possible. Even if some problems exist with both specificity and sensitivity in terms of the GHQ, the results indicate that only a minority of families are free of psychopathology either before or after the birth of twins. Group 3, with classic postnatal depression, is much smaller than group 4, who experienced depression both before and after the birth. Although the rates of problems are lower in the fathers than previous work had suggested[38], they are still sufficient to indicate that fathers may not always be a resource, despite spouse support being a key issue in reducing the risks of postnatal depression in mothers[39]. Accordingly, the role of the partner as a critical provider of marital satisfaction and support needs even more emphasis, especially considering that these families were getting a high level of support, regular access to a role model (a mother who had healthy multiples) and frequent opportunities to have queries answered.

If one or both parents have behavioral problems, it raises significant issues about their ability to cope with any of the additional stressors if there are complications pre- or postnatally. Simply providing more resources is, at best, going to be of modest help if families have such difficulties in coping. Fortunately for some families, circumstances improve, and there is a significant reduction in the percentage of parents who remain depressed 6 months after the delivery. The distinction of short-term versus chronic postnatal psychopathology and the determinants of this distinction are beyond the scope of this chapter (see Chapter 96), but a longer-term follow-up of these families would be invaluable.

## THE LONG-TERM EFFECT OF MULTIPLES WITH SPECIAL NEEDS

While it is patently obvious that additional services should be given by health-care providers and governmental agencies to multiple birth families, a key question is the aim of such services. These may be directed to the parents, the twin(s) or higher multiples with disability, the other twin and/or siblings, or family functioning as a whole. Are they aimed at psychopathology, e.g. to reduce depression, or more generally at coping skills and self-concept?

Ideally, this approach could be used with everyone, but it is not so easy to identify those who most need the help but may not seek it. To be effective as a

**Table 99.2** Notional areas of increased financial costs for families with twins (costs increase exponentially for higher multiples)

| | *Community/health-care system* | *Family* |
|---|---|---|
| *Antenatal care* | | |
| Classes/medical appointments | * | * |
| Fetal and maternal monitoring | *** | * |
| Bed-rest | ** | * |
| Relocation to tertiary service | | ** |
| Disruption of paid employment | * | ** |
| Household expenses | | *** |
| *Perinatal* | | |
| Obstetric intervention | ** | |
| Days in hospital (mother) | * | * |
| NICU/SCN | **** | ** |
| Surgery | * | |
| Stillbirth/neonatal death | ** | * (counseling) |
| Disruption of paid employment | * | ** |
| Care for other siblings | | * |
| *Postnatal* | | |
| Preterm/OC consequences | * | * |
| Parental depression | * | * |
| Cerebral palsy | * | ** |
| Intellectual disability | * | ** |
| Child abuse/family support | * | * |
| Behavior | | |
| language | * | * |
| learning | * | ** |
| ADHD | ** | * |
| Child accidents | * | * |
| Employment/child-care | * | * |
| Household expenses | | * |
| *Reduced earning capacity of twins* | | |
| Death | | |
| Physical/intellectual disability | | |
| Delay in starting/finishing school | | |
| Learning/behavioral problems | | |
| Psychiatric disorders | | |

*Represents increase in financial impact (cost × incidence) over two singletons; NICU, neonatal intensive-care unit; SCN, special-care nursing; ADHD, attention deficit hyperactivity disorder

tool to gauge the extent of the problem, such a model must have a representative sample of multiples[40], so as not to limit the range of behaviors and coping strategies being sampled. In terms of intervention, not only the families who seek information are needed, but also those who, because of mental-health problems or financial or other circumstances, do not seek support.

## COMMENT

The aim of this chapter has been to emphasize that there is more to the management of multiples than mere medical issues. Long after the specialists have ceased to see the family, debilitating consequences can remain and affect all of its members. Two points need to be stressed:

(1) This chapter takes a very broad focus on special needs in order to include not just the physical and intellectual disabilities, but also the more common behavioral ones such as ADHD. With its enormous and continuing impact on the family, the question of whether there are higher rates of autism and schizophrenia in multiple-birth families also needs urgent attention.

(2) The impact of the disability differs greatly between different members of the family. Effects on the mother, the father, siblings, and the affected and unaffected co-twins are all distinct

and must be recognized separately, even though this is unlikely to be part of standard consultations or costings in health-care plans.

One way of emphasizing the economic benefits of such an approach is to try to quantify the costs of multiples. Although the UK study of higher multiples aimed to address this issue, it did restrict its coverage. The section on costs (by Mugford in reference 5) dealt only with obvious costs (e.g. nappies) and not with more general health costs such as disability and loss of lifetime earnings. The one article to address this issue in twins[41] confines itself to the costs of the NICU and (undefined) 'deep handicap', indicating that twins cost some ten times what singletons cost. This is an extremely narrow definition of additional costs and does not consider the emotional costs to both parents and children, with long-term financial consequences of depression and low esteem. Even granting that the effects on the parents and their income-generating capacity are difficult to assess, even more significant is the effect on the children over their life span.

Ultimately, the major cost both to the community and to the families with disabled multiples is in psychopathology. The afflicted twin may be dead with no further cost to the system, but with great and long-term cost to the family, or disabled, where the impact upon the family and co-twin may continue for 50 or more years. There must be a greater commitment by mental-health professionals to the needs of the multiple-birth family and a similar commitment by medical specialists caring for the physical needs of the family to involve mental-health professionals when appropriate. The importance of such a program must be seen within the context of both an increasing number of multiple-birth families and their exceptionally high cost to the health-care system[4,41]. Such a financial investment in improved management of physical needs should be associated with a corresponding focus on the psychological needs and the behavioral aspects of their quality of life.

Table 99.2 is a preliminary attempt to indicate the long-term costs to both the community and the family of having a multiple with a disability. It takes into account such issues as repeating a grade in school or needing extra educational support, which Anderson and co-workers[12] identified as issues for their ELBW cohort. It is even more difficult to include such issues as the association of ADHD with criminal behavior and the disruption to life and career development associated with contributing to the care of your disabled twin or higher-order multiple siblings. However, these are the type of topics which a full costing of the impact of a disabled multiple needs to consider.

To some readers, such issues may seem remote from those of the medical staff dealing with the immediate physical needs of a critically ill newborn twin or higher multiple, or of the family coming to terms with the likelihood that one or more of their multiples are disabled or may be dead or about to die. Yet, the multiple with special needs will be with the family and community for a lifetime. It is time that more thought was given to these often unrecognized multiple-birth priorities.

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# Education of Multiples

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100

IDENTITY DEVELOPMENT AND DEPENDENCE

INTERACTION BETWEEN MULTIPLES AND EDUCATIONAL INFLUENCES

PRESCHOOL FOR MULTIPLES

TWINS' LANGUAGE AND EDUCATIONAL SITUATION

MULTIPLES AT SCHOOL

MULTIPLES AT RISK

Monozygotic triplets at the ages of 4 and 9 years, from the longitudinal Stockholm study. Pictures published with parents' permission. Photographs: Britta Alin Åkerman

## INTRODUCTION

Much research has been conducted on populations of young twins, of which most is oriented towards the genetic aspects of twinship. Monozygotic twins (MZ) are compared with dizygotic twins (DZ). Only a few empirical studies have examined the twin situation itself, comparing twins with singletons. During the past 30 years, several studies have shown a lag in the development of twins compared with singletons[1–4], accompanied by a difference of opinion as to whether this lag is an inherent feature of twinning, or whether due to postnatal factors.

Because twins are commonly born prematurely, are immature at birth and are predisposed to delays in development, educational adjustment, both at preschool and in school, is often problematic.

For 18 years, from 1982 until 2000, a group of Stockholm twins was followed with the aim of describing their mental and identity development, as well as their school adjustment (The Stockholm study). The first aim was to clarify the psychosocial situation of the pregnant mother and her feelings about expectations of twins, including both partners' perception of delivery. A further concern involved the possibility of preventing future problems by providing information to parents about the implications of having twins, and share the experiences of parents-to-be at the time they were informed about the twin pregnancy[5,6].

During this project the question arose whether the situation is similar for couples pregnant with triplets. The only known longitudinal study concerning the mental development and school adjustment of triplets was that of Gonen and associates[7]. These investigators followed 57 sets of triplets, eight sets of quadruplets and five sets of quintuplets, but the study does not describe the follow-up examination.

Moreover, the study period was from 1978 to 1988, and the results are now outdated. Regardless, triplet pregnancies present obstetric and perinatal risks that are considerably higher than those for twins. Although the chances of a good outcome have increased as a result of advances in obstetric management and neonatal care[8–10], triplet deliveries continue to be associated with problems, first because of prematurity and the requirements for neonatal care, and second because of the psychological strain on the family[11].

Several researchers question whether the extent of problems for twins is related to social background. It could be argued that a more stimulating and favorable home environment might reduce or even abolish an existing difference between twins and singletons. Zazzo[1], Koch[12], Mittler[2] and Fischbein[13] all suggest that differences exist irrespective of social background. In the SLU study (Skolöverstyrelsens och Lärarhögskolans Utvecklingsstudie (Board of Education and the Stockholm School of Education), see below), for example, a comparison was made of school achievement for twins and singletons in relation to social background. The difference between twins and singletons was of the same magnitude in all social groups[14]. Additionally, Wilson[3,15] compared twins with low (< 1750 g) and normal birth weight from different social groups, finding that the difference between low-birth-weight and other twins on a mental development scale was larger for lower social classes and tended to disappear for higher social classes. Furthermore, Alin Åkerman and Fischbein found that low birth weight (< 2.5 kg) seemed to have a lasting impact on mental development[4]. In particular, twin boys with low birth weight seemed to be at a disadvantage. This difference tended to disappear, however, in more stimulating home environments. Among twins as well as among singletons, girls develop earlier than boys during the preschool years. These differences between the sexes occur in all children and in all cultures, and are related to the later evolution of physical growth of the brain for boys than for girls[16]. In the Stockholm study, twin boys of all ages show a developmental lag in skills related to locomotor ability and perception.

The prenatal and perinatal damage experienced by many twins may have negative implications for later development. Twins in general may score poorly on developmental tests, compared with singletons, since a larger proportion of prematurely born infants are included in the twin group. Measures of mental development in the Stockholm study show significant differences between the preterm and full-term test groups during school ages. In this analysis, twins born with pregnancy duration shorter than 37 weeks and with birth weight less than 2500 g were compared with full-term twins. Full-term twins with a birth weight more than 2500 g had equally good results as those of singletons, whereas preterm twins presented lower results in all areas. In general, growth-restricted twins achieved lower scores than preterm twins. In particular, gross and fine motor and practical-logistic tasks were most difficult to solve for both preterm-born and growth-restricted twins.

## IDENTITY DEVELOPMENT AND DEPENDENCE

All young people need to be independent of their parents and to develop a personal feeling of identity, specifically a deep feeling about who they are as individuals, and what their values, attitudes and goals are.

The development of identity starts before birth[6]. There is reason to believe that differentiation begins in the uterus. Using ultrasonography, Piontelli found that co-twins differed from each other in activity patterns at an early fetal stage[17]. Such differences persisted when studied in the home environment until 4 years of age. Although the sample size of this study was small[17], similar results were observed in the Stockholm study in that the mothers indicated which fetus was less active *in utero*, and the more active fetus continued to be more active during the first years of life.

The following example illustrates how twins start to differentiate from each other after birth[6]:

> *'A twin pair about 3-months old are sleeping side by side with one twin's thumb in the other twin's mouth. At 7 months the same twin pair are sitting face to face examining each other's bodies in the same way as a single child examines his own body. This play is interrupted by a high scream when a finger that had been placed in the "mirror-like" person's mouth is bitten.'*

A further example was provided by Zazzo[1] when a pair of twins were observed in front of a glass and a mirror which were switched. A hidden camera recorded the change in facial expression upon realizing that the face seen through the glass was not the same face that had been seen in the mirror. Experiences such as these make it possible for twins to be aware of the other twin existing as a separate individual, and not an extension or a reflection of him/herself.

People pay much more attention to twins than to singletons. Through this attention, twins develop a feeling of being different from singletons. Parental attitudes and patterns of upbringing are very important for each twin's possibility to develop a separate identity. If, from the beginning, parents forget to accentuate

individuality by giving each twin different clothes and names as well as a feeling of being separate individuals, then the growth period can be very distressing. One result can be that the twins view each other as one person. If parents and other important individuals always compare the twins' physical and mental abilities, this too aggravates the development of personal identity.

Family conflicts can self-generate if parents fail to see that it is important for each child to be private and develop a sense of independence. This process is more difficult for twins and triplets than for singletons, because multiples must 'double-differentiate' and fight for independence from parents and the twin/triplet sibling(s). This is sometimes made more difficult because multiples are often very strongly attached to each other, despite fights and controversies[18] as might be expected in a love–hate relationship. Both pair members want to be alone and to be together, and do not know how to cope with this situation. This behavior is similar in MZ and DZ twins of the same gender (both males and females), but not in twins of opposite gender. On the other hand, the twins can thrive in each other's company, and the co-twin is often a twin's best friend, even if she/he has other friends.

A comparison of twins in Sweden and Israel revealed that people often view MZ twins as one and the same person, whereas they will treat DZ twins differently[19]. Both restrictive and permissive treatments influence the twins' identity and attitudes towards themselves and towards other people. A more stimulating environment, whether permissive or restrictive, increases the twins' self-confidence. A more restrictive treatment decreases the influence of genetic factors. The most important factor for developing self-confidence is to be treated individually.

The Stockholm study showed that DZ twin girls are less dependent on each other, but it is common that one twin girl in a pair is more dependent on her sister than the reverse[20]. As most DZ twin girls differ in appearance and adults can always differentiate between them, they often have the feeling of just being siblings and not twins. In this manner they develop a more positive identity of being an individual and not mixed with the other. All of the DZ twin girls in this study had a best friend who was not their twin sister, as in the case of MZ twin girls[20].

DZ twin boys are even more like other siblings than DZ twin girls. They are not as dependent on each other, and often have different interests and different friends. This can perhaps be explained by their relations with their peers. For girls in puberty, it is important to have one close friend. For boys in puberty, who often meet others in groups, it is not so important to have one so-called best friend.

DZ girls and boys from opposite-sex pairs present a quite different situation. In particular, a girl is more physically mature in comparison with her brother, often acting as a 'little mother' and taking care of her brother, who complies. But this will often increase her feelings of responsibility, which, in reality, she is not able to cope with. For the boy depending on his sister, self-confidence can decrease, and the result for both opposite-sex twins can be a feeling of failure. This may profoundly influence their identity in a negative way.

## INTERACTION BETWEEN MULTIPLES AND EDUCATIONAL INFLUENCES

In one longitudinal Swedish twin study (the SLU project), which started in 1964, continued until 1975 and had a follow-up 25 years later, over 300 pairs of twins and more than 1000 controls (classmates to the twins) were followed through compulsory school from age 10 to 16 years[13]. In addition to a comparison between mental and physical development of the twins and controls, this study also investigated genetic influences in relation to school and home environment. Three types of results were important from an educational point of view (Figure 100.1):

(1) Genetic influences varied with type of characteristic studied. Logical-abstract thinking was more genetically influenced than verbal ability.

(2) Genetic influences were larger in a permissive compared with a restrictive environment. For example, school achievement was more genetically influenced in a permissive home environment than in a restrictive one in which parents told children how to manage at school.

(3) A stimulating environment (whether permissive or restrictive) was more conducive to optimal development. This stimulation could be adjustment of content, method or psychosocial treatment.

These results were later developed into a model of interaction between individual prerequisites and educational influences, incorporating not only the immediate classroom situation, but also important factors at institutional, regional and societal levels[21]. The educational setting can fluctuate owing to pupil variation, teacher characteristics, content, organizational factors, etc. In a permissive-stimulating situation, the educator functions as a tutor, providing feedback and supplying freedom for individual choice. In a permissive-non-stimulating situation, freedom of choice exists in the presence of very little

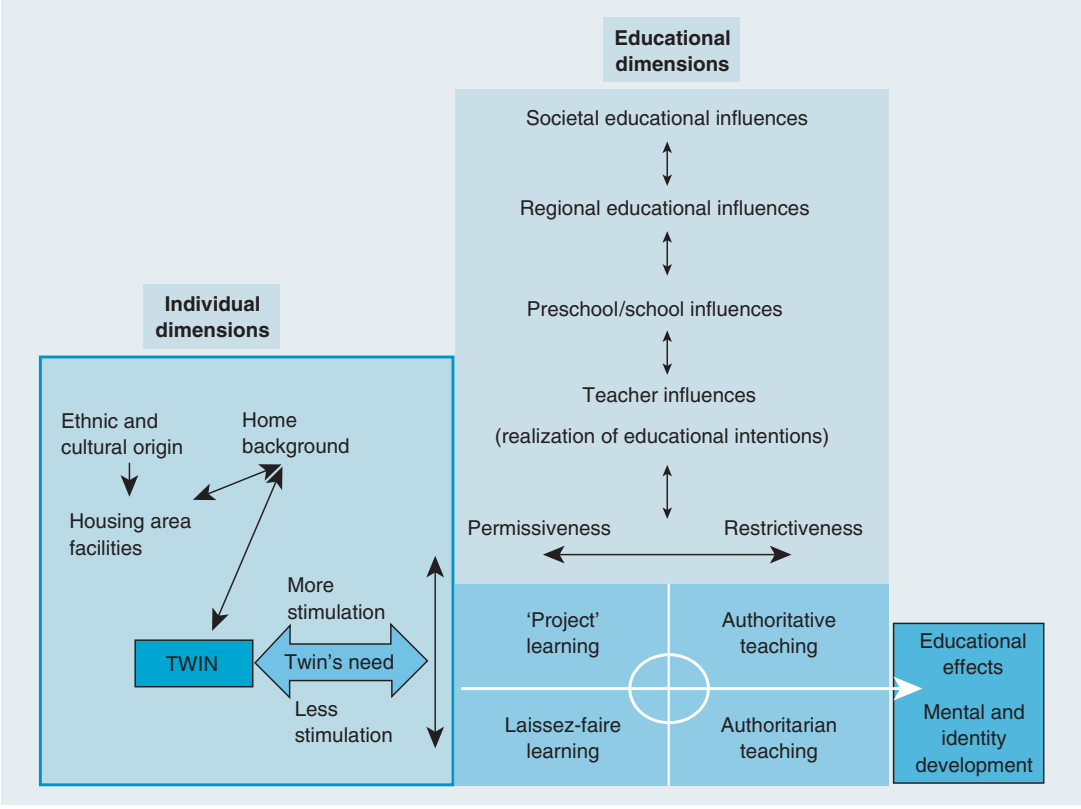


**Figure 100.1** Interaction between multiples and educational influences

feedback, which may cause indifference and insecurity. In a restrictive-stimulating situation, the educator structures the environment in relation to a predetermined goal but also adjusts the setting according to personal requirement. Finally, in a restrictive non-stimulating situation, the educator is controlling and demands that everyone follows his directives. Depending upon the educator, the educational setting will normally fluctuate between these different situations, the group, the content and the goal, but in general, genetic influences tend to be larger in permissive situations and smaller in restrictive.

This model has been used in many different types of studies, and it is also evident that pupils, whether twins or singletons, experiencing difficulties at school need a more structured and stimulating setting to develop to their full potential[22–24].

## PRESCHOOL FOR MULTIPLES

Preschool or day care may assume a great importance for the twins' cognitive, mental and identity development, and, in a way, support their curiosity and desire for knowledge. As one twin can be delayed in his/her development, or be immature for some reason, twins can be better stimulated in preschool than by staying at home during the daytime. This education should, however, be individualized according to the twins' needs. Most preschools in Sweden have well-educated staff. It is important that the staff have sufficient knowledge about twins, and can provide adequate intervention for stimulating development. This intervention should include an appreciation of twinship *per se* by the personnel, and, at the same time, should support all efforts to develop the twins' individuality.

If the family has children other than the twins, preschool or day care is of particular importance, as the parents often lack sufficient time to give all the children the attention and stimulation they need. Educational intervention and stimulation is not the parents' primary task. What parents need to do is to develop a good and satisfying child–parent relationship. This is especially true for mothers who are still at home and not gainfully employed, in order to have time for their own development and interests.

Whether the multiples should be in the same preschool group must be decided on the basis of their personalities. If they are very dependent on each other, there is an advantage of placement in separate groups where they have more opportunities to develop individual characteristics and experiences without being interrupted by their co-twin[5].

Placement in separate groups can also be motivated for psychological reasons. When twins remain in the same group, there is a risk that both twins rush home to tell the same story, each screaming to be the first to relate a particular event to their parents.

Preschool attendance has great importance for social development, as shown in a study of MZ twin girls in the age group 5–6 years[12]. Twins are often very popular among other children, and this popularity strengthens their self-confidence, a result that also was found in the Stockholm study.

## TWINS' LANGUAGE AND EDUCATIONAL SITUATION

It is usual to believe that twins have their own special language. Today it is not as common, as parents are more conscious of the necessity to address their infants separately. In the past, twins were often left alone and, in this circumstance, tended to develop a special type of communication. Sometimes this is called an autonomous language. More often twins create special words that they use together, and nobody else, not even their parents, can understand them. This often happens during a short period when language development starts with words; whereas a singleton child usually imitates the parents or an older sibling, twins tend to imitate each other. In terms of language development, twins use shorter sentences and often have more problems with pronunciation, compared with singletons[6]. The La Trobe study in Australia showed that, at the age of 30 months, twin boys were 8 months delayed in their language development, compared with singletons[25]. This study also revealed that twins with delayed language development had deficiencies in motor ability. In particular, twin boys had problems with articulation at 3–4 years of age[25].

Garitte and colleagues[26] studied a particular twin sample, i.e. those who still had linguistic impairment at school age and were in need of speech therapy. In this survey, there was no clear link between prematurity and linguistic disorders, although there were more premature births in the twin sample. Same-sex pairs and opposite-sex pairs differed in that same-sex pairs had more linguistic impairments than opposite-sex twin pairs. According to the authors, one explanation for this difference may concern the mothers' perceptions regarding twinship and twin differentiation. Mothers' descriptions of the twins' personalities for opposite-sex pairs contrasted with those for same-sex twins[26]. Mothers also had varying attitudes towards same-sex and opposite-sex twins regarding physical help in the home environment. Same-sex twins were allowed to engage in similar physical activities, whereas opposite-sex twin girls were told what was dangerous. This suggests that the way and extent to which the mother individualizes speech directed at each child play an important role in how each child approaches the language-learning situation. This can only be possible if the mother herself has a clearly differentiated representation of the twins, and this is particularly the case for opposite-sex twins. Another difference is that girls are generally more developed in language than boys from the beginning, which will affect them in school situations. A twin boy has a better possibility of imitating his more advanced twin sister than is the case for a pair of less advanced twin boys.

## MULTIPLES AT SCHOOL

To start school is of course as important for multiples as it is for singletons. However, some problems can arise as a result of the twin situation. The first issue to be considered revolves around different classes for starting school. The difference in development in a twin pair can be so great that one of the children is still not mature enough for school but the other is. Moreover, one of the children can be dependent on his twin sister or brother or parents, a circumstance which may cause problems at school from the start. At some schools, during certain periods, the policy has been to place all twins in separate classes from the beginning.

When there are two children, additional problems surround class placement. Should twins of the same sex be placed together and those of different sex placed separately? Should emotionally dependent twins be placed close to each other and others in different classes?

Owing to possible complications at birth, one child in a pair of twins could be developmentally delayed and perform much worse than the other. This will be very difficult for the teachers to handle when they start comparing. The greatest problem is for schools in small communities, lacking two parallel classes, which makes it impossible to place twins in separate classes. In such circumstances they could be placed in different schools, but this would be practically impossible for the families. If the children must be placed in the same class, they should not sit near each other and preferably not at the same table.

Another situation that might arise at school, particularly with male twins, is that they compete with each other. This presents great difficulties not only for the twins themselves but for the teachers as well, especially if one twin feels at a disadvantage and engages in destructive activities to enhance his self-confidence.

Teachers often complain that they cannot distinguish one twin from another when they are monozygotic. This creates insecurity in the teacher, and

increases the possibility that twins will be considered and evaluated as a pair rather than as separate individuals. Sometimes the twins reinforce these tendencies by changing places with each other and taking advantage of their similarity[27–29]. By contrast, however, MZ twin girls are disturbed when teachers are unable to tell them apart. This is especially true at puberty when girls often struggle to be different by using different clothes, having different haircuts and hair colors and also enhancing their different temperaments, aptitudes and career ambitions. At upper secondary school they choose different programs so as not to be too close to each other. Transition from primary school to upper secondary school gives them other options that can reflect their preferences. DZ twin girls can also choose different programs at upper secondary school based upon different abilities and interests, rather than just to separate from each other.

The situation for MZ twin boys is similar to that for MZ twin girls. The teachers often mix them up and give them the same credits, not because they have similar knowledge of a subject, but rather the teachers are not able to distinguish them. This is often the case in written tasks. Twins indicate that it is frustrating to be confused by the teachers and cannot understand why, since all of their friends always know who is who. Another result from the Stockholm twin study is that all the MZ twin boys were aware that one in a pair knew the answer to verbal questions better than the other, even if they produced similar results in written tasks. All of them chose different programs at upper secondary school, which was also the case for DZ twin boys.

Twins from opposite-sex pairs have different problems at school. The girls are often more conscientious and more ambitious. For them it is not important to be placed in separate classes, and most of them have always been in the same class as their twin brothers. Some choose the same programs at upper secondary school, as they believe that they can get help from their co-twin when it becomes more difficult to study.

## MULTIPLES AT RISK

A twin born with a functional disorder induces the same parental grief reaction as the loss of a child[30]. Denial, anger, guilt and grief are feelings in both situations. The parents mourn the 'healthy child' they expected to have. When one of the twins is born without any disorder, it is easy for the parents to imagine how the situation would be with two healthy twins. Experience with the healthy child is always a reminder when the parents nurse the twin with a functional disorder. Quite unconsciously, parents blame the healthy child for the difficulties they have had to cope with in caring for the disabled child.

Other problems can also arise. If parents wish to aid progress in the unhealthy twin's development, they may overlook progress in the healthy child. They can feel guilty if they are happy about the healthy child's progress, which may influence the relationship with both twins. It is easy to deny the happiness as well as the pain and grief. When the twins become older, it is often the case that the development of the healthy child deteriorates, and he/she may start to imitate the less advanced behavior of the unhealthy child. This reaction can be a sign of jealousy about the attention that the parents give to the unhealthy twin.

Twin parents who have a child with a functional disorder require support and help, both psychologically and practically. They need to talk to professionals about mixed feelings of guilt and grief. This need persists for years.

## SUMMARY

There is a need for more knowledge and appreciation of the specific situation that multiples experience in educational settings. Placement can be an intricate question, and should be considered not only from the viewpoint of the multiples themselves but also on the basis of what is convenient for the whole family. The enhancement of separate identities and strengthening of self-confidence are important issues of which educators need practical knowledge and understanding. It is important to address the twins by their first names and not to confuse them, if possible.

Most twins do not have specific educational problems, but there is an increased risk of developmental delay or functional impairment. In most Western societies today, school has become more individualistic, and pupils are expected to seek their own information in books or by computer. This will present problems for children who have reading and writing difficulties or a growth deficit, which means that they will need concrete and structured direction at school. A restrictive and stimulating educational environment at the start of their schooling will be necessary for these children to develop to their full potential. They have a right to feel safe and self-confident at school, and gradually a more permissive approach can be introduced with project-based learning.

Co-operation between parents and the school is necessary to improve the situation for twins. Teachers have a duty to inform both pupils and parents about the school situation. Ideally, parents and teachers should work together to design a program that will support each child.

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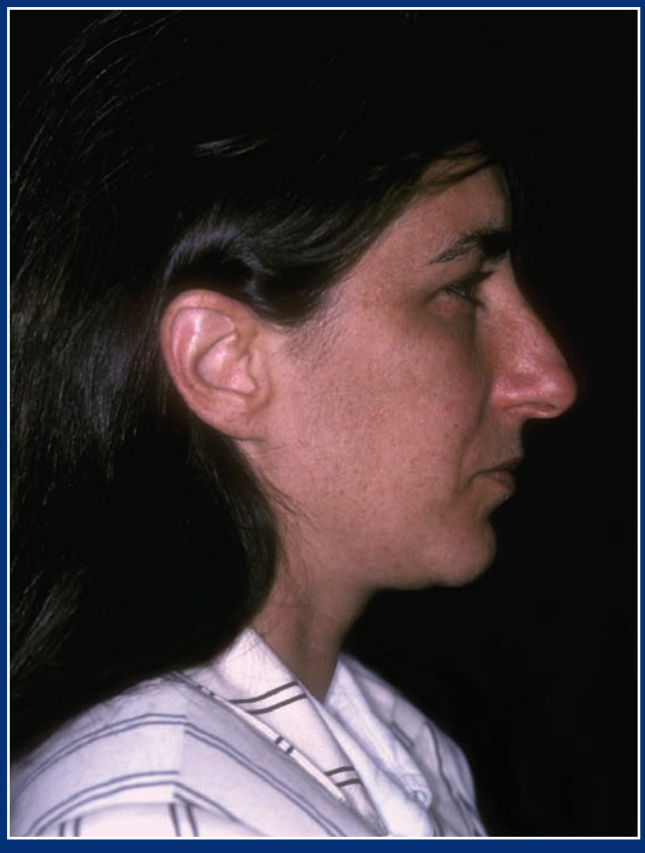
## COMMENT

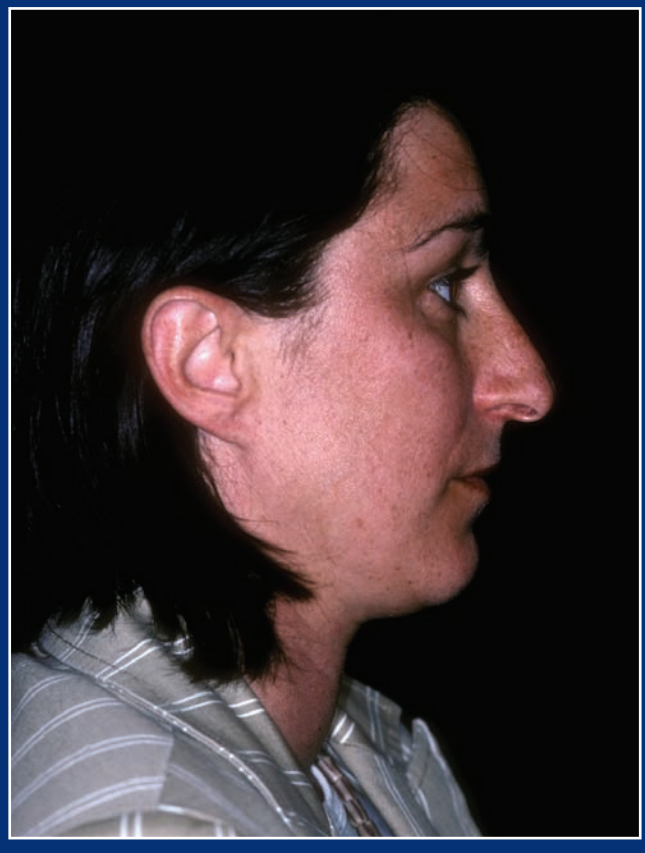
One of the most frequent problems I see is a letter or call from a distressed mother who states that the school wishes to separate her twins for administrative convenience. I have written many letters to officials reminding them that such action will most likely be received as punishment by the twins who will not understand what they have done to deserve this. Most efforts on my part have been successful, but it seems unfortunate to my way of thinking that school officials do not see the twins' perspective from the outset.

Louis Keith

# SECTION X

# FAMILIAL CONCERNS





**35-year-old female monozygotic, monochorionic, non-mirror twins, Belgium, 2004.**

Participants since birth in the East Flanders Prospective Twin Study. Twin A left, Twin B right.

*Woman with twins.* Cameroon, wood

**DOUBLE TROUBLE**

**Double trouble, Double toys**
**Double mess and Double noise.**
**Double tears from Double spills,**
**And Double on the doctor's bills.**
**Sometimes it seems we'll never win**
**The constant challenge of raising twins.**
**Yet there is not a day goes by**
**That I don't look up to the sky,**
**And Thank the Lord in Heaven Above**
**For Blessing me with "Double Love"**

***(Unknown author)***

'The constant challenge of raising twins', so vividly expressed in the poem cited above, is often a battle the parents never win. All major areas of concern for the parents of multiples seem to revolve around the so-called 'parental energy crisis', a direct result of fatigue and sleep deprivation. Even under ideal circumstances, the time required to provide adequate care for multiples and, at the same time, to maintain a quasi-normal household, may exceed 24 hours per day. This concern is obviously 'dose'-dependent, with more time required for triplets than for twins.

When most of available time is spent with the multiples, less is left for other family members. This may result in insufficient attention given to older siblings, who might feel discounted and isolated when the attention of the entire family is redirected to the new members of the family. Again, this concern is 'dose'-dependent, related to the number of multiples as well as to the number older siblings in the family. Finally, but no less important, maintaining the marital relationship and the integrity of the family is a constant challenge.

This section discusses the major familial issues related to multiple births.

*I.B. and L.G.K.*

# Contents of Section X

# Adaptation and Maladaptation in the Multiple Birth Family

*D. A. Hay and L. Steed*

**101**

**PERSPECTIVES ON GOOD ADAPTATION**

**THE ABCX MODEL AS CLINICAL TOOL**

**PRE-, PERI- AND POSTNATAL CONTRIBUTIONS TO GOOD ADAPTATION**

**PARENTAL DEPRESSION**

**ADAPTATION OF THE CHILDREN**

**STEREOTYPING MULTIPLES**

**CHILD ABUSE**

**COPING STRATEGIES**

## INTRODUCTION

For some mothers of infant twins, life is described as follows:

> *'They make all the work worthwhile when they smile and cuddle you. You feel like your heart could burst. I never knew I could love anyone so much as these two little people in my life who are my LIFE.'*

For others, it is like this:

> *'I feel as if everything is getting on top of me and it is worse because I have no help at all. I feel very isolated and as if the world is passing me by. I don't get out very often which I think is causing me to be very depressed. I'm starting to feel like a hermit. Would love to get away for a couple of days but that's impossible, which makes it worse because I have nothing to look forward to.'*

These two quotes from mothers in the study 'Having twins: how does the family cope?' described in Chapter 99 identifies the major theme of this chapter – why do some mothers adapt better than others to the birth of their multiples, and what are the effects on the entire family?

Without doubt, a multiple birth influences many people, not just the parents and siblings. Although only one child in 35–40 is a twin, approximately one person in 12 has their life directly affected by the birth of twins or higher-order multiples. To provide but a few examples of effects on the rest of the family, consider the following points:

(1) Maternal depression is more common, both when mothers of twins are compared with mothers of singletons, and when multiparous women compare their depression after their twin and singleton deliveries[1].

(2) The high rate of child abuse in multiple birth families identified in population-based studies is often directed at an older sibling[2], another index of stress.

(3) Older siblings exhibit increased internalizing and externalizing behavioral problems which worsen rather than improve as the twins get older[3].

(4) The arrival of multiples places stress on the marital relationship[4] and perhaps more importantly limits the capacity of a partner to cope not only with the additional stresses of the multiples but also with problems at work and at home. A father from our study says it all:

> *'The almost constant tiredness – I'm tired at work and tired at home. This causes great difficulty in keeping enough patience to deal with very ordinary problems in an even way.'*

This chapter examines why some families adapt better than others to the diagnosis and birth of multiples, and what can be done to identify at an early stage those families least likely to cope well and to propose cost-effective interventions. Unfortunately, it is not possible to quantify what exactly is 'adaptation'. Although adaptation means more than diminished depression and other psychopathology, such problems are easier to assess than quality of life. As the examples above show, 'good' adaptation may have different meanings for the mother, the father, family functioning and for the children.

One of the potentially most important recent studies examining adaptation is that of Piontelli[5], who followed 30 sets of twins (15 monozygotic and 15 dizygotic) from 10 weeks' gestation (with repeated ultrasound scans during the pregnancy) and continued until the children were 3 years old, mainly by videotaping the twins and the parent–child interactions. The book provides a useful insight into the stages of development of multiple birth children as well as the multiple birth family, as indicated in the following quote:

> *'Being away with my husband without the twins made me realise how much our life as a couple has changed forever. I needed a break and some freedom and intimacy, but I also missed the children. We are a family now and the twins are inextricably part of our existence'*[5].

Unfortunately, the book lacks a longitudinal perspective on these 30 families. Each epoch from diagnosis to starting nursery school is treated as a discrete period with no relationship between intrauterine activity and later temperament or between postnatal depression and later temperament. Such a perspective would have been particularly useful as a background to this chapter with its emphasis on later adaptation to earlier stressors.

## PERSPECTIVES ON GOOD ADAPTATION, PRE- AND POSTNATALLY

Reasons for increased psychopathology in multiple birth families are unclear, both pre- and postnatally. Merenkov[6] adopted a psychodynamic view to problems in pregnancy, where the prospective mother of twins finds more difficulty, both in relating her own birthing experience backward to that of her mother and forward in bonding with two or more fetuses, rather than the one she and her partner had intended. She also raises the issue of 'loss of control', with the involvement of more medical technology and specialists in a multiple pregnancy. Previously, Robin and colleagues[7] had provided the most complete survey of the impact of twins after birth upon the family in terms of economic and behavioral consequences, although they do not relate this specifically to psychopathology.

One issue which has met with less consideration as a predictor of postnatal difficulties is that of anxiety during the pregnancy[8]. Although the available study was of women expecting singletons and was written almost three decades ago, it is one of the few to raise the question of whether anxiety during the pregnancy was predictive of later depression. In this regard, it differs from the many studies that examined prior periods of depression as a predictor of postnatal depression[9]. Given that an obvious source of anxiety with multiple pregnancies is the potential for adverse outcome in terms of mortality and morbidity, this would seem to be a valid and potentially major predictor of subsequent depression. Patients describe their feelings as follows:

> *'Doctor tends to say, "Don't worry about things till they happen", instead of just answering my questions.'*

or:

> *'I can't imagine ever being able to sleep well again or feel normal. I have never felt so uptight or anxious as I have the last two to three weeks.'*

There are specific grounds for pessimism about the efficacy of approaches which simply think that providing information and support for prospective families of multiples is enough. Hay and colleagues[10] emphasize two key points:

(1) Before the birth, families greatly underrate the impact which two or more babies may have upon their coping strategies and see less need to plan adequately.

(2) As discussed in Chapter 96, the high rates of psychopathology pre- as well as postnatally make it even more difficult for families to plan and later to adjust to life with multiples.

## THE ABCX MODEL AS A CLINICAL TOOL

Although many potential stressors for the multiple birth family exist, each is often approached in a different way, and no means exists for identifying common themes and strategies for intervention that may be more broadly applicable. The model outlined below offers a systematic view of the multiple factors that impinge upon the family. This ABCX model has been widely used to assess stress and coping in families with disabled children and in a whole range of other stressful situations. To our knowledge, it has not been used specifically with multiples. We outline the general features of the model, before considering specific applications to the multiple birth family.

Hill[11] proposed a conceptual foundation to the variability found among families in their adaptation to stressful situations, beginning with the identification of four components of the family experience of stress: A (the stressor event) interacting with B (the family's resources to meet crises), interacting with C (the family's definition of the event) to produce X (the crisis).

Hill's model dismisses the conventional notion of a direct relationship between the stressor event (A) and

the resulting family crisis (X). Instead, he proposes that factor B, which comprises available family resources and support networks, and factor C, which is the subjective meaning assigned to the stressor event by the family, act as buffering variables. As such, these variables either increase a family's resilience and facilitate positive adaptation to a stressful event, or may add to a family's vulnerability. Hill's ABCX model is based on the assumption that a stressor event is a discrete event, that is, having a beginning and an end. Hill's model is static and applicable for short-term crisis only and is, therefore, inappropriate for studying the pregnancy, birth and ongoing care of multiples which in fact represents chronic and ongoing demand on the parents. McCubbin and Patterson[12] added a new dimension to Hill's ABCX model to account for such chronic life stressors. They incorporated post-crisis variables in an effort to accommodate chronic life stressors and to describe[12]:

(1) aA the additional life stressors shaping the course of family adaptation;

(2) bB the family and social resources that families develop to manage crises;

(3) cC the perceptions that families develop to make sense of their predicament;

(4) The coping strategies that families employ;

(5) The range of outcomes of these family efforts.

This model has been applied in many situations[13], and becomes clearer when applied to multiples (Figure 101.1). The actual diagnosis of multiples may fit the original ABCX model. Perceptions of the diagnosis differ between a couple with a long history of infertility treatment compared with an unplanned pregnancy in an already large family, and resources differ between a single mother and a professional couple, etc., as the following quote indicates:

> *'Cried – did not want twins. Not ready for two babies … not sure if able to cope as a mother of twins. Financial worries overwhelming – change of lifestyle frightening.'*

Then, as medical and other demands develop during the pregnancy, the situation changes. In accordance with the double ABCX model, a family adapts to the stressors and strengths over a period of time, instead of experiencing one crisis followed by change as in the ABCX model. Adaptation is dependent on the resources available to the family, the family's appraisal of the situation and the family's ability to cope with the stressor. The concept of family adaptation describes a continuum of outcomes from positive to negative, which the family may pursue in order to restore equilibrium[13].

## PRE-, PERI- AND POSTNATAL CONTRIBUTIONS TO GOOD ADAPTATION

The particular value of this model is that individual stressors can be seen against a background of additional resources and problems, both pre- and postnatally. Although this model may seem simplistic, therein lies its strength. Many more complex models of family functioning under stress are available, but these often have too many potential contributing factors to be clinically useful across a wide range of contexts. Moreover, they often focus around one aspect of functioning, such as predicting parental depression. The present model is more robust and thus is also more widely applicable across a range of situations, whether this be effects on the parent or non-twin sibling or on a co-twin after an illness or disability is diagnosed in the other twin. At a clinical level, it offers an easy way of extending one's view of the family's needs beyond the focus on the immediate stressor to consider:

(1) What resources are available to cope with the stressor?

(2) What coping mechanisms exist?

(3) How does the family perceive all of this?

Our longitudinal program 'Having twins: how does the family cope?' has been described previously[10] as well as in Chapter 99. Families had monthly semi-structured interviews by trained mothers of twins, with back-up from midwives when queries that were more complex arose. Mothers completed personal diaries with their thoughts of what happened in the month between the interviews. In this regard, they were often disarmingly honest in their diaries, including discussions on sexual tensions because of their growing size. Data on fathers are less systematic. At least one was in jail from soon after the conception, and in many cases it was difficult to fit interviews with the fathers' work schedules.

The application of the double ABCX model described here is based on 51 families with complete data from the time of diagnosis of twins through the pregnancy and delivery until the children were 6 months old. Particular emphases were placed on encouraging low-income and rural families to participate. Of the 51, 18 families had assisted reproduction, 18 were a planned pregnancy and 15 were unplanned. Twenty sets of twins were delivered by cesarean, 14 sets of twins spent some time in neonatal intensive care or special care nurseries and for three sets only one child needed such care.

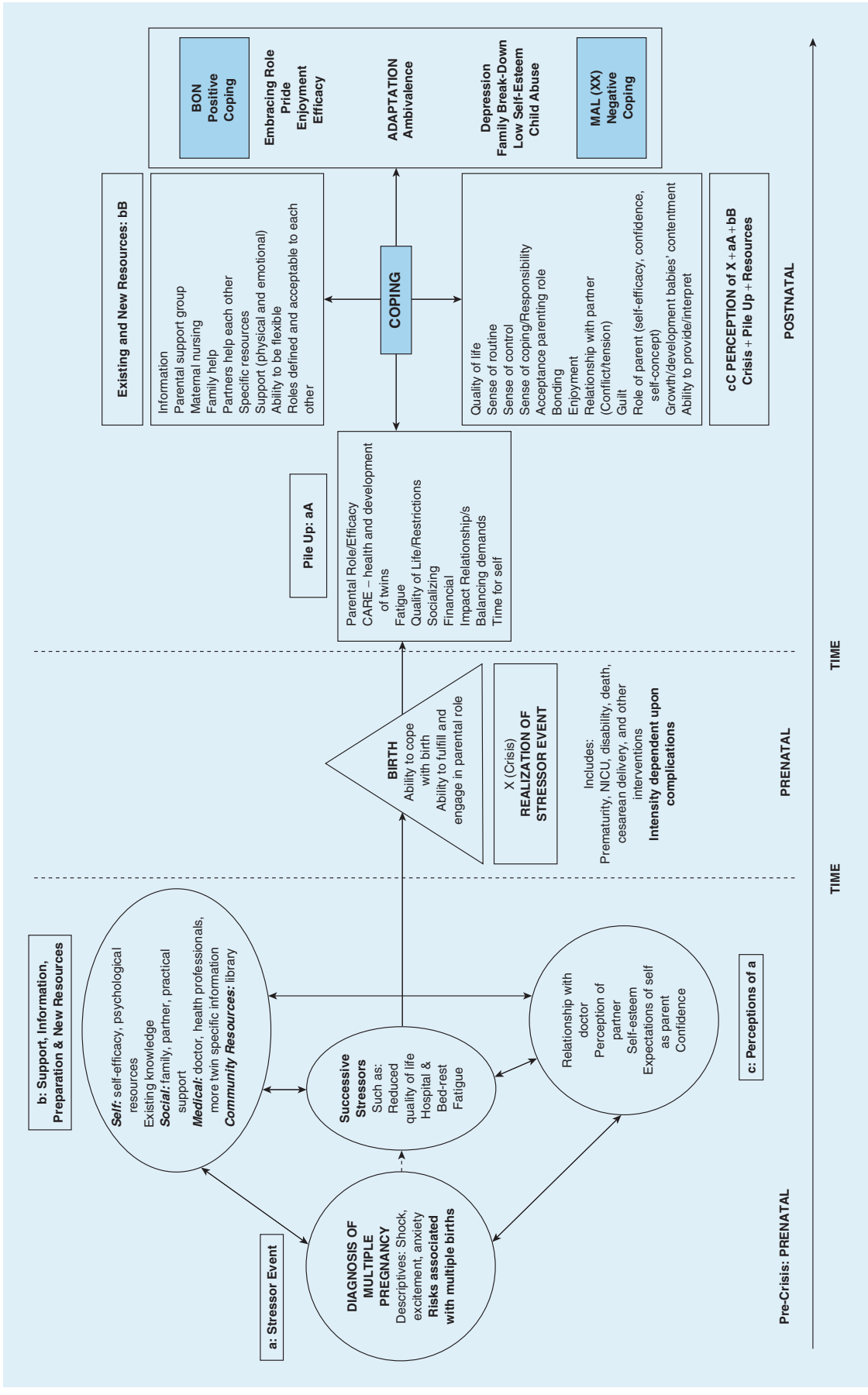



**Figure 101.1** The double ABCX model of adjustment and adaptation[12]

Figure 101.1 starts with the themes identified in the antenatal interviews and diaries and classified according to the ABCX model. These themes were derived through a standardized content analysis. Reading and rereading transcripts to identify themes preceded organization into clusters and master themes. Two individuals, with no communication until all the coding had been done, accomplished this work independently. Then there was discussion to agree on the key themes.

It is obvious that one cannot talk simply of the stress caused by the diagnosis of a multiple pregnancy. Too many events can intervene between conception and the birth. One particular issue in Australia is the size of the country and the fact that high-level neonatal intensive care is rarely available outside state capitals. From early in pregnancy, mothers in rural and remote regions may be aware of the possibility of spending the latter part of the pregnancy in a city perhaps as much as 2000 km or more away from her family:

> *'It has been difficult being separated from my husband and children. I see them about weekly and talk to them by phone each evening.'*

One common and recurring theme was that of quality of life. This included not only such obvious issues as having to organize the budget to plan for two (or more) of everything, but also finding the pregnancy difficult:

> *'I'm not enjoying the pregnancy any more. I am too worried and too uncomfortable about everything.'*

and:

> *'… feeling estranged from my husband. Even hugs are more difficult because of my size! He is nervous about touching me with twins on board, which is different from my previous singleton pregnancy.'*

## PARENTAL DEPRESSION

A key element of the ABCX model is the coping style of the parents. Essentially all psychoeducational models for prospective families with multiples are based around their capacity to seek information. As already indicated, there is growing evidence[13,14] that not all families cope well. One issue, which deserves more consideration in the case of multiples, is that the pregnancy takes control of the daily life of the mother:

> *'I think I've had to learn one of my hardest lessons – to put aside my expectations and desires and assess my situation and maternity. I had always expected that I'd work whilst pregnant with twins to 24/40 – no problems, I'd exercise, swim regularly, find no restrictions. I wanted to continue a "normal" life – no restrictions.'*

The measure of distress used in our study was based on the appropriate clinical cut-off scores of the General Health Questionnaire (GHQ) a commonly used screen for anxiety, depression, and psychosomatic and sleep problems. Chapter 99 includes a discussion of how many mothers and fathers had identifiable problems on the GHQ before or after the birth. The data here are temporal, focusing on changes as the parents adapt to the pregnancy and later to the management of multiples after the birth. In this study, we used the 30-item version of the GHQ prior to the birth and the 60-item version thereafter, to give more precise information on how changes were happening as the couple adjusted to the arrival of multiples. Of particular concern is the high level of problems at 4 months into the pregnancy. Such a result cannot be explained by the somatic problems that may predominate later in a multiple pregnancy, e.g. difficulty in sleeping. Women who have previously had a miscarriage or who received assisted reproduction to initiate their pregnancy could be expected to have higher levels of stress, as could their partners. In fact, the families who used assisted reproduction had very few differences from other multiple birth families, consistent with the Japanese data of Yokoyama[15].

Returning to the ABCX model, simply providing more resources is going to be of only modest help at best if families are having such difficulties in coping. While things do improve for some families by 6 months, the data of Thorpe and colleagues[16] indicate that mothers of twins are still significantly worse off emotionally when the multiples are aged 5.

## ADAPTATION OF THE CHILDREN

Little formal research exists on the needs of older siblings of multiples. Issues for the siblings start well before the birth and the extra attention that multiples receive. Stewart[4] gives an intriguing example where her own daughter was ridiculed at school for 'imagining' her mother was going to have twins! Although consideration is given to how the diagnosis of multiples is related to parents (see Chapter 99), perhaps more attention is needed to how it is communicated to siblings. The negative effects on siblings can continue into the preschool years, well beyond the pregnancy and the first few months, when the focus of the parents and the wider family is

on the needs of the multiples[3]. However, Katie Wood (unpublished thesis) found that by the time siblings and twins were into the school years, only the siblings of monozygotic twins had any continuing problems. By this stage, dizygotic twins are just like any brothers and sisters, whereas monozygotic twins continue to attract attention.

As regards the development of the multiples themselves, Pulkkinen and colleagues[17] provide a perspective, challenging the one we use in Chapter 99, where some of the behavioral problems in multiples are introduced. In an extensive survey of studies of behavioral development in multiples, they contrast such a 'psychopathological hypothesis' with an 'adaptive hypothesis' which is 'couched within the context of the favorable social environment twinship offers for development of socio-emotional behavior, via interactions with, and social support of, the co-twin'. Her argument is that the exposure to another child since such an early stage (and Piontelli[5] would argue this is from well before birth) fosters socio-emotional development. As Pulkkinen says, 'twinship provides opportunities for shaping, imitating and practicing social skills'. Although the generalizability of this result may be limited (Finland is unusual in that over 90% of twins are in the same class) and the nature of the data is unusual (peer nomination), it is an important illustration that not all adaptation of multiples may be bad.

Akerman (in reference 18) provides some examples of this in her survey of 9-year old triplets, where their comments included:

(1) 'We're never alone';

(2) 'When we are afraid there is always someone there';

(3) 'If someone quarrels with me at school there is always someone there to defend me'.

Regardless, the question remains whether good adaptation for multiples may not be good adaptation outside the multiple birth family. The best example would be the issue of language development in multiples, reviewed by Mogford-Bevan (in reference 18), regarding the long-running debate whether multiples have a language delay or a more specific language impairment (SLI). The evidence for a basis in pre- and perinatal events is small, except for the most preterm multiples. SLI could be related to aspects of the twin situation with factors such as reduced motivation and need to communicate, no need to communicate as the other one(s) can do it for you, using each other as the model for language development giving the reduced time that multiple birth parents have to communicate with their children on a one-to-one basis, and needing to get something in first before the other(s) can initiate dialog. Even the relatively rare autonomous language developed by some multiples is an adaptation to their specific situation. The problem is that many of these circumstances may be maladaptive when it comes to communication outside the family.

Stewart[4] gives an excellent account of twinship and social adaptation or maladaptation, including its relationship to language development. As so much has been done in the language area with twins over the past 70 years, it may be the best basis of a more general explanation of good or bad adaptation in the development of multiples. She includes one of the more publicized examples of the latter, namely the Gibbons twins, or the so-called 'silent twins'. This twin pair has probably contributed more than any other to suggest maladaptation of multiples in the minds of the public, but as discussed elsewhere (Hay in reference 18), such significant psychiatric vulnerability was present in these two women that they may have developed equally serious problems if they had not been members of a twin pair.

## STEREOTYPING MULTIPLES OR THE DIFFERENCES BETWEEN MULTIPLES

One of the potentially most pervasive maladaptations in the multiple birth family concerns negative perceptions of the entire multiple birth or of one specific child. Some time ago we demonstrated that issues such as birth order could be fundamental to how parents and the community in general perceived their multiples[1]. Management of the multiple pregnancy has moved a long way from the times when there were significant medical advantages in being the first-born. Despite this, often when asked to rate the twins, parents reported the first-born as 'better' in many ways especially in monozygotic twins, i.e. they were more responsive, more alert, etc. In dizygotic twins, other differences apparent to parents could distinguish their multiples, so the role of birth order was much less, and non-existent in opposite-sex pairs. In monozygotic pairs where fewer obvious differences exist, then birth order may be the catalyst for a whole set of expectations and stereotyping – 'he's the second-born, so you can't expect as much of him' being the kind of response heard all too often. Few obstetricians may realize how pervasive the issue of birth order is for multiples, especially in grandparents whose knowledge of medical outcomes is both old and anecdotal. Medical specialists have an obligation to reduce some of the family concerns about birth order. When addressing

multiple birth mothers on this topic, there would hardly be one who had not been asked in the street or the shopping mall, 'which was the first-born?' In reply, my advice would be to ask, 'why do you want to know?' And it is not just birth order. Spillman (in reference 18) develops a similar scenario around birth weight. That the twin who is perhaps only 20–30 g heavier than the other is perceived differently as being the 'bigger' twin is a good example of potentially maladaptive stereotyping in multiples. As psychologists working with multiples and carrying out assessments, we regard it as bad practice to give parents exact intelligence quotient (IQ) scores. If one has a score of 114 and the other 116, not only are these above-average children, but also their scores are identical as regards standard deviations. Under these circumstances, one should not be perceived as the 'brighter'. With early development indices such as the Bayley tests, the standard deviations are much larger, and even more care is needed in giving families numerical data rather than just broad descriptors.

The problem with multiples is that they are always compared with each other, not with people of the same age in general. True, one may be slightly 'better' than the other on whatever index (school performance, athletic ability, etc.) selected, and it is this that matters. From the very first postnatal check-up, this is an issue of which every practitioner needs to be aware, as the parents(s) provide 'helpful' advice on what their children are like and how they differ from each other. Our website[19] provides a useful model of how multiples may be too close, too far apart or just right in terms of how they or their parents perceive things.

Although the focus of this chapter is on early development, it is important to consider the long-lasting nature of perinatal practices. In our chapter in Sandbank's[18] book dealing with adolescent twins, we demonstrate that decisions such as releasing one newborn twin home from hospital before the other can establish a pattern of how young people are seen throughout childhood.

## CHILD ABUSE: THE WORST MALADAPTATION

Clearly there is much more to child abuse in multiple birth families than can be explained by the fact that such abuse is more common in larger families. As Groothuis and colleagues[2] emphasize, there is something specific to twinship as a predictor of child abuse over and above other variables, especially as it may not be directed to the twin but to an older sibling. Unfortunately, the studies that confirm high rates of child abuse have not sought to identify its etiology. Is it specifically in the extra demands of multiple births, a direct consequence of postnatal depression, an indirect consequence of such depression through a failure to bond or a general attachment problem? Stewart[4] discusses the older work by Broadbent on why mothers of twins may fail to bond, which is consistent with many of the points raised about parenting multiples[1]. The earlier section on stereotyping suggests why there may be much better attachment with one than with both multiples. Unfortunately, the major reports on child abuse in multiples are now some 20 years old. As this is such an important issue for child protection, current epidemiologic data are urgently required, not only for more information on the etiology in multiples, but for comparison with the situation in very preterm births, where significant problems also exist in attachment. The double ABCX model may be a useful approach in that it puts some of the parental stressors after a multiple birth, such as isolation and forced lifestyle changes which may lead to resentment (and potentially abuse), in the context of support and general coping strategies.

## RESOURCES FOR THE MULTIPLE BIRTH FAMILY

Whereas it seems obvious that services should be provided both pre- and postnatally for multiple birth families, a key question is the aim of such services, in terms of to whom they should be directed: the parents, the twin(s) or higher multiples, the other siblings or family functioning in general. Then comes the question of which behaviors a service should address. Should it aim at psychopathology, e.g. to reduce depression, or more generally at coping skills and self-concept? A further question is whether the family already has experience of child-rearing or whether they need support and training in the basics of caring for any child:

> *'I have no experience in regards to child-raising and I live week to week, but I don't know what kind of questions to ask. I feel that people expect you to know, and I think guidelines should be set out for people with twins.'*

Although the amount of written and video material for families with multiples is increasing, dilemmas exist over how much to cover and what might go wrong. The Australian Multiple Birth Association (AMBA) include a section on a mother with postnatal depression in their video, but one mother with such depression in our study expressed no interest in joining AMBA:

> *'I don't need any more fears from other people's experiences.'*

## COPING STRATEGIES FOR GOOD ADAPTATION

> *'… Everyone painted such a black picture of what it would be like and it hasn't been so bad! No one tells you it could be easy – not a big drama.'*

Obviously not every mother of newborn multiples shares the optimistic coping style of this mother. This raises the question of what can be done to target support at the appropriate level for any one family.

Apart from issues specific to the ABCX model about how to identify areas to target, four key points emerge from our work to date concerning how to target information to both families and professionals:

(1) The high rates of depression seen pre- as well as postnatally in one or both parents have implications for their ability to prepare appropriately for the multiple birth and respond to stressors afterwards.

(2) It is necessary to insure that information reaches all families and not just those who actively seek information. Key groups who may miss out are the depressed, the socially disadvantaged and, especially in Australia, the non-English speakers.

(3) Information must be presented cumulatively during the pregnancy. Families complained of too much or irrelevant information as well as too little information and of information being presented at what they (the families) believed was an inappropriate stage of pregnancy.

(4) Recognition of differences between families is important. Not all families will receive the information in the same manner, and we need to determine how best to identify features in families that challenge their potential to adapt.

Given the international concern over the cost of services, a key aim must be to provide only the level of support that a given family wants, needs or can tolerate. The Triple P program[20] is being widely implemented in Australia as a cost-effective intervention strategy across a range of families with problems, as it identifies five successively more intensive strategies, ranging from just the provision of information through to intensive family support. It has never been applied to multiples specifically, but its model is very useful. Following our experience with families with newborn twins[10], plus the studies of Thorpe and colleagues[16] the first stage of simply providing information may not be effective if multiple birth parents have significant levels of depression. The programs would also have to be modified to account for the presence of two or more children, possibly differing in degree of disability, a topic raised in Chapter 99.

To illustrate the Triple P philosophy, the five potentially more intensive (and costly) stages of intervention are:

(1) The provision of information to families through written materials and group meetings. This will have to change from the current initiatives in most countries to:

  (a) Cover a wider range of families rather than just those who actively seek information;

  (b) Provide appropriate information at different stages of pregnancy rather than in one session to avoid saturation and to reflect developing knowledge needs.

(2) Home visits at suitable intervals before and/or after the birth by suitably trained lay-individuals, most likely mothers of multiples from our earlier program[10]. These mothers have to receive appropriate training in such areas as not focusing on their own experiences and having guidelines as to when to refer for more professional assessment. At this and the higher levels of intervention, there would be an emphasis on regular screening for fears, for adequate coping styles and for psychopathology.

(3) Similar visits but by appropriate health or mental-health professionals, following the model which Papiernik[21] found so effective in his study of French women expecting twins in reducing preterm delivery.

(4) Group family sessions to help each family realize they are not the only ones in such a situation and to illustrate strategies that other families have found useful. Such sessions should be led by someone experienced in group counseling, as there can be too many pitfalls for the unwary when families with behavioral problems are brought together.

(5) Psychotherapy at the individual, couple or family level. One of the most major questions here would be: who would provide such support – will they know anything about multiples or simply approach counseling in a more general perspective?

Few families would need more than level (1) or (2), except possibly for a brief time, but such a protocol really does establish a framework for best practice. As well as developing such a program, it also has to

be implemented on a sufficiently large scale, which means improving awareness of both families and professionals. One possibility is the same strategy used in our 'Twins in school' program[22], a nationwide initiative with the parents' organization AMBA in the early 1990s aimed at both parents and educational professionals, with workshops, written information targeted at specific groups, a public awareness campaign and resources for trainee professionals. Bringing it into the 21st century has been the creation of a website www.twinsandmultiples.org[19].

## COMMENT

Whereas so much of this text is devoted to the successful delivery of multiples, this chapter has introduced the question of quality of life of the parents, the multiple birth children and their siblings, even in the absence of definite physical, intellectual or behavioral psychopathology, our topic of Chapter 99.

In addition, this is only the simplest view of the situation. Little is known about additional issues such as assisted reproductive technologies (ART) and its impact on different aspects of the ABCX situation. Obviously, ART is associated with major changes in such aspects as perceptions of pregnancy and of both mortality and morbidity of the multiple(s), an issue identified by Yokoyama[15]. Whereas Yokoyama[15] found less anxiety prenatally in mothers who had infertility interventions, it is not clear what information these women had about multiple birth issues. It is difficult to believe that families who have been trying for years to have a child will respond in the same way as other families to information about potential intervention and risks[23]:

> *'We attended an information night at hospital for expectant twin parents and we both felt this was a real eye-opener … I would like to discuss more about the twins and what to expect.'*

Our data for the 'Having twins' study were collected in the early 1990s. Although the parental comments are still relevant, the amount of information available to families undergoing infertility treatment was much less. Even though they are required to have counseling before treatment, there is no monitoring of the extent to which multiple birth issues were covered, and as Gleicher and colleagues[24] pointed out, the desire of such couples to have a child (or children) has no relationship to best medical practices, nor to what information they are given. There is a fundamental need for health promotion research in this area to insure a suitably 'titrated' amount of information is available to each family at appropriate times, taking into account their resources and coping mechanisms, since:

> *'I am still at a stage of pure panic, when I think about the birth. Not being sure what it is actually like – delivering two babies not one. Especially when most of the time I am so tired.'*

However, Malmstrom[25] raises a significant issue about who can provide the information and, even more importantly, the potential resources:

> *'I feel that there is a lack of information available to mothers/fathers of twins. In retrospect I don't believe nursing staff fully understand the care of twins in preparing me for discharge from hospital (feeding techniques, etc.) The local health-center sister, although very supportive, cannot offer me specific information in caring for twins.'*

The present text and other resources provide ample information for the medical specialist dealing with multiples. At the same time, it is not clear how this is translated to the community nurses and the other primary health-care staff such as general practitioners who are the most frequent point of contact for the family. As Malmstrom emphasizes, there may be areas that have a formal hospital-based multiple birth clinic, a particularly active multiple birth parent support group or some other resource on which training can be based. In other areas, especially rural Australia and even rural America, there is very little or nothing. The most extreme example in Australia, and probably elsewhere, is the difference between states or municipalities in the policies for making home-help and similar support for multiple birth families a priority compared with other deserving groups such as the frail elderly. There have been few effective lobbies by the professionals working with multiples that increase their recognition by those who decide funding priorities.

Quite deliberately, this chapter takes an approach that focuses on the family in the management of multiple pregnancies and uses their words to illustrate the common or important issues. Figure 101.1 focuses on a particular model of family stress, which hopefully indicates clearly the number of issues which impinge upon families over the first year or so after the diagnosis of multiples[26,27]. It should provide the professional with a good start at working out what is needed to support this multiple birth family psychologically as well as medically. It demonstrates three things for those managing the multiple pregnancy and delivery:

(1) The importance of considering prenatal as well as postnatal psychological problems[28];

(2) Recognizing psychosocial needs in fathers as well as mothers[29];

(3) Appreciating that the consequences of your present actions will be interpreted in the context of other stressors, resources and coping styles and may have long-term impact.

The message for clinicians and for researchers alike is to take a more ecologic approach to the family. In our study of the loss of a multiple[30], on average 11 years after the loss, we involved co-twins, siblings and fathers as well as mothers. Many of the mothers had discussed their loss previously. For the others this was the first time that they had the opportunity to communicate their loss to people outside the family (and in the case of the children, often inside the family). When focus groups were run for the participating families to meet each other and to discuss our finding, many fathers encountered for the first time other men who had lived through the same experience. Although parent support groups are increasingly available to multiple birth families, they are predominantly perceived as being for mothers. Our focus groups for fathers of multiples were often the first time that many had been in a male-only group with permission to reveal their feelings.

If we are to achieve better adaptation of multiple birth families, we need to support their communication, whether it be by facilitated groups (as in the case of fathers discussed above), through trained mothers of twins who would come to discuss their concerns (as in our 'Having twins' project) or through visiting nursing staff as described by Papiernik[21]. These must extend the informal chats, anetnatal nights, etc. provided by volunteer multiple birth support groups. Given the enormous investment in the medical management of multiples, an additional need exists for complementary investment, first in identifying what helps adaptation for these families and second in providing such support. At the same time, a triage system is needed to identify which families need the most intensive psychosocial support. The Triple P program was introduced as an appropriate method of resource allocation, so that the more extensive and expensive interventions went only to those who needed them. The ABCX model is a first practical and systematic step to developing such a triage, in identifying what are the more usual factors in the multiple birth family and their medical circumstances which may contribute to adaptation or maladaptation.

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# The Psychological Effects of Multifetal Pregnancy Reduction

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**102**

**DECISION TO UNDERGO MFPR**

**INTERVENTION**

**LONGER-TERM IMPACT**

**CHILDREN'S DEVELOPMENT AND MOTHER–CHILD BONDING**

**WOMEN'S EMOTIONAL REACTIONS**

Multifetal pregnancy reduction (MFPR) is often proposed to deal with the health and social problems associated with pregnancy involving three or more fetuses. Although much is known about the aspects of this procedure, its true impact on women is not well documented. Indeed, it might be expected that women undergoing MFPR are at risk of emotional problems as many of them have a long history of infertility. Under such circumstances, the termination of intensely desired fetuses can be experienced as very painful emotionally and may provoke acute grief reactions. Moreover, grieving during pregnancy can compromise the bonding process and thus jeopardize relationships with surviving fetuses and their subsequent development.

In this chapter we review published surveys of the emotional impact of MFPR from the moment of decision to the years after birth. We studied ten surveys conducted in Europe, in the USA and in Israel. In general, they dealt with small samples of patients interviewed retrospectively by the team having performed the MFPR. Most were published in the mid-1990s, after the dramatic increase of multiple pregnancies and the development of MFPR. Their characteristics are presented in Table 102.1. To this review we added clinical observations and comments from French psychiatrists and psychoanalysts working with families with children born from a multiple pregnancy.

## THE DECISION TO UNDERGO MULTIFETAL PREGNANCY REDUCTION

Surveys generally indicate that most women report guilt and mixed feelings when faced with a decision about MFPR[1–5]. Investigators note the 'agonizing emotional work' that couples face[4] and the paradox of being 'forced to abort after having fought so hard to become pregnant'[3]. McKinney and colleagues[1] describe 'the bitter irony that couples trying desperately to conceive have to consider terminating some of the embryos to allow the others to survive'. All authors mention that fear was the foremost of the emotions described, the most pervasive aspect of which was that all the fetuses would be lost. Using a psychoanalytic perspective, McKinney and Leary[6] suggest that women undergoing the procedure are already vulnerable to lowered self-esteem related to their problems conceiving, and that the diagnosis of multiples and the need for MFPR were often perceived as one more thing that had gone wrong with their body, as it were a 'final injustice' and the end of a difficult ordeal[6,7].

Such thoughts and feelings are not universal, however, as many women also explained that they had no alternative and that the decision was relatively easy to make[1,3]. Expressing no emotion and using neutral, technical language supporting the procedure, they repeated the medical reasons explained by their physicians[1,2], including 'avoidance of risk and preservation of health' of the mother and surviving infants[1,4], the emotional stress of parenting multiples and financial worries[1,2].

## THE INTERVENTION

Most studies note that the actual procedure was emotionally trying for mothers, who experienced acute psychological distress in the form of sadness, depression, guilt feelings and fear of losing the remaining embryos[2,3,8,9]. In the study by McKinney and colleagues[1], one-third of the patients spontaneously used the terms 'murder', 'shooting' or

**Table 102.1** Characteristics of reviewed surveys. Case reports have not been included

| *Authors* | *Country* | *Method* | *Number and time of assessment(s)* | *Number of patients* | *Infertility treatment* |
|---|---|---|---|---|---|
| Brandes *et al.*, 1990 | Israel | comparative (matched-control children)<br>physical, psychomotor evaluation | one assessment,<br>12–38 months of age | two groups of<br>7 children | induction |
| Nantermoz *et al.*, 1991 | France | prospective<br>retrospective<br>interviews | one assessment after intervention<br>one assessment, 9–24 months post-reduction | 12<br>7 | — |
| Vauthier-Brouzes and Lefebvre, 1992 | France | self-administered questionnaire | one assessment after delivery | 22 | 20 IVF, two inductions |
| Kanhai *et al.*, 1994 | The Netherlands | retrospective<br>semi-structured interviews at home | one assessment, 9 months–6 years post-reduction | 21 | 18 inductions,<br>three IVF |
| McKinney *et al.*, 1995 | USA | retrospective<br>comparative (singleton or twin pregnancy)<br>telephone interviews<br>depression (DSM III) and brief symptoms inventory | one assessment within 1 year post-reduction | two groups of 44 patients | 62% induction 38% IVF or GIFT |
| Schreiner-Engel *et al.*, 1995 | USA | retrospective<br>semi-structured interviews at home | one assessment 1.3–5 years post-reduction | 100 | 27% IVF |
| Garel *et al.*, 1995, 1997 | France | prospective<br>comparative (triplet mothers)<br>semi-structured interviews in hospital and at home | six assessments, post-reduction–2 years of age | 18 patients<br>+<br>11 triplet mothers assessed at 2 years | 18 IVF<br>ten IVF or GIFT<br>one spontaneous |
| Bergh *et al.*, 1999 | Sweden | retrospective<br>interviews and scales (well-being and depression) | one assessment, 2.5 months–4 years post-reduction | 13 | six IVF |
| Maifeld *et al.*, 2003 | USA | prospective<br>interviews by telephone or in person | three assessments, 2 weeks post-reduction, 6 weeks and 6 months postpartum | 11 | 10 IVF, one induction |
| Britt *et al.*, 2003 | USA | prospective<br>self-assessment of anxiety | four assessments, multifetal pregnancy diagnosis post-reduction | 66 | — |

IVF, *in vitro* fertilization; GIFT, gamete intrafallopian transfer

'killing' when talking about MFPR. The intervention intensified and brought to the surface conflicts that might have remained unconscious during a normal pregnancy. In particular, ambivalence about pregnancy could explain the intensity of guilt and why many women perceived MFPR as a hostile act[6].

## AFTER THE INTERVENTION

The level of anxiety dropped immediately after the procedure was over[9], but negative feelings were pervasive in the weeks following MFPR. Nearly all patients reported being 'sad, scared, tired and weak, nauseated, depressed, angry, guilty, crying'[4]. They thought about the lost fetuses. In the survey by Schreiner-Engel and associates[8], 70% of respondents reported mourning that most often lasted a month. Mothers asked themselves tormenting questions about the choice of embryo selected, the most accessible, the weakest[10], and expressed guilt that they had killed – 'sacrificed' – one so that the others might live[3,11]. Nevertheless, they expressed relief, repeating the medical justifications and the social, economic and psychological problems created by triplets or higher-order births[3,10,12].

## LONGER-TERM IMPACT

### Pregnancy

Only a few studies have explored the experience of pregnancy after MFPR[10,11]. In the first months, the women feared an adverse outcome, and thought of their pregnancy as fragile, in need of careful attention[2]. However, for some mothers, the continuing pregnancy became a partial reparation and provided a sense of being special and worthwhile[6]. Grief seemed to be suspended at the end of pregnancy, because the mothers were in the process of attaching themselves to the living, developing fetuses[2,11,13]. They may also have been preoccupied by the frequent medical complications at the end of a twin pregnancy. Most of the women in our study expressed relief that they were not bearing triplets in view of their worries about the twin pregnancy[2].

### After birth and in the years that follow

Negative feelings related to MFPR reappear after delivery, mainly guilt and grief about the missing children. The surviving children represent living reminders of the loss of the others[2–4,11]. The frequency and intensity of these negative reactions vary substantially by study, being more predominant in prospective investigations. At 4 months after birth, half the mothers expressed negative feelings related to MFPR[2], and at 6 months postpartum, mothers reported negative feelings more frequently than they had after delivery[4]. Several investigators also observed that mothers worried about the remaining babies, were anxious that something bad would happen to them, had fantasies of punishment or needed forgiveness for the MFPR[4,6,10,11], also wondering, albeit more rarely, what to tell the remaining siblings[1,4,5].

Although these negative feelings appear to decrease with time. One year after birth, one-third of the mothers in our study reported occasional dysphoric feelings about the reduction, mainly sadness and guilt[10]. At 2 years, however, these symptoms had disappeared for all but two women. When compared with mothers of triplets interviewed in a previous study, mothers in the MFPR group appeared to show fewer depressive symptoms.

A minority of mothers reported persistent dysphoric feelings in retrospective studies. In the study by Schreiner-Engel and associates[8], a group of patients contacted from 1.3 to 4.5 years after delivery mentioned lingering sadness and guilt feelings, insisting that whereas they had not forgotten the lost fetuses, they thought about them only rarely. Such MFPR-related depressive symptoms were relatively mild, and regrets were extremely rare in most studies. Kanhai and colleagues[14] found that when the children were between 9 months and 6 years of age parents felt no regrets, although two couples reported occasional grief reactions. In many studies, some mothers expressed relief that they were not trying to parent three or four infants simultaneously[1,3,8,10].

Some researchers measured the psychiatric morbidity associated with MFPR. In particular, McKinney and colleagues[1] studied the emotional effects of MFPR by comparing patients who underwent MFPR with patients who had become pregnant after fertility problems but who had singleton or twin pregnancies and did not require MFPR. Interviews conducted within 1 year of the procedure indicated that although 88% of the pregnant or postpartum patients reported fantasies about the lost fetuses, the two groups did not differ in their rates of depressive disorders. The same proportion (14.7%) of both groups met the criteria for an episode of major depressive disorder (according to the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edn revised (DSM-III-R)) during the 9 months before the interview. These authors concluded that although MFPR is a stressful and distressing experience, it did not pose a significant mental health risk. Another study, conducted between 2.5 months and 4 years after delivery, found no psychiatric morbidity related to MFPR[3]. Similarly, Schreiner-Engel and colleagues[8] found retrospectively that patients had experienced dysphoric feelings but that these were not indicative of a depressive syndrome.

## THE CHILDREN'S DEVELOPMENT AND MOTHER–CHILD BONDING

According to Kanhai and colleagues the initial emotional conflicts seemed to have no deleterious effect on the mother's bonding with the children[14]. Brandes and co-workers[15] assessed the physical and mental development of seven co-sibs surviving reduction of one quintuplet and two quadruplet pregnancies (one set of triplets and two sets of twins); at 12–38 months their development did not differ from that of matched controls. We compared mothers who underwent MFPR with mothers of triplets from a previous study. Two years after delivery, the former reported better psychological health and more satisfactory relationships with their children[10].

Longer-term consequences for the surviving co-sibs remain unknown. Psychoanalysts have reported psychological difficulties among some older children[13,16]. During therapy sessions, mothers have sometimes associated the children's problems, mainly nightmares, with their own emotional distress about the procedure. McKinney and Leary[6] mentioned women who fantasized that the remaining living babies might somehow 'know', and be upset about the reduction.

## FACTORS ASSOCIATED WITH WOMEN'S EMOTIONAL REACTIONS

A few studies examined factors associated with mothers' reactions, suggesting that the final outcome of the procedure is an important factor. As expected, patients who subsequently aborted the entire pregnancy mourned and grieved their fetuses for considerably longer, and reported significantly more major depressive disorders than their peers who did not experience this outcome[1,8]. We also noted that when reduction to twins was followed by the spontaneous abortion of one of the two survivors, maternal anxiety and overprotective behavior increased with the remaining singleton[10].

The conditions surrounding the MFPR are important. On the one hand, receiving full information and comprehensive support from the doctor makes the decision easier for women[2,13]. On the other hand, women who viewed the ultrasound images of the embryos before or during the procedure found it more difficult and continued to be the most affected[4,8]. Furthermore, the number of initial fetuses appears to be associated with depressive symptom scores, i.e. the highest scores were among women who had more fetuses[8].

Schreiner-Engel and associates[8] noted several maternal specific characteristics among the possible negative factors: women who were younger, were religious, came from large families or wanted more than two children were most likely to have depressive symptoms. In contrast, duration of infertility did not appear to be related to the intensity of the persisting depressive feelings.

The experience of MFPR was also shaped by the women's interactions with their partner, family, friends, physicians and other members of the medical team[6]. Good marital relationships were associated with more positive reactions among women[10], but in couples, women reported more worries than did men[4]. A major limitation of many of the results presented here is that the subsamples are very small. They might best be considered as hypotheses to be tested, and need confirmation from further research.

## COMMENTS

On the whole, published surveys suggest that, with time, most mothers believe that they made the correct decision for themselves and their families in terms of MFPR. Of equal importance, MFPR does not appear to present a significant mental health risk nor does it adversely affect the process of mother–child bonding during or after pregnancy. Nonetheless, all surveys consistently mention the emotional work that couples were forced to face, and their lingering feelings of sadness and guilt.

Most authors observed that many of the open-ended survey responses were rather positive, and that the patients, expressing no emotion, noted the rational reasons (medical, economic, familial) for MFPR. Despite this, it is difficult to know whether these responses reflected true psychological integration of the procedure or a transient defense mechanism to protect against overwhelming negative emotions. According to McKinney and Leary[6], 'anticipation, intellectualization, suppression, denial, and isolation of affect were the most widely used and more successful defensive strategies'. This observation alone may explain why most women were able to cope with the procedure. Another possible explanation is that most infertility patients are ready to endure substantial reproductive risk to achieve a biological pregnancy[17]. The present review points to the need for longer-term assessments as well as more clinical observations and reports from psychiatrists about psychological consequences of this procedure, as grief in MFPR is very specific. The loss for the mother is not an object distinct from her but the amputation of a part of herself during the process of its differentiation into an object. Classic descriptions of the grieving process do not fit this situation in which a partial, internal object disappears. Moreover, grief may be complicated or suspended, and the mothers may feel the negative emotional consequences of a 'pathological grief' later.

Longer-term effects on bonding between mother and child and on children's behavior and development remain relatively unexplored. A few small studies report that, overall, MFPR did not affect the process of mother–child bonding, during or after pregnancy. These instruments tended to assess the quality of the relationship with the infants using a rather simplistic method based only upon the mothers' responses[10,14,15]. Often, psychiatrists working with families with children from multiple gestations observe that difficulties present themselves later[13,16]. It is highly probable that the more the parents repress their emotions about MFPR, the greater is the risk of conflict between them and their surviving children. Thus, the inevitable conflicts between parents and children, inherent in every family, may renew guilt feelings about the choice of embryo so that the 'lost' child may be idealized and fantasized by the parents as 'better' than the surviving children[6]. Unfortunately, the guilt associated with such fantasies may have severe consequences on parental attitudes and the survivors' development. Finally, several sensitive issues are involved. For instance, referring to the 'guilty survivor syndrome', Bryan[5] noted that 'any of the survivors could feel their own survival was achieved at the expense of a sibling and hence carry lasting guilt over it'.

The studies reviewed in this chapter are not without inherent methodological weaknesses. They most often failed to include mothers who lost the entire pregnancy or did not wish to talk about what they recalled as a traumatic experience and thus did not participate. The failure to include all patients who underwent MFPR must inevitably lead to underestimating its negative consequences. In addition, in most studies, the mothers or families were contacted by the team that performed the MFPR. This methodology raises issues of bias: patients may tend to minimize their difficulties for the team that helped them to achieve their goal of having a family. Furthermore, most studies considered samples of patients from only a single assisted reproductive technologies (ART) department. The characteristics of the population and the department's practices may be rather specific, and it is thus difficult to generalize the conclusions.

Assessments at a variety of time periods also represent a problem in that it is inappropriate to lump together for combined analysis the emotional reactions of patients whose experience was a few months earlier and those whose experience was several years ago. This method results in minimizing negative answers, as bad memories may fade with time. Furthermore, women expressed fewer negative feelings during their pregnancy than they did several months after delivery. Prospective studies conducted by psychologists and studies of consecutive series of women from the beginning report more negative answers than retrospective studies[2,4,10]. The former protocols may allow patients to express their negative feelings more freely.

To overcome such difficulties one could compare families that did and did not undergo MFPR. Such a comparison would be difficult today, however, as couples embarking on *in vitro* fertilization (IVF) or intrauterine insemination (IUI) tend, on the whole, to be favorable towards fetal reduction in cases of high-order multiple pregnancies[18]. In our study we compared families at 2 years after MFPR with families of triplets[19] who were interviewed, according to the same protocol, in a previous study that took place before MFPR was available. We noted that family relationships and satisfaction were better among mothers who had undergone MFPR. Today, reduction is proposed to mothers carrying three embryos. We do not know, however, whether the extent of difficulties and emotional distress among mothers of triplets who choose not to have a reduction differs from that of mothers who did not have the choice.

In a Cochrane Review, Dodd and Crowther noted the absence of randomized controlled trials about the risks and benefits of MFPR[20]; they observed the insufficiency of the available data to support a policy of MFPR for women with triplet or higher-order multiple pregnancies, and finally pointed out that reduction may not be acceptable to women with a history of infertility. Recruitment into such a trial may prove exceptionally difficult, however. The study of the impact of MFPR should therefore be based on observational studies that use quantitative and qualitative methods and clinical observations.

## RECOMMENDATIONS

All reports insist wisely on the need for psychological support before and after MFPR[1,3–5,8,10,14,21]. The simultaneity of grief for the lost embryos and a life project for the others can result in massive repression of the depressive effects inherent in – and necessary for – healing. The family circle, health professionals and our society (which offers no relevant ritual) accentuate this phenomenon. Guilt feelings and worries about the sacrificed victim may be evidence of repressed affects. Thus, interventions encouraging parental involvement and narration are recommended. These may be conducted by the health-care personnel dealing with ART patients before, during and after pregnancy: physicians, nurses, social-workers, psychologists or psychiatrists. They would facilitate the parents' emotional recovery and prevent adverse effects on the infants and their families.

Britt and colleagues[22] recently described an intervention towards this end, designed to reduce anxiety in patients and focus attention on the surviving twins or singleton. To facilitate bonding, the sonographer invited the couple to look at the surviving twins on the screen immediately after the MFPR procedure. The second stage of the intervention consisted of taking and sharing pictures of the surviving embryos with the couple, and encouraging the couple to make a commitment to send baby pictures. The investigators conceded, however, that 'the sequence might break down at any point'. In their comments they acknowledged the fragility of such an action-oriented intervention. 'Success' must be examined over time, they concluded, given the complexity of the psychological process in which parents cope with the loss of some fetuses and bond with the survivors at the same time. Despite these important limitations, the paper contains valuable recommendations including the development of 'training and practice for sonographers along the lines of physician/patient communication training in critical situations'.

## CONCLUSION

Multifetal pregnancy reduction is a complex issue. The studies reviewed here show that most women find it a highly stressful event, but are able to accept the termination of some fetuses to achieve their goals of parenthood. For a minority of families, MFPR appears to leave deep psychological sequelae. Further surveys, using cohort studies and clinical observations, are needed to evaluate its longer-term psychological consequences. MFPR should not simply be considered as an acceptable part of infertility treatment; instead, prevention of multiple pregnancy should be mandatory. Such a policy has been implemented in some countries where the transfer of three or more embryos per IVF cycle has become exceptional, but the delivery rates per transfer remain high[23].

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# Bereavement: Grief and Psychological Aspects of Multiple Birth Loss

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**103**



## INTRODUCTION

The rising incidence of multiple births increases the likelihood that care-givers will encounter death among a set of multiples. Although many advances have occurred in the management of multiple pregnancies and in the care provided to newborns, circumstances such as those listed in Table 103.1 continue to sadden many families each year[1,2]. Indeed, some parents experience more than one type of bereavement with the same set of multiples, and complicated grief is especially likely with multiple birth loss[3,4]. This chapter reviews the factors that influence a family's reactions to a multiple-birth loss, and offers practical strategies to care-givers who strive to ease suffering.

**Table 103.1** Circumstances for loss of one or more multiples

| |
|---|
| Miscarriage of all fetuses |
| First-trimester loss of some fetuses ('vanishing twin/triplet') |
| Later intrauterine demise of some or all fetuses |
| Multifetal pregnancy reduction (MFPR) |
| Selective or complete termination for anomalies (ST) |
| Expectant management with one or more anomalous fetuses |
| Delayed-interval delivery |
| Twin-to-twin transfusion syndrome (TTTS) |
| Monochorionic complications (monoamniotic, conjoined, other) |
| Intrapartum demise |
| Delivery before viability |
| Delivery at limits of viability |
| Sudden infant death syndrome (SIDS) |
| Accidental death |

## OVERVIEW OF MULTIPLE BIRTH LOSS

### Grief characteristics

Each bereaved family of multiples brings a unique perspective to their loss, and parents with similar circumstances often exhibit different reactions, as they lose not only their fetus(es) or child(ren), but also the challenge of raising the original number of multiples[2,5]. Their responses to loss are influenced by their feelings about having multiples[1], as well as ethical, logistical and medical dilemmas that arise, and the need to juggle feelings and decisions for many children at once[2].

### Loss of all multiples

Couples who lose all of their multiples, especially after treatment for infertility, often mourn more intensely, and for longer, than parents who endure a singleton demise. Low self-esteem, a sense of failure and depression are common[1,6,7]. The loss must be recognized as that of several unique children and not as a 'collective baby', as deaths may occur simultaneously, or one at a time over weeks or months[1,2], and grief resolution may take at least 18 months[1]. Recovery, as defined by traditional grief theory, is an unrealistic expectation that may put additional stress on bereaved parents[8], whereas accommodation to multiple losses, rather than recovery, may be more achievable[8].

Delaying the next pregnancy attempt for up to a year may improve attachment to subsequent children and decrease maternal psychological pain[3,5,7,9]. However, this may be impractical for many infertile couples, who often express anger towards their reproductive specialist for the multiple pregnancy and resultant loss, and at the same time may feel compelled to try promptly for another pregnancy[2,7].

## Loss of some multiples

Mothers and fathers who lose one twin or triplet grieve as intensely as parents whose singleton baby dies[4,5,10]. However, mourning may be delayed for several years while parents are preoccupied with the care of surviving children[1,2,7]. In contrast to the more common 1–4-year grief process for singleton loss[1,3], 3–5 years or more may be required for grief resolution in the case of a twin loss[2,5]. Indeed, 5 years after delivery, depression is more prevalent in parents who lost one twin neonatally, compared with parents of intact twin pairs[4].

Parents often find it confusing to raise survivors after the death of co-multiples, as they are torn between grief and joy[4,10], with the living child(ren) seen as a daily reminder of what could have been[11]. Sometimes parents 'see' a dead child in a living one, even if the children are of opposite gender[4]. Parents differ on whether to refer to a survivor as one of the number conceived or one of the number remaining, although most, especially after later pregnancy loss, consider the remaining child(ren) to be survivors of the original number[1].

Ambivalent interactions between parents and survivors are common, as some parents resent or reject survivors[5,10–14], and others may fear the deaths of the remaining children and resist attaching to them[5,10]. Occasionally, parents feel that attending to a dying fetus or child is initially more important than relating to the healthier child(ren)[11]. In other circumstances, parents describe heightened appreciation for their survivors, feeling excessively attached and overprotecting them[14,15].

## Factors that influence mourning

Table 103.2 lists many factors that affect familial reactions to multiple birth loss. Societal attitudes may influence mourning, as some cultures revere multiples as godly, and others fear them as evil[16]. Cultural practices include the use of special rituals to acknowledge or atone for a twin's death, carving of figurines to represent a deceased child and infanticide or neglect for cultural reasons[16].

Many psychosocial factors influence grief. Some parents are actually relieved by the loss of one twin, as it can lessen the financial, marital and parenting stresses inherent with multiples[1,10]. More often, however, depression, anxiety, isolation, substance abuse, marital conflict and parenting difficulties begin or worsen after a loss[2]. Religious faith may affect mourning and grief recovery[2,5,10,12]. Some parents who are spiritually oriented may be less likely to feel prolonged anger, guilt or blame[10], while others face conflicts as they try to reconcile their experience with traditional religious precepts[6,8].

**Table 103.2** Factors influencing grief after multiple birth loss

| |
|---|
| Cultural beliefs about multiples |
| Psychosocial circumstances |
| Number of survivors and older siblings |
| Previous losses |
| Gestational or postnatal age of loss |
| Zygosity of multiples |
| Gender of deceased or surviving children |
| Other multiples in the family |
| Difficult medical and ethical decisions |
| Contemplation of legal action against care-providers |
| Ill health in mother following delivery (loss of well-being) |
| History of infertility (loss of spontaneous family planning) |
| Premature delivery (loss of rest of pregnancy and normal early parenting) |
| Disability in survivors (loss of child's normal potential) |

Parents with no living children following a multiple-birth loss go home to a deafening silence[2], while parents who have children, including surviving multiples, need advice on helping their children to grieve[1,5]. Although parents of two or more surviving multiples experience the uniqueness and stress of raising the surviving children together, they still miss those who died. Their particular grief is often unjustly minimized[1].

Without doubt, reactions to a new loss are influenced by parents' previous loss experiences[1]. Previously bereaved parents frequently feel devastated when another death occurs, and they are often outspoken regarding the memories and mementos they wish to have as they cope with their most recent loss[8].

The gestational or postnatal age at which loss occurs clearly influences mourning[5,10]. Early loss may assume greater significance to parents after additional losses later in pregnancy or infancy[17]. Losses that occur one by one over a period of months constitute more tragedy than most families suffer in a lifetime[2,17]. Although some parents with a vanishing twin are heartbroken[2], early pregnancy losses in general may be grieved less severely than later losses, or they may be accompanied by relief[1,10].

Knowledge of zygosity helps parents to conceptualize their deceased children's unique relationship, appraise their risk of spontaneously conceiving multiples again and answer questions from survivors as they mature[5,10]. Monozygotic adolescent and adult bereaved twins feel deeper grief than their dizygotic counterparts[18].

Gender also influences grief. Parents of mixed-gender multiples may express disappointment at the death of a child of preferred sex[10], leading a female

survivor to feel, for example, that she could never be her parents' much-desired son[14]. As adults, female surviving twins tend to grieve more intensely than male survivors[14,18].

The existence of other multiples in the family plays a role in mourning. Parents who have close exposure to twins may feel especially well prepared to raise them. Bereaved parents who have an intact set of multiples, plus surviving multiples after a loss, must strive to make all of their living children feel valued as both individuals and/or multiples[5]. A bereaved parent who is a twin may find the relationship with his or her co-twin changed[8]. One bereaved mother rarely speaks to her twin brother about the loss[8], while another believes her twin sister's demonstrative mourning encroached on her own grief for her twins' deaths.

Difficult prenatal and neonatal decisions trouble families, and certain choices may benefit some fetuses or children while resulting in the deaths of others[7,17,19]. Some may mull over their decisions, wondering if their choices were truly best for their children[5,7,19].

Legal action is occasionally contemplated against care-providers, who still may be caring for surviving children. Parents who ultimately pursue a lawsuit may find their anger, grief and stress to be prolonged[20].

Other considerations complicate the grieving process. For example, a mother in critical condition from perinatal complications whose children are dying not only loses precious moments with her babies, but also has her own health at risk[4]. In addition, infertility may cause grief, depression, anger, sexual dysfunction and a sense of failure[21], and it raises the risk of pathological grief after pregnancy loss[22]. Furthermore, premature delivery replaces a normal birth experience with the stressful environment of neonatal intensive care[1]. Finally, disability in a survivor may be mourned indefinitely as the loss of normal capacities[23,24].

## Situations that parents find painful

Common sources of discomfort for bereaved parents of multiples include the failure of care-givers to acknowledge grief, as well as comments that may be considered insensitive (Table 103.3)[1,10]. Staff members often try to minimize grief or deflect parental attention to survivors, when parents actually need and want encouragement to express their feelings to the fullest extent[10,22]. As a prime example, inaccurately labelling two surviving babies as twins, when they are in fact part of a set of higher-order multiples, discounts the meaning of the dead children to the family[1,7]. Encounters with intact sets of multiples or their parents can also be painful to bereaved parents[1,2,10], regardless of whether they occur during an out-patient obstetric visit, during prenatal hospitalization or when their survivors are placed near intact sets of multiples in the nursery.

Parents can feel frustrated when clinicians do not communicate with each other about the loss[6,10]. One woman, whose premature twins died neonatally, was readmitted for postpartum complications. A medical student, who did not know about the twins or their death, asked her how the 'baby' was[6]. The care-givers of many survivors in a neonatal intensive-care unit (NICU) are unaware of a loss, or they do not discuss it. A nurse told a mother whose survivor's isolette was labelled 'twin B': 'This baby is so unique, you'll never have another one like him.' The mother wanted to scream, 'I *did* – he's an identical twin.' Relatives of intact sets of multiples in the nursery may also utter hurtful remarks if they are uninformed about a family's loss.

Parents are particularly distressed when they are deprived of interactions with their deceased multiples or prevented from obtaining mementos of them[5]. Families should be allowed to accept or reject keepsakes, photographs and private time with their deceased children, including a fetus papyraceous or

**Table 103.3** Comments used in discussions with bereaved parents

| *Hurtful comments* | *Helpful comments* |
|---|---|
| Humans aren't meant to have litters | I'm so sorry for your loss |
| God must have known you couldn't handle them all | Some tragedies happen for no good reason |
| It's for the best. They would have been severely disabled | I can't imagine how you feel |
| You're young enough to have other children | I wish things had turned out differently |
| Be strong, your survivor needs you | How are you feeling and coping? How can we help? |
| At least you have two lovely babies | I'm thrilled you have Jacob and Madison, but very sad that Matthew and Amber died |
| Since they were identical, you'll always have a living reminder in Mary | This must be so hard for you |

anomalous fetus, rather than have them withheld by well-meaning staff[1,4,22]. If parents are overwhelmed by perinatal events, more time than usual may be needed for these opportunities[1].

## IMPACT ON THE FAMILY

### Gender differences in grief of parents

Maternal and paternal adjustments to loss are characterized by similarities[4] as well as differences[2,5,10,22]. Differences are primarily due to greater acute grief or longer duration of depressive symptoms among mothers[2,5,10]. Because a multiple-birth family may be physically separated soon after a premature delivery owing to the mother's or babies' medical condition[2], the father must often discuss painful decisions about resuscitation or withdrawal of life support without his wife's input[5]. Staff support of the father at this time is crucial[1], as his presence and comfort are 'of paramount importance' in maternal resolution of grief[10]. Clinicians would do well to warn parents that their grief will probably not be synchronized in its timing, intensity or expression, a difference in grieving style that often causes some estrangement for a certain period of time[3,25]. Up to 12% of couples separate after a perinatal loss[22], and delayed marital breakdown is well documented among couples taxed by multiple-birth losses[2,7].

### Grief of survivors and siblings

Numerous anecdotes suggest that young surviving multiples experience distress related to their loss, with several infants reportedly screaming at the moment of a co-multiple's death, or at the sibling's grave. One neonate's medical status improved when her deceased brother was placed in her isolette for pictures[26]. Toddlers whose twins die from accidents often search for their twin and express missing their twin during daily routines[25,27]. Conversely, surviving conjoined twins may fare well after separation surgery that resulted in the death of their sibling, although as they grow up, they may ask about their twin and have questions about the surgery that separated them[5].

Caution is needed in interpreting childhood behaviors of surviving multiples that might also be seen in singleton children and are not necessarily manifestations of grief[1,2]. Parents of young survivors have described staring episodes, mirror fascination, fantasy playmates, shyness, loneliness, rapid developmental progress and unique artistic representations[5,27]. Older children may express survivor guilt or loneliness, sometimes blaming parents for the death[5,15,28,29]. Personality changes may include assumption of the deceased child's characteristics, risk-taking, withdrawal and refusal to mature without the co-multiples[14,15,29]. Even some surviving twins who are not told about their twin until adulthood report lifelong loneliness or a sense of something missing[14].

As parents struggle with their own grief, the siblings' sense of loss and emotional needs may be overlooked, especially if the parents are depressed[1,3,9,28]. Alternatively, parents may overprotect the survivor(s)[3,15]. Brothers or sisters may believe they caused a loss by wishing the child dead[3,9], express anger about the gender of the deceased or surviving child or fear their own death or that of other family members[3], including surviving multiples. Occasionally, older siblings each choose to help care for a specific multiple. If one baby dies, however, the sibling who had planned to care for him or her may feel empty-handed, guilty or jealous[5,27]. Counselling may be required for successful adjustment to any of these new family dynamics[5].

### Subsequent pregnancy and children

Parents may be anxious when raising children born after the multiples, even to the extent of exhibiting disorganized attachment[9]. In our experience, several parents who conceived or adopted soon after a multiple birth loss experienced postpartum depression or difficulty in attaching to the new child(ren), obviously to their chagrin and disappointment. Although delay of parenthood for at least a year after loss might decrease some of these adverse sequelae[7,9,22], couples who cannot conceive again must come to terms with the grief of childlessness, or consider other parenting options[5]. Some parents greatly desire another multiple pregnancy after suffering a loss[5,7,19], although it may be frightening, and they inevitably come to realize that no children, even another set of multiples, can replace those who died[2,5].

## OPTIMAL RESPONSE TO LOSS

### General recommendations

General recommendations for management of perinatal bereavement have recently been reviewed[9,22]. Empathy from care-givers trained to understand the effects of multiple loss may facilitate parents' attempts to cope. Table 103.4 presents a management checklist of interventions specific to multiple loss. Asking the parents open-ended questions that elicit their values and opinions, and giving them information and options particular to their situation, will help them to choose what is most appropriate for them[1,22].

**Table 103.4** Management checklist for multiple pregnancy loss

| |
|---|
| Elicit parent concerns, values and choices. Encourage parents to write birth plans |
| Reassure parents about the normalcy of their grief responses |
| Discuss the appearance of a fetus papyraceous, anomalous child or stillborn |
| Discuss disposition options |
| Discuss autopsy and zygosity testing |
| Discuss feasibility and preferences for organ donation or breast-milk donation |
| Clarify confidentiality of infertility or loss scenarios |
| Suggest that parents name deceased fetuses or children, which may help survivors and siblings cope with their loss |
| Offer private experiences with multiples individually and together (including the dead children with the living): viewing, holding, bathing and dressing |
| Offer prenatal mementos (e.g. ultrasound photos), and matching mementos for each neonate |
| Offer photos of multiples alone, together and with parents: color, black-and-white, digital or 35-mm. Suggest computer-manipulated photos, sketches or pastels |
| Offer to discuss deceased multiples, and respond when parents mention them |
| Communicate loss history to all personnel caring for family |
| Clarify parent preferences for the survivor's crib label, such as 'twin A' with the child's name, or, alternatively, posting only the child's name |
| Clarify whether parents want to refer to survivors by the original or the remaining number of multiples |
| Help to reduce parental encounters with intact sets of multiples and their parents |
| Offer multiple-specific grief information, support resources and counselling |
| Plan ongoing contact during the first year |

## Death investigation

Autopsy and careful placental examination are recommended for all unexplained stillbirths and neonatal deaths. This information is not only valuable for resolution of parental grief, but may also assist with medical care of survivors[5]. An autopsy may reveal unexpected findings in morphologically normal fetuses or infants in up to 44% of cases[3,5,30,31], and somatic tissue must be obtained promptly for genetic testing and zygosity determination[32]. If a mother is critically ill and has not yet seen her child, a more thorough autopsy can be deferred for a few days if the child's body is refrigerated[5]. In the case of sudden infant death syndrome (SIDS) and apparent accidental deaths, careful death-scene investigations and autopsy are mandatory, especially with near-simultaneous deaths[32–34], because child abuse is more common in multiples than in singletons[23,35,36]. The clinical evaluation of apparently healthy co-multiples is also useful, as it may reveal signs of abuse[37].

## Counseling and confidentiality

In their initial meetings with bereaved parents, professionals can stress that a wide range of emotional responses is normal, and that specific support may be available for their type of multiple birth loss[1,22]. Supportive and disheartening comments are compared in Table 103.3. It is ideal for care-givers also to acknowledge loss, express sincere sorrow, provide medical and grief support information and ask what other assistance parents might need. Parents especially appreciate receiving literature specific to their situation, along with information about relevant peer-support organizations, such as the Center for Loss in Multiple Birth (CLIMB) (see Chapter 104). Peer-support is an invaluable aid to grief resolution, and may indeed lighten the parents' sense of isolation[8,15,22,33].

Professional counselling is strongly advised for unabated depression lasting 6 months, for low self-esteem due to failure to bear a living child and for prolonged guilt or anger[9]. Some parents also desire mental health support for complicated pregnancies and bereavement. After a loss, all parents need to be aware of the symptoms of depression and post-traumatic stress disorder. Early and repeated offers of counselling, with encouragement to try a second or third counsellor if no benefit is perceived with the first, is highly recommended. Judicious use of medication is indicated for parents with postpartum depression, post-traumatic stress disorder or complicated grief, but this should be provided by a professional with experience in psychopharmacology[4,9].

Confidentiality is crucial when interacting with bereaved parents and their family members, as some parents have not discussed their history of fertility treatment or iatrogenic loss outside their marriage. In many cases parents do not want delivery-room personnel to be aware of an early gestational loss, especially a pregnancy reduction, although it is good for birth attendants to know of such events in case

fetal remains are identifiable[1]. All personnel should be well informed about any limits that parents place on the discussion of sensitive topics. Ensuring privacy from the media is a particular concern when parents have controversial or high-risk pregnancies that may invite publicity[4].

### Memories and mementos

Owing to medical complications, drug effects or psychological shock, parents may have difficulty recalling details of the birth or death of their multiples, and they appreciate help from care-givers in reconstructing these events[3,8]. Viewing, holding, washing or dressing their deceased child's body often makes the pregnancy and loss more tangible for parents, who may have reduced anxiety and better grief resolution if they are able to see their dead children as much as desired and obtain tokens of their existence[8,10,22]. Even with significant maceration or malformations, parents who are adequately prepared are often glad to see their child[22]. Such interactions may carry a risk of depression, anxiety, post-traumatic stress or difficulty attaching to a subsequent child, albeit these problems were observed in only one study[9].

Although coercing reluctant parents to spend time with a deceased child may cause emotional disturbance without aiding their grief recovery[9], parents may need to see multiples together to comprehend the loss of the multiple birth unit[11]. A lack of concrete experiences with deceased multiples often causes confusion or unacknowledged grief[10,22]. For instance, a mother who did not see her deceased son felt that she was dressing his surviving twin to attend his own funeral[38]. In our experience, parents are satisfied when they make a decision based on accurate information about the probable appearance of their child(ren).

Some hospitals have retained bodies in the morgue for several weeks until a critically ill mother can see her children, or to allow parents with survivors several opportunities to have all children together. Deceased children's bodies can be brought to room temperature before viewing, and when necessary, can be draped to hide abnormal features[22]. Parents and/or dead or living children have been transported to other hospitals to facilitate time together with all multiples, dead and living[4]. Mementos of all children together help parents to commemorate them as a group. Plaster molds or prints of feet and hands may be obtainable even after prolonged demise or termination[5].

### Photography and images of the multiples

Deceased infants can be photographed alone, with living and dead co-multiples and with parents and siblings. Even when parents initially refuse photographs, they often later enquire whether photos of the deceased were obtained[1,22]. Black-and-white photos minimize discoloration from maceration or anomalies[5]. Computer-merged photos, sketches or pastels such as Figure 103.1 may be powerful substitutes when photographs cannot be obtained, or when original photos could be disturbing[4,7]. If parents are too ill or distraught soon after delivery or death to pose for a family photo with their multiples, they can be photographed later at the funeral home or hospital, as in Figure 103.2. Photos similar to Figure 103.3 may be feasible with a fetus papyraceous, or macerated or anomalous fetus.

**Figure 103.1** Pastel sketch of quadruplets. One (far right) died *in utero* in the second trimester and was born with the other quadruplets in the third trimester

## PRENATAL CONSIDERATIONS

When a fetal demise or anomaly is discovered during an ultrasound scan, parents should be promptly notified together by the attending physician in sympathetic but straightforward terms[5,22]. Discussion of the impact, if any, of the deceased or abnormal fetuses on the healthy fetuses, as well as reassurance that close surveillance is available for the remainder of the pregnancy, helps parents to cope[1]. Written birth plans may include a brief summary of the anticipated or actual loss, and the parents' concerns about the approaching birth, while also indicating the support-persons who parents wish to be present during delivery, and plans for mementos, autopsy, zygosity determination and final arrangements[5]. Parents need to know that a fetus papyraceous may be visible when intrauterine demise occurs after 12–15 weeks' gestation, although the fetus may appear tiny, flattened and/or macerated[1,31]. Parents of fetuses with lethal anomalies can choose resuscitative and comfort-care options[1].

**Figure 103.2** Nancy and Randy Martin holding Elijah Christopher, Melia Margaret and Samuel Anthony (left to right) at funeral home

### Disposition options

When death occurs prior to 20 weeks, or if the birth weight of a fetus papyraceous is less than 500 g, parents in some jurisdictions must choose between private disposition by burial or cremation, hospital burial in a group grave with other miscarried fetuses or hospital disposition by incineration with other pathology specimens[1]. Some parents are greatly disturbed to learn that their dead multiple's body was incinerated with other human tissues; therefore, hospitals should not incinerate fetal remains without informed parental consent[5]. A minority of parents consider private disposition of fetal remains, even after an early reduction or termination[1].

In delayed-interval delivery, a woman may be hospitalized to await the birth of remaining fetuses after the premature delivery and death of one or more children. Hospitals, funeral homes, clergy and clinicians must work together to help a mother plan and attend her child's funeral when prompt services are desired[1]. Embalming can be considered for delayed burial, so parents may view multiples together after delivery of the remaining children, and bury them together if the others do not live.

**Figure 103.3** Elijah Martin's feet with flower petals

## NEONATAL CONSIDERATIONS

It is particularly difficult for parents to cope with the loss of one or more babies in the neonatal period, when maternal illness or transport of neonates to a distant hospital interferes with time together. The following suggestions help to optimize management of these circumstances.

### Parent preferences for death process and notification of death

Parents welcome multidisciplinary team discussions regarding resuscitation and end-of-life decisions and care[26]. Parents desire to be promptly informed of an impending death, as most greatly value time with their babies while they are still alive[3,4,26]. Many parents appreciate a discussion of organ donation, even when it is not feasible[3,27]. If a child dies while parents are away, they can be summoned and notified privately. Care-givers must avoid blaming a survivor indirectly in poorly worded explanations of medical processes, such 'He starved his twin', or 'She strangled her sister'[5].

### Hospitalization of survivors

Some parents find use of appropriate labels such as 'twin B' on an isolette or crib an important validation of their survivor's multiple birth status, and they feel

offended when care-givers remove this marker after one baby's death[1]. In contrast, others feel that this label is an unwanted reminder of death when they visit their living baby or babies. To avoid unnecessary conflict, parents should be asked their preferences for labelling their children's bassinets or isolettes. Use of the child's name, with or without the multiple birth label, is usually appreciated and rarely considered offensive[1]. When feasible and desired by parents, placing surviving multiples away from intact sets of multiples minimizes painful encounters[1].

### Breast-feeding

Breast-feeding of surviving infants after a loss may be emotionally difficult. Stress or grief can overwhelm a mother to the point that production of breast milk is hindered[1,11]. Lactation consultants need to be informed of the loss, respecting the mother's grief and stress while, at the same time, informing her of optimal ways to enhance milk production[1]. Donation of surplus milk to other neonates after a multiple-birth loss is meaningful for some bereaved mothers[1].

### Discharge planning

Parents who lose all of their multiples should be seen within a few weeks after discharge[3]. They often appreciate 'phone calls from hospital personnel or counsellors. On the other hand, parents with surviving multiples must confront the reality of their losses when the living babies are discharged. The sorrow of not bringing home all of the multiples is superimposed on the stressful emotions surrounding the homecoming of a premature or ill child. Parents bringing more than one child home display correspondingly higher levels of stress[1]. Helpful interventions include parental rooming-in with infant(s) before homecoming, written instructions and assistance in arranging home equipment, nurse visits and out-patient follow-up appointments[1].

## DILEMMAS AND DIFFICULT DECISIONS AFTER LOSS

Although Table 103.4 is meant to outline ideal management, many challenging situations arise, especially when the family is physically scattered or deaths occur at different times. Creative alternatives, such as a memorial service for all multiples following the last child's death, commemorative jewelry or sketches of all members of the set, often comfort families with asynchronous bereavement[7].

Ethical dilemmas can be agonizing. Parents may disagree with each other on decisions such as multifetal pregnancy reduction or withdrawal of life support, or such options may contradict their beliefs[3,7,10,39]. Facing such choices repeatedly, or witnessing the struggle of two or more babies clinging to life, can be overwhelming[7]. To involve parents in decision-making effectively, care-givers must offer accurate information, clergy involvement and an opportunity to obtain second opinions or bioethical discussions[1,3,26,33].

Logistical dilemmas also arise. When critically ill multiples are transported to sites far removed from the mother and from each other, care-givers at each site need to be aware of the existence and status of other children from the pregnancy[7]. Parents may have difficulty spending adequate time with each child, especially with a dying baby. The father sometimes is the only one who has seen the children alive[4]. At other times, a healthy child may be at home while a dying neonate is hospitalized. Arranging for the healthy child to be at the hospital, in a visitation room with a parent or staff, enables a mother to spend more time with both her healthy and dying babies[1].

A final dilemma involves disposition. Many parents must decide when to schedule a funeral after one child dies while others remain very ill[1,7]. Although most couples proceed promptly with services, a delayed burial or cremation of all deceased children together, reopening of a casket later or acknowledgment of the group in one service can be comforting. Parents may want to reserve adjacent cemetery plots or leave extra room on an urn nameplate in case additional children die.

## GRIEF AND INTERVENTIONS FOR SPECIFIC CIRCUMSTANCES

### Early losses

Viewing multiples during an ultrasound scan enhances attachment[22,39]. Not infrequently, one or more fetuses are reabsorbed early in gestation. Some parents accept this loss with relative ease, albeit expressing 'deep wistfulness or regret'[10]. Clinicians can offer parents an ultrasound photo of all fetuses, and they can enquire whether the parents wish to refer to the pregnancy as including the original or the remaining number of fetuses. After either spontaneous or iatrogenic loss, parents may wish to acknowledge a deceased fetus with a memorial ritual[4].

During multifetal pregnancy reduction (MFPR), some parents feel psychological or physical pain and need to say either 'goodbye' or 'I'm sorry' to reduced fetuses[7,19]. The psychological sequelae of MFPR are discussed elsewhere in this book (see Chapter 102). Although post-reduction children appear to fare well, no studies of long-term outcome exist. Likewise, no data are available to advise parents on whether and how to inform survivors of

the reduction[7]. The potential also exists for survivor guilt or anger towards parents[7]. If parents elect never to inform their remaining children of the reduction, care-givers and others who know the facts must maintain strict confidentiality[7].

### *Selective or complete termination for anomaly*

Selective termination of an anomalous fetus, as well as complete termination of pregnancies complicated by conjoined twins or severe twin-to-twin transfusion syndrome (TTTS), represents a significant loss. Although most parents do not regret their decision, they mourn nevertheless[5]. Private disposition after the birth of survivors, or memorials shortly after the termination, can be arranged to ease this burden.

## Second- and third-trimester perinatal losses

Later pregnancy losses, especially complete losses near term, are felt more intensely than earlier losses[1,2,5,10]. Although complete losses are overwhelming to parents as well as to providers, ongoing pregnancy with survivors after the detection of an actual or inevitable loss may result in psychological conflicts and attachment difficulties[1,10,13]. Parents may attach more to one child than to another during the ongoing pregnancy[10,13], and they tend to react in one of three ways. They can become primarily concerned with the deceased child, focus exclusively on their healthy or surviving fetus(es) or work through a period of initial fear and sorrow to be able to attend equally to both their living and dead children's needs[5].

### *Spontaneous intrauterine demise*

Intrauterine demise before viability generates both medical and emotional concerns for parents. Frequent monitoring may reassure parents about the health of their remaining fetuses[5], and parents should be asked whether they wish to see the deceased fetus, or know his or her measurements, during subsequent ultrasound scans. Sonographers must be informed of a prior demise to avoid conveying judgemental or unpleasant reactions to the couple[1,19].

As delivery approaches, it is important to discuss the probable appearance of the deceased fetus[31], and to enquire what advance arrangements, if any, the parents wish to make for the fetus's disposition. Parents who cannot cope with such discussions during pregnancy will need to review these issues with a sensitive support-person after birth. Parents may wish to see or hold their living child first, even if the deceased fetus is the first to be born[4].

### *Delayed-interval delivery*

Grief for the birth and death of one fetus before its viability must be balanced with concerns that maternal stress may provoke labor and the birth of the rest of the children. A mother who is still pregnant with the remaining multiples may find it very meaningful to spend time with a critically ill firstborn multiple, even if her visits must be on a stretcher[5]. In contrast, planning for a funeral or memorial may be limited by the gravida's high-risk status. Some mothers resist attaching to remaining fetuses, given their guarded prognosis.

### *Delivery at the limits of viability*

Parents whose children are born at the borderline of viability confront anxiety, uncertainty and the need to make decisions for or against aggressive care[26]. All staff caring for survivors must be aware when a loss has occurred, as support is needed for all aspects of the experience: prematurity, worries about the children's survival and quality of life and grief if any of the multiples die or if they survive with disabilities[1].

### *Intrapartum demise*

Parents must be honestly and compassionately informed when death occurs in the delivery room[3,5]. Such situations include previously unsuspected multiple gestation, cord prolapse, abruption or difficult version of a second- or third-born multiple. Caregivers need to inform parents clearly whether the child was born alive or dead, as this fact may hold great emotional significance for the family[26]. A support mechanism for health-care workers to cope with their own feelings is helpful after any perinatal death[3], and a meeting for the entire health-care team to debrief and discuss their own feelings of loss and grief may be particularly beneficial after these distressing, traumatic births.

## High-risk scenarios

### *Anomaly*

When one fetus in a multiple gestation has a serious abnormality, the parents must consider the options of selective termination or expectant management[1], weighing the potential impact of the abnormal fetus on the healthier fetuses and the family, if the child were to survive with disabilities[1]. Grief for loss of the child's normalcy, and preparatory grief for the expected perinatal death, may begin soon after diagnosis[3]. Many parents are in denial, hoping that the problem is not as serious as suspected or that high-risk treatment will succeed[1].

Anxiety is likely when parents choose expectant management, and approaching delivery may be

**Figure 103.4** Jacob and Riley Sheridan, monoamniotic twins of Mark and Lynne, deceased from acute twin-to-twin transfusion syndrome

greeted with ambivalence, as it represents the inevitable separation, by death, of two or more fetuses that are alive together in the womb[1]. Parents need accurate information about the expected appearance of their child before he or she is born.

Caregivers and parents alike must be prepared for the possibility of prolonged survival of an affected child. Aggressiveness of neonatal care, details of comfort care and availability of home care or hospice support can be discussed long before birth[1].

### *Monochorionic complications*

Unique risks arise in multifetal pregnancies with monochorionic placentation (Figure 103.4), as discussed elsewhere in this book (Chapter 65). The children's individual identities must be valued in situations such as with conjoined twins[5], and the ethics of interventions that result in one child's death in order to save the others must be carefully discussed[5,17]. Intrauterine death of one fetus in a monochorionic gestation results in a greater likelihood of neurological morbidity in the surviving fetus[40]. The inability to predict which fetuses will be affected, or how severely, with the extent of the injury sometimes unknown until months or years later, make decisions regarding management even harder. Peer-support groups for specific complications may provide information or bereavement support.

## Neonatal, infant and childhood loss

### *Sudden infant death*

Twins have about twice the singleton risk of sudden infant death syndrome (SIDS), mainly owing to the higher prevalence of prematurity and low birth weight in multiples[41]. After one child's sudden death, the parents' first worry is whether the other twin will also die of SIDS[41]. The rate of concordancy for twin SIDS has been estimated at 0.9–2.8%, with a relative risk of 8.17 for the second twin's death compared with singletons[41]. Simultaneous SIDS is extremely rare. Although child abuse and toxic environmental factors must be considered in sudden infant twin death, especially with simultaneous deaths[34], professionals must interact with parents empathically, supportively and non-judgementally[42]. Prompt evaluation of a survivor's health is warranted[34,37,42], and parents may benefit from contact with a SIDS support organization. On occasion, parents may be too distraught to care effectively for their surviving child(ren), whose own grief reactions may reflect both the parents' distress and an awareness that their co-multiple is missing[1,15]. A social-worker may help parents to contact family or friends, to care for children while they cope with early grief and arrange the funeral or memorial service. Cardiorespiratory monitoring has not been shown to prevent SIDS in subsequent or surviving siblings, although it has been suggested for surviving twins[1]. The risk for SIDS in the surviving twin may be greatest in the month following the first twin's death[1]. If two or more children are monitored at home, the parents' stress levels will be increased, and parents may benefit from frequent 'phone contact or a visiting nurse[1].

### *Accidental death, disability and child abuse*

Although no studies have compared incidences of accidental injuries in multiples with those in singletons, factors that increase the risk of injury have been examined in twin pairs[43]. In one Finnish study, the fathers' favorite twins were less prone to accidents[44]. Aggression is a risk factor for injury, and the more aggressive child of a twin pair is more likely to be injured[43]. However, social and environmental factors remain more important than child-specific factors[43]. Some circumstances that are common in multiple-birth families, e.g. noisy, confused households, poor supervision and family stress, also increase the chance of injury[1,43]. When an accidental

death of a twin or higher-multiple child occurs, it is important that care-givers attend to the guilt and grief expressed by parents and co-multiples[15,29]. Parents sometimes respond to an accidental death by becoming advocates for child safety.

Quite apart from death, disability is grieved as a loss in itself, increasing familial stress[1,7,23]. Specific support for parents with disabled survivors is available through CLIMB. The family dynamics of raising disabled multiples has been elaborated in detail[23,24].

Child abuse, including shaken-baby syndrome, is more common in multiples than in singletons, and it often occurs in only one twin, generally the smaller or more disabled one[23,35–37]. Extreme stress caused by an infant's crying, rather than intent to harm, often provokes shaken-baby syndrome[36]. Parental-grief support throughout the death investigation is needed, and adequate social support is essential if surviving children remain with their parents[36,37].

## CONCLUSIONS

In our years of working with bereaved parents, we continue to be amazed by their resilience in tragic circumstances. Clearly, those who receive sensitive care after their loss have fewer regrets[10], and they tend to offer abundant praise for their care-givers. We hope that our work will assist in providing a firm, evidence-based foundation for excellence in clinical responses to bereavement in multiple births. With the many excellent resources and compassionate interventions available, these parents no longer need to suffer alone.

## ACKNOWLEDGMENTS

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# Coping with the Impacts of Death in a Multiple Birth

*J. A. Kollantai*


While society recognizes the joys and challenges of multiple births, a significant number of families confront the most dark and problematic side of 'the world of multiples', that is, the death of one, perhaps all of their babies at some time during pregnancy, at birth, in infancy or during childhood.

After finding myself back in my hospital room after a full-term, uneventful pregnancy with fraternal twin boys, holding one in each arm – one alive, and one equally handsome and well grown, but dead – I began to search for what I imagined would be one or two other mothers and families who had experienced this shocking, bittersweet, and simultaneously agonizing kind of parenthood. I could not possibly have known at that time that oncoming changes in fertility technology might mean that the risks for multiples could not decrease as much as the numbers of multiple conceptions could increase, and that prematurity was only one of the risks associated with these pregnancies.

My personal search led to the founding of CLIMB, Inc., the Center for Loss In Multiple Birth. In the 15 years since that time, I have spent full time and a bit more in contact with as many as 8–10 000 families throughout the USA, Canada and beyond, who experienced the death of one or both of their twins, or one or more or all of their triplets or other higher-order multiples at any time from conception to childhood, placing them in contact with each other and developing our journal and other resources for parents, care-givers and multiples organizations. Some parents have witnessed the deaths of both or all of their multiples after years of infertility, and may or may not ever have living children. Others may have two, three or more survivors, but wonder if the day will ever come that they do not cry for the one who died. Some brought their babies home only to experience sudden infant death syndrome (SIDS), illness or an accident. Although socioeconomic, cultural and personal backgrounds are quite diverse among these families, as are people's coping styles and ability to speak of their experience I, nonetheless, think it is safe to say the following in regard to loss during pregnancy, birth and infancy:

(1) The impacts of multiple birth loss are severe and ongoing over a period of years. The death of two or more babies and/or the realities of grieving for a multiple while raising one or more survivors, coupled with the general lack of understanding and appropriate support for multiple birth loss are enormous. Many parents face the additional ongoing impact of one or more handicapped or medically fragile survivors.

(2) The degree of bonding that results from ultrasonography contributes to the severity and duration of the parents' grief. To those pregnant with twins or triplets after years of infertility, 21 weeks *is* really close to having their children, and many couples have made complete preparations in anticipation of a successful birth. For all, especially after the period of prematurity, it is impossible to believe that these babies would not be here.

(3) The positive impact on the grieving process of sensitive, knowledgeable care-giving at the time

of the loss and afterward by hospital and other professionals cannot possibly be underestimated. The same may be said regarding the adverse impact of treatment which is insensitive or does not take into consideration the entire situation. The opportunity to have concrete experiences with each and all of the babies and do various things that are necessary for all bereaved parents, adapted to complicated circumstances, is even more important here. The lack of these opportunities imposes a hurdle to healing which is extremely difficult for many to overcome. The future emotional health of any survivors, as well as that of the parents and any subsequent or current children, is directly at stake, even though those who are care-givers at the time are not usually in a position to see how things will reverberate in a family over 3–4 years.

(4) Isolation, combined with often being considered 'rare', is detrimental to parents' becoming mobilized to do what is necessary to begin to cope and heal, especially when coupled with the media and other attention focused on only successful multiple births.

(5) Many parents feel betrayed by the technology which helped them conceive their children and manage the pregnancy, but was not sufficient to ensure all of them being born alive and healthy. The same is true regarding the general lack of statistics and of information about specific risks, especially for monozygotic twins, and the uneven levels of care given to certain types of pregnancies. (Nowhere is this more evident than in the management of monoamniotic pregnancies, at least in the USA, as well as those with twin–twin transfusion syndrome.) Many feel that their twin or triplet pregnancy was trivialized by the success of some very high-order pregnancies.

(6) Parents' medical experiences are integral to how their loss is experienced, and relevant medical information after the loss is essential to being able to process it all mentally *and* emotionally.

(7) Any ambivalence or guilt about the decision to undergo (or not undergo) multifetal pregnancy reduction (MFPR) is magnified if there is death later of a remaining baby/ies. A significant subgroup of parents undergo long-term emotional aftermath of MFPR despite a 'successful' pregnancy outcome.

(8) Parents, especially those with a survivor, are at risk for clinical depression, anxiety and difficulties in parenting, as well as marital problems, even more so 3–4 years later than in the immediate aftermath.

(9) All the emotions of loss are underscored completely by the preciousness and irreplaceability of multiples. People grieve intensely for 'my twins' or supertwins and their status as the parent of living multiples, or an intact set, and do not expect to have them again 'next year', or harbor the illusion that their next child will even the score for what was lost. Those who do have multiples again, usually through fertility technology, find that their living multiples make them even more aware of the loss of their first set. Most parents believe that they have squandered an incredible once-in-a-lifetime opportunity for which they thought they had been specially chosen. Direct and indirect encounters with intact sets of living multiples, especially of the same number and type, are extraordinarily painful and problematic for most mothers, even many years after the loss.

The combination of appropriate medical information, informed care and the opportunity to know that their feelings are normal and that their realities, sadly, are not rare enables parents to recognize the things they need to do actively to cope and adapt to an irreparable loss, ultimately incorporating it into their personal experience and perspective, and into the life of their family. Sensitive professional counseling is indispensable, especially with regard to some of the 'sticking points' and additional issues which arise. With time and appropriate support, the babies' memories become part of lives that are still satisfying, even though we will always wish that things had turned out differently. Grieving for the loss of multiples is a tough, endlessly complicated and intensely demanding process emotionally, intellectually, physically and spiritually. One of the many unofficial mottos of our group is that *anything* with regard to raising both or all of them would have been easier than the situation into which we were thrust.

Table 104.1 lists some of the primary groups specific to the needs of bereaved multiple-birth parents, and which may also be helpful to medical and other care-givers; some of these contain additional resource listings. The usual net cautions apply to all internet resources in relation to multiple birth loss.

**Table 104.1** Groups specific to the needs of multiple-birth parents: prepared and accurate as of 30 September 2003

*eLIMBO (electronicLoss In Multiple Birth Outreach)*
www.groups.yahoo.com/group/eLIMBO
e: Terryc45@hotmail.com, Terry Callaghan
an e-mail support group of bereaved multiple-birth parents, most with the loss of one of their twins or higher multiples in pregnancy or infancy

*LAMBS (Loss of All in Multiple Birth Support)*
www.public.iastate.edu/~cjenks/lambs.html
e: cjenks@iastate.edu, Cynthia Jenks
an e-mail support group of parents who have experienced the death of both twins or all their higher-order multiples (and the only one of its kind)

*Elizabeth A. Pector, MD*
www.synspectrum.com/multiplicity.html
includes articles on many aspects of multiple birth loss for parents and care-givers, and an extensive resource listing, by a physician and bereaved multiple birth parent; also,
www.synspectrum.com/multiplicity.html, 'Rebuilding a Life …'

*Center for Loss in Multiple Birth (CLIMB), Inc.*
www.climb-support.org
e: climb@pobox.alaska.net, Jean Kollantai
peer support for multiple-birth parents bereaved at any stage of gestation to childhood, in the USA, Canada and beyond; *Our Newsletter* (quarterly since 1987), parent contact network, and assistance to care-givers and multiples organizations

*M-BABS (Australian Multiple Birth Association Bereavement Support)*
www.amba.org.au/bereavement
e: bereavement@amba.org.au, Simone Zmood
affiliated with the Australian Multiple Birth Association (AMBA): peer support for loss in a multiple birth at any stage of gestation or age, quarterly newsletter *Multiple Dreams*, assistance to care-givers

*Twin and Multiple Birth Loss NZ (Inc.)*
www.twinloss.org.nz
e: twinloss@xtra.co.nz, Rosemary Smart and Jan Liddell
peer support network in New Zealand for multiple birth loss at any stage of gestation or age; quarterly newsletter *Hearts & Wings*, assistance to care-givers and multiples organizations

*Lynda Haddon*
www.multiplebirthsfamilies.com/bereavement.html
a site which includes a large section on bereavement, by a childbirth educator who is also the bereavement co-ordinator for Multiple Births Canada/Naissances Multiples Canada (e: loss@multiplebirthscanada.org)

*TAMBA BSG (Bereavement Support Group)*
www.tamba-bsg.org.uk
affiliated with the Twins And Multiple Births Association (England): peer support for loss in pregnancy and infancy, quarterly Newsletter, contact network, periodic meetings

*The Twin to Twin Transfusion Syndrome Foundation*
www.tttsfoundation.com
… information and support for parents and care-givers involved in TTTS pregnancies, including some bereavement support

*Monoamniotic.org – Monoamniotic Monochorionic Support*
www.monoamniotic.org
peer support and information for parents undergoing monoamniotic pregnancies, including a bereavement support section 'Lost Angels'

*Multiple Births Foundation*
www.multiplebirths.org.uk
among its publications, booklets for parents and professionals on complications of monochorionic twinning, bereavement, fetal reduction (multifetal pregnancy reduction) and selective fetocide (selective termination)

# A Personal Perspective on Multiple Pregnancy and Birth


*J. L. Bleyl*

In my role as the author of this chapter, I would like to be a voice for the *parents* who are asking for help from medical professionals as they seek to realize the best possible outcomes of their multiple-gestation, high-risk pregnancies. I speak from personal experience, having given birth to triplets born at 29 weeks' gestation over 21 years ago, as well as from contact with and the detailed medical questionnaires from approximately 1500 expectant parents of multiple births *each year* (more than 30 000 since 1983). Our detailed medical questionnaires are completed by members and are sent to The Triplet Connection, the largest organization of its kind in the world. From this 'bird's-eye' perspective, I try to keep abreast of what is going on in the medical field of obstetrics concerning multiple births, as well as to read and hear comments and perspectives from thousands of women for whom I act as a quasi-spokesperson. I know of their fears, their need for knowledge and involvement, their sensitivity and need for compassionate and expert care, and of their desire to have healthy outcomes as well as adequate support and resources during pregnancy and afterward. From the beginning of pregnancy to the care of their multiple-birth offspring, these women desperately need the understanding and positive support of those who will guide them through one of the most emotionally charged and physically challenging experiences they will ever undergo.

The numerous excellent practitioners who impart outstanding care for their expectant mothers of multiples are to be commended. In the opinions of their patients they provide compassion and interest, and supply resources and information to help patients become well-informed 'partners' in their medical care and to help them become decisive rather than passive. These physicians are neither unlikely nor too proud to consult with others when challenges arise, nor are they liable to discount seemingly insignificant worries from their patients – or allow their office or hospital staff to prevent them from hearing such concerns first-hand. In my experience, the physician who is knowledgeable yet humble, compassionate yet firm when necessary, who has respect for his/her patients and who is willing to step up to 'bat' and to enlist more qualified help when needed provides for the very best outcomes among mothers of multiples. I salute each of you for your knowledge, skill, compassion and willingness to persevere! I hope that you will take the time to read and think about my voice, a qualified spokesperson for your multiple-birth patients!

First, I would ask you to realize that women expecting multiple babies are a unique group of individuals. While many are undergoing spontaneously conceived pregnancies, others are fertility-induced. This latter group often includes women who, although they have tried for many years to achieve a pregnancy, rarely think about the stark reality of multiples – particularly triplets or more. These women, after years of infertility and subsequent heartache, are often overjoyed finally to have the opportunity to bear children. They are, however, totally overwhelmed with what they are facing: the awesome fear and responsibility of successfully carrying, giving birth and subsequently caring for two, three or more infants. They are sometimes overjoyed, sometimes devastated, but *always* overwhelmed with their new-found knowledge.

*Please* be compassionate and positive with these women! Please inform them of their condition with

sensitivity! *So* many expectant mothers find their doctors' initial reaction to include negativism and immediate advice to 'reduce' their pregnancies to 'something more manageable'. Please be aware that many of these women may be overjoyed at the prospect of welcoming multiple infants into their families, although some may be frightened beyond description. Each understands full well that this may be her only hope of ever having children. Please give these mothers the news tenderly, and then give them what is most important: the knowledge that multiple-birth pregnancies are usually manageable, although they require much more work. Please immediately provide them with *resources,* including support individuals and groups who will help them know exactly what they are up against, and who can testify that there is life and joy after a multiple birth. If, and only if, a woman wants to consider selective reduction, she should be given contacts which include both those who have had selective reductions and who have volunteered to be resources, as well as others who have undergone similar pregnancies successfully (and even unsuccessfully) who want to be resources and share their experiences. Please connect them with individuals and physicians who can help them understand exactly what they are up against, and what they can do to help promote the best possible outcome of their pregnancies. Expectant mothers of multiples deserve to be provided with balanced information and contact resources from the day they receive the news that they are expecting multiple infants. They do not deserve to be treated with pessimism and/or given dire predictions, nor do they need to be treated as though any one of the lives they carry is any less important than a singly conceived infant. These women need support, compassion, resources and immediate connection with other individuals who understand their fears and joys. No resource is as valuable as the opportunity to connect immediately with other mothers of multiples.

Unfortunately, many couples describe feeling that they felt pressured to reduce their pregnancies by their reproductive endocrinologists and/or physicians, being told that 'there is no other way' to achieve a healthy outcome. Many had been told that they were 'guaranteed' poor outcome by their physicians, and went on to reduce their pregnancies before ever realizing that the majority of mothers, do, indeed, have good outcomes to their multiple-birth pregnancies. Many of these ill-advised couples experience tremendous anger and resentment because they were not given balanced and sufficient information and resources to help them make their decisions before it was too late to change their minds. Furthermore, few women who undergo selective reduction are warned of the increased likelihood of problematic pregnancies in spite of the reduction, nor are they adequately prepared for the ill-reported total loss after reduction.

Once you have delivered the news of multiples and your patient has been provided with every resource available, please be prepared to help her accomplish the choice of her heart. If you are not well experienced in positive outcomes with pregnancies similar to this patient's, *please* immediately refer her to someone who is very well experienced, or work closely with a well-experienced physician to co-manage her care. There is always a learning curve for management of multiple-birth pregnancies, and this should never be a time for inexperienced care-givers to keep patients who deserve to be treated with experience and competence if and when unexpected problems arise.

Likewise, please be sure that your patient is prepared to deliver at a hospital that is well equipped and experienced in delivering and caring for multiple-birth infants. Even when not born prematurely, multiple-birth infants frequently present unique challenges at the time of birth, and deserve to be delivered in a hospital prepared immediately to meet the needs of infants born with unexpected problems. It is unfortunate to see multiple-birth infants delivered in less than adequate hospital facilities and not have immediate, experienced and qualified care available when needed.

Please be sure that each of your patients desires to understand thoroughly and precisely what potential problems *may* be associated with multiple-birth pregnancies, and what she should watch for and report to you. Assure her that, although she may never face any serious problems, it is important that she be cautious, aware and communicative. Very often, women who are well informed and well motivated are able to report early on insidious symptoms which, when attended to early enough, can result in prolongation of their pregnancies. Every physician should encourage patients to become as well informed as possible when it comes to multiple-birth pregnancy. Books, web sites, support organizations and other sources help a woman to recognize potential problems and identify resources.

Please be sure to give your patients the opportunity to report their concerns to you, first-hand. You might be surprised to know how many women tell their concerns to an office worker or a nurse, only to be told that 'this is normal', or 'not to worry', with the doctor never being involved or informed. Very often, important symptoms are passed off when immediate attention might have saved a pregnancy or prevented a premature birth.

While I hear of hundreds and hundreds of wonderful, competent physicians who manage multiple

pregnancies, both I and many of the members of our scientific advisory panel and those who enter data from our medical questionnaires can attest to many, many stories of less than ideal care and outcome. We hear from women who have been ignored, chastised for 'bothering' their physicians and patronized to the point of neglect. We hear of women whose babies have been born at home, when they were told to lie down and take ibuprofen for what they reported to their physicians. We hear of physicians who refuse to take action when problems arise early on, sometimes sentencing women to inevitable loss. We sometimes hear from women who are in such dire circumstances that they ask us to help them find other, more proactive and supportive care-givers during the last days of their pregnancies.

When you have a patient whose pregnancy *is* in trouble, *please* do all which can reasonably be done to help! Please be the best advocate possible for your patient, and provide her with every advantage currently available. I am personally aware of countless women who have had multiple-birth pregnancies fraught with serious complications from very early on until the day of delivery, yet still had positive outcomes of pregnancies that other doctors would have 'let go', never providing the help and support needed to see them through. Every physician needs to understand that most women are willing to walk through the proverbial fire in order to protect their babies, and I believe that every physician should be prepared to help them when that becomes necessary.

When physicians and care-workers have provided every possible opportunity to ensure a good outcome, and when a woman has been informed and motivated and has become a 'partner' with her physician, even a poor outcome can be accepted. In contrast, it is when a doctor or medical facility has refused to do all that is possible that couples feel they have been cheated, and their grief and anger are unmanageable.

In the sad instances when these risky pregnancies do not turn out well, *please* do not turn your back on your grieving patient! Unfortunately, this often happens. When a patient feels as though those who tried to help her did everything possible, and when she realizes that they *care*, she feels much more peaceful about her outcome than when her medical-care providers stay away after the event.

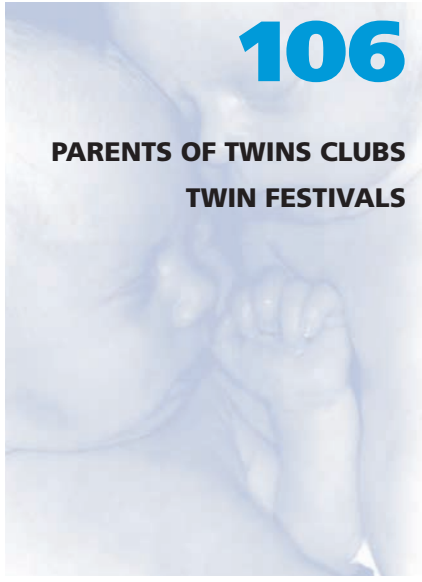
Thankfully, the majority of multiple-birth pregnancies do end successfully. Each experience presents unique obstacles and requires much work on the part of both patient and physician. It is crucial that *every* care-giver understand that there is *great joy* in parenting multiple-birth children! It *is* difficult in many ways, but what you must understand is that there is no way to convey the extraordinary love and joy that also accompanies the experience! Whereas there is incredible joy in holding a single, wanted baby in one's arms, there is simply no way to describe the joy in holding two or more infants in one's arms. Healthy multiply-born infants, children and adults are, indeed, a joy. The joy is *worth* all the challenges involved in their care and keeping.

I sincerely hope that you will work diligently and sensitively with every expectant mother of multiples to help her realize the joy of multiple-birth children!

Janet L. Bleyl is founder and president of The Triplet Connection, a national, non-profit organization providing a 'network of caring and sharing for multiple birth families'. Members of The Triplet Connection are informed, motivated, 'partners' with their physicians. For a free physician's copy of our books, *Exceptional Pregnancies: A Survival Guide to Parents Expecting Twins,* and *Exceptional Pregnancies: A Survival Guide to Parents Expecting Triplets or More*, contact The Triplet Connection: www.tripletconnection.org. Many physicians and hospitals provide every expectant mother of multiples with our brochures, books and resource packets.

# Forming and Using Parents of Multiples Clubs: Advice for Health-care Professionals

*D. M. Keith and N. Keith Hall*




## PARENTS OF TWINS CLUBS

Parents of Twins Clubs, or their more recent counterpart, Parents of Multiples Clubs (POMCs), are not a new concept. In the early 1970s, prior to the growth of political correctness, these parental support groups were called 'Mothers of Twins Clubs', as high-order multiple births were still quite rare, and the vast majority of multiple births were governed by nature and calculated by the now obsolete Hellin's Law. Eventually, Mothers of Twins Clubs were supplanted by Parents of Twins Clubs in the name of gender equality, which in turn were succeeded by Parents of Multiples Clubs when the explosion of high-order multiple births stole the limelight from the once rare twin sets. No matter the name, the purpose and format are almost identical.

It is reasonable to ask why should you as a health-care professional suggest that your patients join or, in the same instances, form a club that exists solely for parents of multiples? There are many reasons, only some of which are enumerated below.

First and foremost is the fact that the vast majority of expectant parents rely heavily on their physicians and other health-care professionals, in particular their obstetricians or midwives, for information and support on major and minor issues as they go through the antenatal period. This includes such mundane topics as where best to purchase equipment, car seats and cribs. Unfortunately, you may not have all the answers, or the time to provide the emotional and psychologic support that they are looking for and have come to expect in the 21st century during an office visit conducted under time constraints set by outside funding agencies.

Simply stated, POMCs can help bridge the information/support gap between the purely medical/physical aspects of an impending or recent multiple birth, and the practical, hands-on know-how provided by parents who have recently experienced the same challenges.

From a parent's point of view, as well as provider's vantage point, parents of twins/triplets/ quadruplets, etc. frequently ask common, repetitive questions that may or may not be medical in nature. From a physician's point of view, a support group can assist and even save the day with many problems, allowing physicians, nurses, midwives and other health-care professionals more time to answer the pertinent medical questions where their training, expertise and interests lie. In the final analysis, the best person to answer questions on co-bedding, breast-feeding two or more infants simultaneously or the social aspects of toilet training is a parent who has 'been there, done that'.

POMCs represent an innovative, ingenious and low-cost/maintenance means to disseminate support information related to a narrow audience. The vast majority of members have experienced the joys and tribulations of a multiple pregnancy, and are able and most willing to answer questions on weight gain, clothing, and where to find strollers for six. To be sure, someone in the organization is familiar with time- and labor-saving techniques for every task that must be accomplished. In larger cities in the developed world, POMCs are the norm. Yet their absence in smaller, rural or isolated areas or in developing nations does not mean that they are not needed in these locations. Just the opposite may be true.

At this point, you may ask, exactly what is a POMC? The answer is simple: a POMC can take any form and serve any function that the members want. Most POMCs serve the needs of diverse groups. Pomp and ceremony may bog down some clubs, with

great attention paid to Roberts' Rules of Order, and where seniority has its privileges. In contrast, other organizations just roll up their sleeves and go to work. This said, and in spite of such minor differences, POMCs are fun and productive, and are an invaluable resource for their members, taking much of the information-passing off the health-care provider's plate.

Hospitals, maternity wards and health-care units are ideal sponsors for a POMC. In addition, health-care institutions can be counted upon to provide a constant flow of new members. All it takes is someone in the hospital and a few interested parents to get a POMC started. These parents can then spread the word in familiar places, e.g. church groups, health clinics, physician offices, libraries and social-service offices. However, even the organizers must be organized. The ideal starting points for a POMC are long-term veterans, parents who have had their multiples for some time. New parents initially tend to feel overwhelmed with financial obligations and demands on their time for infant care and feeding, and are more likely to be participants than initiators.

When forming a new club, the first duty is to appoint temporary officers. The chair will coordinate plans, hold meetings and prepare agendas. The secretary will record the minutes and conduct correspondence. At least one person needs to spearhead publicity measures to 'spread the word', 'seek the media' and 'be a spokesperson'. The treasurer will keep the books. The membership officer will maintain a list of members and prospective members. Temporary officers lay the groundwork in contacting other POMCs for ideas.

The temporary officers also schedule the first meeting. This meeting needs to be publicized as much as possible. The chair should prepare and follow an agenda and assign duties. The new officers should ideally arrive ahead of time to plan for last-minute glitches. The publicity chair is an ideal individual to act as host, to 'meet and greet' and to help new parents feel welcome. The membership chair should obtain new members' contact information. The secretary takes minutes, passes out information and is a general all-around assistant.

The second meeting is the best time to read and approve minutes, choose permanent officers and select a name for the club. This time interval is important for several reasons. Members must decide on a club objective, and establish annual dues, which should be as low as possible. The organization needs someone to draft by-laws and look for inexpensive (free) meeting places. The former usually is accomplished by using the by-laws of an already existing club as a starting point. The latter depends an community resources.


**Figure 106.1** Parents of Multiples Clubs in different countries

A few months are usually required to develop good programs. However, but good programs result in participation and attract new members. All members need to be involved in some way, and meetings are an excellent opportunity to invite participation from the local health-care community, perhaps in an advisory role. The club needs to plan a speaker program as well as a newsletter.

It is important to remember that good officers make things happen. The president must act as the leader to promote, organize and plan. The executive group should have a vision for the organization. The vice-president should help the president. A good secretary is essential to keep accurate, unbiased minutes. And of course, no club is complete without a treasurer to maintain accurate books.

Appendix I contains a list of Council of Multiple Birth Organizations (COMBO) of the International Society for Twin Studies (ISTS) (Figure 106.1). Appendix II contains the 1995 'Declaration of Rights and Statement of Needs of Twins and Higher-Order Multiples', developed and adopted by COMBO. A full reference list for the declaration can be found on the ISTS website (www.ists.qimr.edu.au).

## TWIN FESTIVALS

One of the important activities of many clubs is either to arrange or to participate in festivals of twins and other multiples (Figure 106.2). The most widely


**Figure 106.2** Logo of the Twinsburg twins festival (http:// www.twinsdays.org)


**Figure 106.3** Twin sisters Debbie and Lisa Ganz, authors of The Book of Twins, during their visit to the Szczecin (Poland) Twin Festival

known in the USA is the Twinsburg festival, held for almost 35 years on the first full weekend of August in Twinsburg, Ohio. It attracts about 3000 sets of twins and countless family members and interested public in an outdoor festival atmosphere. It is a wonderful place for parents to bring their children so that they (the children) will know that they are not the only doubles and triples on the face of the planet. One of the most recent and growing festivals in Europe, is held annually in Szczecin, Poland (Figure 106.3).

Finally, many twin festivals are a superb opportunity for researchers in the field of multiples to meet, within a short period of time and within a restricted

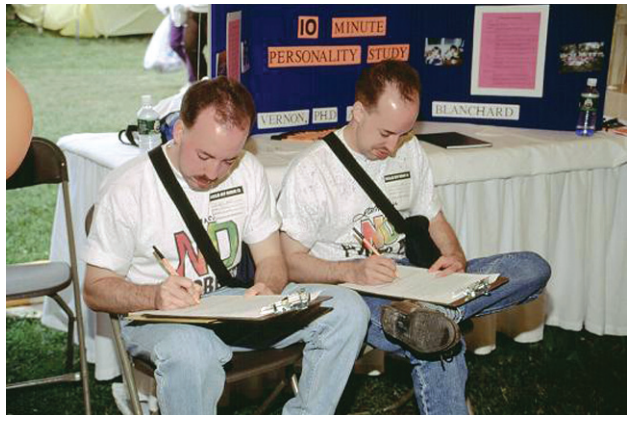



**Figure 106.4** Monozygotic twins replying to a questionnaire in Twinsburg

**Figure 106.5** Anthropometric measurements at Twinsburg

**Figure 106.6** David Teplica (right) with the assistance of Donald Keith (left) sets the stage for the photographic Twinsburg archives

location, a large number of twins. Such research may take the form of questionnaires (Figure 106.4), or measurements (Figure 106.5), and has led to the creation of Twinsburg photographic archives by David Teplica, MD, MFA (see Chapter 38) (Figure 106.6).

## APPENDIX I

Members of the Council of Multiple Birth Organizations (COMBO) of the International Society for Twin Studies (ISTS), July 2004

ABC-Club
30451 Hannover
Bethlehemstr. 8
Germany
www.abc-club.de

Australian Multiple Birth Association
PO Box 105
Coogee
New South Wales 2034
Australia
www.amba.org.au

Centre for Loss in Multiple Birth (CLIMB) Inc.
PO Box 91377
Anchorage, AK 99509
USA
www.climb-support.org

Illinois Organization of Mothers of Twins Clubs Inc.
415 Spaulding Road
Bartlett, IL 60103-0957
USA

Japanese Association of Twins' Mothers
1-5-10-722 Shimo-ochiai
Shinjuku-ku, Tokyo 161-0033
Japan
www.tmcjapan.org

Jumeaux et Plus
28 Place Saint Georges
75009 Paris
France
www.jumeaux-et-plus.assoc.fr

MOST (Mothers of Supertwins) Inc.
PO Box 951
Brentwood, NY 11717-0627
USA
www.MOSTonline.org

Multiple Births Canada
240 Graff Avenue
Box 22005
Stratford
Ontario
Canada
N5A 7V6
www.multiplebirthscanada.com

Multiple Births Foundation
Level 4, Hammersmith House
Queen Charlotte and Chelsea Hospital
Du Cane Road
London W12 OHS
UK
www.multiplebirths.org.uk

Multiple Births Foundation of Sri Lanka
Dr Athula Sumathipala
Institute of Psychiatry
Kings College, University of London
Denmark Hill
London SE5 8AZ
UK

National Organization of Mothers of Twins Clubs, Inc.
PO Box 438
Thompson Station TN 37179-0438
USA
www.nomotc.org

New Zealand Multiple Birth Association
PO Box 1258
Wellington
New Zealand

Nordic Twinnet
2, Fjendstrupvej
DK-4850 Stubbekobing
Denmark
www.tvilling.net

Swedish Twin Society
Svenska Tvillingklubben
Valhallavagen 106
114 41 Stockholm
Sweden
www.tvillingklubben.se

Tamba
2 The Willows
Gardner Road
Surrey GU1 4PG
UK
www.tamba.org.uk

The Lone Twin Network
PO Box 5653
Birmingham B29 7JY
UK

The Twins Foundation
PO Box 6043
Providence, RI 02940-6043
USA

The Twin to Twin Transfusion Syndrome Foundation
411 Longbeach Parkway
Bay Village, OH 44140
USA

Triplet Connection
PO Box 99571
Stockton, CA 95209
USA
www.tripletconnection.org

Triplets, Quads and Quints (TQQ)
2968 Nipiwin Drive
Mississauga
Ontario
Canada
L5N 1X9
www.tqq.com

Twin Hope, Inc.
2592 West 14th Street
Cleveland, OH 44113
USA
www.twinhope.com

## APPENDIX II

Declaration of Rights and Statement of Needs of Twins and Higher-order Multiples

Adopted by the Council of Multiple Birth Organizations (COMBO) (composed of representatives of 16 organizations from ten countries: Australia, Belgium, Canada, Germany, Indonesia, Japan, Sweden, Taipei, United Kingdom, United States) of the International Society for Twin Studies (ISTS) at the Eighth International Twin Congress, Richmond, Virginia, May 31, 1995 (http://www.ists.qimr.edu.au/Rights.html).

WHEREAS myths and superstitions about the origins of multiples have resulted in the culturally sanctioned banishment and/or infanticide of multiples in some countries:

I. Multiples and their families have a right to full protection, under the law, and freedom from discrimination of any kind.

WHEREAS the conception and care of multiples increase the health and psychosocial risks of their families, and whereas genetic factors, fertility drugs, and *in vitro* fertilization techniques are known to promote multifetal pregnancies:

II. Couples planning their families and/or seeking infertility treatment have a right to information and education about factors which influence the conception of multiples, the associated pregnancy risks and treatments, and facts regarding parenting multiples.

WHEREAS the zygosity of same sex multiples cannot be reliably determined by their appearances; and whereas (1) the heritability of dizygotic (two-egg) twinning increases the rate of conception of multiples; (2) the similar biology and inheritance of monozygotic (one-egg) multiples profoundly affect similarities in their development; (3) monozygotic multiples are blood and organ donors of choice for their co-multiples; and (4) the availability of the placenta and optimal conditions for determining zygosity are present at birth:

III.

A. Parents have a right to expect accurate recording of placentation and the diagnosis of the zygosity of same sex multiples at birth.
B. Older, same sex multiples of undetermined zygosity have a right to testing to ascertain their zygosity.

WHEREAS during World War II twins were incarcerated in Nazi concentration camps and submitted by force to experiments which caused disease or death:

IV. Any research incorporating multiples must be subordinated to the informed consent of the multiples and/or their parents and must comply with international codes of ethics governing human experimentation.

WHEREAS inadequate documentation, ignorance, and misconceptions regarding multiples and multiple birth increase the risk of misdiagnosis and/or inappropriate treatment of multiples:

V.

A. Multiple births and deaths must be accurately recorded.
B. Parents and multiples have a right to care by professionals who are knowledgeable regarding the management of multiple gestation and/or the lifelong special needs of multiples.

WHEREAS the bond between co-multiples is a vital aspect of their normal development:

VI. Co-multiples have the right to be placed together in foster care, adoptive families, and custody agreements.

### Statement of needs

Summary: Twins, and higher-order multiples have unique conception, gestation and birth processes; health risks; impacts on the family system; developmental environments; and individuation

processes. Therefore, in order to insure their optimal development, multiples and their families need access to health care, social services, and education which respect and address their differences from single-born children.

WHEREAS twins and higher-order multiple births are at high risk of low birth weight (< 2500 grams), and very low birth weight (< 1500 grams), disability, and infant death:

I. Women who are expecting multiples have a need for:

   A. Education regarding the prevention and symptoms of preterm labor;
   B. Prenatal resources and care designed to avert the preterm birth of multiples, including:

      1. Diagnosis of a multiple pregnancy, ideally by the fifth month, which is communicated tactfully, with respect for the privacy of the parents;
      2. Nutrition counseling and dietary resources to support a weight gain of 18–27 kilos (40–60 pounds);
      3. Obstetric care which follows protocols of best practice for multiple birth; and when the health of the mother or family circumstances warrant:
      4. Extended work leave;
      5. Bed-rest support; and
      6. Child-care for siblings.

WHEREAS breast-feeding provides optimal nutrition and nurture for preterm and full-term multiples; and whereas the process of breast-feeding and/or bottle-feeding of multiples is complex and demanding:

I. Families expecting and rearing multiples need the following:

   A. Education regarding the nutritional, psychologic, and financial benefits of breast-feeding for preterm and full-term infants;
   B. Encouragement and coaching in breast-feeding techniques;
   C. Education and coached practice in simultaneous bottle-feeding of co-multiples; and,
   D. Adequate resources, support systems, and family work leave to facilitate the breast-feeding and/or bottle-feeding process.

WHEREAS 60% of multiples are born before 37 weeks' gestation and/or at low birth weight and experience a high rate of hospitalization which endangers the bonding process and breast-feeding; and whereas newborn multiples are comforted by their fetal position together:

I. Families with medically fragile multiples need specialized education and assistance to promote and encourage bonding and breast-feeding. Hospital placement of medically fragile multiples and hospital protocols should facilitate family access, including co-multiples' access to each other.

WHEREAS multiple-birth infants suffer elevated rates of birth defects and infant death:

II. Families experiencing the disability and/or death of co-multiples need:

   A. Care and counseling by professionals who are sensitive to the dynamics of grief associated with disability and/or death in co-multiples; and
   B. Policies which facilitate appropriate mourning of a deceased multiple or multiples.

WHEREAS the unassisted care of newborn, infant, and toddler multiples elevates their families' risk of illness, substance abuse, child abuse, spouse abuse, divorce, and potential for child abuse:

I. Families caring for multiples need timely access to adequate services and resources in order to:

   A. Insure access to necessary quantities of infant and child clothing and equipment;
   B. Enable adequate parental rest and sleep;
   C. Facilitate healthy nutrition;
   D. Facilitate the care of siblings;
   E. Facilitate child safety;
   F. Facilitate transportation; and
   G. Facilitate pediatric care.

WHEREAS families with multiples have the unique challenge of promoting the healthy individuation process of each co-multiple and of encouraging and supporting a healthy relationship between the co-multiples; and, whereas the circumstance of multiple birth affects developmental patterns:

I. Families expecting and rearing multiples need:

   A. Access to information and guidance in optimal parenting practices regarding the unique developmental aspects of multiple-birth children, including the processes of: socialization, individuation, and language acquisition; and
   B. Access to appropriate testing, evaluation, and schooling for co-multiples with developmental delays and/or behavior problems.

WHEREAS twins and higher-order multiples are the subjects of myths and legends and media exploitation which depict multiples as depersonalized stereotypes:

I. Public education, with emphasis upon the training of professional health and family service providers, and educators, is needed to dispel mythology and disseminate the facts of multiple birth and the developmental processes in twins and higher-order multiples.

WHEREAS twins and higher-order multiples suffer discrimination from public ignorance about their biological makeup and inflexible policies which fail to accommodate their special needs:

II. Twins and higher-order multiples need:

A. Information and education about the biology of twinning; and
B. Health care, education, counseling, and flexible public policies which address their unique developmental norms, individuation processes, and relationship. For example by permitting and/or fostering:

1. The treatment of medically fragile co-multiples in the same hospital;
2. The neonatal placement together of co-multiples in isolettes and cribs to extend the benefits of their fetal position together;
3. Medical, developmental, and educational assessment and treatment which is respectful of the relationship between co-multiples;
4. The annual review of the classroom placement of co-multiples, and facilitation of their co-placement or separate placement according to the particular needs of each set of co-multiples;
5. The simultaneous participation of co-multiples on sports teams and other group activities;
6. Specialized grief counseling for multiples at the death of a co-multiple;
7. Counseling services addressing the special needs of adult multiples.

WHEREAS the participation by multiple-birth infants, children, and adults as research subjects has made important contributions to scientific understanding of the heritability of disease, personality variables, and the relative influence of nature and nurture on human development; and, WHEREAS relatively little is known about optimal management of plural pregnancy and the unique developmental patterns of multiples:

I. Scientists must be encouraged to investigate:

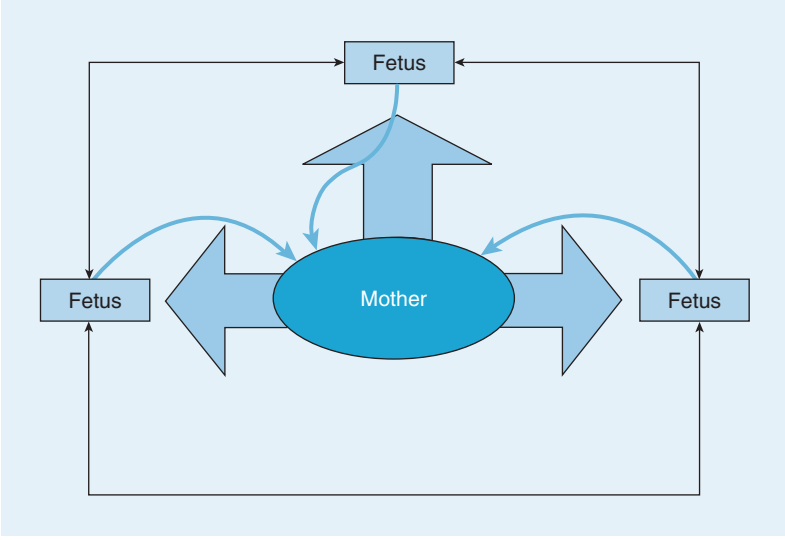
A. The optimal management of plural pregnancies;
B. Norms for developmental processes which are affected by multiple birth such as: individuation, socialization, and language acquisition;
C. Benchmarks of healthy psychological development, and relevant therapeutic interventions for multiples of all ages and at the death of a co-multiple.

# SECTION XI
# ECONOMIC, ETHICAL AND LEGAL CONCERNS

**16-year-old female monozygotic, dichorionic, non-mirror twins, Belgium, 2004.**

Participants since birth in the East Flanders Prospective Twin Study. Twin A left, Twin B right.

Few areas exist in which ethical and medicolegal aspects are so entwined as in Maternal–Fetal Medicine. Whereas in singletons, the maternal–fetal relationship is bidirectional, the situation in multiple pregnancies is multidirectional and far more complex. This complexity is primarily because the special interfetal relationships are superimposed on the double (or triple) relationships that exist between each fetus and the mother (Figure).




This section also discusses the economic aspects of multiple pregnancy. Intuitively, some patients may think that having twins or triplets is kind of a 'bargain', whereby money is saved because, for the same price of infertility treatment and with a somewhat higher cost for pregnancy care, she gets two or three babies instead of one. The fact is that the risk of preterm birth, with a prolonged stay in the NICU and the potential need to care for handicapped children, much increases the cost of multiples, not only for individual parents but for society as a whole, as the final bill often comes to rest in the public purse. The net result is that it is much more cost-effective to have one child at a time.

*I.B. and L.G.K.*

# Contents of Section XI

# Economic Considerations

*J. E. Hall and T. L. Callahan*

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## INTRODUCTION

During the past three decades, dramatic changes have occurred in the therapeutic methods available for the treatment of infertility, beginning with the use of gonadotropins for induction of ovulation in the 1960s[1] to the current use of these agents in combination with sophisticated *in vitro* techniques[1–3]. It is axiomatic that the treatments for infertility not only have the potential to alleviate this condition, but also carry with them the risk of inducing multiple pregnancies, as is discussed repeatedly in this volume. The importance of providing treatment for infertile patients cannot be underestimated from either a personal or a societal perspective. For reasons that are as yet unclear, infertility is associated with increased medical risks for women. Although it is difficult to quantify the spectrum of the benefits of infertility treatments, it is of increasing importance to understand the costs of the treatment *per se*, as well as the costs associated with side-effects, and to examine the impact of mandated infertility coverage on a variety of outcomes. This chapter reviews available data addressing these issues.

## COST OF OVULATION INDUCTION

Clomiphene citrate (CC) and exogenous gonadotropins are the medications used most commonly for ovulation induction (OI). The cost of CC is low, both because of the cost of the medication itself and because of the almost universally held opinion that intensive monitoring is not necessary owing to the low risk of ovarian hyperstimulation syndrome (OHSS) and/or multiple gestation. Unfortunately, not only are the studies of this drug dated, but the risk of both complications is grossly underestimated.

The cost of exogenous gonadotropin therapy depends on the amount of medication required, the intensity of post-stimulation monitoring and the source of the drug (i.e. urinary or recombinant)[4]. Overall estimates for each cycle of OI range from as low as $US600–700[5,6] to as much as $US5795[6]. In our center, in over 800 cycles of OI with gonadotropin therapy in patients with ovulatory disorders as well as unexplained infertility, the median number of ampules used was 14 during an average 8 days of treatment. With gonadotropin costs ranging from $US35 to $US60 per ampule, medication costs alone are $US500–850. Given the significant risks of OHSS and multiple follicular development with exogenous gonadotropins, intensive ultrasound and estradiol monitoring are necessary, accounting for the remainder of the costs. Capitated health-care plans currently allow up to approximately $US1200 per cycle to cover the clinical monitoring of gonadotropin therapy.

Although pulsatile gonadotropin-releasing hormone (GnRH) is much less popular in the USA, this form of therapy is widely used in Europe. Pulsatile GnRH is the treatment of choice in patients with various ovulatory disorders. Treatment cycles are considerably less expensive than gonadotropin cycles, largely because on-line estradiol measurements are not required and fewer ultrasound scans are required.

## COST OF ASSISTED REPRODUCTIVE TECHNOLOGIES

In 1988, the US Office of Technological Assessment estimated that less than 50% of infertile couples were

successful in achieving a live birth with conventional methods of treatment including OI, donor insemination and surgery, and thus were candidates for *in vitro* fertilization (IVF) treatment[7]. Recent reports of the cost of each IVF treatment cycle range between $US6200[8,9] and $US8071[10,11].

Additional useful information can be obtained by attempting to quantify the economic impact of IVF services by estimating the cost per live delivery resulting from IVF. The study of Neumann and colleagues developed cost estimates per successful delivery (defined as at least one live birth) of between $US66 667 and $US80 000, depending on the number of cycles and the likelihood of conceiving under various combinations of clinical conditions[11]. However, more recent data indicate that these costs represent marked overestimates of actual costs. The study of Griffin and Panak determined that the cost of assisted reproductive technologies (ART) per delivery in Massachusetts, a state in which support for infertility services is mandated, ranged between $US47 677 and $US106 667, depending on clinical factors[12]. An additional Massachusetts-based study determined that costs per delivery associated with ART were $US36 417, using data from a single health maintenance organization (HMO)[9]. These results are similar to those of Van Voorhis and colleagues, who analyzed the first 1000 oocyte retrievals in their program in Iowa, and further determined that costs per delivery were reduced by 15% when cryopreserved embryo transfers were included in the analysis[10]. Goldfarb and co-workers included the initial delivery and neonatal hospitalization charges and determined that per-cycle costs for singleton or twin pregnancies were $US39 249, but increased by almost a factor of ten with higher-order multiple pregnancies[13].

The health economics of IVF and intracytoplasmic sperm injection (ICSI) involving cost, cost-effectiveness and ability to pay are different in Europe. In the UK, where there is limited availability of IVF from the National Health Service, the average cost of one private IVF cycle is over £2000 (about $US3700), and often closer to £4000 (about $US7300), but in Hungary and Slovenia the cost could be much lower, as the price of the drugs is cheaper. According to estimates coming from the European Society of Human Reproduction and Embryology (ESHRE), the average cost per IVF–ICSI cycle in 2002 would be $US9547 in the USA, and $US3518 in 25 other countries[14]. The average cost-effectiveness ratios in 2002 would be $US58 394 per live birth in the USA, and $US22 048 in other countries. In three randomized controlled trials, incremental costs per additional live birth with IVF compared with conventional therapy were $US26 586, 79 472 and 47 749[14]. The costs to individual couples range from 10% of annual household expenditures in European countries to 25% in Canada and the USA[14].

## MATERNAL COSTS ASSOCIATED WITH MULTIPLE PREGNANCIES

### Prenatal costs

The increased incidence of maternal complications associated with multiple gestation is well documented (see Section IV). The economic impact of multiple pregnancies, prior to delivery, includes the cost of treating complications and the cost of preventing complications. Increased in-patient and out-patient costs, with the use of additional laboratory services and procedures, all increase the economic impact. Preventive strategies include earlier and more frequent monitoring, home bed-rest, cervical cerclage, tocolytic therapy and home uterine activity monitoring. Although these modalities have been used with varied degrees of success, they contribute significantly to the prenatal cost of multiple pregnancies, just as do increased in-patient costs and additional procedures should complications occur. Finally, the potential for loss of wages and/or the requirement for increased support in the home must be factored into overall economic assessments.

In a study of 20 triplet pregnancies between 1992 and 1993, the average gestational age was 30.7 weeks, and the average birth weight of the surviving fetuses was 1764 g[15]. Nine of the women had antepartum admissions separate from the delivery admission, and five had more than one. Total prenatal maternal costs were determined for 16 patients who received their care at a single institution, and were $US13 110 per mother with $US5227 for prenatal professional fees, $US4256 for in-patient charges and $US3577 for laboratory and imaging studies. Unfortunately, this study provides no comparative data for singleton pregnancies[15].

### Delivery charges

We previously reported that multiple pregnancies result in increased hospital delivery charges per mother, per neonate and per family unit[16]. The medical and billing record of 13 206 pregnant women admitted to the Brigham and Women's Hospital between 1986 and 1991 were examined, and results were compared for mothers of singletons ($n = 11\,986$), mothers of twins ($n = 1135$) and mothers of higher-order multiples ($n = 244$). In-patient hospital charges were analyzed from the date of admission for delivery until discharge. Hospital charges included nursing care, room and board charges,

ancillary services including respiratory, laboratory and radiology, supplies, pharmaceuticals and charges for operative delivery. Data did not include charges for ART services, physicians' charges or prior hospital admissions.

When controlled for variables known to affect hospital charges including age, race, ethnicity, type of insurance and year of admission, the average length of stay for a singleton mother was 4.0 days, compared with 6.8 days for twin mothers and 14.1 days for higher-order multiple mothers. Average total maternal hospital charges were $US4838 for singleton mothers, compared with $US7991 for twin mothers and $US15 379 for mothers of higher-order multiples (Figure 107.1)[16]. It is likely that the increased incidence of cesarean section in mothers of twins and higher-order multiples (67% and 93%, respectively), compared with singletons (24%), contributed significantly to the difference in length of stay and total maternal in-patient charges.

## NEONATAL AND TOTAL FAMILY COSTS OF MULTIPLE PREGNANCIES

Although multiples constitute a relatively small percentage of births nationwide, they are disproportionately represented among low-birth-weight (LBW) and very-LBW infants and among infants requiring intensive care (see Chapter 90). The decrease in the median birth weight and gestational age for surviving twins in the past 40 years[17] is a testament to the impact of advances in neonatal intensive care. In 1987, a study of neonatal intensive-care unit (NICU) charges among 48 000 newborns in Maryland revealed that premature neonates constituted 5% of neonatal discharges, but generated 36% of all neonatal hospital charges[18]. In our more recent study of singleton, twin and higher-order multiple pregnancies, we showed that the average length of stay for twins was 8.2 days compared with 10.0 days for higher-order multiples and 4.6 days for singletons[19]. Average charges for each neonate in our study were $US5007 for singletons compared with $US14 978 for twin births and $US31 462 for higher-order multiples (Figure 107.1). These data represent extremely conservative estimates of total cost, as we also showed that 24% of twins and 60% of higher-order multiple neonates were transferred to step-down or community nurseries, compared with 6% of singletons[19], and data following transfer were not included in our analysis. Much of the increase in hospital costs for multiple gestation neonates relates to the need for NICU services. In our initial study, we found that only 15% of singletons required NICU admission, whereas more than 48% of twins and 78% of higher-order multiples required at least 1 day in the NICU[16]. These results are supported by those of Keith and colleagues, who used US vital statistics to investigate the costs of preterm delivery and NICU use[20–22]. Once admitted to the NICU, our studies indicate that multiple neonates use the same resources as singletons, when adjusted for birth weight and gestational age[19]. Taken together, these studies suggest that if prematurity and/or low birth weight could be avoided, so would many of the costs associated with the sequelae of multiple pregnancy[19,23].

### Total family charges

Because multiple gestation impacts on maternal as well as neonatal health, the most meaningful examination of charges should consider total family charges[16]. After controlling for variables that might independently affect charges at the Massachusetts General Hospital, the average total charge per family unit in 1991 was $US9845 for a mother and her singleton child, compared with $US37 945 for a mother and her twin children and $US109 765 for a mother and her triplet children (Figure 107.1). It was previously believed that multiple gestation would be less expensive than having two or three successive singleton deliveries. Expressing these data in relation to each baby born shows clearly that a twin delivery doubles the charges per baby, whereas delivery of triplets increases the charges for each baby born four-fold.

A recent study from The Netherlands intended to determine the difference in medical costs per singleton and twin pregnancies after IVF treatment from pregnancy to 6 weeks after delivery[24]. This study confirmed that maternal and neonatal hospital admissions were the major cost drivers. The medical cost per twin pregnancy was found to be more than five times higher than per singleton pregnancy. The authors concluded that a reduction in the number of twin pregnancies by elective single embryo transfer (SET) will save substantial amounts of money, which may be used for the additional IVF cycles that will probably be needed to achieve similar success rates between single- and two-embryo transfer[24].

### Contribution of birth weight and gestational age to increased in-patient costs for multiples

Results of our initial study indicated that maternal and neonatal charges contribute equally to total family charges for singletons, whereas neonatal charges contribute disproportionately to total family charges for twin and higher-order multiple gestations (78% and 86%, respectively) (Figure 107.1)[16]. We hypothesized that both birth weight and gestational age are potentially independent mediators of

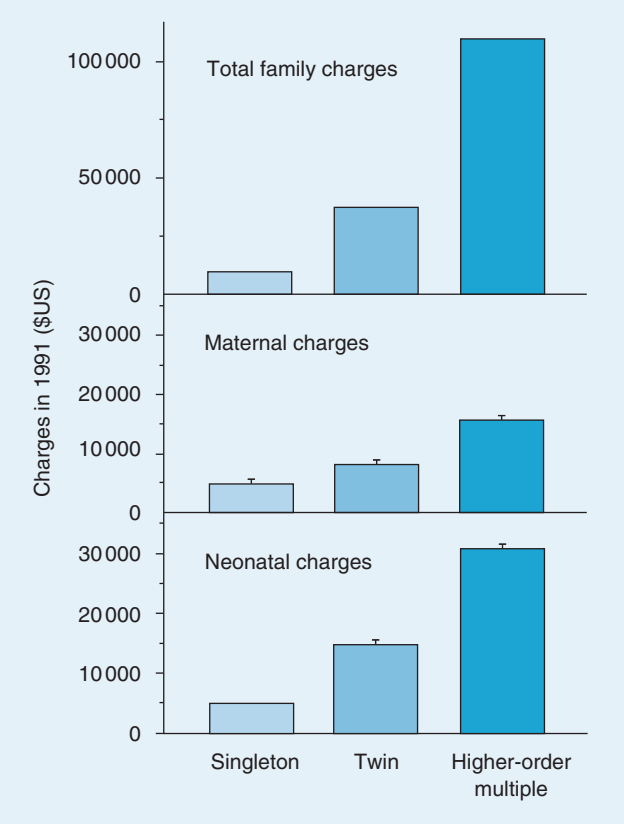


**Figure 107.1** Hospital charges for singleton, twin and higher-order multiple-gestation pregnancies. Total family charges include all neonatal and maternal charges resulting from a single delivery; maternal charges are expressed per delivery; and neonatal charges are expressed per baby. Standard errors are shown for the maternal and neonatal charges. From reference 16, with permission

the effect of multiple gestation on economic outcomes. In addition, we hypothesized that there are additional effects of multiple gestation not mediated through birth weight or gestational age, and constructed a model which took into account all three possibilities. This model was used to analyze the detailed data on neonatal hospital charges derived from our initial study of singleton and multiple gestation outcomes[19]. Our results indicate that, after controlling for other relevant demographic and socioeconomic characteristics, gestational age accounts for 50% of the increase in total charges due to multiple gestation, birth weight accounts for 40% and neither gestational age nor birth weight account for the remaining 10% (Figure 107.2). This 'direct' effect of multiple gestation is due primarily to longer hospital stays among twins and higher daily charges among higher-order multiples. Our study suggests that strategies designed to increase gestational age will have the most dramatic effects on health-care costs. However, even strategies that increase birth

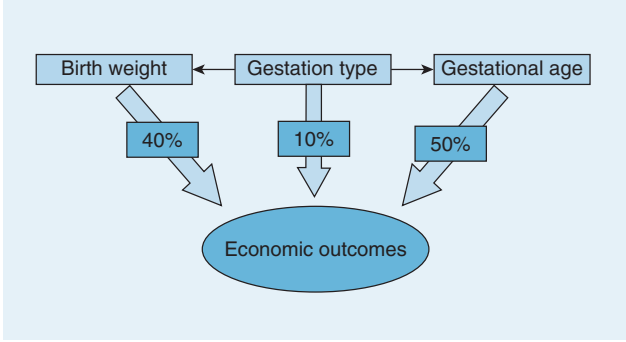


**Figure 107.2** Effect of gestation type on economic outcome is largely mediated through decreased gestational age and decreased birth weight with a minor effect, which cannot be accounted for by either of these factors. Adapted from reference 19, with permission

weight without increasing gestational age, as shown in some reports of bed-rest (see Chapter 74), may have substantial benefit. According to Ettner and colleagues, delaying birth by an extra week would be expected to reduce neonatal charges by $US699 per infant, and increasing birth weight by 500 g would reduce charges by $US900 per infant[19].

## CHILDHOOD COSTS OF MULTIPLE PREGNANCIES

### Medical costs following hospital discharge

After discharge from the NICU, premature and LBW infants continue to experience high rates of morbidity. Such infants are more likely to require more intensive out-patient services and recurrent hospitalizations and are at risk for long-term handicap and disabilities (see Chapter 97). Admittedly, these costs have not been well quantified, but they include the potential need for surgery, specialized health-care providers, surveillance for sight and hearing abnormalities, and physical therapies and treatments related to developmental delay, learning difficulties, decreased motor skills and speech and language difficulties (see Chapter 95). Monthly costs for very-LBW infants are estimated to be 3–60 times those of the average child during the first 3 years of life[25]. Moreover, studies have indicated that direct medical costs in the first year of life average $US10 139 for very-LBW infants, compared with $US179 for control term infants[26]. This assessment does not include expenditures associated with transportation and child care. Interestingly, in this study, the differential was greatest in the first two quarters and virtually disappeared thereafter[26]. Despite the fact that data from these studies apply specifically to very-LBW infants, the implications for all multiple gestation infants are abundantly clear.

### Costs associated with neonatal disabilities and handicaps

Dramatic improvements in neonatal intensive care allow survival of infants of very low birth weight and gestational age who previously would not have lived. Unfortunately, many of these survivors are affected by physical and neurologic handicaps (see Chapter 97). The projected costs of medical care, rehabilitation and special education during the lifetime of a child with cerebral palsy are estimated at $US445 000 per child[27], while those for the care of a severely handicapped child and adult are as high as $US1 million per individual[28].

These cost estimates reinforce the impression that the economic implications of multiple gestation are profound, but do not address potential social implications of severe developmental problems associated with prematurity and very LBW, both of which are over-represented in multiple pregnancies.

## THE MANAGED-CARE ENVIRONMENT

### Insurance coverage for infertility treatment

Insurance coverage for fertility services is available in only 13 states in the USA. Even in those in which it is available, coverage is often limited. Several studies address the cost of providing insurance coverage for infertility services within group insurance plans. In 1982, before the widespread use of ART and the enactment of state mandates to regulate access to ART with health-care plans, it was estimated that expenditure for infertility services was about $US3.29 for each woman aged between 15 and 44 years, and accounted for 1% of reproduction-related health-care expenses in that year[29]. More recent analysis by Collins and associates, based on nationwide utilization of IVF in the USA, indicates that the cost of providing insurance coverage for IVF services would be $US2.79 per annum, i.e. $US0.23 per month, less than 0.1% of the total health-care premium in the typical family health-care benefits plan[8].

Data from eight HMO plans in Massachusetts and the Blue Cross/Blue Shield indemnity plan show that, in 1993, infertility services accounted for 0.41% of total expenditures or approximately $US1.71 per contract-month[8,12]. In a relatively small study[9], which included various ART, the HMO cost for these procedures was $US2.49 per member per annum. These authors found the ART costs per member per annum to be similar to HMO costs for nutrition and podiatry, approximately one-third of that for organ transplants, 14% of that for physical therapy and 5% of HMO costs for mental health. Importantly, they also found that the cost per member per annum was increased by 27% if higher-order multiples resulted from the ART.

### Impact of insurance coverage on utilization of services and multiple gestation

It is commonly presumed that increased access to infertility treatment automatically results in an increase in the use of these services (see Chapter 19). Data from the World Health Organization suggest that IVF utilization increases when these services are added to health benefits plans[30]. In their examination of the effect of the Massachusetts infertility insurance mandate, Griffin and Panak noted an increased utilization of IVF procedures in Massachusetts compared with the rest of the USA and Canada, and a similar utilization to that eported in France[12]. These authors suggested that the ability to contain costs despite increased utilization was probably due to the use of low-cost conventional intervention for the majority of infertile couples, the improving success rates associated with ART and the adoption of provider arrangements and capitation plans within HMO groups. The authors cautioned against the likelihood that more embryos would be transferred per cycle as a way of increasing success rates for couples unable to afford repeated ART attempts[12].

Preliminary data from Frankfurter and colleagues provide support to this latter contention[31]. The result of their study indicated that, in states with mandated infertility and IVF coverage, a decrease in the mean number of embryos transferred is associated with a significant decrease in the rate of multiple births per cycle. A recent study used 1998 data reported to the Centers for Disease Control and Prevention by 360 fertility clinics in the United States to determine utilization and outcomes of IVF services according to the status of insurance coverage[32]. Clinics in states that required complete coverage performed more IVF cycles than clinics in states that required partial or no coverage. The percentage of cycles that resulted in live births was higher in states that did not require any coverage than in states that required partial or complete coverage, but the percentage of pregnancies with higher-order multiples was also higher. The number of fresh embryos transferred per cycle was lower in states that required complete coverage than in states that required partial or no coverage. The authors concluded that state-mandated insurance coverage for IVF services is associated with increased utilization of these services but with decreases in the number of embryos transferred per cycle, the percentage of cycles resulting in pregnancy and the percentage of pregnancies with three or more fetuses[32]. Even more recently, Reynolds and

colleagues used a population-based sample of IVF procedures performed in three states with mandated insurance coverage compared with three states without coverage[33]. They concluded that insurance appears to affect embryo transfer practices, but the effect on multiple birth risk was less clear, as the insurance states all had protective odds ratios for higher-order multiple births, but only the odds ratio for Massachusetts was significant.

[Editorial note: This chapter has been updated and adapted from Hall JE, Callahan TL. Economic considerations. In Blickstein I, Keith LG, eds. *Iatrogenic Multiple Pregnancy: Clinical Implications*. London: Parthenon Publishing, 2001:185–96.]

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# Ethical Issues in Multiple Pregnancy

*F. A. Chervenak and L. B. McCullough*

**108**



## INTRODUCTION

In this chapter we provide a clinically applicable account of current ethical issues in the management of multiple pregnancy. We start with an introduction to clinical ethics and its two fundamental principles, beneficence and respect for autonomy. On the basis of these ethical principles we then explicate the important concept of the fetus as a patient. We present and justify three indications for fetal reduction and selective termination of multiple pregnancy based on this central concept of obstetric ethics. We then present a preventive ethics approach to avoiding unwanted multiple pregnancy. We conclude with a discussion of the management of premature delivery of multiple pregnancies.

## CLINICAL ETHICS

The basic reference point for clinical ethics in the global history of medical ethics has been the physician's obligation to protect and promote the health-related interests of the patient. This ethical obligation is quite general, however, and needs to be made specific so that it becomes more clinically applicable. To accomplish this task, we interpret it in terms of two perspectives relating directly to the patient's interests, that of the physician and that of the patient[1].

The ethical principle of beneficence translates medicine's perspective on the interests of the patient into clinical practice. This ethical principle obligates the obstetrician, as it does all physicians, to seek the greater balance of clinical benefit over clinical harm or risk for the patient as a consequence of the physician's behaviors. On the basis of rigorous clinical judgement, informed by current standards of evidence-based medicine and a commitment to excellence in clinical practice, the obstetrician should identify those clinical strategies that are expected to result in the greater balance of benefits, i.e. the protection and promotion of health-related interests, over harms, i.e. impairments of those interests. The principle of beneficence has an ancient pedigree in global medical ethics. In the West, these roots go back to the time of Hippocrates[2]. Specifically, the Hippocratic oath enjoins physicians to act in a manner that will 'benefit the sick according to my ability and judgement'[3].

In obstetrics, the principle of beneficence should be distinguished from the principle of nonmaleficence, also known as *Primum non nocere* or 'First, do no harm'. It is interesting to note that *Primum non nocere* appears neither in the Hippocratic oath nor in the texts that accompany the oath. Rather, the principle of beneficence was the primary consideration of the Hippocratic writers, as is clear from the language of the oath, just quoted. In addition, another Hippocratic text, *Epidemics*, reads: 'As to diseases, make a habit of two things – to help or to at least do no harm'[4]. Although the historical origins of *Primum non nocere* may be in the far distant past, our point is not just historical, but conceptual and clinical as well. If *Primum non nocere* were to be made the primary principle of obstetrics, virtually all invasive aspects of obstetrics would be unethical.

A rigorous clinical perspective on the interests of the patient is but one possible legitimate perspective on those interests. The patient's perspective on her own interests must also be considered by the physician[1], because, before encountering the physician, the patient has developed a set of values and

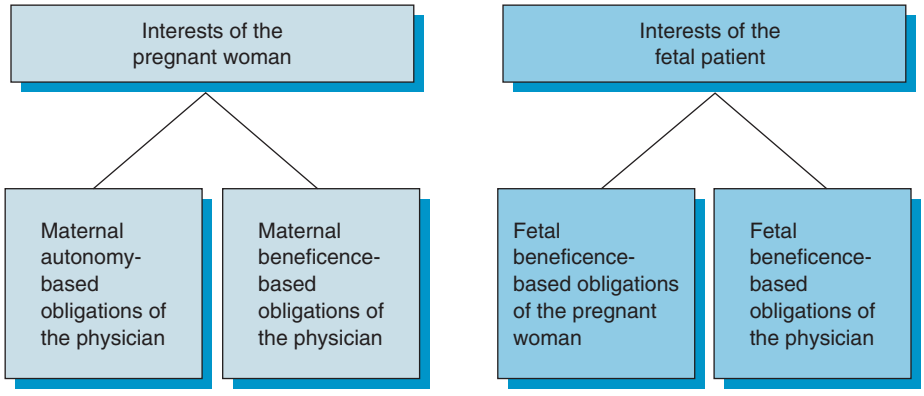


**Figure 108.1** The fetus as a patient

beliefs according to which she is capable of making judgements about what will and will not protect and promote her health-related and other interests. It should be assumed that the adult pregnant woman is competent to determine which clinical strategies are consistent with her interests and which are not. In making such judgements, values and beliefs may be utilized that go far beyond health-related interests, e.g. religious beliefs or beliefs about how many children she wants to have. Both are relevant to initiating and managing pregnancy, especially multiple pregnancy. Beneficence-based clinical judgement is limited by the competencies of medicine, and therefore gives the physician no intellectual or moral authority to assess the worth or meaning to the patient of the patient's non-health-related interests; these are matters solely for the patient to determine for herself, drawing on whatever sources of meaning and instruction she deems relevant and useful.

The patient's perspective is translated into clinical practice by the ethical principle of respect for autonomy[2]. This principle obligates the physician to respect the integrity of the patient's values and beliefs, to respect her perspective on her interests and to implement only those clinical strategies authorized by her as the result of the informed consent process. The informed process is usually understood to have three elements: disclosure by the physician to the patient of an adequate amount of information about the patient's condition and its management at a level the patient can reliably be expected to understand; understanding of that information by the patient; and a voluntary decision by the patient to authorize or refuse clinical management[1,5].

## THE FETUS AS A PATIENT

The obstetrician's perspective on the pregnant woman's health-related interests and the commitment to protect and promote those interests generate beneficence-based obligations (Figure 108.1). The woman's own perspective on her interests and the physician's commitment to respect her values and preferences generate autonomy-based obligations. In contrast, the fetus cannot meaningfully be said to possess values and beliefs because of its insufficiently developed central nervous system. Thus, there is no basis for saying that a fetus has a perspective on its interests. As a result, there can be no autonomy-based obligations to any fetus[1]. The obstetrician has a perspective on the fetus's health-related interests, and therefore can have beneficence-based obligations to the fetus, but only when the fetus is a patient. Because of its importance for the ethics of management of multiple pregnancy and obstetric ethics generally, the concept of the fetus as a patient requires detailed consideration. We explain this concept below in ethical terms that should be acceptable in multicultural contexts.

It is important to recognize that one can become a patient without having rights. A critical advantage of the concept of the fetus as a patient is that the language of fetal rights or personhood has no meaning and, therefore, no application to the fetus in obstetric ethics, despite its popularity in public and political discourse in many countries. Thus, current controversies about 'right to life', which usually end in gridlock, can be avoided in clinical judgement and decision-making.

The authors have argued elsewhere that beneficence-based obligations to the fetus exist when the fetus can later, after birth, become a child and subsequently achieve independent moral status[1]. That is, the fetus is a patient when the fetus is presented to the physician and there exist medical interventions, whether diagnostic or therapeutic, that reliably can be expected to result in a greater balance of good over harm for the fetus in its future as a child. The ethical significance of the concept of the fetus as a patient therefore depends on links to achieving independent moral status in the future.

One such link is viability, introducing the first ethical sense of the fetus as a patient. Viability means that the fetus can exist *ex utero*, albeit with full technological support. Viability is not, however, an exclusively biological property of the fetus, because viability must be understood in terms of both biological and technological factors. It is only in virtue of both factors that a viable fetus can exist *ex utero* and then achieve independent moral status. Moreover, these two factors do not exist as a function of the autonomy of the pregnant woman. In countries with different levels of technological capacity, viability will be a function of access to that technological capacity. When there is access to achieved technology, which is the case in the USA, viability occurs at approximately the end of 24 weeks of gestational age[6,7].

The only possible link between the previable fetus and the child it can become is the pregnant woman's autonomy, introducing the second ethical sense of the fetus as a patient. This is because technological factors cannot result in the previable fetus becoming a child. This is simply what previable means. The link, therefore, between a fetus and the child it can become, when the fetus is previable, can be established only by the pregnant woman's decision to confer the status of being a patient on her previable fetus. This is because the previable fetus has no reliable claim to the status of being a patient independently of the pregnant woman's autonomy, despite the endless disputes about the independent moral status of the fetus. The pregnant woman is therefore free to withhold, confer or, having once conferred, withdraw the moral status of being a patient on or from her previable fetus according to her own values and beliefs. This has direct clinical application to the clinical management of multiple pregnancy, as discussed below. The previable fetus is presented to the physician solely as a function of the pregnant woman's autonomy. In deciding about the moral status of the previable fetus, a pregnant woman is free to draw on whatever sources of meaning and instruction that are acceptable to her.

Because the pregnant woman controls the decision to confer moral status on her previable fetus, respect for autonomy means that the physician should not judge the reasons a woman has for aborting a previable pregnancy, including a multiple pregnancy. Respect for autonomy also means that the physician should be alert to coercive influences on her decisions about the clinical management of a multiple pregnancy, such as might derive from her husband or potential grandparents, and should advocate for her preferences to protect her from such coercion[1].

Before viability, the management of a multiple pregnancy complicated by fetal anomalies is ethically straightforward. The pregnant woman is free to withhold or withdraw the moral status of being a patient from any previable fetus, including the fetus with anomalies. For this reason, when an anomaly is detected in a previable fetus, counselling by the physician should be rigorously non-directive out of respect for the pregnant woman's autonomy. The woman should therefore be given the choice between selective termination and continuing her pregnancy to viability and thus to term, regardless of the physician's personal views about rearing a child with such an anomaly, or about abortion. If the woman elects selective termination of an affected fetus in a multiple pregnancy, the procedure should be performed or an appropriate referral made, as a matter of professional obligation. If the woman elects to continue her pregnancy, she should be apprised about decisions that will need to be made later, so that she can begin to plan the rearing of her child[1].

After viability, aggressive obstetric management is the ethical standard of care. By aggressive obstetric management, we mean optimizing perinatal outcome by utilizing effective antepartum and intrapartum diagnostic and therapeutic modalities. A subset of such aggressive management is fetal surgery. Most of this is experimental and should be governed by applicable human-subjects-research law and regulation. Such research can only be offered, not recommended, to patients[1,8].

One important exception to aggressive obstetric management is termination of pregnancy after fetal viability. This exception applies when there is certainty of diagnosis, and either certainty of death as an outcome of the anomaly diagnosed or, in some cases of short-term survival, certainty of the absence of cognitive developmental capacity as an outcome of the anomaly diagnosed[9–11]. When these criteria are satisfied, recommending a choice between non-aggressive management and feticide of the affected fetus is justified, provided there is a careful discussion of the risks. Anencephaly is a classic example of a fetal anomaly that satisfies these criteria[9].

A second exception to aggressive obstetric management is non-aggressive obstetric management. This exception applies when there is a very high probability but sometimes less than complete certainty about the diagnosis, and either a very high probability of death as an outcome of the anomaly diagnosed, or survival with a very high probability of severe and irreversible deficits of cognitive developmental capacity as a result of the anomaly diagnosed[1,12]. When these two criteria apply, a choice between aggressive or non-aggressive management should be offered, including when the fetus is in distress intrapartum. Encephalocele is a classic example of a fetal anomaly that satisfies these criteria.

Any directive counselling for fetal benefit should occur only after balancing beneficence-based obligations to the fetal patient against beneficence-based and autonomy-based obligations to the pregnant woman[1]. It cannot be overemphasized that any such balancing needs to recognize that a pregnant woman is obligated to take only reasonable risks of obstetric interventions that are reliably expected to benefit the viable fetus or child later. These include alternatives for the clinical management of multiple pregnancy.

Obviously, any strategy for directive counselling for fetal benefit that takes account of autonomy-based obligations to the pregnant woman is open to the possibility of conflict between the physician's recommendation and a pregnant woman's autonomous decision to the contrary. Such conflict is best managed preventively through informed consent as an ongoing dialog throughout the pregnancy, augmented as necessary by negotiation and respectful persuasion[1,13]. This is an unappreciated aspect of the informed consent process.

A subset of the previable fetus as a patient concerns the *in vitro* embryo. In terms of beneficence, whether the fetus is a patient depends on links that can be established between the fetus and its later achieving independent moral status. Consequently, the reasonableness of medical interventions on the *in vitro* embryo depends on whether that embryo later becomes viable. Otherwise, no benefit of such intervention can meaningfully be said to result. An *in vitro* embryo becomes viable only when it later survives *in vitro* cell division, transfer, implantation and subsequent gestation to such a time that it becomes viable. This process of achieving viability occurs only *in vivo,* and is therefore entirely dependent on the woman's decision regarding the status of the fetus(es) as a patient, should assisted conception result successfully in the gestation of the previable fetus(es). Whether an *in vitro* embryo will become a viable fetus and whether medical intervention on such an embryo will benefit the fetus clinically are both functions of the pregnant woman's autonomous decision to withhold, confer or, having once conferred, withdraw the moral status of being a patient on or from the previable fetus(es) that might result from assisted conception. It is therefore appropriate to regard the *in vitro* embryo as a previable fetus rather than as a viable fetus. As a consequence, any *in vitro* embryo(s) should be regarded as a patient only when the woman into whose reproductive tract the embryo(s) will be transferred confers that status.

## PREVENTIVE ETHICS APPROACH TO AVOIDING MULTIPLE PREGNANCY

This chapter starts with an emphasis on preventive ethics, the use of ethical reasoning and decision-making in the informed consent process to prevent ethical conflicts between the pregnant woman and her obstetrician. Multiple pregnancy can be prevented by transferring no more pre-embryos than supported by current evidence regarding the minimum number needed to achieve live birth[14].

In addition to this beneficence-based consideration, there is an important autonomy-based issue: whether the woman wants to avoid having to consider or elect fetal reduction after successful embryo transfer. In such cases, she should be offered transfer of only one or two pre-embryos. If she elects this option, she should be provided with evidence-based information about the possible effect on live birth specific to her clinical situation[14].

The preventive ethics approach to the use of superovulatory drugs, which can result in iatrogenic multiple pregnancies, is to satisfy fully the requirements of the informed consent process. The woman should be informed about the occurrence rate of iatrogenic multifetal pregnancies and about selective termination versus non-intervention to manage such pregnancies when they occur. In this manner, the woman is alerted to the possibility of having to confront a decision about fetal reduction, a decision some women will want to avoid. This approach also has the advantage of preventing the surprise diagnosis of iatrogenic multiples later.

## THREE INDICATIONS FOR FETAL REDUCTION AND SELECTIVE TERMINATION OF MULTIPLE PREGNANCIES

Fetal reduction and selective termination are now a recognized ethical dimension of the clinical management of multiple pregnancies[15–19]. We turn now to the ethical justification of three clinical indications for reduction or selective termination of multiple pregnancies. These indications are related to three possible goals for a multiple pregnancy: achieving a pregnancy that results in a live birth with one or more infants with minimal neonatal morbidity and mortality; achieving a pregnancy that results in a live birth of one or more infants without anomalies detected antenatally; and achieving a pregnancy that results in a singleton live birth.

We base this ethical justification on the ethical principles of beneficence and respect for the autonomy of the pregnant woman and on the concept of the fetus as a patient as explained above. In obstetrics, beneficence applies to the pregnant woman who is always a patient, and to the fetus when it is a patient. According to this approach to obstetric ethics, the fetus is a patient only in pregnancies being taken to term. The moral status of the previable fetus as a patient depends upon the pregnant woman's decision to confer such status. Thus, the previable fetus has no independent moral status or rights.

### First indication: achieving a pregnancy that results in live birth of infant(s) with minimal neonatal morbidity and mortality

In cases of wanted pregnancies being taken to term, the goal of obstetric management is delivery of an infant with minimal neonatal morbidity and mortality. In triplet pregnancies, while this goal is more than remotely possible, there are nonetheless significant increased risks of fetal morbidity and mortality. In multiple pregnancies of high order (four or more), this goal is only remotely possible, or even impossible, to achieve, depending on the number of fetuses. Fetal reduction either makes it possible to achieve, or increases the likelihood of achieving, the goal of live birth of infant(s) with minimal neonatal morbidity and mortality[20]. The first indication applies to cases in which the woman's goal is to maximize the probability of live birth. In current clinical judgement, this is best achieved by having two fetuses remain after the procedure has been performed.

At first it may appear that this first indication for fetal reduction is ethically unjustified because it violates beneficence-based obligations to the fetus as patient. However, on closer examination this is not the case, because the moral status of being a patient is conferred on the previable fetus only as a function of the pregnant woman's decision to do so, as explained above. The clinical reality is that, for pregnancies in this category, the pregnant woman's decision to confer such status on all of the fetuses will jeopardize all of the fetuses. For some of the fetuses to become patients, the moral status of being a patient must be withheld from others. Thus, fetal reduction does not involve the killing of patients, and is therefore ethically justified in obstetric and medical ethics.

A related and important justification for fetal reduction in this category has been offered in the pioneering articles by Evans and colleagues[21,22]. These authors apply the ethical principle of proportionality of benefits and risks, an application of the ethical principle of beneficence: 'Proportionality is the source of the duty, when taking actions involving risks of harm, to balance risks and benefits so that actions have the greatest chance to cause the least harm and the most benefit to persons directly involved'[21]. They conclude that fetal reduction of multifetal pregnancy is permissible in the clinical ethics of obstetric practice.

### Second indication: achieving a pregnancy that results in live birth of infant(s) without antenatally detected anomalies

In these cases the goal of obstetric care differs from that of the first indication: live birth(s) without antenatally detectable fetal anomalies. Given the widespread use of antenatal diagnosis and legal access to abortion in developed countries, this is already an accepted practice. The ethical challenge in this category is the possibility of increased morbidity and mortality to the remaining fetus(es).

When a woman elects selective termination of a fetus with a detected anomaly, she, in effect, withholds from that fetus the moral status of being a patient, and thus cannot reasonably be thought to be violating, in any way, beneficence-based obligations to that fetus. Presumably the remaining fetus(es) will be taken to term and thus have conferred on it (them), by the pregnant woman's decision to do so, the moral status of being a patient. The possible risks of increased morbidity and mortality for the remaining fetuses must be evaluated in the particular context of whether the anomaly is of such severity to justify possible compromise of the beneficence-based obligations to the remaining fetus(es). At present, risks of the selective termination procedure to the survivor fetus(es) are so infrequent that one cannot justify overriding beneficence-based obligations to the remaining fetuses not to perform the procedure[23].

### Third indication: achieving a pregnancy that results in a singleton live birth

These cases do not involve fetal reduction as a means of having a successful pregnancy, as was not done for the first indication. Nor do they involve selective termination after the antenatal diagnosis of fetal anomalies, as was done for the second indication. Rather, they involve the pregnant woman's decision to have a single child rather than more than one child from her current pregnancy.

The woman's decision to reduce her multiple pregnancy to a singleton pregnancy withholds the moral status of being a patient from one or more of the fetuses. This is clearly something she is free to do as a matter of exercising her autonomy to set her own goals for her pregnancy. The pregnant woman also confers the status of being a patient on the fetus that survives reduction to the singleton she intends to take to term. As a consequence, there are beneficence-based obligations on her part and her physician's part to the singleton fetus to avoid significant harm that might result from the reduction. Clinical experience at this time does not support the likelihood that harm will occur with high probability[16]. In the case of fetal reduction of twins to a singleton, a randomized clinical trial would be necessary to assess clearly whether the survivor would fare slightly better or slightly worse than twins without intervention. Given that the alternative to reduction of twin gestation is often complete termination, any minor risk

of harm of the procedure becomes moot under beneficence-based judgement when balanced against 100% mortality. Therefore, there are no beneficence-based obligations to the surviving singleton fetus not to terminate a multiple pregnancy to a singleton when the woman elects this option after a thorough informed consent process that reviews these matters.

### Individual conscience and fetal reduction and selective termination of multiple pregnancies

The basic clinical strategy for implementing the ethical justification of multiple pregnancies is the informed consent process. As the outcome of this process, the pregnant woman may make a decision that the physician cannot accept as a matter of individual conscience, distinct and apart from professional conscience[1]. The consciences of many physicians have been formed by the moral teachings of the various religions of the world. There will also be a spectrum among physicians of the acceptability of fetal reduction or selective termination, and wider variation in the acceptability of these procedures depending on the original number of fetuses, the number resulting from the procedure and the presence of anomalies.

It is a standard principle of medical ethics that the exercise of autonomy by a patient cannot justifiably oblige a physician to act in a way that is unacceptable as a matter of individual conscience, with the exception of grave emergencies when no other physician can take over the patient's care rapidly[1]. This exception does not apply to the reduction or selective termination of multiple pregnancies, because this is an elective procedure. It follows, therefore, that a physician legitimately exercises his or her own autonomy when it is found that this sort of moral incompatibility exists between himself/herself and his/her patient.

The response to such a situation should be for the physician to explain why the incompatibility exists, and to emphasize to the patient that she is not acting in a morally unjustified manner. That is, respect for the integrity of the patient's values and beliefs requires the physician to be non-judgemental about them in the informed consent process. One should also seriously consider making a referral to an appropriately trained and experienced colleague for whom such an incompatibility may not exist, so that the woman's autonomous decision can be effectively implemented.

## CLINICAL MANAGEMENT OF PREMATURE DELIVERY OF MULTIPLE PREGNANCIES

Preventive ethics is especially relevant to the management of premature delivery of multiple pregnancies. Every woman who intends to take her pregnancy to term should be informed that premature labor can occur. The increased occurrence of prematurity must therefore be explained and, indeed, emphasized to all women who experience multiple pregnancy. The information to be provided should reflect the obstetrician's obligations to the fetus and the pregnant woman when premature delivery occurs.

In the setting of premature labor, tocolytic therapy should be recommended if it is clinically indicated. If tocolysis fails and the fetuses are previable, then there is no obligation to attempt resuscitation of the delivered fetuses, because there do not exist interventions that are reliably expected to benefit the fetuses clinically. This is just what previable means. If tocolysis fails and the fetuses are viable, i.e. fetal patients, resuscitation and subsequent neonatal critical care are obligatory, and should be initiated in the absence of lethal anomalies. The involvement of a neonatologist in the decision-making process about the management of premature delivery of viable fetuses would enhance that process, and also help prepare the woman for the resuscitation of her infants and their rapid transfer to the neonatal intensive-care unit.

## CONCLUSION

The authors provide a preventive ethics approach to the management of multiple pregnancy, an ethical justification for three indications for fetal reduction and selective termination of multiple pregnancies and a preventive ethics approach to the management of prematurity. Because medical procedures are typically evaluated in terms of their reduction of the risks of morbidity and mortality, their indications tend to be mainly justified in terms of the ethical principle of beneficence. The distinctive feature of the indications identified in this chapter is that, whereas their justification takes beneficence-based considerations into account, ultimately that justification is based upon the ethical principle of respect for the autonomy of the pregnant woman. The indications for fetal reduction and selective termination discussed in this chapter expand the concept of 'medical indications' to include those that are based ultimately on respect for autonomy.

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## COMMENT

### Some examples where ethical issues may influence clinical management

The fate of surplus embryos in an IVF cycle
The number of embryo transfers in an IVF cycle
Reduction of high-order gestation to twins
Selective termination of an anomalous fetus in a multiple gestation
Reduction of a twin gestation to a singleton
Management of discordant fetal conditions remote from term
Sacrificing a twin during the separation of a conjoined set

### Glossary of ethical terms

| | |
|---|---|
| *Respect for autonomy* | An ethical principle that obligates the physician to seek a greater balance of good over harm as defined from the patient's perspective |
| *Beneficence* | An ethical principle that obligates the physician to seek a greater balance of clinical good over clinical harm in patient care |
| *The fetus as a patient* | The viable fetus is a patient; the previable fetus is a patient as a function of the woman's autonomy; in all cases, obligations to the fetal patient should be balanced against obligations to the pregnant woman |
| *The informed consent process* | This process has three components:<br>(1) providing the patient with an adequate amount of information about her condition or disease and the medically reasonable alternatives for managing them<br>(2) the understanding of this information by the patient<br>(3) a voluntary decision by the patient |
| *Preventive ethics* | This involves practices and policies that anticipate the potential for ethical conflicts and seek to prevent them |
| *Primum non nocere ('First, do no harm')* | This defines a limiting condition on the principle of beneficence: when the limits of medicine to alter disease processes are reached, the physician should avoid unnecessarily harming the patient |

# Ethical Issues: a Non-essentialist Point of View

*Y. M. Barilan*



## INTRODUCTION

Pregnancy in general and multiple pregnancy in particular raise three basic ethical questions:

(1) What is the moral status of the embryo/fetus?

(2) How do we settle maternal–fetal conflicts?

(3) What is the moral significance of intrauterine life (in contrast to 'ordinary life')?

The lion's share of the literature treats these questions in this order, the moral status of the embryo being the most important. If we hold the embryo to be a human person, the argument goes, it deserves consideration equal to that given to any other person, its embryonic life being merely a contingent epiphenomenon. Despite so many differences among individuals, every person is endowed with human dignity and human rights. Accordingly, his or her interests deserve equal consideration among the interests of all other persons. Some persons are young; others are old. Some depend on life-support; others depend on charity. Some live in houses, others in wombs. All deserve equal respect and equal consideration. This is, for example, the official doctrine of the Catholic Church and some Kantian and neo-Aristotelian ethicists. They all base their ethics of pregnancy on the proposition that the embryo (during most if not all of its intrauterine life) is a human person. Utilitarians and other ethicists establish their ethics on the opposite assertion, namely that the embryo (at least during part of fetal life) is not a human person, and that our duties to embryos are of a different kind and a different degree from our duties to persons. The interests of embryos rank lower than those of persons. Possibly, we do not owe embryos any duties at all.

I will refer to these schools of ethics as *essentialistic*, because their position with regard to the moral status of the embryo shapes their ethics of pregnancy.

On the other hand, *non-essentialism* will be defined as any system of ethics crafted from the answer to the remaining questions. That is, what is the implication on the moral status of the relationships one has with others, and how do the circumstances of existence bear on morality? A non-essentialist ethics of pregnancy might find specific circumstances in which an embryo deserves respect as if it were a human being like you and me, whereas on other occasions it is given little respect. In either instance, the biologic and metaphysical standing of the embryo would be the same, but the moral attention it would receive would differ in accordance with the kind of relationships it has with its mother and its extra- and intrauterine siblings, as well as with the constraints imposed on all parties involved by the unique environment, which is the human womb.

In this chapter I describe the ethics of multiple pregnancy mainly from a non-essentialist point of view.

## FETAL LIFE AS A PARTIALLY INDIVIDUATED LIFE WITHIN A COMPACTED AMBIENCE

From an interpersonal perspective, multiple pregnancy carries with it two fundamental differences compared with ordinary life. These are *non-individuation* and *compactedness*. Since I draw a

conceptual line between fetal life and extrauterine life, the non-essentialist ethics I propose tends to disregard developmental considerations. The ethical conclusions I arrive at apply both to young embryos and to viable fetuses. Therefore, I employ the terms 'embryo' and 'fetus' interchangeably. Despite an obvious wish to write in gender-neutral language, I refer to embryos and children as males in order to avoid confusing mothers with children.

## THE PROBLEM OF MORAL INDIVIDUATION

As McCloskey[1] points out, moral rights are 'rights to', not 'rights against' someone. Thus, a right does not lay a claim on others to yield their vital interests to the holder of that right. Rather, a right protects the vital interests of its bearer *from* the actions (sometimes from the inactions) of a third party. In order to be able to ask the essentialist question: 'What is the moral status of X?', X must be individuated from non-X. If X has no clear boundaries separating it from other persons or claimants to personhood, it makes little sense to talk about its moral rights. We cannot differentiate the protected party from potential violators, the protected rights from encroaching interests. Even if we put aside the language of rights, deliberating the moral status of X means that X deserves moral attention from all *others*. As respect for personal autonomy is a fundamental of ethics, it necessitates a clear distinction between the voice representing the autonomy of a given person, and all other persons and voices that are bound to respect the personal autonomy in question. As 'autonomy' means 'self-governance', the value of respect for autonomy is dependent on separation between the thing governed and the rest of the world.

The right to privacy provides the most illuminating example of the importance of complete and unambiguous individuation. Privacy is the exclusion of others from intimate affairs. Hence, the fence of privacy must be built precisely on the division between the personal and the non-personal. In the absence of unambiguous and complete individuation, the construction of a private sphere and its protection are meaningless, both conceptually and practically.

Conjoined twins are a case in point. Sometimes it seems that they are merely two persons who happen to be joined to each other. Chang and Eng Butler, the Siamese twins (19th century USA), were connected by a narrow band of skin and liver tissue, but otherwise they had separate bodies. They also had distinct personalities. Each married a wife, entertained his own preferences and practiced his own habits. Sometimes the picture is more complicated, as occurs with an anencephalic twin attached to a healthy one, or when two heads share a single heart.

Pregnancy is a similar condition. Although the fetus and the mother are two distinct organisms, they are attached to each other and share almost the same fate. Himma[2] belabors the analogy from conjoined twins to pregnancy. He argues that if they can go on living attached to each other, it is unethical to separate the twins when this results in the death of the weak twin. Following this line of thinking I have argued that if one conjoined twin wishes to have an operation, we will not carry it out *without* the consent of the other twin[3]. If one conjoined twin wishes to consult a certain doctor, whereas the other twin prefers a different physician, neither doctor may treat either of the twins. These simplistic examples illustrate that a single conjoined twin cannot be regarded as a 'patient' in the full sense of the word. From an essentialist point of view, because a conjoined twin may have his own mind, personality and wishes, he may be considered a moral person. But his physical attachment to another person makes him ineligible for being taken as a moral person, as an autonomous agent and having a discrete focus of privacy and well-being.

If the autonomous conduct of one person *typically* encroaches upon or dispossesses the privacy or autonomy of another person, neither may be separately considered a moral person. Lack in individuation not only comes in the way of one conjoined twin becoming a patient of medicine, but it also affects fetuses in a similar manner. In order to treat a fetus as a patient, one must either secure the co-operation of its mother or *coerce* her to comply. Administering a drug to a fetus and operating on it is not like caring for an ordinary patient. Another person, the mother, has to ingest the drug or to take it intravenously. Along the same lines, an operation requires cutting of the body of the mother as well. Using another person is an *inevitable* step in the care of a fetus. Mature twins may disagree with each other, but a mother is the sole voice of her own self and her pregnancy. In many cases of conjoinment we have no compelling reason to prefer one voice or one set of interests to the other. In the case of maternal–fetal conflicts, the mother's voice and interests must have the upper hand, because the mother had been morally individuated before the embryo came into existence. Besides, the fetus derives its life from its mother, from her choice to have it, from her dedication and from her bodily resources and vitality. He owes everything that he has to his mother.

Moreover, whereas conjoined twins are affected merely by insufficient individuation, in the case of pregnancy, not only is the fetus not fully individuated from its mother, but the body of its mother is also the *ambience* in which the fetus exists and the sources of its nourishment. Ordinary life is composed of people

acting upon their environment in a relationship of manipulation and consumption. We breathe the air around us; we defecate on the ground; we burn fire and make instruments. A person must never treat a fellow human being as an environmental resource. The embryo has no choice, however, since his mode of existence is founded on the kind of life which is incompatible with the fundamentals of morality. Consequently, the fetus cannot be regarded as a moral person.

Multiple pregnancy creates an even more complicated problem of individuation. In addition to being attached to the body of the mother, multiple embryos often share so many vital resources and so much biologic tissue so as to be implicated in circumstances of compactedness.

## THE PROBLEM OF COMPACTEDNESS

'Lifeboat ethics' is a paradigmatic example of a compacted environment, in which a group of people occupy a small lifeboat, which can sustain only a few of them. The metaphor of the lifeboat is in widespread use with regard to the ethics of multiple pregnancy[4]. Multiple pregnancy is a compacted situation because the human womb cannot properly sustain more than one or two fetuses. Simply stated, the healthy survival of one or two embryos *obliges* the loss of others.

A close look at the principles of our ethics reveals that they all imply existence within a non-compacted world as a precondition to ethics being practical, reasonable, non-alienating and consistent. In a compacted environment, on the other hand, ethical values typically collide with each other or end up in self-contradiction. A non-compacted environment is a world in which every person has a right to life, respect and bodily integrity. Lifeboat situations occasionally happen, but *typically* there is no need to kill people in order to save others. Typically the respect for the personal autonomy of one person does not entail violation of personal rights of others. In contrast, in a compacted environment, acting in manners that promote the *vital interests* of one individual and his or her dignity is *expected* to frustrate the rights and *vital* interests of another.

We believe that medical beneficence and respect for personal autonomy of one patient do not *by nature* harm another person or trample on his personal autonomy. If daily life really required the sacrifice of the innocent, the moral maxim against their killing would not make sense unless we take morality to be an alienated and impossible standard of conduct. Ethics is about making choices within life, not about choosing between life and ethics. Occasionally one faces a terrible dilemma; for example: shall I accept death or shall I kill an innocent person? But such dilemmas do not define ordinary human society and ordinary moral life. Rather, they define compacted life. Rare cases of lifeboat ethics are the exceptions that underline the rule.

Intrauterine life is different from extrauterine life. Intrauterine life is compacted, whereas most usually extrauterine life is not compacted. Most people lead their lives from birth until death without ever experiencing lifeboat dilemmas. We find it a moral goal to free the few who happen to be entrapped in lifeboat situations from these dire straits. In a better world, no lifeboat situations exist. None of this makes sense in the context of pregnancy. It is a simple and well-accepted fact that in the beginning of its life every human being must pass through a stage of compacted and partially individuated life. We do not find this circumstance a target for change. Rather, the tight intimacy of creating new human life becomes a powerful source for love, affection, solidarity and sense of continuity. Fetal life is not an accidental deviation from 'normal' life. It is a different kind of life altogether. It is a compacted stage of human existence. Hence it has its special set of moral principles and ways of reasoning about it.

We cannot extrapolate the principle of not harming the innocent into most cases of multiple pregnancy, because in human multiple pregnancy innocent embryos will certainly be harmed. The only questions are: how and which? Typically, medical beneficence strives to promote the well-being of each and every patient. But beneficence at the personal level, beholding the fetus as a patient, cannot be a reasonable agenda for medicine. It is an impossible mission both practically and morally. Does it make sense to seek the good life for a group of individuals most of whom will certainly not have a good life, not even life at all? I do not see how 'a right to life' can be meaningful when so many of those who purportedly have it will certainly die. Beneficence and non-maleficence (avoidance of harm) inevitably collide with each other whenever we try to apply them to moral problems of pregnancy in general and to multiple pregnancy in particular, as many interventions in the benefit of one party are quite harmful or distressful to another.

The lifeboat analogy is also potentially misleading because it presents us with actors who had been individuated as moral persons and agents prior to boarding the lifeboat. They also expect rescue at every moment. A set of four embryos had never been persons – they actually never existed at all prior to entering the compacted milieu of the womb. No rescue awaits a quadruplet in a womb, for whom the 'lifeboat situation' is the normal and only way of life. It is in their best interest to remain *in utero*.

Therefore, I contend that their compacted circumstances prevent embryos and fetuses from being moral persons. The very notions of moral personhood, moral rights, the principle of not harming the innocent, the calling to assist and help the needy, belong to a non-compacted world, a reality that fetuses enter only upon birth.

In sum, embryos and fetuses are thricely removed from the preconditions of ordinary ethical life: they are not fully individuated; their very existence is derived from instrumentalizing a human being and her body; third, the only environment that can sustain fetal life is compacted. The compactedness is much enhanced in settings of multiple pregnancy.

## WHO IS THE PATIENT OF PRENATAL CARE?

Since fetal life is both non-individuated and compacted, we cannot regard fetuses as patients of medicine.

Decisions of health care are based on the weighing of risks, suffering and values. Each person has his or her own point of view and his or her axis of evaluation. The fetal aspect is different from the mother's. Being a patient of medicine is being at the focus of individual health care. If the fetus is at the focus of care, his mother is out of focus. I contend that it is immoral to empower someone as a patient by marginalizing another person. Therefore, the only patient of prenatal care is the pregnant mother, holistically considered. Usually her well-being and the well-being of her pregnancy overlap. Sometimes a conflict ensues, however, such as might occur when the health of the fetus requires unusual efforts and sufferings on behalf of the mother. Since medicine must not assist one patient at the expense of another, doctors are forbidden to give noxious medicine or to operate on a body even if this saves the life of another patient. Whereas some generous people might accept the considerable risk and inconvenience as a personal gesture to a needy fellow, it is immoral to *force* unwilling people to do so. In the same vein it has been argued that any medical act that thwarts the autonomy of the mother with regard to her bodily integrity is immoral even when done in order to save the life of her fetus. Over 30 years ago, Thomson elaborated this line of reasoning, thus inaugurating non-essentialist ethics of abortion within applied ethics[5].

Multiple pregnancy throws Thomson's arguments into relief. If an embryo is a patient, any form of fetal reduction and any other intervention that harms embryos are immoral. Chervenak and McCullough contend in this volume (see Chapter 108) that a mother may designate only some (or none) of her embryos as patients. The remaining will be treated as non-persons. I wish to disagree. Moral status is too important and fundamental a concept to be determined by a personal, sometimes idiosyncratic, choice. A woman's power to seek abortion stems from the *pregnancy* being *hers*, not from any special entitlement to confer and to withhold moral status.

Multiple pregnancy carries the idea of the embryo as a patient to an absurdity. At week 10, a mother of a quadruplet might tell her doctors: 'I love them all. All four are my children. I accept your recommendation for fetal reduction. But I am not going to sentence any of my children to death. Do whatever you have to do.'

From a deontologic point of view, all four embryos have been designated as patients by their mother, none of whom may be deliberately put to death. This would be an odd conclusion when both doctor and mother opt for reduction for so obvious reasons. Alternatively, we might say that the mother has relegated the decision on patienthood to the doctors. Whichever fetus they abort is *ipso facto* a non-patient. This renders the argument about choosing embryos as patients tautologic (circular and hence empty). In sum, an embryo can be neither a moral person nor a patient. The subject of prenatal care is the pregnant woman *qua* a pregnant woman. She and the doctors are free to trade one embryo for another and to intervene in ways that promote the overall well-being of the mother and her offspring.

A mother may insist on a strategy of care that the prenatal experts find detrimental to her pregnancy; for example, she might wish to abort a healthy female embryo and keep an intrauterine growth-restricted (IUGR) male embryo. In such cases the doctors will have to choose between respecting the autonomy of their patient and their duty not to harm. An unjustified demand for abortion is similar to insistence on having futile surgery. In my view, a mother may exercise a personal choice (male rather than female) when physicians intend to perform a random selection. I do not think that doctors have a duty to comply with personal requests that are certain to bring about a less healthy child or children. I believe that the well-being of the mother comes before that of the embryo. But this case (sex selection) is purely about personal choice that leads to a diseased child. The woman might choose to abort the pregnancy should her reductive preferences not be met. She might also demand money and other benefits on the threat of abortion. Generally speaking, each doctor and health-care provider needs a policy that helps to distinguish between the rights to privacy and autonomy from their abuse.

In sum, doctors should provide care for the mother and her *pregnancy* not for individual embryos or fetuses. The subject of care in a case of toe infection is the whole person. The person is the

patient, not her leg or her toe. Similarly, an embryo is not the patient of prenatal care, but his pregnant mother is.

## DISCORDANT GROWTH

The rate of major malformations among twins is 7–11%, much above the rate for singleton pregnancies. The risk is significantly increased among triplets and quadruplets. Therefore, many multifetal pregnancies host healthy and afflicted embryos simultaneously, as discussed elsewhere in this book.

Discordance may be an acquired condition as well, when one (or more) fetus crowds out one (or more) sibling. The 'weak' fetus enjoys too little amniotic space and insufficient blood supply from the chorion. An analogy from extrauterine life would be two mentally retarded persons sharing a room in an asylum. The 'stronger' one steals the food of his room mate. The 'strong', retarded person is not morally accountable for this aggression. Nonetheless, we will remove either him or his victim to another room, and not let the two be engaged in a Darwinian game of power and survival. Such a policy is of no avail in the case of discordant growth. We cannot 'remove' any of the fetuses. It is pointless to abort the 'strong' fetus, thus 'saving' the 'victim' whose well-being is already compromised. We openly allow the 'strong' fetus to prevail. Moreover, if the 'weak' fetus becomes so weak so as to endanger the survival of the 'strong' one, many find it ethical to abort the 'weak' fetus and save the only fetus that is healthy and salvageable. From an ethical point of view I do not think it makes any difference whether the source of discordance is intrinsic (malformation affecting the lagging fetus), extrinsic (a maternal condition or pressure from the other fetus or fetuses) or some combination thereof. The subject of care is not a group of fetuses and not even a single fetus singled out by the mother, by the doctor or by nature. The subject of care is the pregnant woman and her pregnancy. The goal is to bring forth healthy progeny at the lowest possible risk to the mother's health and well-being. This usually implies the reduction of multiple pregnancies to either a twin or a singleton pregnancy. Such a strategy relies on a comparative evaluation of the embryos, using methods such as 'embryo quality scores'[6]. Hospital policy that chooses patients according to a 'quality score' is highly objectionable. Even when a hospital tries to tackle a dilemma of allocating scarce resources using utilitarian scoring scales, attention is given to prognosis, to the utility of *therapy*, not to the 'quality' of *patients*. A blind fetus ranks low in an embryonic quality score. A blind patient is a moral person. His blindness does not detract from his standing in a competition with other patients over a very expensive anticancer drug. Prioritizing people according to their 'quality' is dehumanizing. Indeed, such an attitude suits only *compacted dilemmas that entrap partially individuated persons*.

## ABORTING A 'DEFECTED' FETUS AND FETAL REDUCTION

When a singleton is diagnosed with a malformation, the mother faces an excruciating dilemma: to accept the life given to her or to abort it. Since the ethics of abortion falls outside this discussion, I wish only to highlight a key difference between the moral dilemma of a malformed singleton and the problem of fetal reduction[7]. Once we realize that the subject of medical care and moral attention is the pregnancy, not the embryo or embryos, we realize that killing a singleton terminates the pregnancy whereas fetal reduction protects and promotes it.

There is nothing one can do to alter the pregnancy of a malformed singleton. It is either accepted or aborted. Since the fetus is not a moral person, nobody owes it any personal duties. One cannot violate a right of someone who has never existed as a moral person and who will never exist as a moral person either. Obviously, we must always keep in mind that wanton destruction of embryos is abhorrent, not only because it often involves harm to women, but also because of the loss of human life. Even so-called 'defected' babies are precious and unique, albeit their preciousness is not the only factor in deliberating abortion.

If a pregnant woman abuses alcohol while pregnant, she commits a personal offense against a person, a future person. This is borne out by the fact that there will be a man who will suffer the consequences of her alcoholism. He could point to his mother and ask, 'Mom, why did you do this to me?'

A woman accepting a malformed fetus is making an existential choice. The born child cannot protest against his mother's decision not to abort (a claim of wrongful birth)[8]. Nor can he blame his parents for begetting a genetically affected child. If his mother had conceived by a different man or even by a different sperm cell, the born person would have been someone else. As Kripke notes, personal identity is *rigidly designated*[9]. My embodied self is located on an uninterrupted time–space continuum, which began with one specific fertilized ovum. At the time of conception, the fertilized human egg in question was not yet 'me'. It could have died or split into twins. Regardless, my personal and biologic identity is traceable retrospectively to that fertilized egg and only to that egg and not to any single embodied

human life antecedent to it. Anything done to that continuum at any time during its existence is something done *to me*.

An embryo that is going to develop into a child is a fixed human organism. If the mother hurts that embryo, she offends the future person. Therefore, although embryos are not fully individuated to qualify as moral persons or as subjects to individual moral attention of the kind given to patients of medicine, they are individuated to the degree that harming them is an offense against the future children, if and only if a future child or children ever come into existence.

Stated another way, a person who suffers the consequences of the actions of his mother while pregnant can point to an alternative course of action. Had she behaved differently *he* would have fared better. A person who suffers from his mother's decision to give birth to him cannot point to an alternative course of action. Had his mother acted differently *in this matter* he would not have existed at all. The child she might have instead is not him. It follows that it is better to abort a fetus rather than act in ways that significantly harm him as a future child.

The ethics of ordinary life does not accept such reasoning. Killing is a graver felony than maiming. Life with a disability is usually better than death. But I persist that the ethics of intrauterine life is quite different from the ethics of ordinary life. An existential choice with regard to an embryo – keeping it or aborting it – is never a personal benefit or a personal injury to that embryo. Such a decision might be an extremely grave personal moral issue for the mother, though. An existential choice with regard to a born human being – killing it – is possibly the gravest interpersonal decision one can ever make.

In sum, abortion of a whole pregnancy (singleton or multiple) is an existentially moral choice. Fetal reduction and similar treatments and interventions are practical moral decisions whose sole justification is the benefit of persons: the mother and/or the future child or children.

## INTRAUTERINE SURGERY AND OTHER TREATMENTS THAT ARE AIMED AT ONE EMBRYO BUT ALSO HARM ITS SIBLINGS

The very need for an intrauterine operation creates a compacted situation for the mother and for the afflicted fetus. His condition implicates her body and health. It cannot benefit from medicine *unless* at the price of discomfort or injury to another person, to its mother. I do not believe the mother has a moral *duty* to risk her health for the sake of rescuing her pregnancy, because in democratic cultures not only is there not moral duty to procreate and have children at all, but also there is no moral duty to sacrifice one's life for the sake of saving the life of another person. A mother who accepts the travails of intrauterine surgery may, nevertheless, wonder whether it is ethical to risk a healthy fetus for the benefit of a sick one.

The loss of fetal life is never a personal loss to the fetus. Therefore, I believe it is wrong to perform *life-saving* intrauterine surgery on a fetus whenever the surgery is likely to have a detrimental effect on the other fetus (or fetuses) *in its capacity as a future person*. Losing one fetus harms nobody, although it might be very painful for the mother and even to the extended family. Performing the surgery will harm somebody. In that respect even a *minor* harm to a future person does not justify saving the *life* of a fetus. In ordinary life, fear of a minor harm is set aside for the sake of saving life. If both fetuses are expected to survive even without surgery, the best decision is the one that will optimize the outcome of the pregnancy. Maternal health and well-being are key factors in such optimization.

Goldstein and colleagues[10] reported successful insertion of a ventriculoamniotic shunt in a twin, with an excellent outcome for mother and both twins. Although achievements such as Goldstein's are commendable, they do not set a moral standard for all. Aborting the fetus in need of surgery could be a morally acceptable option as well. In extrauterine life we never kill the weak for the benefit of the strong. Intrauterine life, however, is a different setting, where we aim at protecting the fit, even at the expense of the survival of the weak.

The same considerations apply not only to fetal surgery but also to similar situations such as fetal distress affecting only one fetus: induction of labor is in the best interest of the fetus in danger, whereas it is detrimental to the other one. If both fetuses are going to survive, the mother may wish to optimize the outcome of her pregnancy. She might also opt for aborting one fetus in order to give birth to only one albeit healthy child.

Since selective termination of an abnormal twin is a safe procedure for both the mother and the other twin[11,12], any attempt at saving an affected twin is bound to meet this standard of safety. The mother may submit herself to excessive suffering and to increased risk in an attempt to save her fetus. Risking the health of one fetus while trying to save another is a more complicated issue.

Women and ethicists might call our attention to personal devotion, hope, faith, love, self-sacrifice and refusal to accept calculations of survival as key virtues in procreation and family life. Post-structuralist sociologists and historians may remind us

of the work of Elias and Foucault who argued that the idea of a core 'self' or 'person' that is encapsulated in a shell of a physical body is a modern figment, and that alternative discourses of ethics need to be developed, particularly to dilemmas of human intimacies.

Overt rationalization of pregnancy, and a system of ethics that merely strives to optimize outcome, might undermine the very motivation to become a parent, to love and to be giving from the depth of one's heart and with commitment that transcends any consideration of utility. Levinas writes, 'life is love of life, a relation with contents that are not my being, but more dear than my being'[13]. Such noble words, however, do not shed light on how we may resolve conflicts *that arise from and within* such concepts of life, love and ethics – dilemmas of maternity in general[14] and of multiple pregnancy in particular.

## THE BITTER IRONY OF INFERTILITY TREATMENTS

Evans and colleagues[15] highlight a 'bitter irony' affecting couples whose infertility treatments lead them to abortion in the form of fetal reduction. Some of these situations can and need to be avoided. Circumspect use of hormones that induce ovulation and implantation of one embryo at a time will certainly reduce some medical complications associated with iatrogenic multiple pregnancy. Such a policy, however, boosts costs, protracts the duration of therapy and, possibly, will also cause some women to miss their final opportunity to have biologically affiliated children. Experts and ethicists still debate the best ways to prevent the multiple pregnancies of infertility treatments[16].

I now wish to revisit the distinction propounded between existential and non-existential moral choices in reproduction. If a woman has to choose between barrenness and aggressive infertility treatments, she might wish to take the risks and not lose her only chance of having biologic children. This might be the situation for women approaching the menopause or for women who have serious difficulties with ovulation. Both sorts of women face an existential decision: to have a child or not to have one. A carrier of a genetic defect is not obliged to refrain from having children. Similarly, a woman whose *only* means of having children is aggressive infertility treatments has no duty to forgo them either.

Most women undergoing infertility treatments have a choice. They can ask for lower doses of hormones and for the transfer of only one embryo. In the case of a young woman with a good prognosis, I see no justification for employing anything but the most conservative therapeutic strategy. A woman might, nevertheless, wish for an aggressive infertility treatment, pledging to undergo early reduction to a singleton pregnancy as well. In my view, doctors should consider to decline plans that take overtly unnecessary toll on the human body. A right to privacy and to autonomous reproduction does not render self-injury and futile procedures moral.

## JUDAISM AND ISLAM

Both Judaism and Islam have developed systems of positive law according to which abortion is an offense against the Word of God.

In Judaism, fetuses have no independent moral status. Protection of maternal health is a cogent justification for abortion at any time during pregnancy. This includes fetal reduction as well. When reduction is not indicated on maternal grounds, the rabbis permit performing it in multiple pregnancies that are not likely to bring all fetuses to term. Rabbis debate the number of embryos that may be aborted. Some forbid the reduction of embryos that will survive even without reduction. Others advocate an 'unsentimental trade-off' that will promise 'reasonable chances' to those remaining alive[17].

Most schools of Muslim religious law permit abortion during the first 120 days of pregnancy. The most common justification for abortion in Muslim societies during pre-modern times was fear for an infant sib. Pregnancy might diminish maternal milk and jeopardize him[18]. In contemporary Muslim bioethics, poverty and too-big sibship are frequently mentioned as justified reasons for abortion. Muslim law is also relatively lenient with regard to the abortion of disadvantaged fetuses[19]. This paves the way to fetal reduction until the fifth month. Some contemporary rulings tend to be on the stricter side. Serour writes, 'multifetal pregnancy reduction is only allowed if the prospect of carrying the pregnancy to viability is very small. It is also allowed if the life or health of the mother is in jeopardy'[20].

## ESSENTIALIST APPROACHES TO THE ETHICS OF MULTIPLE PREGNANCY

According to the official position of the Catholic Church[21], the fertilized ovum has a moral standing as if it were a moral person, like any other human being. Other schools of ethics operating in the spirit of natural law regard the embryo as a moral person, although opinion varies as to when exactly it begins to be a person: some point to the appearance of the primitive streak; others focus on the maturation of the central nervous system, or on the stage of viability. Many Catholic and Protestant theologians follow the Augustinian teaching that formation (the development of a human frame), which was believed to

take place at day 40, marks the beginning of the human person.

Alternatively, we may define the moral standing of the fetus according to its *potentiality* to become a full human person, rather than according to its temporal stage of development. Either way, it is held that the person that is the embryo, or the future person now inherent within the embryo, has a right to life which is rather strong, even if not as strong as the right to life of born persons. I refer to these schools of ethics as *affirmative essentialists* because they are essentialists who hold that the embryo, at least during part of its fetal life, is a moral person.

The vast majority of past and present ethicists and theologians do not grant the vital interests of fetuses and born persons equal consideration. In many circumstances the policy advocated by affirmative essentialism is not much different from the opinions articulated in this chapter. Whereas I have stressed the disparity between fetal life and ordinary life, affirmative essentialists employ various conceptual tools in order to endorse acts that, even though not deliberately, brings about the death of embryos. Hence, these ethicists propound an ethics which practically brings about discrimination against the unborn in most cases of life-and-death maternal–fetal conflicts and which resolve intrauterine conflicts differently from conflicts of ordinary life [22].

## Self-defense

Some ethicists believe that medical complications of pregnancy should be conceptualized as an unjust aggression of the fetus on the mother. In that case the fetus may be killed, directly or only indirectly. However, as pointed out above, care of pregnancies complicated by discordant growth is often biased in favor of the 'aggressor', the 'stronger' embryo. In order to save the pregnancy we tend to protect the most promising embryo or embryos.

Ethicists debate whether the right to self-defense includes permission to kill an *innocent* aggressor. Many believe that it is always immoral to kill an innocent human person directly and actively. Some schools of ethics endorse *self-preferential homicide* (i.e. if someone must die, let it not be me) within the framework of the principle of double effect.

## The principle of double effect

According to this principle, it is permissible to bring about *unintentionally* a violation of an ethical duty by means of a *morally neutral act* when the violation is a *foreseeable* side-effect of an act whose value *significantly outweighs* the gravity of the violation. The 'morally neutral act' condition excludes harnessing *bad acts* in the service of good ends.

Aggressive pain relief for the dying is a paradigmatic model. Although morphine might kill patients (the unintended but foreseeable bad act), relief of suffering (the good act) justifies its use in terminal care. The mitigation of suffering significantly outweighs the few hours or days a dying patient might lose. Administering morphine is morally neutral. It is not in itself bad. On the other hand, the principle of double effect does not permit euthanasia in which a bad act, killing, is the means to a good end, comfort of the dying.

Similarly, we may treat a pregnant woman with chemotherapy (chemotherapy is not intrinsically bad and the treatment serves a worthy goal, cure of cancer) although the chemotherapy might induce a miscarriage (the unintended but foreseeable bad act). The loss of the mother along with her embryo is disproportionately worse than losing only the embryo. Some would even argue that the loss of a woman is disproportionately worse than the loss of a fetus. The disproportionality condition within the principle of double effect actually introduces utilitarian considerations into a deontologic (duty-bound) ethics[23]. In my view, multiple pregnancy poses a serious challenge to the attractiveness of combining a belief in the embryo being a person with the principle of double effect. Suppose we have to choose between saving the mother and saving her near-term healthy twin or triplet fetuses. If indeed a near-term fetus is a human person, one might argue that the death of two or three human persons is disproportionately worse than the death of only one woman. Essentialists would reject counting lives, arguing that an *intention* to take a human life is *always* immoral. However, Catholic and other ethicists who subscribe to the doctrine of double effect must reckon with the fact that counting lives is a component – even if not the most important one – in the deliberation of *foreseeable but not intended* killing. Meaning to save two fetuses, doctors may harness the principle of double effect to an unintentional but foreseeable killing of the mother. Facing the same situation, the doctors might also employ the principle of double effect in order to save the mother, while *unintentionally* bringing about the death of the fetuses. Thus, different and opposing acts might both fall under the principle of double effect. In such cases, counting lives seems to me to be the only reasonable way of action. Essentialists are expected to intend the saving of the many (fetuses) and tolerate the unintended loss of the one (mother). I have not found affirmative essentialists who carry their essentialism all the way to this kind of conclusion.

It is almost universally held that one should save the life of the mother even if the only way of doing so is by losing the fruit of her womb, may it be one, two or more fetuses. Care-givers are always *mindful* of the pregnant mother; in cases of maternal–fetal conflicts she is never beyond the focus of their intentions. Essentialists tolerate courses of action in which fetuses fall outside our ethical focus – an asymmetry which is incompatible with essentialism. This contradiction sheds light on a key weakness of essentialism. Fetal reduction cannot fall under the ambit of the principle of double effect, though, because in fetal reduction, killing embryos is not an 'unintentional side-effect' but the very act in question.

## Opting for the lesser evil

When one cannot escape an evil outcome, one often chooses the least immoral path. We may abort a fetus in order to save its mother, whenever inaction brings with it the loss of both mother and fetus. Many ethicists employ this concept only as a mitigating factor or only when no active killing is involved. For example, withholding care for the fetus is permissible in order to save the mother, but active abortion is not. This leads us to another distinction, that which is between *action and inaction*.

Ethicists debate whether acts of commission are morally different from acts of omission[24]. Life-and-death dilemmas underline the relevance of this distinction. Virtually every school of ethics teaches that I do not have to sacrifice my own life even if this is the only way to save the life of a friend. In the absence of any other alternative course of action, I may sit passively and watch him die. If I am the endangered person and my friend is the one who refuses to sacrifice his life for me, I am strictly forbidden to kill him in order to save my own life.

## The defense of necessity

In extraordinary circumstances people may violate moral rules in order to escape a very great injury. For instance, a person may break into his friend's house in the course of running away from a ferocious animal. The imminent danger of falling prey to a beast justifies the suspension of property rights. Yet a popular saying declares that 'necessity knows no law', virtually all schools of ethics accept the defense of necessity[25] in *killing a non-aggressor person* only as a mitigating argument, not as a justification. The defense of necessity can, therefore, justify harming fetuses in order to save the health or the life of the mother. According to official Catholic doctrine this is acceptable only within the framework of the principle of double effect. The defense of necessity is irrelevant when we harm one fetus in the benefit of others. Neither the mother nor the doctor acts under necessity.

Some philosophers believe that the defense of necessity justifies the killing of one person *only* if this saves the life of many other persons who would otherwise die, thus incorporating the motif of *disproportionality* in their reasoning. This argument also combines the defense of necessity with the opting for the lesser evil. If the extreme necessity does not need to be the perpetrator's, such combination can justify most forms of fetal reduction.

## Utilitarianism

Utilitarianism is committed to the course of action that leads to the greatest happiness overall. Utilitarianism focuses on consequences of action, not on deontologic issues such as veracity, and fiduciary and other values pertaining to *the kind of action* or to *the personal attitude* of the moral agents. Therefore, utilitarianism disregards the above considerations of 'double effect', 'necessity', etc. In utilitarian ethics the only relevant kind of argument is the ultimate impact on well-being. Utilitarianism is essentialist because it regards the capacities to suffer and to be happy as the loci of the kind of well-being which morality reckons with. The relationships among these loci and the ambience of their existence play at best a secondary role. The vast majority of utilitarians are *negative essentialists* because they believe that the fetus is not a locus of well-being deserving equal consideration of its interests and preferences.

The non-essentialist ethics promulgated in this chapter is explicitly utilitarian with regard to intrauterine life. I do not believe that utilitarianism is suitable for many ethical problems that beset ordinary life[26]. But extrauterine life is beyond the topic of this chapter.

Non-utilitarians believe that certain virtues or duties compel us to act in ways that do not necessarily result in the highest level of happiness possible. They claim that duties such as the duty not to harm the innocent, or the call of love, prevents us from exploiting the few in the benefit of the many *even* when such a conduct is *guaranteed* to produce the greatest level of happiness possible.

I have shown that multiple pregnancy is too compacted and too complicated a condition to allow for a non-utilitarian policy of care. Even those who subscribe to deontologic (duty-bound) or virtue ethics quite often resort to philosophic constructions, such as the principle of double effect, in order to refrain from rigorous implementation of a right-based ethics to the fetal side of multiple pregnancy.

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# Common and Emerging Legal Implications

*B. Tauber and H. Raziel*

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## INTRODUCTION

> *'Be fruitful and multiply and replenish the earth and subdue it'*
>
> *Genesis* 1:29

With the advancement of numerous technological and biotechnological developments surrounding fertility, conception, pregnancy and birth, this simple instruction has caused a host of legal implications and the claims that hotly pursue the same. A vivid example of the current dichotomy surrounding medicine is the virtually simultaneous unsuccessful attempt to separate the Iranian Bijani conjoined twins and celebration of the 25th anniversary of the world's first 'test-tube' baby – Louise Brown – on 25 July 2003.

This chapter does not propose to analyze the rights and wrongs of scientific advancements, nor to seek to determine what the the most appropriate approaches might be. Rather, its purpose is to seek to identify various legal issues that have evolved and that may evolve when dealing specifically with multiple pregnancies, especially twins, whether they be the result of assisted reproductive technologies (ART) or of spontaneous conception.

## GENERAL PRINCIPLES OF MEDICAL NEGLIGENCE

Before considering some of the difficult situations that confront the medical as well as the legal profession when dealing with multiple pregnancies, it is useful to consider briefly medical negligence or malpractice from a general point of view. As this is an enormous and ever-growing subject, this chapter can only provide a very general overview of major principles and their specific application to multiple pregnancies, with an indication of the more complex problems that can arise.

It is trite to state that the general approach of legal cultures based on or deriving from the system of common law (such as those of England and Wales, USA and Israel) is that the liability of the medical profession under medical negligence is not strict. In simple terms, it means that it is not sufficient for damage to occur for liability to attach in medical negligence (except for issues of presumed strict liability as might occur when using defective medical devices). What is required for liability to attach is that there must be a finding of negligence on the part of the medical practitioner involved.

The legal concept of negligence is not static, and advances as technology and medical knowledge advance – albeit not always at the same pace. The practical standards against which the medical profession would have been measured 50 years ago for the purposes of determining negligence are not necessarily those against which the profession is measured today. With specific reference to pregnancy and multiple pregnancies, account has to be taken of advances in the fields of ART, diagnostic techniques and devices relating to the health and development of the fetus, among other things. In addition, legal developments in the medical field in general, or in other areas of the law in particular, can and do impact upon the manner in which medical negligence is to be measured. For example, the increasing awareness of information rights and the enactment of laws to protect the same (see below on informed consent) may come into play in consideration of the

standards against which medical practitioners are to act. Examples of specific enactments in this regard include the Israeli 'Basic Law: The Respect for Man and his Freedom' and the 'Israeli Patients' Law', 1996, the English Human Rights Act 1998 and the Patients' Charter/National Health Service Guidelines.

The basic approach of the legal cultures referred to above is that in order to establish a case in negligence, certain factors in addition to damage must be proven. Each is discussed in detail in the following sections.

## DUTY OF CARE

A duty of care must exist between the person suffering the damage and the person alleged to have caused it, as it must exist between the patient and the medical practitioner involved. The general common law principles for determining the existence of the duty of care are based on the concept of proximity – not necessarily physical proximity but legal proximity, the basic test being whether the parties involved are in sufficient degree of proximity, that one party owes a duty of care to the other[1].

The general approach of the legal cultures to which this chapter refers is that medical practitioners owe a duty of care to their patients. However, there are special circumstances whereby it may be decided that such a duty of care does not exist, thus denying the primary basis for negligence. Using an example from Israeli law, the accepted opinion until 1986 was that genetic counsellors did not owe any duty of care towards a child born with disabilities, even if those disabilities could have been discovered at an early stage of the pregnancy; similar approaches were used in other jurisdictions, including the USA[2]. However, this approach changed in 1986 when the Supreme Court of Israel decided that a genetic counsellor owed a duty of care not only to the parents, but also to the child, thereby establishing the grounds for a 'wrongful life' claim on the part of the child in such circumstances[3]. Wrongful conception/ birth claims have long been recognized in the context of sterilization cases in many jurisdictions; yet this was a landmark decision by allowing a 'wrongful life' claim to proceed on behalf of the child itself for the recovery of damages. Although the question before the Israeli court was about the duty of care and whether a claim indeed existed, the court did not actually rule on the facts, and thus it did not award damages but sent the claim back for trial. This decision on the part of the Supreme Court in Israel departed from the present trend in the USA and from the single case reported in England, as well as from the accepted jurisprudence on the point[4–7]. It can be argued, however, that adoption of the Israeli decision essentially reflects recognition that technological advances may enable earlier and more accurate diagnosis of fetal health and development, and that the use of such technology should come under closer scrutiny by all parties involved.

Whereas the Israeli case involved a singleton pregnancy, the implications of such a case are amplified in multiple pregnancies. For example, the correct treatment of a multiple pregnancy depends upon the diagnosis of the pregnancy as such. In one instance, a failure to diagnose twins, and subsequently to treat the pregnancy accordingly, ended in one stillborn and one brain-damaged twin. This case was settled out of court for $US1.8 million[8].

Even when the correct diagnosis of multiple pregnancies is made, the possibility still exists that a problem may arise *en route* to birth, with the potential for legal liability. If a problem such as potential disability could be diagnosed at an early stage, issues arise concerning the doctor's duty to discuss with the parent(s) the possibility of multifetal pregnancy reduction (MFPR) or selective termination of one or more of the fetuses, and the parent(s)' rights with respect thereto, as well as the rights of the unborn child[9]. In the US Healy case[10], the plaintiff and her son sued their doctors for injuries which allegedly were sustained by the son *in utero* and after birth. The plaintiff conceived triplets, and the son shared a placenta with a fetus that died during pregnancy. The plaintiffs alleged that MFPR should have been conducted while still viable, and that they should have been advised of this possibility.

Although in the Healy case the plaintiffs lost on the facts of the case, it sheds light on the legal issues that can arise in this context. Does the doctor owe a duty of care to the parent(s) and thus need to raise the possibility of MFPR? Against the legal background of legislation promoting and protecting the patients' rights to know and to be informed, the general answer to such a query would have to be in the positive. But how will the law analyze the situation if the parent(s) want to seek a second opinion (in these cases, time can be essential, since the longer the pregnancy continues the greater are the risks in performing MFPR)? What if the opinions differ – on what basis can any tribunal elect one opinion over the other? Indeed, is the court the best forum for resolving such a dispute? If the parents decide against MFPR and the infant suffers injury or disability as a result of this decision, should the legal system allow the infant to sue not only the medical profession but also its parents for such injury or disability?

In this context, it is relevant to introduce the concept of civil assault, which is an alternative ground available to patients to claim compensation from the medical profession. Technically, any interference or dealing with the body of a person without the

consent of that person amounts to an assault. Accordingly, if an operation is conducted without the patient's consent, an assault is committed. With this in mind, the medical practitioner has to be wary of carrying out MFPR without the consent of all those parties capable of providing consent.

Although medical evidence suggests that MFPR can be more successful at an early stage in pregnancy, risk-related issues can become problematic as the pregnancy continues. For example, consider a twin pair discordant for Down's syndrome. If the only option for terminating the malformed fetus is to induce abortion, issues arise concerning the right of the doctors and/or parents to abort the healthy fetus by terminating the imperfect one. If all parties capable of decision-making in this situation are not in agreement, concerns can arise as to what should be done in such a case: can the termination be ordered? Perhaps more important, should the termination be ordered, whereby the healthy fetus is doomed?

## BREACH OF DUTY

A breach of the duty of care on the part of the medical practitioner must be proven. The general approach is that not every mishap constitutes negligence. The medical profession is not required to abide by a perfect standard; in other words: 'The doctor does not warrant or insure either a correct diagnosis or a successful course of treatment'[11]. In essence, medical practitioners are required to comply with an objective, reasonable standard – that of the reasonable practitioner[11–14]. In the USA, this standard requires a medical practitioner to act in accordance with the best standards adopted by practitioners in his/her field[11]. Similarly, in England and Wales, this requires the medical practitioner to act in accordance with a practice accepted as proper by a responsible body of medical men skilled in that particular art[12,13]. The law looks to determine how logical was the decision to act/failure to act and weigh the risks and benefits involved[15]. The more specialized is the field of medicine, the more specialized the standard of care will be.

In terms of a generally accepted standard (England and Wales) or the best practice standard (USA), the introduction of other laws (as noted above) may affect the issues considered in this chapter. For example, in England and Wales, the Human Rights Act 1998 initiated a discussion of whether the enactment of this legislation had in effect brought in the best practice standard, at least with respect to the duty to inform[16]. As is acknowledged in one consideration of the Human Rights Act 1998, these two standards are not synonymous[16]. Arguably, the best practice standard imposes a higher duty on the medical professional than that of the generally accepted standard. Furthermore, enactment of the Human Rights Act in England and Wales introduces an additional basis – independent from medical negligence claims – for claims against medical practitioners based on breach of a statutory duty, in much the same manner as the enactment of the Patients' Rights Law 1996 has done in Israel.

The discussion of duty becomes more complicated if one considers sources other than primary legislation. For example, one of the legal issues that arises in this context concerns the extent to which the potential parent(s) can insist upon having a multiple pregnancy, aiming to secure the chance of at least one healthy child (it is beyond the scope of this chapter to consider the legal debate on the fate of 'surplus' embryos created during ART procedures). However, in the more common circumstance, multiple pregnancies bring with them their own medical complications, leading to recent legal developments seeking to reduce the incidence of multiple pregnancies. For example, in August 2001, the UK Human Fertilisation and Embryology Authority (HFEA) recommended that no more than two embryos – unless exceptional circumstances exist, in which case a maximum of three embryos – are to be returned, in any given *in vitro* fertilization attempt. The implementation of such a recommendation gives rise to numerous legal issues. For instance, if a doctor refuses to act in accordance with the recommendations, and a multiple pregnancy follows with complications, the existence of such a recommendation could provide grounds for claims of negligence, as the recommendation may be treated as the mandatory standard of care, and perhaps breach of statutory duty if the recommendation is treated as more than a mere guideline. As at the time of writing this issue is untested. The other side of the coin is whether potential parent(s) in the UK can dispute this recommendation on the basis that a government authority (HFEA in this instance) cannot eliminate the right of potential parent(s) to have a multiple pregnancy, to increase the chance of a pregnancy in an ART cycle by transferring more embryos, or on the basis that such a recommendation cuts across human rights laws and the autonomy of a woman's body. Such a dispute could lead to vastly different opinions between potential parents, as in the Israeli case where family members (wife and father-in-law) disputed the posthumous use of sperm from a deceased husband[17]. Clearly, by seeking to limit the medical problems involved in multiple pregnancies, any order or law limiting the number of transferred embryos may awaken other dormant legal issues.

A further concern arises as to when and whether the courts will intervene and diverge from the

standard adopted by the medical profession. In one case in the USA, the court was prepared to indicate that the standard adopted by the medical profession was not adequate, and to require a higher standard[18]. A potential legal question might be whether courts should follow general legal practice or push the medical profession towards adopting a different (perhaps higher) standard – with all the budgetary issues that might involve. The standard of care requires that the medical profession will keep updated on developments in the field. Again, the degree of required updating depends on the degree of specialization that a particular practitioner has acquired. Hence, the higher is the specialization, the more the practitioner is expected to be updated within that specialization.

Finally, the generally accepted legal approach is that the standard of care relates to the knowledge available at the date of the incident. If, after the incident, further knowledge becomes available and demonstrates that a once acceptable course of action should no longer be used, such knowledge will not be applicable to the incident under review. In this respect, the law of negligence does not operate with the benefit of hindsight.

## CAUSATION

The putative breach of duty caused the damage alleged by the patient. The generally accepted test here is the 'but for' test, i.e. but for the negligent act or omission of the medical practitioner the damage suffered would not have occurred.

## DAMAGES

It is critical to negligence claims that damage be suffered. If there is no damage, then no claim is warranted, irrespective of how negligent the medical practitioner may have been. However, the absence of a claim in negligence does not exclude the possibility of disciplinary proceedings against the practitioner in question.

In cases of pregnancy/multiple pregnancy, wrongful birth/wrongful life claims illustrate some interesting issues. For example, the 1986 decision of the Israeli Supreme Court regarding 'wrongful life' enabled the submission of claims not only by the parents but also by the children[3]. The Court's decision could be viewed as a rather courageous one, because it extended beyond the existing jurisprudence as well as the trend of case law in the USA and England.

Wrongful birth and wrongful conception are used interchangeably in English law, but in the USA they refer to birth following negligent abortion and birth subsequent to negligent sterilization, respectively. Both are brought by the parent(s). Wrongful life, on the other hand, refers to claims that might be brought by the child itself. In the USA there have been a number of cases dealing with 'wrongful birth', 'wrongful conception' and 'wrongful life' claims, whereas in England there is only one reported case dealing with the same. There is no reason why such claims would be limited to negligent sterilization/abortion processes, as the Israeli Zeitchov case demonstrates[3].

In addition to the question of whether there exists a duty of care by the medical practitioner towards the child, concerns exist about the amount of recoverable damages. The courts are often requested to consider whether damages should extend not only to those derived directly from the pregnancy, but also to damages for the maintenance and care of the child or, in the case of multiple pregnancies/births, children. The general approach adopted in the USA (albeit not all of the states: in Nevada, neither wrongful conception nor wrongful birth are legally recognized types of damage[19]) and in England[20] is that if wrongful birth and wrongful conception cases are proven, recovery will be allowed for all damages flowing directly from the pregnancy. However, as a general rule, damages for the maintenance and care of the child will not be awarded. The latter damages may be awarded where the child in question suffers a handicap. In contrast, the Israeli courts have been prepared to award damages not only for losses flowing directly from the pregnancy but also for the maintenance and care of the child[21].

No better summary can be provided than the comment made by the English House of Lords on the McFarlane case, namely that this area of the law is in a state of flux.

## OTHER LEGAL ISSUES

The legal system is confronted on a daily basis with complicated and often heart-rending issues. In these instances, negligence is not necessarily the issue, and the discussion leads in different directions.

In one instance in the USA, the so-called Donna Fasano incident, a doctor working in an ART facility had inserted a number of embryos – including some that did not belong to the patient. The error led to a mother carrying two fetuses, one of which was her husband's and another which was not. The mother ultimately gave birth to so-called 'twin' boys – one black and one white (see Chapter 16). After appropriate DNA testing, the patient elected to give the black boy over to its 'biological' mother, and kept her own child. Similar cases are reported from The Netherlands. Fortunately, perhaps, the courts were

not required to determine as a matter of law to whom each embryo and resulting child belonged and who were the parents of each circumstance. It is also perhaps fortunate that, during the course of the pregnancy, none of the interested parties sought a court order for the mother carrying the child to terminate the pregnancy (as was suggested by the attending physician). Having said this, it is reported that, after the child was handed over to its biological mother, attempts to work out visitations on behalf of the gestating mother resulted in a restraining order.

More recently, a not dissimilar mix-up occurred in the UK where, following *in vitro* fertilization (IVF) treatment, a white couple gave birth to mixed-color twins. In this instance, however, the mother's egg had been fertilized with the sperm from the husband of another couple undergoing IVF treatment at the same clinic, rather than her own husband's sperm. After appropriate DNA testing, the case was taken to a court that ruled: first, the gestating mother is the mother of each of the twins (based on the Human Fertilisation and Embryology Act, 1990); and second, the legal father of each of the twins is the man from whom the sperm came rather than the legal mother's husband[22]. This conclusion was reached by a clinical analysis of Section 28 of the Human Fertilisation and Embryology Act and the 'consent' provisions thereof. Essentially, the court determined that the husband had not consented to treatment with sperm other than his own. This conclusion as to paternity could give rise to numerous follow-on queries: the father's right to access and visit the children, potential maintenance rights, the potential rights and claims that the children may have. Section 29 of the Human Fertilisation and Embryology Act provides that where, by virtue of its application, a person is to be treated as a father, he will be the father of the child *for all purposes*. In the case itself, the court effectively surmounted the problems posed by reliance on said Section 29 by turning to a different statutory regime: the Children Act 1989 (by terms of which the sperm donor is an unmarried father who, by the 1989 Act, has no parental responsibilities). Whereas the court acknowledged that the rights of the husband, wife and twins under the human rights legislation were engaged (those of the sperm donor were not) and interfered with, it concluded that this was in accordance with the law, and thus could be properly cured by legal remedies (i.e. adoption). Interestingly, in the case itself, the sperm donor/legal father was not contesting paternity rights (as Dame Elizabeth Butler-Sloss pointed out: 'Everyone … agrees the twins should remain with the family into which they were born'), and one wonders how the arguments could have differed had such rights been fully contested and the statutory inconsistencies on fatherhood and its effects ironed out. As the court pointed out: 'Behind the legal arguments which occupied the court for three days lies a tragic human story of two families trying to come to terms with the consequences of the mistake.' What seems to be apparent from the case is that the Human Fertilisation and Embryology Act, when enacted, did not contemplate or regulate those circumstances where mistakes are made – surely this is an issue that cannot afford to be ignored by legislators in the future, either in the UK or elsewhere.

It would be inappropriate to complete this chapter without consideration of two additional and particularly difficult instances. The consequences of multiple pregnancies do not stop with birth, as the recent case of unsuccessful separation of the Iranian conjoined twins so tragically demonstrated. From a legal perspective, one has to ask whether the twins were as fully informed as they could have been of the risks, and given the opportunity to weigh the risks of the operation. Assuming that they were, can society and its legal system ask whether the twins themselves took a calculated risk, and could their decision, in the knowledge that the chances of success were low, be viewed as an election to die if the operation failed? If the answer to the latter question is 'yes', then it is logical to ask whether the medical practitioners' activities could be classified as active assistance to almost inevitable death and, if so, what should be done about it?

One way in which medical practitioners may seek to avoid or pre-empt possible legal action is to approach the court directly, as the doctors did in the Maltese twins case[23] (see Comment on page 919). However, such an approach – apart from being impracticable – is hardly a desirable method of practicing medicine. Moreover, as noted above, it is not clear whether the courts are any better equipped to address the complex legal, ethical and medical professional issues that may arise than are the individuals who petition the courts. In the above case, the twins were joined in such a manner that general medical opinion was that, so one twin may obtain a chance of survival, an operation to separate them should be carried out, even though the death of the other twin would be an inevitable consequence of that operation. The parents, a Catholic couple from Malta, did not share the views of the doctors and did not want the operation. The doctors decided to ask the court for an order to proceed with the operation, notwithstanding the parents' wishes. The issue eventually reached the Court of Appeal in England, and was presided over by three Court of Appeal judges[24]. The Court of Appeal unanimously upheld the trial judge's decision to allow the operation to proceed, although all four judges (the trial judge and the three appellate

judges) adopted various reasons for their decision. The trial judge concluded that the operation would amount to passive euthanasia of the one twin rather than killing her. At the appellate level, the judges each adopted a different rationale. Lord Justice Alan Ward basically elected for the lesser of two evils. Since continued united existence would lead to the death of both twins, the operation and inevitable death of the weaker twin was a form of justifiable homicide. Lord Justice Robert Brooke relied on the concept of legal necessity, and justified its application here since 'Mary is, sadly, self-designated for a very early death'. Lord Justice Robert Walker, after concluding that analogies were not helpful to the case and that the doctors' duties to the twins were in conflict, chose in favor of surgery, without which neither life would have the bodily integrity which it was due (even if, in the one case, such integrity or wholeness was only for a brief spell). George Annas in a widely publicized discussion of this case[24] indicated that, in the USA, the parental decision would have been final, unless the physicians or the state could have persuaded a judge that this was a case of child neglect. The authors of this chapter assume that the US application of parental decision would apply where there are no differences of opinion between the parents, and also where there are no complications arising from mishaps during ART procedures (such as in the Fasano and the recent UK cases).

## CONCLUSION

This chapter has sought to review and also demonstrate the complexity of legal issues that can arise when dealing with complications associated with multiple pregnancies. Whereas this is vividly seen in the Maltese twins case, other cases concerning medical negligence claims show that, not infrequently, the medical profession is walking through a legal minefield.

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## COMMENT

The Maltese conjoined twins Mary and Jodie discussed in this chapter were of the ischiopagus type, a variety constituting about 6% of all conjoined twins. Ischiopagous twins are joined end-to-end with the spine in a straight line, united from the umbilicus to a large conjoined pelvis, and usually have a single external genitalia and a single anus. Ischiopagous twins have four arms and a variable number of legs. In the Maltese twins there were four legs, a condition termed 'ischiopagus tetrapus/quadripus', the most common type representing 70% of all ischiopagus twins.

Mary had an underdeveloped brain, described as 'extremely primitive', and received oxygenated blood from Jodie's aorta. Jodie was bright, alert and of normal intelligence.

The illustration of ischiopagous twins with three legs (tripus) comes from the famous description of the various types of conjoined twins by the French Renaissance surgeon, Ambroise Paré. Paré was chief surgeon to both Charles IX and Henri III, and tried to explain birth defects in his illustrated encyclopedia of curiosities *On Monsters and Marvels* (1573)[1].

Isaac Blickstein

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# Index

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The first edition of this book was a landmark publication in establishing the study of multiple pregnancy and the perinatal care of children from multiple births as a recognized subspecialty within obstetrics. The book presented many facets of the clinical, psychosocial and practical issues of multiple gestation.

The new edition has been fully revised in line with modern obstetrics and perinatology and will include the evidence base to current practice, where available. The text has been expanded in scope to include more on epidemiology, biologic mechanisms, the impact of infertility treatments, prenatal diagnosis (including a more extensive and detailed coverage of ultrasound imaging in multiple pregnancy), and fetal therapy.

Isaac Blickstein, from the Kaplan Medical Center and the Hadassah-Hebrew University School of Medicine, Jerusalem, is Chairman of the Working Group on Multiple Pregnancy of the International Society for Twin Studies (ISTS) and one of the most widely quoted contemporary authorities on multiple gestation.

Louis Keith, the President of the Center for Study of Multiple Birth, the past co-President of the ISTS and long-standing member of the Faculty of the Feinberg School of Medicine, Northwestern University, Chicago, is a world-renowned authority on multiples.

Both have published many studies on almost every clinical aspect of multiples and co-edited *'Iatrogenic Multiple Pregnancy: Clinical Implications'* and *'Triplet Pregnancies and their Consequences'* – unique contributions to the field.

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