A Textbook of
POSTPARTUM HEMORRHAGE

A comprehensive guide to evaluation, management and surgical intervention

HRH The Princess Royal

BUCKINGHAM PALACE

It is a pleasure to assist in the promotion of improvement in maternal and child health, both in the developed and the developing world. One of the tragedies of modern life is that 90% of maternal deaths are due to delays in decision making, transfer and treatment of critically ill patients who have bled after childbirth. Many of the mothers who die because of these delays die unnecessarily and the tragedy results in the loss of a mother to her whole family.

This textbook is unique because it is the first effort to bring together information on how to treat significant bleeding after childbirth, and I am confident that this British initiative will make an important contribution to the better understanding of how to save these women's lives.

I hope that heathcare communities worldwide will use this material to save lives, and encourage appropriate authorities to provide essential services which will improve the health of both women and their families.

This book is dedicated to all women who have died from postpartum hemorrhage and to those who strive to prevent and overcome it.

A Textbook of POSTPARTUM HEMORRHAGE

A comprehensive guide to evaluation, management and surgical intervention

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***With a Special Message from* HRH The Princess Royal**

***and a Foreword by* Arnaldo Acosta, President of the International Federation of Gynecology & Obstetrics, FIGO, *and* André B. Lalonde, Co-Chair of FIGO Save The Mother and Newborn Health Committee**

SAPIENS PUBLISHING

All the authors and editors have contributed to this publication on a strictly charitable basis and have received no remuneration of any kind for their contributions.

This book, and other elements in the programme, are being produced and published on a not-for-profit, charitable basis by the proprietors of Sapiens Publishing in loving and grateful memory of their daughter ABIGAIL BLOOMER, who worked alongside them in medical publishing for a number of years and who sadly died at the early age of 31 from breast cancer in December 2001. Abigail was especially involved in publishing on women's health issues. She is greatly missed.

Abigail Bloomer, 1970–2001

The book, which is available through the normal commercial channels in the Western World, is being provided free to a large number of selected physicians in developing countries and at a special low price to members of all national obstetric and gynecological societies worldwide. The whole book is also available entirely free of charge on the internet, via the Publishers' website, where it may be read or downloaded chapter by chapter by anyone at any time.

A CD-ROM of the book, designed as a resource for lecturers and teachers, is being produced. In addition, an aide-mémoire poster on surgical techniques and also practical ***Guidelines for Immediate Action*** leaflet/wallchart for midwives and clinical assistants are both being published. All these items are being made available free of charge, on a selective basis. Please contact the Publishers at the address below for further information.

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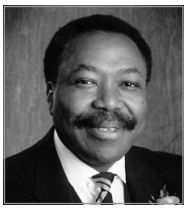

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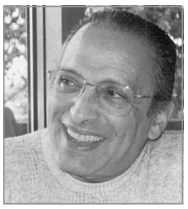

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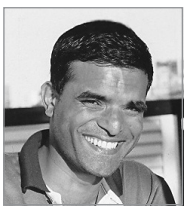

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The surgical illustrations (in color) in this book have been prepared by Philip Wilson, Medical and Scientific Illustrator, Old Coulsdon, Surrey, UK.

Foreword

This book, launched at the Presidential Symposium at the XVIII World Congress of the International Federation of Gynecology and Obstetrics (FIGO) in 2006 in Kuala Lumpur, Malaysia, marks an important day in the battle for improved treatment possibilities for postpartum hemorrhage. Beginning in October 2003 at the World Congress in Santiago, Chile, FIGO launched an international effort with other partners and donors to develop strategies to prevent postpartum hemorrhage and, in the cases where it still occurred, to identify effective medical and surgical treatments.

There is no controversy about the need for prevention and treatment of postpartum hemorrhage. Recent evidence from the World Health Organization strongly suggested that deaths due to postpartum hemorrhage were underestimated and could reach as high as 40% of all maternal mortality in some African countries as well as South Africa, South-East Asia and Latin America. Indeed, postpartum hemorrhage is the cause of close to 50% of maternal mortality in Guatemala and Afghanistan.

In the last 25 years, the world has seen only minimal progress in low-resource countries to reduce the incidence of postpartum hemorrhage and the resulting maternal mortality and morbidity. This new book is part of a world-wide effort to prevent postpartum hemorrhage and offer new perspectives in the medical and surgical treatment options. The first and foremost problem that is addressed is the lack of definition and the difficulty in assessing blood loss during delivery. Amazing as it may sound, blood loss is most often underestimated, and the clinical evaluation is very inaccurate. In the second section of the book, causation is presented, from basic physiology to obstetric trauma. The third section discusses the entire issue of prevention, with an excellent description of the active management of the third stage of labor and how this initiative, undertaken by a number of partners, including the International Confederation of Midwives (ICM), FIGO and the Prevention of Postpartum Haemorrhage Initiative (POPPHI), is beginning to make a difference in many countries. Misoprostol and its use for prevention and treatment are outlined and this will bring the discussion to the forefront on why this low-cost alternative is not more widely used.

Lacerations and trauma following spontaneous instrument delivery are highlighted as well as the management of adherent placenta. Coagulation disorders and disseminated intravascular coagulation are fully reviewed, with a strong chapter on therapy with factor VIIa. Therapy for uterine atony is well illustrated, with a proposal for a postpartum hemorrhage tray in order for midwives and physicians to be prepared for this emergency. In addition, the B-Lynch brace suture is described by the surgeon who first demonstrated its utility. Other new procedures, such as intrauterine tamponade and conservative surgical therapy, are also proposed in detail, with a call for more clinical research about these possible low-cost-effective therapies.

The consequences of postpartum hemorrhage for maternal mortality and morbidity are presented, along with the experiences of Poland, Iran, India and Africa with postpartum hemorrhage.

The FIGO Board, at its December 2005 meeting, approved a motion that calls on all its member countries to delegate to nurses and midwives the use of oxytocin without a doctor's prescription. FIGO has also requested its member countries to work with other health professionals and regulators to ensure that misoprostol is approved for inclusion on the essential drug list. FIGO further developed a questionnaire to evaluate the use of oxytocin and misoprostol as well as the management of the third stage of labor.

Postpartum hemorrhage continues to threaten women's lives in low- and high-resource countries and is the most important cause of maternal mortality in low-resource countries. The majority of cases of postpartum hemorrhage are due to uterine atony and the prevention and treatment are simple, using low-cost technology that unfortunately is not applied.

ICM and FIGO have joined international agencies, in particular USAID, to train and implement active management of the third stage of labor as well as propose low-cost technologies to be used by health-care professionals. FIGO and ICM are calling upon UN agencies and major donors from high-resource countries to support the ongoing effort to reduce maternal mortality due to postpartum hemorrhage. As part of this effort, we heartily endorse this book which is the first-ever compendium of information on a topic that is of vital interest to the medical professions world-wide.

Arnaldo Acosta, MD
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Editors' Foreword

The genesis of this book is unusual in that it was not conceived by any Institution, Organization or Medical College. Rather, it came forth from a perceived need by three individual physicians working in separate institutions (LK, MK and CBL). They decided to initiate the effort and act as Editors. The fourth editor (AL) joined later when he was informed of the project.

Each author who was asked to contribute enthusiastically agreed to do so, often at very short notice in view of the desire to distribute this volume at the XVIII World Congress of the International Federation of Gynecology and Obstetrics (FIGO) in Kuala Lumpur, Malaysia in early November, 2006. Moreover, every author agreed to write with no remuneration whatsoever, having been informed from the outset that the entire project was charitable in nature. With this in mind, decisions were eventually made to make the book available on the internet and to make translation rights by any of the national member societies of FIGO possible at a nominal charge.

The Editors were extremely fortunate to find a like-minded publisher, David Bloomer of Sapiens Publishing in the United Kingdom, who undertook this project in memory of his late daughter, Abigail, who died well before her time of that other scourge of women, namely breast cancer.

The careful reader will undoubtedly note certain duplications in the text. These could have been removed if the book were meant to be read seriatim from cover to cover. However, the Editors are of the opinion that many readers will focus on specific chapters or series of chapters, at least in the beginning, so the duplications were left to stand. We apologize for any inconvenience this may cause an individual reader.

As with any dynamic topic, last-minute changes had to be made to accommodate 'late-breaking news', foremost of which was that which came to light at the International Congress on the Prevention of Post Partum Hemorrhage, held in Goa, India, July 12–16, 2006. Although the manuscript was already in pages, a new section on Specific preventive measures was added to reflect evidence which was not known when the chapters were commissioned. Credit for the incorporation of these changes into the already completely set book goes to Mrs Jean Wright, a senior and experienced editor *par excellence*, who has worked with David Bloomer for many years. Credit and many heartfelt thanks are also due to Mrs Nora Horner, private secretary to Mr B-Lynch, who managed all the e-mail traffic between the Editors and authors connected with the transmission of all manuscripts in electronic format, a formidable task to say the least.

Finally, the Editors join David Bloomer in thanking HRH The Princess Royal for writing a Special Message for this volume and for speaking at the launch held at Chandos House, the Royal Society of Medicine, London, on October 11, 2006.

We sincerely hope that our effort helps all levels of health-care practitioners to work more effectively to save women's lives when postpartum hemorrhage occurs. If that happens but once, then our combined efforts will have been worthwhile.

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September, 2006

Maternal mortality in the developing world – and the special challenge in Africa

The publication of this textbook marks a great milestone in our joint efforts at achieving the Millennium Development Goal 5, which aims to reduce maternal mortality by three-quarters, a daunting task indeed for most developing countries. The African region, especially Eastern and Western Africa, has the highest ratio of women dying as a result of pregnancy or childbirth in the world, estimated at an average of 1000 per 100 000 live births. Half of all the maternal deaths world-wide occur in the African Region, a region that accounts for only 12% of the world's population and about 20% of births. A lifetime risk of 1 in 3000, as is the case in high-income countries, represents a low risk of dying from pregnancy and childbirth, while 1 in 100 is considered a high risk. In Sub-Saharan Africa, for every 16 women, one will die of pregnancy and childbirth-related conditions. It is obvious that a lifetime risk of 1 in 16 is extremely high. This is a direct result of the defects in the social, cultural and economic status of women as well as inadequacies in existing health systems. Available evidence shows that the causes of maternal death include obstructive labor (8%), hypertension disorders (12%), abortion (13%), sepsis (15%), indirect causes such as malaria, anemia and HIV/AIDS (20%) and other direct causes (ectopic pregnancy, embolism and anesthesia-related problems (7%)). Postpartum hemorrhage accounts for 25% of the etiology of maternal mortality; however, it accounts for a third or more maternal deaths in certain countries of the Region. Malaria in pregnancy predisposes women to a number of complications including anemia, which places them at a higher risk of mortality from hemorrhage. Only an estimated 46% of the deliveries in the African Region are assisted by qualified health personnel.

The above situation makes reduction of maternal mortality one of the priorities of the WHO Regional Office for Africa – and we are making strenuous efforts towards improving maternal health and reducing maternal mortality.

This book provides evidence-based practical guidance to build the capacity of health providers in the management of postpartum hemorrhage in both pre-service and in-service training of health providers. As developing countries gear up to increase the availability of qualified personnel with the necessary skills to provide safe motherhood services, drawing on the guidance that this book provides will further urge us to promote safer practices.

The gap between the mortality rates from postpartum hemorrhage in developed countries and developing countries underscores the need for effectiveness and timeliness of the health systems in responding to pregnancy and childbirth-related complications. There is also an urgent need to find low-cost interventions that can

be implemented in resource-poor settings. This text book provides such options. I encourage practitioners, tutors and trainers to apply this book at all levels of care, along with other interventions, such as community participation, to increase the timely and appropriate utilization of health services.

Finally, I would like to assure readers that WHO will continue to work hand-in-hand with all partners, including the research and academic communities, to promote the implementation of evidence-based interventions to improve maternal health in the world.

Dr Luis Gomes Sambo
Regional Director
World Health Organisation Regional Office for Africa

Section I

Demographic and logistical considerations

1

POSTPARTUM HEMORRHAGE TODAY: LIVING IN THE SHADOW OF THE TAJ MAHAL

A. B. Lalonde, B.-A. Daviss, A. Acosta and K. Herschderfer

'Women are not dying because of a disease we cannot treat. They are dying because societies have yet to make the decision that their lives are worth saving.'

Mamoud Fathalla, President of the International Federation of Gynecology and Obstetrics (FIGO), World Congress, Copenhagen 1997

INTRODUCTION

The wife of the Shah Jahan of India, the Empress Mumtaz, had 14 children and died after her last childbirth of a postpartum hemorrhage in 1630. So great was the Shah Jahan's love for his wife that he built the world's most beautiful tomb in her memory – the Taj Mahal[1]. Far away and to the north, another country was taking a different approach: in 1663, the Swedish Collegium Medicum was established. The Swedish clergy created an information system that by 1749 provided the first national vital statistics registry in Europe; by 1757, a national training was approved for midwives in all parishes of Sweden. The resulting infrastructure – a comprehensive community midwifery system, with physician back-up expertise and an outcome reporting system – is today considered responsible for reducing the maternal mortality in Sweden from 900 to 230 per 100 000 live births in the years between 1751 and 1900[2]. To this day, Sweden enjoys the lowest maternal mortalities in the world.

In 2006, each nation must decide whether it is going to build monuments to hardship and suffering or take the steps to avoid it. Although a full 10 years remain until the target date of 2015, it is already predicted that the Millennium Development Goal (MDG) number 5 to reduce maternal mortality (MM) by 75% will not be reached. Maternal mortality is currently estimated at 529 000 deaths per year, a number that translates into a global ratio of 400 maternal deaths per 100 000 live births[3]. Another way to characterize these deaths is to say that one woman dies every minute of every hour of every day.

Most of the deaths and disabilities attributed to childbirth are avoidable, because the medical solutions are well known. Indeed, 99% of maternal deaths occur in developing countries that have an inadequate transport system, limited access to skilled care-givers, and poor emergency obstetric services[4]. It is axiomatic that each and every mother and newborn require care that is close to where they live, respectful of their culture, and provided by persons with enough skill to act immediately should an unpredictable complication occur. The challenge that remains internationally is not technological but strategic and organizational[4].

Postpartum hemorrhage is the most common cause of maternal mortality and accounts for one-quarter of the maternal deaths worldwide[5]. The optimal solution for the vast majority, if not all, of these tragedies is prevention, both before the birth, by assuring that women are sufficiently healthy to withstand postpartum hemorrhage should it occur, and at the time of the birth, by the use of physiological or active management of labor, a management strategy that unfortunately is dependent on circumstances and the availability of oxytocics. To their credit, the International Confederation of Midwives (ICM) as well as the International Federation of Gynecology and Obstetrics (FIGO) are engaging their membership in a world-wide campaign to address this travesty.

DEFINITION AND INCIDENCE

The World Health Organization (WHO) has examined studies on postpartum hemorrhage published between 1997 and 2002 in order to arrive at more precise definitions of postpartum hemorrhage and its incidence[6]. Available resources – data from 50 countries, 116 studies and 155 unique data sets – were reported to be poor in quality. Definitions of postpartum hemorrhage were lacking in 58% of the published studies and, in the population-based surveys of medium quality, the prevalence ranged from a low of 0.55% of deliveries in Qatar to a high of 17.5% in Honduras. Preliminary findings suggest that excessive bleeding was reported between 0.84% and 19.80% of the time, but the majority of studies were reported as low in quality and had problems defining and diagnosing postpartum hemorrhage.

One of the major problems plaguing the research is how to measure postpartum hemorrhage with accuracy. Published data are scant, and an adequate and accurate gold-standard method is lacking. Clinical visual estimation of blood loss is not reliable[7]. As is often the case, necessity becomes the mother of invention. In the rural areas of Tanzania, the use of 'Kanga' has been adopted as a valid instrument tool[8]. Convenient because it is produced and sold locally, the pre-cut Kanga is a standard-sized rectangle (100 cm × 155 cm) of local cotton fabric. When three to four soaked Kangas are observed at a delivery, the trained traditional birth attendant (TBA) is entrusted to transfer patients to a health center.

Even when a good measurement methodology is in place, there is still difficulty in defining postpartum hemorrhage simply as blood loss greater than 500 ml because it fails to take into account predisposing health factors that are reflected in such a definition. Since the quantity of blood loss is less often important than the actual effect that it has on the laboring woman, it has been suggested that the definition take into account any blood loss that causes a major physiological change, such as low blood pressure, which threatens the woman's life. These issues are discussed in greater detail in Chapters 2–6.

POSTPARTUM HEMORRHAGE: WHEN, WHY AND WHERE

Sixty percent of all pregnancy-related maternal deaths occur during the postpartum period and one source suggests 45% of them occur in the first 24 h after delivery[9].

The risk of dying from postpartum hemorrhage depends not only on the amount and rate of blood loss but also the health status of the woman[10]. Poverty, lifestyle, malnutrition, and women's lack of decision-making power to control their own reproductive health are some of the broad issues that have unfortunately come to be accepted as inevitable and unchangeable. In a busy urban maternity hospital, in the country where the Taj Mahal acts as a testament to contravention of this problem, nurses in a labor ward may not complete patient case notes for low-caste women, depriving them of the safeguards of other women[3]. But India's problems are merely a symbolic representation of a problem that faces both high- and low-resource countries[3,4,11]. The insidious reality about having a postpartum hemorrhage is that two-thirds of the women who experience it have no identifiable clinical risk factors such as multiple births or fibroids[12]. In this regard, postpartum hemorrhage is a veritable equal-opportunity occurrence. However, it is not an equal-opportunity killer because it is the poor, malnourished, unhealthy woman who delivers away from medical care who will die from it, whereas those who are fortunate enough to deliver in a well-supplied and staffed medical facility most likely will survive three delays at the actual time of birth: delay in the decision to recognize a complication and seek help; delay in accessing transportation to reach a medical facility, and, finally, delay in receiving adequate and comprehensive care upon arrival.

About 95% of maternal deaths in 2000 were equally distributed between Asia (253 000) and sub-Saharan Africa (251 000)[13], but the risks are higher in Africa because it has a smaller population than Asia. For decades, sub-Saharan Africa has been the region with the highest maternal mortality ratio in the world, at over 900/100 000 live births. In this region, the numbers of births attended by skilled health personnel and life

expectancy at birth strongly correlate with maternal mortality.

As an example, the increased ability to measure maternal mortality in Afghanistan has revealed a heretofore suspected but unconfirmed reality. The Center for Disease Control and Prevention's retrospective cohort study of women of reproductive age in four selected districts in four provinces reported an astounding maternal mortality of 1900 per 100 000 live births[14]. Another group of authors, working in the same country, describes reasons for such a high maternal mortality ratio in the Province of Herat:

> '. . . conditions for individual and community health often depend on the protection and promotion of human rights. The findings of this study identify a number of human rights factors that contribute to preventable maternal deaths in Herat Province. These include access to and quality of health services, adequate food, shelter, and clean water, and denial of individual freedoms such as freely entering into marriage, access to birth control methods and possibly control over the number and spacing of one's children'[15].

In many other countries, hemorrhage accounts for more than half of the maternal deaths, rather than the quarter of maternal mortality usually cited world-wide. For example, in Indonesia it has been reported at 43%, in the Philippines at 53%, and in Guatemala at 53%[4].

Within given countries, certain populations are also at increased risk. In Latin America, for example, the Pan American Health Organization (PAHO) has identified reasons why maternal mortality is higher among the indigenous populations:

(1) The professional teams in charge of maternity care underrate or are ignorant of traditional cultural practices;

(2) The health team and pregnant women often communicate poorly, a principal factor behind the low maternity coverage;

(3) Public policies for consensus building and intercultural dialogue on maternal health are in conflict over objectives and goals and the allocation of resources[16].

EXISTING EVIDENCE FOR PREVENTION OF HEMORRHAGE

In September 2004, Litch provided a summary of the evidence base for the active management of the third stage of labor[17]. The following excerpt summarizes these data:

> 'From 1988 to 1998, four large, randomized, controlled studies conducted in well-resourced maternity hospitals (two in the UK, one in the United Arab Emirates and one in Ireland) compared the effects of active and expectant management of the third stage of labor. In all four studies, active management was associated with a decrease in postpartum hemorrhage and the length of third stage of labor . . . A Cochrane Library systematic review and meta-analysis also concluded that active management of the third stage in the setting of a maternity hospital was superior to expectant management in reducing blood loss, incidence of postpartum hemorrhage and duration of the third stage. It was also associated with reduced postpartum anemia, decreased need for blood transfusion, and less use of additional therapeutic uterotonic drugs'[17].

To a certain extent, the same caveat holds for the usage of prostaglandins where at least two Cochrane Reviews have addressed the issue of this drug as a choice for use in active management. A review in 2003 suggests rectal misoprostol 800 μg may be a useful 'first-line' drug for the treatment of primary postpartum hemorrhage, but that further randomized controlled trials are required to identify the best drug combinations, route, and dose for the treatment of postpartum hemorrhage. In 2004, a review says 'Neither intramuscular prostaglandins nor misoprostol are preferable to conventional injectable uterotonics as part of the active management of the third stage of labor, especially for low-risk women. Future research on prostaglandin use after birth should focus on the treatment of postpartum hemorrhage rather than prevention where they seem to be more promising'[18]. However, this review should be read in the context that many countries do not have the infrastructural elements to provide uterotonics.

Even a WHO multicenter, randomized trial left some issues unresolved. This study concluded that 10 IU oxytocin (intravenous or intramuscular) was preferable to 600 μg oral misoprostol in the active management of the

third stage of labor in hospital settings where active management was the norm[19]. The possible troubling 'secondary effect' of oxytocin on manual removal of the placenta needs clarification, however, as a 2004 Cochrane Review suggested that, with prophylactic use of oxytocin, 'the risk of manual removal of the placenta may be increased'[20]. In high-resource countries, where embolism rather than postpartum hemorrhage is the major cause of maternal mortality, hemorrhage requiring hysterectomy is considered one of the most life-threatening conditions experienced by women during the perinatal period[21]. Retained placenta represents a serious complication requiring manual removal and such a 'secondary outcome' could be as critical to consider when deciding on third-stage management protocols. Because the picture is not yet entirely clear, practitioners should continually update themselves as to available options, and health-care agencies and government planning units should be equally vigilant about what is the best approach considering the available resources.

Thus, although the literature suggests that active management using the standard oxytocics can reduce postpartum hemorrhage by 40%[22], this methodology is far from ideal for use in low-resource countries where the lethal postpartum hemorrhages are occurring, and where many births take place away from medical facilities and are supervised solely by traditional birth attendants who do not have access to medications or the right to use them.

The WHO study did not investigate whether misoprostol was better than placebo. Two recent trials with misoprostol, however, suggest favorable results for the use of this agent in low-resource countries. One was a field intervention trial in Tanzania after home births that demonstrated that implementing the use of 1000 μg of rectal misoprostol administered by TBAs to women with 500 ml or more blood loss decreased referral and need of further treatment when compared to a non-intervention group[23]. The second trial was a randomized, double-blind, placebo-controlled trial that took place among women attended by midwives at local health centers in Guinea-Bissau. Here it was concluded that routine administration of 600 μg of sublingual misoprostol after delivery reduced the frequency of severe postpartum hemorrhage[24]. Both studies state these promising results suggest increased safety of deliveries using misoprostol even when attended by practitioners not considered by the WHO/ICM/FIGO definition to be 'skilled'. Further discussion of ongoing field work with misoprostol is provided in Section IV.

An even more promising alternative method to deal with postpartum hemorrhage was undertaken in Indonesia, where 1811 women were offered counselling about the prevention of postpartum hemorrhage and use of misoprostol by trained and supervised volunteers. This study demonstrated that misoprostol was safely used in a self-directed manner among study participants who had home deliveries in the intervention area[25].

Although misoprostol is available in most countries in Asia and the Americas, there are restrictions to its use in many countries resulting from the fear that it will be used as an abortifacient. There is no access to this agent in most of Africa and much of the Middle East and only three countries have approved the obstetric use of it: Brazil, Egypt and France[26]. Given the potential benefits of misoprostol to the major goal of the MDG #5 (maternal mortality), and the fact that the WHO has added it to its list of 'essential medicines'[27], there appears to be a role for FIGO, ICM and the research community in closing the gaps on research as well as the barriers to availability of this medication.

ONGOING INITIATIVES TO PREVENT POSTPARTUM HEMORRHAGE

Every child-bearing woman is potentially at risk for postpartum hemorrhage, but biological/physiological considerations are only a part of the picture. Broader issues suggest that heath-care workers should assume more of an attitude of service and responsibility in the larger public health issues, empowering women to seek help because the health-care culture is acceptable to them. With respect to indigenous populations and minority groups forgotten or subjugated by a dominant culture, more sensitive approaches that respect pregnancy and birth as a social and cultural rather than a medical act and incorporating traditional practitioners, e.g. the 'partera'

in Central America, into the health-care team, are an important step forward. It is crucial that physicians, midwives, and nurses work with communities and women's groups to bridge existing gaps in care.

An international group including the ICM, FIGO members, researchers and experts met in Ottawa, Canada, in August 2003 to craft the Ottawa Statement on prevention of postpartum hemorrhage and offer new options for its treatment. At the last World Congress of FIGO in Chile in 2003, President Arnaldo Acosta announced that FIGO, in partnership with ICM, would launch an initiative that would promote active management of the third stage of labor (AMTSL) to prevent postpartum hemorrhage and increase the knowledge of nurses, midwives and physicians in the medical and surgical treatment of postpartum hemorrhage. Both FIGO and ICM are collaborating with the Program for Appropriate Technology for Health (PATH) to conduct a project: Prevention of Post Partum Hemorrhage Initiative (POPPHI), launched in October 2004. The program has created tool kits and educational modules for implementation of the AMTSL. POPPHI is also providing small grants to countries for FIGO and ICM members to collaborate on scaling up the use of AMTSL. These initiatives have been prompted in large part by the fact that past efforts have not decreased maternal mortality and morbidity substantially. Postpartum hemorrhage prevention and treatment procedures are well known and are proven to be scientifically beneficial but not readily available to health workers and pregnant women.

The following Joint Statement and Action Plan was launched in 2004 by ICM/FIGO.

JOINT ICM/FIGO STATEMENT AND ACTION PLAN

Management of third-stage labor should be offered to women since it reduces the incidence of postpartum hemorrhage due to uterine atony.

Active management of the third stage of labor consists of interventions designed to facilitate the delivery of the placenta by increasing uterine contractions and to prevent postpartum hemorrhage by averting uterine atony. The usual components include:

- Administration of uterotonic agents,
- Controlled cord traction, and
- Uterine massage after delivery of the placenta, as appropriate.

Every attendant at birth needs to have the knowledge, skills and critical judgement required to carry out active management of the third stage of labor and access to appropriate supplies and equipment.

How to use uterotonic agents

- Within 1 minute of the delivery of the baby, palpate the abdomen to rule out the presence of an additional baby(s) and administer oxytocin 10 units intramuscularly. Oxytocin is preferred over other uterotonic drugs because it is effective 2–3 minutes after injection, and has minimal side-effects so that it can be used on all women.
- If oxytocin is not available, other uterotonics can be used such as: ergometrine 0.2 mg intramuscularly, syntometrine (1 ampoule) intramuscularly or misoprostol 400–600 μg orally. Oral administration of misoprostol should be reserved for situations when safe administration and/or appropriate storage conditions for injectable oxytocin and ergot alkaloids are not possible.
- Uterotonics require proper storage:
  – Ergometrine: 2–8°C and protect from light and from freezing
  – Misoprostol: room temperature, in a closed container
  – Oxytocin: 15–30°C, protect from freezing
- Counselling on the side-effects of these drugs should be given.

Warning! Do not give ergometrine or syntometrine (because it contains ergometrine) to women with pre-eclampsia, eclampsia or high blood pressure.

How to perform controlled cord traction

- Clamp the cord close to the perineum (once pulsation stops in a healthy newborn) and hold in one hand.

- Place the other hand just above the woman's pubic bone and stabilize the uterus by applying counter-pressure during controlled cord traction.
- Keep slight tension on the cord and await a strong uterine contraction (2–3 minutes).
- With the strong uterine contraction, encourage the mother to push and very gently pull downward on the cord to deliver the placenta. Continue to apply counter-pressure to the uterus.
- If the placenta does not descend during 30–40 seconds of controlled cord traction, do not continue to pull on the cord:
  – Gently hold the cord and wait until the uterus is well contracted again;
  – With the next contraction, repeat controlled cord traction with counter-pressure.

Never apply cord traction (pull) without applying counter-traction (push) above the pubic bone on a well-contracted uterus.

- As the placenta delivers, hold the placenta in two hands and gently turn it until the membranes are twisted. Slowly pull to complete the delivery.
- If the membranes tear, gently examine the upper vagina and cervix wearing sterile/disinfected gloves and use a sponge forceps to remove any pieces of membrane that are present.
- Look carefully at the placenta to be sure none of it is missing. If a portion of the maternal surface is missing or there are torn membranes with vessels, suspect retained placenta fragments and take appropriate action[27].

How to perform uterine massage

- Immediately massage the fundus of the uterus until the uterus is contracted.
- Palpate for a contracted uterus every 15 minutes and repeat uterine massage as needed during the first 2 hours.
- Ensure that the uterus does not become relaxed (soft) or 'boggy' after you stop uterine massage.

In all of the above actions, explain the procedures and actions to the woman and her family. Continue to provide support and reassurance throughout.

IMPORTANT CHANGES TO CONSIDER IN ACTIVE MANAGEMENT PROTOCOLS

As the evidence suggesting immediate cord clamping can reduce the quantity of red blood cells an infant receives at birth and result in potential short-term and long-term problems, and because prior concerns about polycythemia have not been documented[28], the collaborative ICM/FIGO group decided not to include early cord clamping in the active management protocol. This decision means that the present definition of active management promulgated by ICM/FIGO differs from that described in the early literature.

FIGO now also advises that, in the absence of oxytocin or misoprostol at delivery, skilled birth attendants should use physiologic management of the third stage to avoid overexertion through cord traction until the uterus has contracted and the placenta has begun being expelled. This is best described as allowing the mother to expel her own placenta without interference from the practitioner.

THE ROLE OF NATIONAL PROFESSIONAL ORGANIZATIONS

The following points outline the ten key action imperatives that are being promoted world-wide by FIGO/ICM to prevent postpartum hemorrhage and manage postpartum hemorrhage when it occurs.

(1) Disseminate and secure support for the joint statement from UN agencies, and international and national organizations.

(2) Recommend that this Global Initiative on the Prevention of Postpartum Hemorrhage be integrated into the curriculum of medical, midwifery and nursing schools.

(3) Work toward the goal of offering uterotonic drugs for prophylactic treatment of postpartum hemorrhage to every

mother giving birth anywhere in the world.

(4) Ensure that every skilled attendant at a birth will have uterotonic drugs and know how to administer them.

(5) Ensure that every hospital birthing unit and every birth center will have uterotonic drugs and a protocol to prevent and manage postpartum hemorrhage.

(6) Give adequate training to every skilled attendant that attends births (including doctors, nurses and midwives) in uterine massage, bimanual compression, and manual removal of the placenta.

(7) Make the use of new simple medical and surgical therapies available to skilled attendants, including the use of intravenous infusion, tamponade balloons, and shock pants[29] (see Chapters 5, 14, 21 and 28).

(8) Provide every doctor who can perform a laparotomy and basic clinical officers who are responsible for the surgical management at the peripheral hospital level, with surgical training to perform 'simple conservative surgery', including compression sutures and sequential devascularization (see Chapter 31).

(9) Make blood transfusion facilities with secure blood supplies available in centers that provide comprehensive health care (see Chapter 45).

(10) Make definitive surgery (hysterectomy) and modern clotting factors (recombinant factor VIIa) available in level III (tertiary care) hospitals (see Chapter 26).

National professional associations also have an important and collaborative roles to play in the following areas:

(1) Advocacy for skilled care at birth;

(2) Public education about the need for adequate prevention and treatment of postpartum hemorrhage;

(3) Publication of the statement in national midwifery, obstetric and medical journals, newsletters and websites;

(4) Dealing with the legislative and other barriers that impede the prevention and treatment of postpartum hemorrhage, including dealing with poverty and malnutrition as well as the incorporation of active management of third stage into pre-service and in-service curricula for all skilled birth attendants;

(5) Incorporation of active management of the third stage of labor in national standards and clinical guidelines, as appropriate;

(6) Working with national pharmaceutical regulatory agencies, policy-makers and donors to assure that adequate supplies of uterotonics and injection equipment are available.

CONCLUSION

Tourists flock to the Taj Mahal, largely unaware how often around the world the event symbolized by this monument still occurs in the shadows of a woman's blood-soaked dirt floor, or when a desperate husband's rough cart is dragged over poor roads and fails to arrive in time, or in the sad eyes of a basic health-unit nurse. Governments have been slow to prioritize women's health and donor countries have not shown sufficient commitment to dealing with maternal mortality. This is in a context in which there is supposed recognition that poverty reduction and education are the keys to good health – that there is no health without education and no education without health[30].

To address the issue of postpartum hemorrhage, ICM and FIGO have launched a worldwide initiative to promote the offer of active management to all women. Further research is needed about the benefits of misoprostol, the secondary side-effects of oxytocin, the anti-shock garment, and the balloon tamponade in preventing and treating postpartum hemorrhage. Both organizations need the support of governments, donors and the public to support the campaign that will produce results in addressing Millennium Development Goal number 5. We respectfully request the professional associations to join the ICM/FIGO coalition to prevent and treat postpartum hemorrhage by working with their Ministries of

Health on the broader issues of poverty, nutrition, status of women, and access to medication and education, while they adopt the low-cost medico-surgical approaches we have discussed in this chapter. Since a good community/national infrastructure designed in Sweden in the 1700s still represents a respectable solution to our millennium goal to save mothers, it appears to be time to act upon the answers that have been staring us in the face for some time.

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2

DEFINITIONS AND CLASSIFICATIONS

A. Coker and R. Oliver

INTRODUCTION

Conventionally, the term 'postpartum hemorrhage' is applied to pregnancies beyond 20 weeks gestation. Although bleeding at an earlier gestational age may have a similar etiology and management to postpartum hemorrhage, these are usually referred to as spontaneous miscarriages.

There has been no significant change in the definitions or classification over the past 50 years; this does not reflect the advances made in medical and surgical treatment over this period[1]. A widely used definition currently is that proposed by the World Health Organization (WHO) in 1990 as 'any blood loss from the genital tract during delivery above 500 ml'[2].

The average blood loss during a normal vaginal delivery has been estimated at 500 ml; however, around 5% of women would lose greater than 1000 ml during a vaginal birth[3–6]. Cesarean deliveries are associated with an average estimated blood loss of 1000 ml[7]. There is, therefore, a degree of overlap in the acceptable range of blood loss for vaginal and Cesarean deliveries.

PURPOSE OF CLASSIFICATION

Classification of postpartum hemorrhage is desirable for the following reasons. First, due to the rapidity of disease progression, there is an overriding clinical need to determine the most suitable line of management. The urgency of intervention depends on the rate of the patient's decline or deterioration.

The second reason for classification is to assess the prognosis. This may help to determine the immediate, medium and long-term clinical outcome. Therefore, a prognostic classification will guide the degree of aggressiveness of the intervention, especially as management may involve more than one clinical specialty. It will also help to decide on the optimal site for subsequent care, for example in a high-dependency unit or intensive care unit, if such exist in the hospital.

The third reason is to allow effective communication based on standardization of the estimate of the degree of hemorrhage, thus standardizing differing management options. The initial assessment is usually made by the staff available on site, and these are often relatively junior medical or midwifery personnel. They, in turn, have to assess the severity of bleeding and summon help or assistance as required. Thus, a standardized easily applicable working classification facilitates effective communication and obviates inter-observer variation.

CLASSIFICATIONS IN USE

Conventional temporal classification

Traditionally, the classification of postpartum hemorrhage has been based on the timing of the onset of bleeding in relation to the delivery. Hemorrhage within the first 24 h of vaginal delivery is termed either early or primary postpartum hemorrhage, whereas bleeding occurring afterwards, but within 12 weeks of delivery, is termed late or secondary postpartum hemorrhage[8].

Secondary postpartum hemorrhage is less common than primary postpartum hemorrhage, affecting 1–3% of all deliveries. In both cases, the true blood loss is often underestimated due to the difficulty with visual quantitation[9,10].

Classification based on quantification of blood loss

Amount of blood lost

Blood loss at delivery is estimated using various methods. These range from the less modern methods of counting blood-soaked pieces of cloth or 'kangas' used by traditional birth attendants in rural settings, to more modern techniques such as calculating the blood loss by subtraction after weighing all swabs using sensitive weighing scales[11].

The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM) describes postpartum hemorrhage as a blood loss of 500 ml or more for a vaginal delivery and 750 ml or more in association with Cesarean delivery[12].

Change in hematocrit

The American College of Obstetricians and Gynecologists advocates the definitions of either a 10% change in hematocrit between the antenatal and postpartum periods, or a need for erythrocyte transfusion[13].

Rapidity of blood loss

In attempts to overcome these inconsistencies, the classification of postpartum hemorrhage has also been based on the rapidity of blood loss. Severe hemorrhage has been classified as blood loss > 150 ml/min (within 20 min, causing loss of more than 50% of blood volume) or a sudden blood loss > 1500–2000 ml (uterine atony; loss of 25–35% of blood volume)[14].

Volume deficit

A form of standardized classification described by Benedetti considers four classes of hemorrhage[15] (Table 1). The class of hemorrhage reflects the volume deficit, and this is not necessarily the same as the volume of blood loss.

Table 1 Benedetti's classification of hemorrhage[15]

Hemorrhage class	*Acute blood loss* (ml)	*Percentage lost*
1	900	15
2	1200–1500	20–25
3	1800–2100	30–35
4	2400	40

Class 1 The average 60 kg pregnant woman has a blood volume of 6000 ml at 30 weeks gestation. A volume loss of less than 900 ml in such a woman will rarely lead to any symptoms and signs of volume deficit and will not require any acute treatment.

Class 2 A blood loss of 1200–1500 ml will begin to manifest clinical signs, such as a rise in pulse and respiratory rate. There may also be recordable blood pressure changes, but not the classic cold clammy extremities.

Class 3 These are patients in whom the blood loss is sufficient to cause overt hypotension. The blood loss is usually around 1800–2100 ml. There are signs of tachycardia (120–160 bpm), cold clammy extremities and tachypnea.

Class 4 This is commonly described as massive obstetric hemorrhage. When the volume loss exceeds 40%, profound shock ensues and the blood pressure and pulse are not easily recordable. Immediate and urgent volume therapy is necessary, as this quantity of blood loss can be fatal secondary to circulatory collapse and cardiac arrest.

Classification based on causative factors

The causes of postpartum hemorrhage can also form a basis of classification (Table 2).

Causes of primary postpartum hemorrhage

Primary postpartum hemorrhage is traditionally considered as a disorder of one or more of the four processes: uterine atony, retained clots or placental debris, genital lesions or trauma, and disorders of coagulation. An aide memoire is the four Ts: tonus, tissue, trauma and thrombin. Uterine atony alone accounts for 75–90% of cases of postpartum hemorrhage.

Table 2 Classification of postpartum hemorrhage (PPH) according to causative factors

Causes of primary PPH
Tonus (uterine atony)
Uterine overdistention: multiparity, polyhydramnios, macrosomia
Uterine relaxants: nifedipine, magnesium, beta-mimetics, indomethacin, nitric oxide donors
Rapid or prolonged labor
Oxytoxics to induce labor
Chorioamnionitis
Halogenated anesthetics
Fibroid uterus
Tissue
Impediment to uterine contraction/retraction: multiple fibroids, retained placenta
Placental abnormality: placenta accreta, succenturiate lobe
Prior uterine surgery: myomectomy, classical or lower segment Cesarean section
Obstructed labor
Prolonged third stage of labor
Excessive traction on the cord
Trauma
Vulvovaginal injury
Episiotomy/tears
Macrosomia
Precipitous delivery
Thrombin (coagulopathy)
Acquired during pregnancy: thrombocytopenia of HELLP syndrome, DIC (eclampsia, intrauterine fetal death, septicemia, placenta abruptio, amniotic fluid embolism), pregnancy-induced hypertension, sepsis
Hereditary: Von Willebrand's disease
Anticoagulant therapy: valve replacement, patients on absolute bedrest
Causes of secondary PPH
Uterine infection
Retained placental fragments
Abnormal involution of placental site

Adapted from Wac *et al. Female Patient* 2005;30:19

Classification based on clinical signs and symptoms

Any bleeding that results in or could result in hemodynamic instability, if untreated, is considered as postpartum hemorrhage (Table 3).

PITFALLS OF CURRENT CLASSIFICATIONS

The drawbacks of a classification based solely on blood loss or hematocrit include the fact that this is a retrospective assessment and may not represent the current clinical situation. To a certain extent, any classification is of limited use to a clinician faced with active and continuous bleeding.

The change in hematocrit depends on the timing of the test and the amount of fluid resuscitation previously administered[16]. It could also be affected by extraneous factors such as prepartum hemoconcentration, which may exist in conditions such as pre-eclampsia.

Where the diagnosis is made by a clinical estimate of blood loss, there is often significant underestimation. The WHO definition of 500 ml is increasingly becoming irrelevant, as

Table 3 Symptoms related to blood loss with postpartum hemorrhage

Blood loss		*Blood pressure*	
%	ml	(mmHg)	*Signs and symptoms*
10–15	500–1000	normal	palpitations, dizziness, tachycardia
15–25	1000–1500	slightly low	weakness, sweating, tachycardia
25–35	1500–2000	70–80	restlessness, pallor, oliguria
35–45	2000–3000	50–70	collapse, air hunger, anuria

Adapted from Bonnar J. *Baillieres Best Pract Res Clin Obstet Gynaecol* 2000;14:1

most healthy mothers in the developed world can cope with a blood loss of less than 500 ml without any hemodynamic compromise.

Classifications based on the need for blood transfusion alone are also of limited value as the practice of blood transfusion varies widely according to local circumstances and attitudes to transfusion of both patients and physicians[17].

The clinical application of such a classification may, in addition, be limited because of inherent individual differences in response to blood loss. Hemodynamic compensation depends on the initial hemoglobin levels prior to onset of bleeding, and these vary among healthy individuals. For these reasons, reliance on a classification solely based on the amount of blood loss and without consideration of clinical signs and symptoms may lead to inconsistency with management.

NEED FOR A CLINICAL AND PROGNOSTIC CLASSIFICATION

Universally, guidelines on the management of postpartum hemorrhage have reiterated the importance of accurate estimation of blood loss, and the clinical condition of the hemorrhaging patient. This was further emphasized in the 1988–1990 Confidential Enquiries into Maternal Deaths in the United Kingdom (CEMD)[18] and reiterated in the 1991–1993 report as a list of six bullet points, the first being 'accurate estimation of blood loss'[19].

The ideal classification of postpartum hemorrhage should take into consideration both the volume loss and the clinical consequences of such loss. The recorded parameters should be easily measurable and reproducible. This will help in providing an accurate and consistent assessment of loss, which can readily be communicated and incorporated into most labor ward protocols.

PROPOSED CLASSIFICATION

The 500 ml limit as defined by WHO[2] should be considered as an alert line; the action line is then reached when the vital functions of the woman are endangered. In healthy women, this usually occurs after the blood loss has exceeded 1000 ml.

We propose a classification (Table 4) wherein the volume loss is assessed in conjunction with clinical signs and symptoms. We propose this classification as being mainly useful in fully equipped hospitals and obstetric units. It is not being proposed for full implementation in areas which are resource-poor.

Our adaptation of a previously described classification[15] will fulfil most of these criteria. This guideline adopts a practical approach whereby a perceived loss of 500–1000 ml (in the absence of clinical signs of cardiovascular instability) prompts basic measures of monitoring and readiness for resuscitation (alert line), whereas a perceived loss of > 1000 ml or a smaller loss associated with clinical signs of shock (hypotension, tachycardia, tachypnea, oliguria or delayed peripheral capillary filling) prompts a full protocol of measures to resuscitate, monitor and arrest bleeding.

Table 4 Proposed classification. Adapted from Benedetti[15]

Hemorrhage class	*Estimated blood loss* (ml)	*Blood volume loss* (%)	*Clinical signs and symptoms*
0 (normal loss)	< 500	< 10	none
	ALERT LINE		
1	500–1000	15	minimal
	ACTION LINE		
2	1200–1500	20–25	↓ urine output ↑ pulse rate ↑ respiratory rate postural hypotension narrow pulse pressure
3	1800–2100	30–35	hypotension tachycardia cold clammy tachypnea
4	> 2400	> 40	profound shock

Need observation ± replacement therapy
Replacement therapy and oxytocics
Urgent active management
Critical active management (50% mortality if not managed actively)

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3

VITAL STATISTICS: AN OVERVIEW

M. J. Cameron and S. C. Robson

INTRODUCTION

Postpartum hemorrhage constitutes a major cause of maternal mortality, particularly in the developing world, and of maternal morbidity in both the developed and the developing world. This chapter describes the incidence of primary postpartum hemorrhage, the difficulties in reporting epidemiological data on primary postpartum hemorrhage and the etiology and precipitating factors for primary postpartum hemorrhage. Because of its broad scope, this discussion will invariably include several points that are discussed in greater detail elsewhere. Regardless, these statistics should provide additional insights as many derive from secondary analyses.

DEFINING POSTPARTUM HEMORRHAGE

The traditional definition of primary postpartum hemorrhage used in most textbooks of obstetrics is a visually estimated blood loss of 500 ml or more within the first 24 h after delivery[1]. Secondary postpartum hemorrhage is generally defined as 'excessive bleeding' from the genital tract after 24 h and up to 6 weeks post-delivery (see Chapter 2). As such, this latter definition only contains quantification of the time period rather than the extent of blood loss. However, according to older and commonly quoted data, measured blood loss during a vaginal delivery averages 500 ml whereas that during a Cesarean section averages 1000 ml[2]. Thus, the 'classic' definition of primary postpartum hemorrhage is in reality a reflection of the almost universal tendency to underestimate delivery blood loss (see below and Chapters 4 and 6).

Because a loss of 500 ml at delivery for most women in the developed world does not result in significant morbidity, one might argue that the classic definition of primary postpartum hemorrhage is clinically inappropriate and should be revised to identify a group of women who become 'ill' and at real risk of morbidity after the hemorrhage. If the classic definition were to be changed, definitions of any event leading to severe obstetric morbidity could then be based on 'pathophysiology', 'management' or a combination of both parameters[3]. The problem with using a management-based definition of hemorrhage, such as number of units of blood transfused, is that it can only be used retrospectively and is of no value to the clinician attempting to treat the primary postpartum hemorrhage. Further, such a definition is likely to be highly influenced by local practitioner/hospital beliefs about when to transfuse as well as the local facilities available for transfusion (see Chapter 45). Consequently, according to a recent UK position, it may be better to think of the term 'significant obstetric hemorrhage', using a definition of loss of more than 1000 ml or more than 1500 ml, rather than define primary postpartum hemorrhage as > 500 ml blood loss[4].

In the average non-pregnant adult, circulating blood represents a total of 7% of body weight, or approximately 5 liters. Loss of 30–40% of the circulating volume (1500–2000 ml) results in tachycardia, tachypnea, a measurable fall in systolic blood pressure and alterations in mental state[5]. Therefore, the concept of defining a 'significant primary postpartum hemorrhage' as one resulting in a blood loss of 1500 ml or more is meritorious as this reflects the point when physiological compensatory mechanisms begin to fail. Whether this concept will find universal acceptance remains to be seen, however.

DIFFICULTIES OF COMPARING STUDIES

Two key factors must be considered when comparing published studies of primary postpartum hemorrhage: first, the method used to determine blood loss, and, second, the method of managing the third stage of labor. In addition, confounding represents a potential problem in case-control studies that examine risk factors for primary postpartum hemorrhage.

Determining blood loss: estimating versus measuring

Accurate measurement of blood loss at delivery is possible but must be planned for in advance (see also Chapter 4). The most obvious is collection of blood into receptacles and direct measurement. This can be combined with a gravimetric procedure which depends upon converting the increase in weight of sponges and linen into milliliters of blood on a ml/g basis. Gulmezoglu and Hofmeyr recently proposed a method for directly measuring blood loss objectively which does not interfere with routine care[6]. They suggest 'after delivery of the baby, the amniotic fluid is allowed to drain away and amniotic fluid-soaked bed linen is covered with a dry disposable 'linen saver'. A low-profile, wedge-shaped plastic 'fracture bedpan' is slipped under the woman's buttocks for blood collection, with blood and clots decanted into a measuring cylinder. Weighing of blood-soaked swabs and linen savers occurs, with the known dry weight subtracted and calculated volume added to that from the bedpan.' They particularly recommend this method for all future trials of interventions to reduce primary postpartum hemorrhage. Strand and colleagues suggested a novel method with a combination of a plastic sheet and a bucket below a cholera bed on which the woman rested during postpartum observation[7]. The BRASSS-V collection drape and instructions for use are described in Chapter 4. As with any direct measurement of blood loss, contamination with amniotic fluid and urine is not uncommon.

Laboratory-based methods for measuring blood loss include photometric techniques, whereby sanitary protection is collected and blood pigment converted to acid or alkaline hematin and the concentration then compared in a colorimeter with the patient's own venous blood[8]. Alternatively, volumetric methods involve labelling the woman's plasma or erythrocytes with dyes or radioactive substances and then calculating the reduction in blood volume. Unfortunately, both techniques require expertise and are more time-consuming and expensive to perform than simple measurement of blood loss.

Visual estimation has long been considered to be unreliable, but only recently have data proven this to be the case. Duthie and colleagues compared visual estimation and measured blood loss using the alkaline-hematin method during normal delivery in 37 primigravid and 25 multigravid women. These investigators found that, for both groups, the mean estimated blood loss (261 ml and 220 ml, respectively) was significantly lower than the mean measured blood loss (401 ml and 319 ml, respectively)[9]. This observation is consistent with studies of simulated scenarios that suggest midwives and doctors underestimate blood loss at delivery by 30–50%[10]. Importantly, estimates are particularly unreliable for very small and very large amounts of blood[11] (see Chapter 6).

Reported rates of postpartum hemorrhage also differ widely depending on the method of measuring blood loss. Older studies that directly measured blood loss reported rates of primary postpartum hemorrhage (> 500 ml) of between 22% and 29%[12,13] compared to rates of 5–8% with visual estimation. More recently, Prasertcharoensuk and colleagues compared visual estimation with direct measurement in 228 women who had a spontaneous vaginal delivery[14]. The incidences of postpartum hemorrhage > 500 ml and > 1000 ml were 5.7% and 0.44%, respectively by visual estimation, whereas direct measurements showed incidences of 27.63% and 3.51%, respectively. These differences are five and seven times higher, respectively. The authors concluded that visual estimation underestimated the incidence of postpartum hemorrhage by 89%. Razvi and colleagues conducted a similar prospective study and showed a similar degree of underestimation[15].

Conduct of third stage of labor

Active management of the third stage (AMTSL) involves early clamping of the umbilical cord before pulsations have stopped, controlled cord traction using the Brandt–Andrews technique and the use of prophylactic uterotonics such as syntocinon or syntometrine, usually with the delivery of the fetal anterior shoulder (see also Chapter 11). In contrast, expectant or 'physiological' third stage involves late clamping of the cord after pulsations have stopped, waiting for spontaneous separation of the placenta from the uterine wall and avoidance of synthetic uterotonics. Nipple stimulation has been used to promote the release of endogenous oxytocin and reduce the length and amount of bleeding at the third stage of labor[16], but is not part of active or expectant management. A meta-analysis of five randomized, controlled trials (involving over 6000 women) indicates that active management results in a reduction in maternal blood loss at delivery and a reduction in the risks of postpartum hemorrhage, defined as an estimated blood loss > 500 ml (relative risk (RR) 0.38, 95% confidence interval (CI) 0.32–0.46), severe postpartum hemorrhage, defined as an estimated blood loss ≥ 1000 ml (RR 0.33, 95% CI 0.21–0.51) and prolonged third stage[17].

Clearly, the reported incidence of postpartum hemorrhage in any population is influenced by the conduct of the third stage. As active management is less widely practiced in the developing world, this must be considered when making international comparisons of postpartum hemorrhage rates.

CONFOUNDING FACTORS IN EPIDEMIOLOGICAL STUDIES

Confounding is a potential problem in epidemiologic studies exploring risk factors. A confounder is associated with the risk factor and causally related to the outcome. Thus, a researcher may attempt to relate an exposure to an outcome, but actually measures the effect of a third factor, the confounding variable[18]. As an example, parity, particularly grand multiparity, is generally considered a risk factor for primary postpartum hemorrhage. However, grand multiparas tend to be older and therefore have higher rates of age-related medical diseases, such as diabetes mellitus, which could be the 'true' risk factors for postpartum hemorrhage.

Methods used to control confounders include:

(1) Restriction – in the example cited in the preceding paragraph, women with diabetes mellitus could be excluded. However, restriction limits the external validity of the findings and reduces the sample size.

(2) Matching – here, if diabetes mellitus is deemed a confounder, then for every woman recruited with diabetes mellitus who has a postpartum hemorrhage, she is matched to a control with diabetes mellitus.

(3) Stratification – can be thought of as *post hoc* restriction performed at the analysis phase.

Multivariable analysis is a statistical tool for determining the relative contributions of different causes to a single event or outcome[19]. Epidemiological studies that use multivariable statistical methods are much more likely to eliminate confounders. For readers who require further information about the problems of epidemiological studies, please refer to Grimes and Schultz and Mamdani and colleagues[20,21].

INCIDENCE OF PRIMARY POSTPARTUM HEMORRHAGE

Denominator data

Studies that attempt to quantify the incidence and impact of postpartum hemorrhage need a denominator value over a time period to calculate rates. Common denominators used to calculate maternal mortality and morbidity rates[22] are illustrated in Table 1.

Developed countries, including the United Kingdom, have the advantage of accurate denominator data, including both livebirths and stillbirths. Consequently, the UK Confidential Enquiries into Maternal Deaths have used maternities for denominator data because this enables establishment of a more detailed picture of maternal death rates. However, for many countries, particularly in the developing world, no process of stillbirth (or even livebirth) registration exists. Denominator data are, therefore,

Table 1 Denominators used in calculating maternal mortality and morbidity

Denominator	*Definition*	*Advantages and disadvantages*
Livebirths	Number of pregnancies that result in a livebirth at any gestation	Easier to collect than maternities
Maternities	Number of pregnancies that result in a livebirth at any gestation or stillbirths occurring at or after 24 weeks of completed gestation and required to be notified by law	Includes the majority of women at risk from death from obstetric causes but requires infrastructure for notification of stillbirths
Women aged 15–44 years	Number of women of reproductive age in a given population	Lacks rigor of confining rate to women who were pregnant Enables comparison with other causes of death

likely to be based on livebirths, rather than maternities. Indeed, in some countries even livebirth data collection may not be reliable. As a result, it is often extremely difficult to compare maternal mortality and morbidity from different geographic areas.

Maternal mortality

One method of attempting to quantify the magnitude of postpartum hemorrhage is to look at its contribution to maternal deaths around the world, and in a particular country over time. Trends over time within one country are an important audit tool in examining the care of women with postpartum hemorrhage, as can be seen from the UK Confidential Enquiries into Maternal Deaths. However, differences between countries often reflect differences in health-care provision, general economic prosperity and geographic and climactic conditions that affect access to obstetric care.

Global picture

The WHO estimates that obstetric hemorrhage complicates 10.5% of all livebirths in the world, with an estimated 13 795 000 women experiencing this complication in 2000[22]. Around 132 000 maternal deaths are directly attributable to hemorrhage, comprising 28% of all direct deaths. In comparison, the following numbers relate to other conditions: 79 000 deaths from sepsis, 63 000 deaths from pre-eclampsia/eclampsia, 69 000 from abortion and 42 000 from obstructed labor.

The United Kingdom

A triennial report on confidential enquiries into maternal death has been published since 1985, with reports for England and Wales commencing in 1952. Direct deaths are reported that result from obstetric complications of the pregnant state (pregnancy, labor and puerperium up to 42 days), from interventions, omissions, incorrect treatment or from a chain of events resulting from any of the above. Obstetric hemorrhage (comprising placental abruption, placenta previa and postpartum hemorrhage) is one example of direct deaths[23]. In the 2000–2002 triennium, there were 106 direct maternal deaths. Seventeen (16%) were attributed to obstetric hemorrhage with ten (9.4%) attributed principally to postpartum hemorrhage. Since the UK-wide triennium report began in 1985, 83 deaths from obstetric hemorrhage have been recorded, of which half (41 women) was caused by postpartum hemorrhage, resulting in a death rate for postpartum hemorrhage of 3.1 per million maternities. Calculated death rates for postpartum hemorrhage for each triennium are shown in Table 2.

Although at first glance there appears to be a marked increase in postpartum hemorrhage in the last triennial report compared to the one that immediately preceded it, two patients had no contact at all with health services and two patients refused blood products that would probably have saved their lives. Excluding these four deaths results in a rate per million maternities comparable to the reports published between 1985 and 1996.

Table 2 Maternal mortality from postpartum hemorrhage in UK (extrapolated from CEMACH[23])

Triennium	*Postpartum hemorrhage (n)*	*Total maternities (n)*	*Rate per million maternities*
1985–87	6	2 268 766	2.6
1988–90	11	2 360 309	4.6
1991–93	8	2 315 204	3.4
1994–96	5	2 197 640	2.2
1997–99	1	2 123 614	0.4
2000–02	10	1 997 472	5.0

Of the eight women who sought care in the 2000–2002 cohort and ultimately died from postpartum hemorrhage, elements of substandard care were present in seven (88%) including:

(1) Organizational problems – including inappropriate booking at hospitals with inadequate blood transfusion and intensive care facilities;

(2) Poor quality of resuscitation – including inadequate transfusion of blood and blood products;

(3) Equipment failure, e.g. malfunctioning of specimen transport system;

(4) Inadequate staffing of recovery areas;

(5) Failure to recognize or treat antenatal medical conditions, e.g. inherited bleeding disorders;

(6) Failure of senior staff to attend;

(7) Concerns about the quality of surgical treatment given.

The recognition of these diverse elements provides a blue-print to health-care authorities to institute remedial action (see Chapter 22).

United States of America

The Center for Disease Control (CDC) conducted a pregnancy-related mortality survey in the USA between 1991 and 1999[24]. Hemorrhage in pregnancy was responsible for 17% of maternal deaths, although this figure includes hemorrhage from first-trimester pregnancy complications. Of the 2519 maternal deaths that resulted in a livebirth and the 275 maternal deaths resulting in stillbirth, 2.7% and 21.1%, respectively, were considered to be a direct result from obstetric hemorrhage. Unfortunately, no separate data were provided about postpartum hemorrhage. Comparison with the 1987–1990 data shows a reduction in the percentage of maternal deaths from pregnancy-related hemorrhage from 28.7% to 17%[25].

France

A confidential enquiry into maternal deaths in five of the 22 administrative areas of France found that five deaths from 39 obstetric causes were due to postpartum hemorrhage[26]; implicating postpartum hemorrhage in 13% of the obstetric deaths. No denominator data were collected, and therefore it is not possible to estimate rates.

Africa

Bouvier-Colle and colleagues performed a population-based survey of pregnant women from seven West African areas from 1994 to 1996[27]. Overall, 55 women died from direct or indirect obstetric causes among 17 694 live births. Hemorrhage accounted for 17 deaths (31%), with delivery hemorrhage (third stage) and post-delivery hemorrhage (retention of placenta) accounting for six and four deaths, respectively. This equates to a maternal mortality rate of 565 per 1 000 000 livebirths, a rate approximately 100-fold higher compared to the UK.

Another study in South Africa, involving one tertiary center, reported a maternal mortality rate of 1710 per 1 000 000 livebirths during the period 1986–1992, with 25% of deaths attributed to obstetric hemorrhage[28]. Within this setting, hemorrhage was the leading cause of death.

Maternal morbidity

Because maternal death in the developed world is a rare event, clinicians have attempted to quantify significant morbidity, which is often labelled as a maternal adverse event or a near miss (see Chapter 37). Studies have generally

included massive obstetric hemorrhage as one indicator of severe maternal morbidity. As with mortality, comparisons between studies are often difficult because of variations in definition of 'massive obstetric hemorrhage'. Both antenatal and intrapartum bleeding are sometimes included within the definition of 'obstetric hemorrhage'.

Scotland

The Scottish Programme for Clinical Effectiveness in Reproductive Health (SPCERH) conducted a prospective investigation into 14 severe maternal morbidity categories for all maternity units in Scotland in 2003[3]. Within this audit, major obstetric hemorrhage was defined as estimated blood loss ≥ 2500 ml, or transfusion of ≥ 5 units of blood or the need for fresh frozen plasma or cryoprecipitate. Of the 375 events, 176 (46%) were reported to be related to obstetric hemorrhage. Because some patients experienced more than one morbid event, major obstetric hemorrhage occurred in 65% of 'near-miss patients' (176/270). Using a denominator of 50 157 livebirths, the authors calculated a rate of major obstetric hemorrhage of 3.5/1000 births (CI 3.0–4.1). Of the 176 cases notified to the investigators, full disclosure of data was obtained in 152 cases; 70% of the cases were due to primary postpartum hemorrhage, 26% to intrapartum hemorrhage and 17% to antepartum hemorrhage with some women falling into more than one category.

England

In the South East Thames region, 19 maternity units participated in a 1-year study between 1997 and 1998 to determine the incidence of severe obstetric morbidity[29]. Severe obstetric hemorrhage was defined as estimated blood loss > 1500 ml or a peripartum fall in hemoglobin concentration of ≥ 40 g/l or the need for an acute transfusion of 4 or more units of blood. There were 588 cases of severe obstetric morbidity among 48 856 women delivered over the year, giving an incidence of 12/1000 deliveries. Hemorrhage was the leading cause of obstetric morbidity at 6.7 (CI 6.0–7.5) occurrences per 1000 deliveries, representing nearly two-thirds of cases. However, this study did not include thromboembolic disease, which is the leading cause of direct maternal deaths in the UK.

Canada

Wu Wen and colleagues conducted a retrospective cohort study of severe maternal morbidity involving 2 548 824 women who gave birth in Canadian Hospitals over a 10-year period from 1991, using information on hospital discharges compiled by the Canadian Institute for Health Information[30]. Their criteria for severe maternal morbidity included postpartum hemorrhage requiring hysterectomy or transfusion. Their overall rate of all severe maternal morbidity was 4.38 per 1000 deliveries. Overall rates for severe postpartum hemorrhage in the 10-year time frame are illustrated in Table 3 along with time analysis for rates at the beginning and end of the study. Within this study, rates for postpartum hemorrhage requiring transfusion halved (RR 0.5, CI 0.44–0.55), but hysterectomy rates for postpartum hemorrhage almost doubled (RR 1.76, CI 1.48–2.08). Because the definition of postpartum hemorrhage was based on management rather than pathophysiology, it is difficult to tease out whether the temporal change reflects a true reduction in the incidence of postpartum hemorrhage or simply a change in clinical management.

Africa

Filippi and colleagues conducted prospective and retrospective data extraction on near-miss obstetric events in nine referral hospitals in three countries (Benin, Cote d'Ivoire, and Morocco)[31]. Obstetric hemorrhage was defined as hemorrhage leading to clinical shock, emergency hysterectomy and blood transfusion. The incidence of near-miss cases varied widely between hospitals. Most of the women were already in a critical condition on arrival, with two-thirds being referred from another facility. The study identified a total of 507 cases of late pregnancy obstetric hemorrhage (i.e. previa, abruption and other non-classified hemorrhage and postpartum hemorrhage) from 33 478 deliveries, representing a near-miss late obstetric hemorrhage rate of 15.1/1000 deliveries. In

Table 3 Postpartum hemorrhage (PPH) rates in Canada 1991–2000. Adapted from Wu Wen[30]

	Number of cases (1991–2000)	*Rate per 1000 deliveries (95% CI)*	*Rate per 1000 deliveries (1991–1993)*	*Rate per 1000 deliveries (1998–2000)*	*Relative risk (95% CI)* *
PPH requiring transfusion	2317	0.91 (0.87–0.95)	1.27	0.63	0.5 (0.44–0.55)
PPH requiring hysterectomy	892	0.35 (0.33–0.37)	0.26	0.46	1.76 (1.48–2.08)

*The 1991–1993 period was the reference period

total there were 266 cases of postpartum hemorrhage, representing a near-miss postpartum hemorrhage rate of 7.9/1000 deliveries.

Prual and colleagues examined severe maternal morbidity from direct obstetric causes in West Africa between 1994 and 1996[32]. A severe obstetric event was defined as prepartum, peripartum or postpartum hemorrhage leading to blood transfusion, or hospitalization for more than 4 days or to hysterectomy. A total of 1307 severe maternal morbidity events were identified, with obstetric hemorrhage representing the largest group involving 601 cases, 342 of which were postpartum hemorrhage. The near-miss obstetric hemorrhage rate was 30.5 (CI 28.1–33.0)/1000 live births and the near-miss postpartum hemorrhage rate was 17.4 (CI 15.6–19.3)/1000 live births.

The Pretoria region of South Africa has used the same definition of 'near miss' for over 5 years, allowing comparison of temporal changes[33]. Rates per 1000 births for near misses plus maternal deaths over 5 years from severe postpartum hemorrhage are shown in Table 4. These rates are not dissimilar to those in Canada or the UK.

Table 4 Rates per 1000 births for near misses plus maternal deaths from severe postpartum hemorrhage in Pretoria. Adapted from Pattinson *et al.*[33]

	1997–99	*2000*	*2001*	*2002*
Rate/1000 births	0.96	1.37	2.38	2.28

Table 5 The Four Ts of postpartum hemorrhage (from ALSO[34])

Tone – uterine atony
Trauma – of any part of the genital tract, inverted uterus
Tissue – retained placenta, invasive placenta
Thrombin – coagulopathy

ETIOLOGY AND PRECIPITATING FACTORS

Causes of primary postpartum hemorrhage

In recent years, individual authors and academic groups have used the Four Ts pneumonic to provide a simplistic categorization of the causes of postpartum hemorrhage. This is shown in Table 5[34].

Uterine atony

Uterine atony, the most common cause of postpartum hemorrhage, is reported in 70% of cases[34]. It can occur after normal vaginal delivery, instrumental vaginal delivery and abdominal delivery. A large cohort study found an incidence of uterine atony after primary Cesarean section of 1416/23 390 (6%)[35]. Multiple linear regression analysis demonstrates the following factors as being independently associated with risk of uterine atony: multiple gestation (odds ratio (OR) 2.40, 95% CI 1.95–2.93), Hispanic race (OR 2.21, 95% CI 1.90–2.57), induced or augmented labor for > 18 h (OR 2.23, 95% CI 1.92–2.60), infant birth weight > 4500 g (OR 2.05, 95% CI 1.53–2.69), and clinically diagnosed chorioamnionitis (OR 1.80, 95% CI 1.55–2.09).

Surprisingly, it is much more difficult to find comparable studies of risk factors for uterine

atony in women achieving vaginal delivery. A single center, case-control study from Pakistan reporting on women who had either assisted or non-assisted vaginal delivery found only two factors had a strong association with uterine atony: gestational diabetes mellitus (OR 7.6, 95% CI 6.9–9.0) and prolonged second stage of labor in multiparas (OR 4.0, 95% CI 3.1–5.0)[36]. They found no association with high parity, age, pre-eclampsia, augmentation of labor, antenatal anemia and a history of poor maternal or perinatal outcomes.

Trauma

Trauma is reported to be the primary cause of postpartum hemorrhage in 20% of cases[34] (see also Chapter 9). Genital tract trauma at delivery is associated with an odds ratio of 1.7 (95% CI 1.4–2.1) for postpartum hemorrhage (measured blood loss > 1000 ml)[37]. Similar results were found in a Dutch study with a reported OR of 1.82 (CI 1.01–3.28) for postpartum hemorrhage (≥ 1000 ml) with perineal trauma ≥ first-degree tears[38]. Trauma to the broad ligament, uterine rupture, cervical and vaginal tears and perineal tears are all associated with increased blood loss at normal vaginal delivery.

Inversion of the uterus is a rare cause of postpartum hemorrhage (see Chapter 9). The incidence of inversion varies from 1 in 1584 deliveries in Pakistan[39] to around 1 in 25 000 deliveries in the USA, UK and Norway[40]. Blood loss at delivery with a uterine inversion is usually at least 1000 ml[41], with 65% of uterine inversions being complicated by postpartum hemorrhage and 47.5% requiring blood transfusion in a large series of 40 cases[42].

Tissue

Retained placenta accounts for approximately 10% of all cases of postpartum hemorrhage[34]. Effective uterine contraction to aid hemostasis requires complete expulsion of the placenta. Most retained placentas can be removed manually, but rarely the conditions of placenta percreta, increta, and accreta may be responsible for placental retention (see Chapters 24 and 36). Retained placenta occurs after 0.5–3% of deliveries[43]. Several case–control and cohort studies show that retained placenta is associated with increased blood loss and increased need for blood transfusion. Stones and colleagues reported that retained placenta had a RR of 5.15 (99% CI 3.36–7.87) for blood loss ≥ 1000 ml within the first 24 h of delivery[44]. Bais and colleagues found an incidence of 1.8% for retained placenta in Holland[38]. Using multiple regression, these authors determined that retained placenta was associated with an OR of 7.83 (95% CI 3.78–16.22) and 11.73 (95% CI 5.67–24.1) for postpartum hemorrhage of ≥ 500 ml and postpartum hemorrhage ≥ 1000 ml, respectively. In addition, retained placenta was found to have an OR of 21.7 (95% CI 8.9–53.2) for red cell transfusion in this Dutch cohort.

Tanberg and colleagues reported an incidence of retained placentas of 0.6% in a large Norwegian cohort of 24 750 deliveries and showed that hemoglobin fell by a mean of 3.4 g/dl in the retained placental group compared to no fall in the controls[45]. In addition, blood transfusion was required in 10% of the retained placental group but only 0.5% of the control group. A similar incidence of retained placenta was found in a Saudi Arabian case–control study which demonstrated increased blood loss in women with a retained placenta (mean 437 ml) compared with controls (mean 263 ml)[46]. A large study from Aberdeen of over 36 000 women reported postpartum hemorrhage in 21.3% of women with retained placenta compared to 3.5% in vaginal deliveries without retained placenta[47]. Both studies confirmed that women with a history of retained placenta have an increased risk of recurrence in subsequent pregnancies[46,47]. In the study by Adelusi and colleagues, 6.1% of the patients with retained placenta had a prior history of retained placenta, compared to none in their control group of normal vaginal deliveries[46].

Placental accreta is a rare and serious complication, occurring in about 0.001–0.05% of all deliveries[48,49]. Makhseed and colleagues found an increasing risk for accreta with increasing numbers of Cesarean sections (OR 4.11, 95% CI 0.83–19.34) after one previous Cesarean section and an OR of 30.25 (95% CI 9.9–92.4) after two previous Cesarean sections, compared with no previous Cesarean section. Kastner and colleagues found that placenta accreta was

implicated in 49% of their 48 cases of emergency hysterectomy[50]. Zaki and co-workers found an incidence of 0.05% of placenta accreta in a population of 23 000 women[49]. They found that rates of postpartum hemorrhage and emergency hysterectomy were higher in the accreta group compared to the placenta previa group undergoing Cesarean section. Postpartum hemorrhage occurred in 91.7% of the accreta group compared to 18.4% of the previa group (OR 48.9, 95% CI 5.93–403.25), whereas 50% of accreta cases required emergency hysterectomy compared to 2% in the previa group (OR 48, 95% CI 7.93–290.48). Within the accreta group, 75% of patients had a previous history of Cesarean section, compared to 27.5% in the previa group (OR 7.9, 95% CI 1.98–31.34).

Thrombin

Disorders of the clotting cascade and platelet dysfunction are the cause of postpartum hemorrhage in 1% of cases[34]. Known associations with coagulation failure include placental abruption, pre-eclampsia, septicemia and intrauterine sepsis (see Chapter 44), retained dead fetus, amniotic fluid embolus, incompatible blood transfusion, abortion with hypertonic saline and existing coagulation abnormalities[4,51,52] (see Chapter 25).

ANTENATAL RISK FACTORS FOR PRIMARY POSTPARTUM HEMORRHAGE

Age

Increasing maternal age appears to be an independent risk factor for postpartum hemorrhage. In Japan, Ohkuchi and colleagues studied 10 053 consecutive women who delivered a singleton infant[53]. Excessive blood loss (≥ 90th centile) was defined separately for vaginal and Cesarean deliveries (615 ml and 1531 ml, respectively). On multivariate analysis, age ≥ 35 years was an independent risk factor for postpartum hemorrhage in vaginal deliveries (OR 1.5, 95% CI 1.2–1.9) and Cesarean deliveries (OR 1.8, 95% CI 1.2–2.7). In Nigeria, Tsu reported that advanced maternal age (≥ 35 years) was associated with an adjusted RR of 3.0 (95% CI 1.3–7.3) for postpartum hemorrhage (defined as visual estimation of ≥ 600 ml)[54]. Ijaiya and co-workers in Nigeria found that the risk of postpartum hemorrhage in women > 35 years was two-fold higher compared to women < 25 years, although no consideration of confounding was made in this study[55]. Rates of obstetric hysterectomy have also been reported to increase with age; Okogbenin and colleagues in Nigeria reported an increase from 0.1% at 20 years to 0.7% at ≥ 40 years[56]. However, others have found no relationship between delaying childbirth and postpartum hemorrhage[57].

Ethnicity

Several studies have examined whether ethnicity is a factor for postpartum hemorrhage. Magann and co-workers, using a definition of postpartum hemorrhage of measured blood loss > 1000 ml and/or need for transfusion[37], found Asian race to be a risk factor (OR 1.8, 95% CI 1.4–2.2)). Other studies have observed similar findings in Asians[58] (OR 1.73, 95% CI 1.20–2.49) and Hispanic races (OR 1.66, 95% CI 1.02–2.69)[58] (OR for hematocrit < 26%, 3.99, 95% CI 0.59–9.26)[59].

Body mass index

Women who are obese have higher rates of intrapartum and postpartum complications. Usha and colleagues performed a population-based observational study of 60 167 deliveries in South Glamorgan, UK; women with a body mass index (BMI) > 30 had an OR of 1.5 (95% CI 1.2–1.8) for blood loss > 500 ml, compared to women with a BMI of 20–30[60]. Stones and colleagues reported a RR for major obstetric hemorrhage of 1.64 (95% CI 1.24–2.17) when the BMI was 27+[44].

Parity

Although grand multiparity has traditionally been thought of as risk factor for postpartum hemorrhage, Stones and colleagues and Selo-Ojeme did not demonstrate any relation between grand multiparity and major obstetric hemorrhage[44,61]. This observation was confirmed in a large Australian study which used

multivariate logistic regression analysis and found no association between grand multiparity (≥ five previous births) and postpartum hemorrhage (> 500 ml)[62]. Tsu reported an association with low parity (0–1 previous birth) with adjusted RR without intrapartum factors of 1.7 (95% CI 1.1–2.7) and adjusted RR with intrapartum factors of 1.5 (95% CI 0.95–2.5) but not with grand multiparity (defined as five or more births)[54]. Ohkuchi also found primiparity to be associated with excessive blood loss at vaginal delivery (OR 1.6, 95% CI 1.4–1.9)[53]. Studies from Pakistan[63] and Nigeria[55] have reported an association between grand multiparity and postpartum hemorrhage, but both studies failed to account for other confounding factors such as maternal age.

Other medical conditions

Several medical conditions are associated with postpartum hemorrhage. Women with type II diabetes mellitus have an increased incidence of postpartum hemorrhage of > 500 ml (34%) compared to the non-diabetic population (6%)[64,65]. Connective tissue disorders such as Marfans and Ehlers-Danlos syndrome have also been associated with postpartum hemorrhage[66,67]. Blood loss at delivery is also increased with inherited coagulopathies[52]. The most common inherited hemorrhagic disorder is von Willebrand's disease, with a reported prevalence of between 1 and 3%. Most (70%) have Type 1 disease characterized by low plasma levels of factor VIII, von Willebrand factor antigen, and von Willebrand factor activity. Less common inherited bleeding disorders include carriage of hemophilia A (factor VIII deficiency) or hemophilia B (factor IX deficiency) and factor XI deficiency. In their review, Economaides and colleagues suggest that the risks of primary postpartum hemorrhage in patients with von Willebrand's disease, factor XI deficiency, and carriers of hemophilia are 22%, 16%, and 18.5%, respectively, compared with 5% in the general obstetric population[52]. James also reviewed the numerous case series and the more limited case–control studies of women with bleeding disorders and came to similar conclusions[68] (see Chapter 25).

Prolonged pregnancy

A large Danish cohort study compared a postterm group (gestational age ≥ 42 weeks or more) of 77 956 singleton deliveries and a term group of 34 140 singleton spontaneous deliveries[69]. Adjusted odds ratio for postpartum hemorrhage was 1.37 (95% CI 1.28–1.46), suggesting an association between prolonged pregnancy and postpartum hemorrhage.

Fetal macrosomia

Several studies confirm that fetal macrosomia is associated with postpartum hemorrhage. Jolly and colleagues examined 350 311 completed singleton pregnancies in London[70]. Linear regression analysis suggested that a birth weight > 4 kg was better at predicting maternal morbidity than birth weight > 90th centile. Postpartum hemorrhage was increased in women with fetal macrosomia (OR 2.01; 95% CI 1.93–2.10). In a large cohort of 146 526 mother–infant pairs in California, Stotland and co-workers also demonstrated an adjusted OR for postpartum hemorrhage of 1.69 (95% CI 1.58–1.82) in infants of 4000–4499 g compared to 2.15 (95% CI 1.86–2.48) and 2.03 (95% CI 1.33–3.09) with weights of 4500–4999 g and ≥ 5000 g, respectively[71]. In Nigeria, a case–control study of 351 infants weighing > 4 kg with 6563 term infants found an incidence of postpartum hemorrhage of 8.3% and 2.1%, respectively[72]. Bais and colleagues, in their Dutch study, also demonstrated an increase in risk for postpartum hemorrhage (≥ 500 ml) and severe postpartum hemorrhage (≥ 1000 ml) with infants with weights ≥ 4 kg (OR 2.11, 95% CI 1.62–2.76 and 2.55, 95% CI 1.5–4.18)[38].

Multiple pregnancies

Epidemiological studies suggest twins and higher-order pregnancies are at increased risk for postpartum hemorrhage. Walker and co-workers conducted a retrospective cohort study involving 165 188 singleton pregnancies and 44 674 multiple pregnancies in Canada[73]. Multiple pregnancies were associated with an increased risk for postpartum hemorrhage (RR 1.88, 95% CI

1.81–1.95), hysterectomy (RR 2.29, 95% CI 1.66–3.16) and blood transfusion (RR 1.67, 95% CI 1.13–2.46). Several other studies have estimated the RR of postpartum hemorrhage associated with multiple pregnancies to be between 3.0 and 4.5[44,58,74]. Bais and colleagues, in a Dutch population-based cohort study of 3464 women, used multiple regression analysis and found that the OR for postpartum hemorrhage ≥ 500 ml for multiple pregnancy was 2.6 (95% CI 1.06–-6.39)[38]. Albrecht and co-workers conducted a retrospective review of 57 triplet deliveries and found an incidence of 12.3% for postpartum hemorrhage requiring transfusion[75], and a case series of 71 quadruplet pregnancies conducted by Collins and colleagues estimated that the frequency of postpartum hemorrhage and transfusion to be 21% (95% CI 11–31%) and 13% 95% CI 5–21%), respectively[76]. Magann and colleagues demonstrated an OR for postpartum hemorrhage of 2.2 (95% CI 1.5–3.2) in multiple pregnancies[37], and Stones and colleagues showed a relative risk of 4.46 (95% CI 3.01–6.61) for obstetric hemorrhage with multiple pregnancies[44].

Fibroids

Obstetric textbooks suggest that leiomyomas can be a cause of postpartum hemorrhage. This is mainly based on case reports[77], but one cohort study of 10 000 women in Japan found that women with leiomyomas had an OR of 1.9 (95% CI 1.2–3.1) and 3.6 (95% CI 2.0–6.3) for excessive blood loss at vaginal and Cesarean delivery, respectively[53].

Antepartum hemorrhage

Antepartum hemorrhage has been linked to postpartum hemorrhage risk with an OR of 1.8 (95% CI 1.3–2.3)[37]. Stones and co-workers found a RR for major obstetric hemorrhage (> 1000 ml) of 12.6 (95% CI 7.61–20.9), 13.1 (95% CI 7.47–23) and 11.3 (95% CI 3.36–38.1) for proven abruption, previa with bleeding, and previa with no bleeding, respectively[44]. Ohkuchi and colleagues, in their 10 000 women, demonstrated that a low-lying placenta was associated with odds ratios of 4.4 (95% CI 2.2–8.6) and 3.3 (95% CI 1.4–7.9) for excess blood loss at the time of vaginal and Cesarean delivery, respectively[53]. This study also reported that placenta previa was associated with an OR of 6.3 (95% CI 4.0–9.9) for excessive blood loss at Cesarean delivery.

Previous history of postpartum hemorrhage

Magann and colleagues found previous postpartum hemorrhage to be associated with an increased risk for subsequent postpartum hemorrhage (OR 2.2, 95% CI 1.7–2.9)[37].

Previous Cesarean delivery

The Japanese study demonstrated an odds ratio of 3.1 (95% CI 2.1–4.4) for excessive blood loss at vaginal delivery in women with a previous Cesarean section[53].

INTRAPARTUM RISK FACTORS FOR PRIMARY POSTPARTUM HEMORRHAGE

Induction of labor

Meta-analysis of trials of induction of labor at or beyond term indicates that induction does not increase Cesarean section or operative vaginal delivery rates[78]. However, this meta-analysis did not examine blood loss at delivery. Epidemiological studies suggest a link between induction of labor and postpartum hemorrhage. Brinsden and colleagues reviewed 3674 normal deliveries and found that the incidence of postpartum hemorrhage was increased after induction of labor[79]; among primipara, the incidence was nearly twice that of spontaneous labor, even when only normal deliveries were considered. The study of Magann and colleagues suggested an OR of 1.5 (95% CI 1.2–1.7) for postpartum hemorrhage after induction of labor[37] and Bais and co-workers found an OR of 1.74 (95% CI 1.06–2.87) for severe postpartum hemorrhage of > 1000 ml after induction of labor[38].

Tylleskar and colleagues performed a prospective, randomized, control trial of term induction of labor with amniotomy plus oxytocin versus waiting for spontaneous labor in 84 women and found no difference in the

amount of bleeding at the third stage[80]. A Cochrane review[81] of amniotomy versus vaginal prostaglandin for induction of labor reported no difference in postpartum hemorrhage rates. Another Cochrane[82] review of amniotomy plus intravenous oxytocin included only one placebo-controlled trial, but no data on postpartum hemorrhage were reported. This review compared amniotomy plus intravenous oxytocin against vaginal prostaglandin (two trials, 160 women) and found a higher rate of postpartum hemorrhage in the amniotomy/oxytocin group (13.8% vs. 2.5% respectively, RR 5.5, 95% CI 1.26–24.07)[82].

A review of intravenous oxytocin alone for cervical ripening[83] found no difference in postpartum hemorrhage rates compared to the placebo/expectant management group (three trials, 2611 women; RR 1.24, 95% CI 0.85–1.81) or vaginal PGE_2 (four trials, 2792 women; RR 1.02, 95% CI 0.75–1.4). Use of mechanical methods to induce labor[84] was not associated with any difference in postpartum hemorrhage rates when compared to placebo (one study, 240 women, RR 0.46, 95% CI 0.09–2.31), prostaglandin vaginal PGE_2 (one study, 60 women, RR 3.0, 95% CI 0.33–27.24), intracervical PGE_2 (three studies, 3339 women, RR 0.91, 95% CI 0.40–2.11), misoprostol (one study, 248 women, RR 2.34, 95% CI 0.46–11.85) or to oxytocinon alone (one study, 60 patients, RR 1.0, 95% CI 0.22–4.56).

Meta-analysis[85] of trials of membrane sweeping for induction of labor found a reduction in postpartum hemorrhage compared to no intervention (three trials, 278 women, RR 0.31, 95% CI 0.11–0.89). A review of oral misoprostol for induction of labor[86] did not include any trial that compared this agent with placebo. However, one trial reported in this review, involving 692 women and using PGE_2 in the control arm, found no difference in postpartum hemorrhage rate (RR 0.98, 95% CI 0.73–1.31). Other reviews of induction of labor methods have reported no difference in postpartum hemorrhage rates between vaginal misoprostol when compared to placebo (two trials, 107 women, RR 0.91, 95% CI 0.13–6.37)[87], vaginal prostaglandins (five trials, 1002 women, RR 0.88, 95% CI 0.63–1.22), intracervical prostaglandins (two trials, 172 women, RR 1.62, 95% CI 0.22–12.19), or with oxytocin (two trials, 245 women, RR 0.51, 95% CI 0.16–1.66). Finally, a review of vaginal PGE_2 for induction of labor suggested an increased risk of postpartum hemorrhage compared to placebo[88] (eight studies, 3437 women, RR 1.44, 95% CI 1.01–2.05).

Duration of labor

First stage

Compared with the second stage of labor, limited evidence is available regarding the influence of the duration of the first stage of labor on postpartum hemorrhage[89]. Magann and colleagues defined a prolonged first stage of labor as a latent phase of > 20 h in nulliparous and > 14 h in multiparous and/or an active phase of < 1.2 cm per hour in nulliparous and < 1.4 cm in multiparous patients[37]. These investigators found an OR of 1.6 for prolonged first stage of labor but the 95% CI ranged from 1 to 1.6.

Second stage

Several large studies have explored the relationship between the length of the second stage and adverse maternal and neonatal outcomes. Cohen analyzed obstetric data from 4403 nulliparas and found an increase in postpartum hemorrhage rate after more than 3 h in the second stage[90]. He attributed this to the increased need for mid-forceps delivery. A large retrospective study involving 25 069 women in spontaneous labor at term with a cephalic presentation found that second-stage duration had a significant independent association with the risk of postpartum hemorrhage[91]. A more recent retrospective cohort study of 15 759 nulliparous term, cephalic singleton births in San Francisco divided the second stage of labor into 1-h intervals[92]. Postpartum hemorrhage was defined as estimated blood loss of > 500 ml after vaginal delivery or > 1000 ml after Cesarean delivery. The frequency of postpartum hemorrhage increased from 7.1% when the second stage lasted 0–1 h to 30.9% when it lasted > 4 h. The risk for postpartum hemorrhage with a second stage of > 3 h remained statistically significant when controlled for confounders (including

operative vaginal delivery, episiotomy, birth weight and fetal position) (OR 1.48, 95% CI 1.24–1.78). Myles and colleagues examined 6791 cephalic singleton births and found that the incidence of postpartum hemorrhage was 2.3% in women experiencing a second stage < 2 h compared to 6.2% in women with a longer second stage[93]. Janni and co-workers compared 952 women with a singleton cephalic pregnancy after 34 weeks' gestation with a 'normal' second stage to 248 women with a second stage > 2 h[94]. The median difference between intrapartum and postpartum hemoglobin levels was lower in the normal group (–0.79 g/dl) compared to the prolonged second-stage group (–1.84 g/dl) Multivariate binary logistic regression confirmed duration of the second stage as an independent predictor of postpartum hemorrhage (RR 2.3, 95% CI 1.6–3.3). Magann and colleagues also found an OR of 1.6 (95% CI 1.1–2.1) for prolonged second stage[37].

Third stage

Strong evidence indicates that, despite the use of active management, prolongation of the third stage of labor increases the risk for postpartum hemorrhage. Combs and colleagues studied 12 979 singleton, vaginal deliveries and found that the median duration of the third stage was 6 min (interquartile range 4–10 min)[95]. The incidence of postpartum hemorrhage and blood transfusion remaining constant until the third stage reached 30 min (3.3% of deliveries). Thereafter, it increased progressively, reaching a plateau at 75 min[95]. Dombrowski and colleagues studied the third stage in 45 852 singleton deliveries ≥ 20 weeks' gestation[96]. Postpartum hemorrhage was defined as an estimated blood loss ≥ 500 ml. At all gestational ages, the frequency of postpartum hemorrhage increased with increasing duration of the third stage, reaching the peak at 40 min. Magann and colleagues performed a prospective observational study of 6588 vaginal deliveries[97]. Postpartum hemorrhage was defined as a blood loss > 1000 ml or hemodynamic instability requiring blood transfusion. Postpartum hemorrhage risk was significant (and increased in a dose-related fashion with time) at 10 min (OR 2.1, 95% CI 1.6–2.6), 20 min (OR 4.3, 95% CI 3.3–5.5) and at 30 min (OR 6.2, 95% CI 4.6–8.2). Using receiver operating characteristic (ROC) curves, the best predictor for postpartum hemorrhage was a third stage of ≥ 18 min[97]. Similarly, a Dutch population-based cohort study of 3464 nulliparous women suggested that a third stage of ≥ 30 min was associated with a blood loss of ≥ 500 ml (OR 2.61, 95% CI 1.83–3.72) and ≥ 1000 ml (OR 4.90, 95% CI 2.89–8.32)[38]. Blood loss was determined by a combination of measurement and visual estimation.

Analgesia

A retrospective case–control study involving 1056 and 6261 women with and without epidural analgesia, respectively, found that use of epidural analgesia was associated with intrapartum hemorrhage > 500 ml[98]. Magann and colleagues also found an OR of 1.3 for postpartum hemorrhage with epidural analgesia, but the 95% CI extended from 1 to 1.6[37]. However, if Cesarean delivery is required, regional analgesia is superior to general anesthesia in reducing blood loss, according to evidence from one randomized, controlled trial involving 341 women[99].

Delivery method

The NICE guideline of the UK on Cesarean section examined maternal morbidity in a comparison of planned Cesarean section with planned vaginal birth from available randomized, controlled trials on an intention-to-treat basis[100]. For maternal obstetric hemorrhage (defined as blood loss > 1000 ml), an absolute risk of 0.5% for planned Cesarean section and 0.7% for vaginal birth (RR 0.8, 95% CI 0.4–4.4) was reported, suggesting there is no difference in risk.

Magann and colleagues examined the incidence and risk factors for postpartum hemorrhage in 1844 elective Cesarean sections and 2933 non-elective Cesarean sections[101]. Two criteria were used to define postpartum hemorrhage: measured blood loss > 1000 ml and/or need for blood transfusion and measured blood loss > 1500 ml and/or need for blood transfusion. Six percent of all Cesarean deliveries were complicated by a blood loss > 1000 ml. The postpartum hemorrhage rates for elective Cesarean section (blood loss > 1000 ml –

4.84%, blood loss > 1500 ml – 1.9%) were lower than for non-elective Cesarean delivery (6.75% and 3.04%, respectively). During the 4-year period of this study, there were 13 868 vaginal deliveries with a postpartum hemorrhage rate of 5.15% (blood loss > 1000 ml) and 2.4% (blood loss > 1500 ml)[101]. No data on operative vaginal delivery rate were reported. Although the postpartum hemorrhage rate was higher in women undergoing non-elective Cesarean delivery than after vaginal delivery, the difference in rate for elective Cesarean delivery was not statistically significant different. Using linear regression, risk factors for postpartum hemorrhage at elective Cesarean delivery were leiomyomas, placenta previa, preterm birth and general anesthesia. For non-elective Cesarean delivery, risk factors were blood disorders, retained placenta, antepartum transfusion, antepartum/intrapartum hemorrhage, placenta previa, general anesthesia, and macrosomia.

Combs and colleagues performed a case–control study involving 3052 Cesarean deliveries[102]. They reported a postpartum hemorrhage incidence (based on fall in hematocrit and/or need for blood transfusion) of 6.4% for Cesarean delivery, similar to Magann and colleagues. However, Combs and colleagues did not differentiate elective from non-elective deliveries.

This group also examined 9598 vaginal deliveries and found an overall incidence of postpartum hemorrhage of 3.9%[58]. Using multiple linear regression, they reported an adjusted OR of 1.66 (95% CI 1.06–2.60) for forceps or vacuum extraction use, suggesting that operative vaginal delivery is associated with postpartum hemorrhage. In addition, the use of sequential instruments (forceps after unsuccessful vacuum extraction) to achieve vaginal delivery is a further risk factor (OR 1.9, 95% CI 1.1–3.2)[37] or relative risk of 1.6 (95% CI, 1.3–2.0)[103] for postpartum hemorrhage.

Episiotomy

A Cochrane review argues for restrictive use of episiotomy because this policy is associated with fewer complications[104]. Surprisingly, this meta-analysis does not address the question of postpartum hemorrhage incidence with episiotomy. Iatrogenic trauma by the indiscriminate use of a mid-line or mediolateral episiotomy is associated with increased blood loss and postpartum hemorrhage in most studies, with blood loss increases of between 300 and 600 ml compared with no episiotomy[105,106]. Stones and colleagues reported a relative risk of 2.06 (95% CI 1.36–3.11) for postpartum hemorrhage when episiotomy occurred[44]. Bais and coworkers reported similar results with an OR of 2.18 (95% CI 1.68–-2.81)[38], and Combs and colleagues reported that a mediolateral episiotomy is associated with an odds ratio of 4.67 (95% CI 2.59–-8.43) for postpartum hemorrhage[58]. However, one recent randomized, controlled trial of the use of episiotomy when perineal tears appear imminent suggested no difference in postpartum hemorrhage rates[107].

Chorioamnionitis

Several studies have reported an increased risk for postpartum hemorrhage in the presence of chorioamnionitis, ORs ranging from 1.3 (95% CI 1.1–1.7) at vaginal birth[37] to 2.69 (95% CI 1.44–5.03) at Cesarean section[102] (see Chapter 44).

CONCLUSIONS

Postpartum hemorrhage remains an extremely important cause of maternal mortality and morbidity throughout the world. Sadly substandard care continues to contribute to mortality and morbidity from postpartum hemorrhage, regardless of the country in which death takes place.

Major obstetric hemorrhage complicates around 10% of live births and is responsible for 28% of direct deaths, globally. Marked differences exist between countries; in the UK there are five deaths per million maternities, whereas the figure is 100 times higher in parts of Africa. Severe obstetric hemorrhage is increasingly used as a measure of quality of health care in women. In the UK, severe obstetric hemorrhage occurs in three to seven cases per 1000 livebirths, with postpartum hemorrhage implicated in 70% of cases. In contrast, rates as high as 30.5 per 1000 livebirths are reported in parts of Africa, with postpartum hemorrhage rates of 17.4 per 1000.

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4

PITFALLS IN ASSESSING BLOOD LOSS AND DECISION TO TRANSFER

B. S. Kodkany and R. J. Derman

INTRODUCTION

Pregnancy and childbirth involve health risks, even for women without any pre-existing health problems[1–7]. Obstetric hemorrhage is the single most important cause of maternal death. Of great importance is the inaccurate assessment of blood loss that may result in significant adverse sequelae. Underestimation leads to delayed treatment and overestimation to unnecessary and costly interventions. It is axiomatic that postpartum hemorrhage occurs unpredictably and no parturient is immune from it. Simply stated, postpartum hemorrhage is an equal opportunity killer[8]. Unlike uterine rupture which can precede death by 24 h and antepartum hemorrhage which may lead to death in half that time, postpartum hemorrhage can be lethal in as little as 2 h.

The common definitions of postpartum hemorrhage are described in Chapter 2. Traditionally, blood loss after delivery is visually estimated, with wide variations in accuracy. The importance of accurately measuring vaginal blood loss at delivery was stressed by Williams as early as 1919[9]. The birth attendant grossly makes a quantitative estimate; however, the associated amount of loss is often far greater than appreciated by visual estimation alone[10].

In the past, quantitative methods for estimating vaginal blood loss included direct collection of blood into bedpans or plastic bags; gravimetric methods wherein pads were weighed before and after use and the difference in the weight used to determine the amount of blood lost; determination of changes in blood indices before and after delivery; the acid hematin method, by which blood in the sponges and pads was mixed with a solution that converted hemoglobin to acid hematin or cyanmethemoglobin, which in turn was measured by a colorimeter; plasma volume determinations before and after delivery using radioactive tracer elements; and, finally, measuring blood loss by using ^{51}Cr-tagged erythrocytes.

None of these methods was ever adopted in clinical practice because of their complicated nature or due to the effort, expense and time required to obtain results before beginning interventions. Thus, visual estimation, inaccurate as it may be, continues to be used clinically. Published studies, in which investigators carefully quantified blood loss after delivery, repeatedly indicate that clinical estimates of blood loss are notoriously unreliable, with a tendency to underestimate the incidence of postpartum hemorrhage by 30–50%[1]. As a result, numerous authorities have advocated a more objective approach to the diagnosis of postpartum hemorrhage. Although many studies address this issue, accurate measurement of blood loss by an ideal method remains a gray area.

NORMAL BLOOD LOSS DURING DELIVERY

Investigators report a range of average blood loss during vaginal delivery. For example, at the low end it has been reported as 343 ml in 1000 consecutive term vaginal deliveries, 339 ml and 490 ml, respectively, in two separate studies of 100 and 123 patients using the acid hematin spectrophotometric method, and a 450-ml average blood loss in 123 deliveries using chromium-labeled red blood cells[10–13]. Despite such variations, it is now generally accepted that the average blood loss during delivery is

between 400 and 500 ml, whereas most Cesarean births loose about 1000 ml[14]. Unfortunately, these values are reflective of hospital-based data, primarily among women in the developed world.

PHYSIOLOGICAL ADAPTATIONS IN PREGNANCY

Antepartum adaptations for physiologic blood loss at delivery include a 42% increase in plasma volume and a 24% increase in red blood cell volume by the third trimester[15]. Women who develop pre-eclampsia either experience little or no expansion over non-pregnant levels or lose during the third trimester what gain had been accrued early in gestation[16]. In severe pre-eclampsia, the blood volume frequently fails to expand and is similar to that in a non-pregnant woman[17]. Hemoconcentration is a hallmark of eclampsia with increased sensitivity to even normal blood loss at delivery[18]. Women so afflicted are relatively less prepared to withstand blood loss and may develop life-threatening hypovolemia with smaller amounts of hemorrhage[16].

Progressively complicated deliveries are accompanied by greater degrees of blood loss: vaginal delivery (500 ml), Cesarean section (1000 ml), repeat Cesarean section plus hysterectomy (1500 ml), and emergency hysterectomy (3500 ml)[19–21].

Some of the factors leading to increased blood loss in the third stage of labor are as follows[22–24]:

(1) Mean vaginal blood loss is higher in multiparae than in primiparae;

(2) In primiparae, forceps delivery is associated with greater blood loss than spontaneous delivery; this is related to the episiotomies and other injuries to the genital tract;

(3) Patients with an episiotomy and a laceration lose significantly more blood than those without such insult. Episiotomies contribute 154 ml to the average blood loss[25]. However, forceps delivery does not appear to contribute to blood loss *per se*; any excess bleeding in this instance is due to the episiotomy that is almost always required.

DIAGNOSIS OF POSTPARTUM HEMORRHAGE

Over the years, different methods have been used for estimation of blood loss; these can be classified as clinical or quantitative methods and are delineated below.

Clinical methods

Clinical estimation remains the primary means to diagnose the extent of bleeding and to direct interventional therapy in obstetric practice. Examples include internal hemorrhage due to ruptured tubal pregnancy, ruptured uterus, and the concealed variety of abruptio placentae. The classification of hemorrhage can be based on a graded physiological response to the loss of circulating blood volume (Table 1)[26,27]. This scheme has worked well in the initial management of trauma patients. Knowing that the blood volume of a pregnant woman is 8.5–9% of her weight, one is able to quickly approximate blood loss based on changes in pulse,

Table 1 Classes of hemorrhage

	Class I	*Class II*	*Class III*	*Class IV*
% Blood loss	15	20–25	30–35	40
Pulse (beats/min)	normal	100	120	140
Systolic blood pressure (mmHg)	normal	normal	70–80	60
Mean arterial pressure (mmHg)	80–90	80–90	50–70	50
Tissue perfusion	postural hypotension	peripheral vasoconstriction	pallor, restlessness, oliguria	collapse, anuria, air hunger

systolic blood pressure and mean arterial pressure. Thus, the failure to respond to the initial administration of 3000 ml of crystalloid would suggest a Class II hemorrhage with loss greater than 20–30% of the total blood volume or acute ongoing bleeding[26,27]. A systolic blood pressure below 100 mmHg and a pulse rate above 100 beats/min are late signs of depleted blood volume and indicate commencing failure of compensatory mechanisms[28], whereas acute blood loss might not be reflected by a decrease in hematocrit or hemoglobin level for 4 h or more[26,27]. The importance of diagnosis at a Class I stage cannot be too strongly emphasized as women can progress into Class II rapidly. At level III, unless intervention is rapid and appropriate, women may progress to irreversible shock.

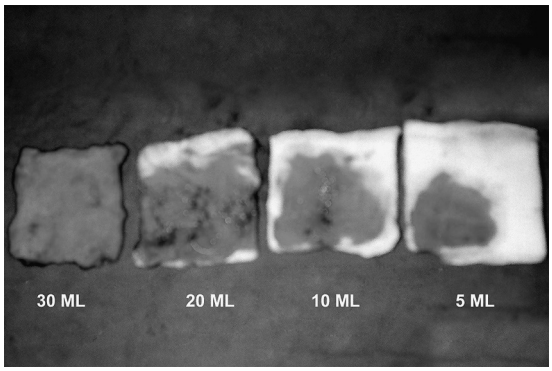

Figure 1 Soakage characteristics of 10 × 10 cm pads

Figure 2 Blood drained into a fixed collecting container

Quantitative methods

Visual assessment

The standard method of observation used for the measurement of blood loss is relatively straightforward and requires no expenditure[8]. Despite its inaccuracy and variation from one care-giver to the next, birth attendants correlate it with clinical signs. A review of the records of 32 799 deliveries at a large municipal hospital during the decade of 1963–1972 found an incidence of postpartum hemorrhage of 4.7/1000 live births or 0.47%. This was extremely low compared to stated rates in the literature, and the author concluded that many cases of postpartum hemorrhage were not recorded due to underestimation of blood loss[29].

The accuracy of this method can be improved by standardization and training. The observer needs to be trained in determining the blood loss using a single collecting container and fixed-sized gauze pads of size 10 × 10 cm. Simulated scenarios with known measured blood volume need to be created and calibrated visually (see Figure 1).

Another method of calculation is by allowing blood to drain into a fixed collecting container (Figure 2) for estimation at the end of 1 h. Blood losses on the delivery table, garments and floor should also be assessed. At the end of 1 h, the total amount of blood lost is estimated by totaling up the blood in the container, in the sponges and secondary blood spillage on the delivery table, garments and floor. How often such calculation is utilized is unknown, but failure to do so undoubtedly contributes to underestimation.

Direct collection of blood into bedpan or plastic bags

This approach was used in the World Health Organization (WHO) multicenter, randomized trial of misoprostol in the management of the third stage of labor[30]. In this trial, blood loss was measured from the time of delivery until the mother was transferred to postnatal care. Immediately after the cord was clamped and cut, the blood collection was started by passing a flat bedpan under the buttocks of a woman delivering in a bed or putting in place an unsoiled sheet for a woman delivering on a delivery table.

Blood collection and measurement continued until the third stage of the labor was completed and the woman was transferred to the postnatal ward. This period was generally up to 1 h postpartum. At that time, the collected blood was poured into a standard measuring jar provided by WHO and its volume measured. To simplify the procedure for measurement of blood loss, any available small gauze swabs soaked with blood were put into the measuring jar and included in the measurement together with the blood and clots. A validity study was performed before the trial to assess the effect of adding the gauze swabs on the estimation of blood loss and was found to result in an approximately 10% increase in the blood loss measurement.

Gravimetric method

This method involves weighing sponges before and after use. The difference in weight provides a rough estimate of blood loss.

Determination of changes in hematocrit and hemoglobin

The changes in values before and after delivery of the hematocrit and hemoglobin levels provide quantitative measurements of blood loss, as depicted in Figure 3.

Acid hematin method

This method is based on collected blood being mixed with a standardized solution which converts hemoglobin to acid hematin or cyanmethemoglobin. This in turn can be measured by a spectrophotometer or colorimeter. Spectrophotometric analysis can be performed by the methods described below[9,31]:

(1) *Preparation of standard* Two milliliters of peripheral blood are collected pre-delivery. The blood standard is prepared with 0.1 ml of the patient's peripheral blood in 9.9 ml of 5% sodium hydroxide solution. The optical density (OD) is read at 550 nm after 30 min;

(2) *Preparation of sample* The collected sample is added to 2 liters of 5% sodium hydroxide and let stand for 15 min. One ml of the filtrate is diluted 10 times in 5% sodium hydroxide and left to stand for another 15 min. The optical density (OD) is read with a spectrophotometer at 550 nm at 30 min after the addition of sodium hydroxide to the sample;

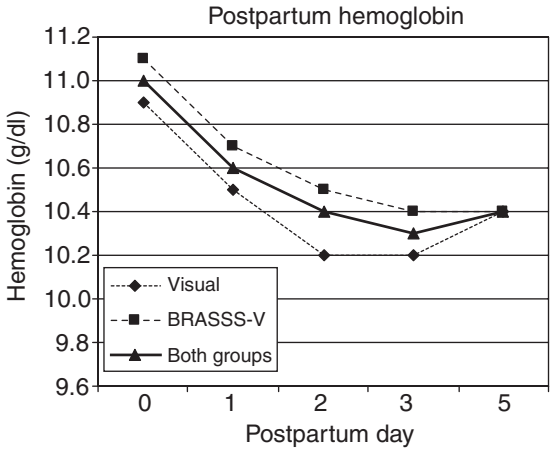

Figure 3 Postpartum hemoglobin changes

(3) *Calculations*

$$\frac{\text{OD sample} \times 2000 \times 10\,\text{ml}}{\text{OD blood standard} \times 100} = \text{Blood volume loss}$$

Plasma volume changes

The plasma volume can be determined before and after delivery using radioactive tracer elements.

Measurement of tagged erythrocytes

Blood loss can be measured by using ^{51}Cr-tagged erythrocytes[13].

Failures of each method

Visual assessment

The major advantage of this method is that it is a real-time assessment and enables the birth attendant to correlate findings, on an individualized basis, with the clinical presentation. However, significant differences between clinical estimates and actual measurements have been consistently demonstrated in several

studies[28]. The most common error is underestimation of blood lost, with an average error of 46% when estimates at the time of delivery are compared with more precise measurements. As might be expected, observers tend to give median or average estimate of blood loss. When losses were large, they were most often underestimated and, when the losses were less than average, they tended to be overestimated[11].

Standardized visual estimation

In an attempt to rectify this error, the use of a standardized visual estimation can be employed as a simple method to be routinely practiced in low-resource setting, albeit based on training the providers and standardization of the pads (size and quality) used during delivery. The accuracy of estimated blood loss is not dependent upon age or the clinical experience of the provider[32–35]. Teaching this tool significantly reduced the error in blood loss estimation for inexperienced as well as experienced clinicians. Of particular clinical importance is a reduction in underestimation of blood loss in the face of greater degrees of measured blood loss; this has the strongest potential to reduce hemorrhage-related morbidity and mortality[36].

Collection in pan or plastic bags

The errors in estimating blood loss arise from failure to collect or note all the blood in stained linen, incomplete extraction from the collection device, ignoring maternal blood within the placenta (approximately 153 ml), confusion related to the mixing of blood contaminated with amniotic fluid and urine, and technical inaccuracies associated with transfer of the collection to a measuring device.

Gravimetric methods

The gravimetric method requires the weighing of materials such as soaked pads on a scale and subtracting the known weights of these materials to determine the blood loss[37]. Inaccuracies can arise at several steps in this procedure, including lack of international standardization of size and weight of gauze, sponges and pads.

Use of blood indices and spectrophotometric measurement of hemoglobin

The first study reporting on measurement of blood loss during surgical procedures employed the colorimetric technique, which required that hemoglobin be washed from surgical materials in a blender and measured in a colorimeter[38]. Clearly, this is impractical in obstetric practice. Routine hematocrit determination, on the other hand, is possible if the equipment is available. However, routine postpartum hematocrits are unnecessary in clinically stable patients with an estimated blood loss of less than 500 ml. After delivery associated with an average blood loss, the hematocrit drops moderately for 3–4 days, followed by an increase. The peak drop may be appreciated on day 2 or day 3 postpartum[39]. By days 5–7, the postpartum hematocrit will be similar to the prelabor hematocrit[15]. Should the postpartum hematocrit be lower than the prelabor hematocrit, the blood loss may have been larger than appreciated[40].

Plasma volume changes and measurement of tagged erythrocytes

Blood volume estimation using dye-dilution or radioisotope dilution techniques is more difficult and requires special equipment and serial measurements[41,42]. Measurement of erythrocytes appears to be more consistent than estimates of plasma volume secondary to physiological hemodilution causing a fluid overload of approximately 1080–1680 ml in pregnancy[14]. Significant cardiovascular changes occur immediately postpartum. The cardiac output remains elevated for 24 h, blood pressure declines initially and then stabilizes on postpartum day 2. Maternal physiological changes of hemodilution lead to reduced hemoglobin and hematocrit values, reflecting the importance of timing of the measurement[43]. In the majority of patients[44], no single timed hemoglobin or hematocrit determination in the first 24 h postpartum will detect the peak.

BRASSS-V DRAPE: BLOOD LOSS COLLECTION TOOL

A randomized, placebo-controlled trial to test the use of oral misoprostol was conducted to

reduce the incidence of acute postpartum hemorrhage and hence maternal morbidity and mortality in women delivering in rural villages (away from major hospitals) within Belgaum District, Karnataka, India. The intervention was delivered by local health-care workers. A critical component of this trial was the development of a specially designed low-cost 'calibrated plastic blood collection drape' that would objectively measure the amount of blood collected in the immediate postpartum period. The BRASSS-V drape was developed by the NICHD-funded Global Network UMKC/JNMC/UIC collaborative team to specifically estimate postpartum blood loss[45,46]. (The name 'BRASSS-V' was coined by adding the first letter of the names of the seven collaborators who developed the drape.) The drape has a calibrated and funneled collecting pouch, incorporated within a plastic sheet that is placed under the buttocks of the patient immediately after the delivery of the baby. The upper end of the sheet has a belt, which is loosely tied around the woman's abdomen to optimize blood collection, particularly for deliveries performed on the floor or on a flat surface at homes or in rural primitive health posts. This simple tool not only has the potential for a more accurate detection of postpartum blood loss, but we hypothesize that this approach will lead to earlier interventions, with an ultimate goal of decreasing maternal morbidity and mortality due to postpartum hemorrhage. Since most developing countries use some form of under-buttock sheet, either at home, in the health center or in hospitals, drape substitution is acceptable and relatively simple. The BRASSS-V calibrated drape used for objective estimation of blood loss is shown in Figures 4 and 5.

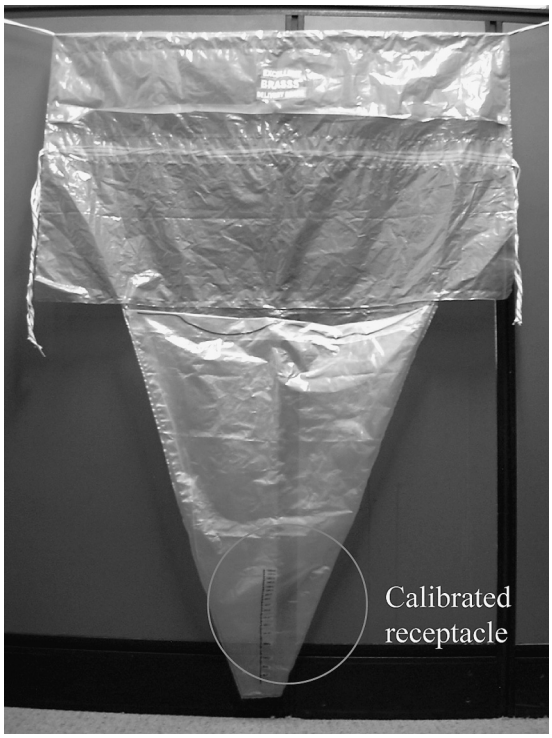

Figure 4 BRASSS-V blood collection drape with calibrated receptacle

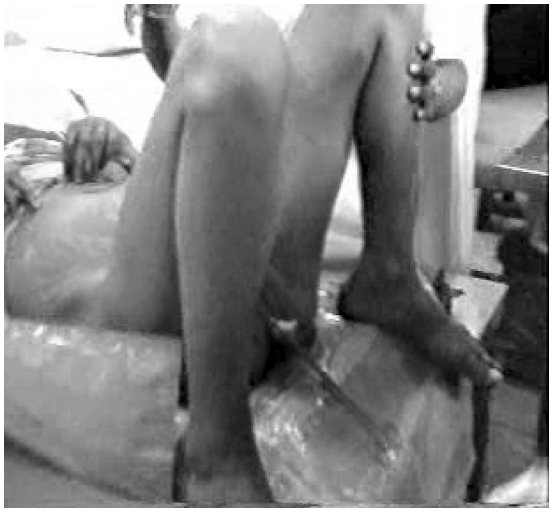

Figure 5 Collection of blood using BRASSS-V blood collection drape with calibrated receptacle

Results of three studies conducted at JNMC, Belgaum, Karnataka, India[4,7] strongly suggest that the BRASSS-V drape is an accurate and practical tool to measure blood loss occurring in the third stage of labor. While, among women with little blood loss, the ranges of blood loss were similar in both visual and drape assessment, the actual visual assessment amount was considerably less compared with the calibrated drape values (Table 2 and Figure 6). This observation further underscores the inaccuracy of the visual estimation method as described in the literature, whereas differences between the drape and spectrophotometry values were found to be 37.15 ml, with the drape having the higher value (an average error of 16.1%). The drape measured blood loss equally and as

Table 2 Distribution of blood loss

	Blood loss (ml)		
	Visual (n = 61)	*Drape* (n = 62)	*All cases* (n = 123)
Mean ± standard deviation	203.11 ± 147.49	302.82 ± 173.28	253.37 ± 168.86
Range	50–950	50–975	50–975

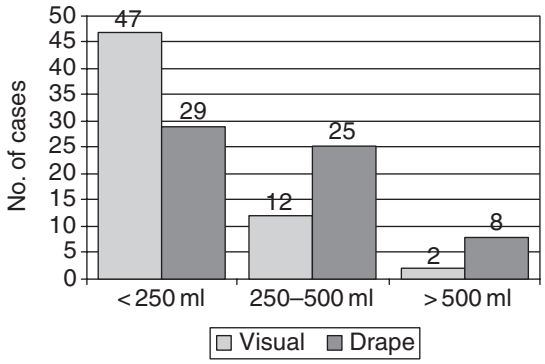

Figure 6 Number of cases detected for specific blood loss ($p < 0.01$). The calibrated drape more accurately determined true blood loss when ≥ 250 ml and more accurately estimated overall levels

Table 3 Comparison between drape-measured and spectrometrically analyzed blood loss

	Blood loss (ml)	
	Drape-measured	*Spectrometry*
Mean ± standard deviation	225 ± 96.10	187.84 ± 61.79
Range	100–350	93.19–285.98

efficiently as gold-standard spectrophotometry (Pearson's correlation coefficient of 0.928; $p = 0.01$, Table 3).

Use of the drape diagnosed postpartum hemorrhage four times as often as the visual estimate. A larger validation study is presently underway at the University of Missouri at Kansas City School of Medicine. In addition, the drape is being tested in a number of international settings including Tibet, Vietnam, Egypt, Ecuador, Brazil and Argentina. Based on the Indian experience, it appears to have great potential for training delivery attendants to determine postpartum blood loss in an accurate and timely manner. The drape, apart from being an objective tool for measurement of postpartum blood loss, also provided a hygienic delivery surface while permitting early management and referral. Residents and nurses in hospital settings and the nurse midwives who used the BRASSS-V drape during home delivery all found it to be a very useful tool to measure blood loss after delivery and for early diagnosis of postpartum hemorrhage; it also led to earlier transfer from rural areas to the higher facility. The women who delivered at home and their family members also appreciated the usefulness of the drape for easy disposal of body fluids after birth[45].

A similar approach has been used in another recently reported study[48]. A plastic collecting bag put under the pelvis of the mother just after delivery can serve as a quantitative and objective method of measuring blood loss. The study goal was to assess sensitivity, specificity, positive predictive value and negative predictive value, including correlation between the bag's volume and hemoglobin and hematocrit variation. The authors conclude that the collecting pelvis bag is a rapid and precise procedure with which to diagnose postpartum hemorrhage in the delivery room. It also enables a visual and quantitative non-subjective estimation of blood loss. Because of its simplicity and very low cost, the pelvis collecting bag may have applicability as a routine preventive measure.

Accurate measurement of blood loss at delivery as a means of early detection of postpartum hemorrhage is necessary for several reasons, not the least of which is the fact that oxytocic agents, while an important component for addressing the third stage of labor, do not address many factors related to postpartum

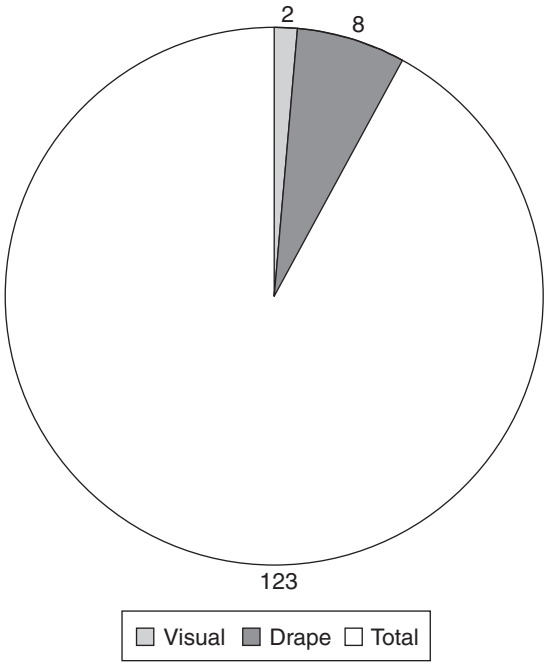

Figure 7 Number of cases of postpartum hemorrhage (PPH) detected for specific blood loss ($p < 0.01$). The calibrated drape diagnosed PPH at a rate four times that of the visual estimate method

hemorrhage in resource-poor areas. Trauma of the birth canal during delivery and retained placental fragments are important causes of postpartum hemorrhage and may occur more often than previously reported. Visual assessment of blood loss in the presence of a contracted uterus may diagnose traumatic postpartum hemorrhage late and therefore result in delayed referrals. In India and many other developing nations, at least half of all births take place in rural areas. Most of these deliveries are conducted by indigenous health-care providers such as dais (traditional birth attendants) or auxiliary nurse midwives having varying levels of training. Blood loss appears to be commonly underestimated, as visual assessment is the only means available to the birth attendant to make this diagnosis. The clinical symptoms of blood loss (low blood pressure, fast pulse, pallor and sweating, signs of hypovolemia and impending shock) are often the primary indicators for intervention. However, relying on the onset of such symptoms may lead to delayed intervention, resulting in increased rates of morbidity and mortality. As other quantitative methods employed have both practical and technical limitations, the employment of simple tools, such as the BRASSS-V under-buttock blood collection drape with a calibrated receptacle, can be effectively employed for objectively assessing the blood loss. It is likely to be of great utility to the midwife/birth attendant and thus help to ensure more timely and accurate patient management. Having identified excessive blood loss, corrective measures can be taken at the earliest time, thus improving outcomes associated with postpartum hemorrhage.

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5

ASSESSING AND REPLENISHING LOST VOLUME

J. G. L. Cockings and C. S. Waldmann

INTRODUCTION

Classically, shock is defined as a state of inadequate tissue perfusion for the metabolic needs of the patient. This state of inadequate blood flow may manifest clinically as tachycardia, pallor, oliguria, the development of lactic acidosis and altered mental status.

Shock is either hypovolemic, cardiogenic, anaphylactic or cytotoxic. Hypovolemic shock classically associated with postpartum hemorrhage is due to loss of circulating blood volume. Hypotension is often present in severe cases, but is a late sign and is a poor guide to the volume of blood lost, as pregnancy is accompanied by an alteration of cardiovascular physiology and the response to blood loss and its management may differ to the non-pregnant situation. Maternal blood volume increases, total red cell mass also increases but to a lesser extent, systemic vascular resistance is reduced, and cardiac output becomes more dependent on body position.

Massive postpartum hemorrhage accounts for 35% of obstetric admissions to intensive care in the UK[1,2]. These patients demand rapid assessment and judicious replenishment of lost circulating volume, albeit within the context of the compensatory effects of hypovolemic shock and the physiological changes seen in late pregnancy.

PHYSIOLOGY

The normal circulating blood volume for a healthy non-pregnant adult is 70 ml/kg, or 7.5% of body weight. Cardiac output is 4–6 l/min, and the non-pregnant adult systemic vascular resistance is 10–15 mmHg/l/min (900–1200 dyne.s/cm^5). Maternal blood volume increases during pregnancy to 40% above baseline by the 30th week, with an accompanying but smaller (20–30%) increase in red cell volume. Cardiac output increases to 50% above pre-pregnancy levels by the 24th week. Systemic blood pressure is more variable in healthy uncomplicated pregnancy, with a small fall in the first and second trimesters, but a return to pre-pregnancy levels by the third. Resting heart rate increases progressively in the first and second trimesters to 15–20 beats per minute above pre-pregnant levels. In addition to these changes, other changes also take place in the autoregulation of intravascular volume and the circulation, both of which affects the body's response to blood loss. Examples include a blunted response to angiotensin II, which may in part be due to an increased production of nitric oxide[3], a decreased tolerance to postural changes and an increased cardiac noradrenaline turnover[4,5].

Circulating volume, clinical signs of hypovolemia and the body's ability to compensate for volume loss are also all affected by pregnancy-related diseases and their treatment, the effects of which continue on into the early postpartum period. Pre-eclampsia, for example, causes a contracted effective arterial blood volume compared with the normal peripartum state. Vascular reactivity is increased, and widely used drugs such as hydralazine and magnesium compromise the body's ability to produce compensatory vasoconstriction in the face of hemorrhage. Indeed, it appears that there is a failure to increase plasma volume and reduce systemic vascular resistance in pre-eclampsia, due to inadequate trophoblastic invasion into the spiral arteries of the uterus[5]. Pre-eclamptic patients thus have an increased tendency to develop pulmonary edema during volume replacement due to many factors, including increased capillary permeability, hypoalbuminemia and left ventricular dysfunction[6].

Normal delivery results in predictable losses of 300–500 ml blood volume for vaginal deliveries and 750–1000 ml for Cesarean section births (see Chapter 4). However, in addition to blood lost from the body, a substantial amount of blood is also redirected into the systemic circulation, often referred to as the autotransfusion effect. This results in an increase in cardiac output by as much as 80%. The effect persists in uncomplicated patients, gradually returning to non-pregnant levels at 2–3 weeks[5].

ASSESSMENT OF CIRCULATING BLOOD VOLUME

Young healthy adults can compensate for the loss of large volumes from the circulation with few obvious external signs. Accurate assessment of blood loss can be difficult for the experienced as well as the inexperienced examiner, as described in Chapter 4.

In cases of hemorrhage symptoms often precede signs. These include unexplained anxiety and restlessness, the feeling of breathlessness (with or without an increased respiratory rate), and a sensation of being cold or generally unwell. For healthy, non-pregnant adults, hypovolemia and associated signs can be divided into four stages (Table 1). These range from the largely undetectable stage 1 with less than 15% loss of volume, to the severe life-threatening stage when more than 40% has been lost. Unfortunately, comparable tables for early and late pregnancy and the immediate postpartum period have not been compiled, but the signs follow a similar pattern.

The most important principle in the treatment of postpartum hemorrhage is early recognition and prompt correction of lost circulating volume, together with simultaneous medical and/or surgical intervention to prevent further loss. Early recognition of life-threatening physiological derangements can be improved by the use of early-warning scoring systems.

Recording physiological observations at regular intervals has long been routine practice in hospitals. Early-warning scores derived from simple routine physiological recordings can identify patients with greater risk of critical illness and mortality. Such scores can be used to flag the early but sometimes subtle signs of concealed but largely compensated hemorrhage in the early postpartum patient and have been recently recommended for use by the Confidential Enquiry into Maternal and Child Health report of 2004[7]. These scores use the physiological parameters most likely to detect impending life-threatening compromise. These usually comprise respiratory rate, heart rate, systolic blood pressure, temperature and mental awareness. Each variable is assigned a weighted score and the total score is the sum of these. This allows a trigger value for ward staff to call for assistance from intensive care or other senior staff. Such systems have been shown to be reproducible and effective at predicting the likelihood of progressing on to critical illness. They are well suited to the early detection of the

Table 1 Stages of shock

Classification	*Class 1*	*Class 2*	*Class 3*	*Class 4*
Blood loss (% volume lost)	10–15%	15–30%	30–40%	> 40%
Conscious state	Alert, mild thirst	anxious and restless	agitated or confused	drowsy, confused or unconscious
Respiratory rate	normal	mildly elevated	raised	raised
Complexion	normal	pale	pale	marked pallor or gray
Extremities	normal	cool	pale and cool	cold
Capillary refill	normal	slow (> 2 s)	slow (> 2 s)	minimal or absent
Pulse rate	normal	normal	elevated	fast but thready
Systolic blood pressure	normal	normal	normal or slightly low	hypotensive
Urine output	normal	reduced	reduced	oligoanuric

Modified from Baskett PJF. ABC of major trauma. Management of hypovolaemic shock. *BMJ* 1990;300: 1453–7

often subtle signs of unappreciated blood loss and can be easily introduced. Altered normal physiology in late pregnancy and the early postpartum period demands that these scores, usually derived from general surgical or medical patients, be modified for this population as shown in Table 2.

Once the possibility of intravascular depletion has been raised, a prompt clinical assessment is urgent, as the clinical condition of the patient can change rapidly. Clinical assessment, in association with non-invasive and invasive monitoring where appropriate, must be made by senior clinicians (if available), with special attention to repeated assessment at frequent intervals to detect the problem as early as possible. If senior clinicians are not available, they should be notified as described in the protocols in Chapters 22 and 50.

Clinical examination is performed simultaneously with incident-related history taking. This history may elicit the more obvious features of shock such as overt blood loss and pain, but may also elicit the more subtle features such as general malaise, anxiety and restlessness, a poorly defined sense of doom and breathlessness. Physical examination is directed to the fundamental areas of vital function, the conscious state and airway protection, the adequacy of respiratory function, oxygenation and circulation. In particular, the following should be assessed and documented:

(1) Early stages of shock are associated with restlessness and agitation, sometimes with a heightened sense of thirst, but these progress to drowsiness when around 30% of blood volume is lost. Loss of consciousness is a very late sign, with significant risk of imminent death.

(2) Tachypnea is an early sign, partly driven initially by the anxiety, but is an independent sign, and the respiratory rate increases with progressive blood loss and will usually exceed 20 breaths/min when 30% of blood volume is lost.

(3) Oxygenation becomes harder to assess clinically as peripheral pallor becomes more marked, and the pulse oximeter becomes less reliable as peripheral perfusion becomes weaker.

(4) A fall in the jugular venous pressure occurs reasonably early, but is partly compensated

Table 2 Modified early obstetric warning system. Reproduced with permission by Dr R Jones, Consultant Anaesthetist, Royal Berkshire Hospital, UK, from unpublished work in progress

	Score						
	3	*2*	*1*	*0*	*1*	*2*	*3*
Respiratory rate (bpm)		< 8		9–18	19–25	26–30	> 30
Pulse rate (bpm)		< 40	40–50	51–100	101–110	111–129	> 129
Systolic blood pressure (mmHg)	< 70	71–80	81–100	101–164	165–200	> 200	
Diastolic blood pressure (mmHg)				< 95	95–104	> 105	
Conscious level	unresponsive	responds to pain	responds to voice	alert	irritated		
Urine hourly (ml/h) or in 24 h	0	< 30 (< 720 ml)	< 45 (< 1000 ml)	> 45 (> 1000 ml)			

Final score = sum of individual scores at any one time

Action:

Score 0 or 1 Repeat observations when appropriate for clinical scenario

Score 2 Inform midwife in charge, repeat in 15 min

Score 3 Inform midwife in charge, obstetric registrar and duty anesthetist

Score ≥ 4 As above but the consultant obstetrician should be informed

Consider informing duty consultant anesthetist and intensive care team

for by a reduction on venous capacitance. However, the jugular veins can be hard to visualize reliably in postpartum women.

(5) A more reliable indication of hypovolemia from the central venous pressure is the poor increase observed following volume administration.

(6) The pulse rate increases after around 15–20% of blood volume has been lost, but this sign can be unreliable as a sinus tachycardia is physiological in late pregnancy and in the early postpartum period.

(7) Capillary refill is slowed after 15% of blood volume is lost and is almost completely absent when 40% of volume is lost.

(8) Blood pressure is well maintained, despite a falling cardiac output and tissue perfusion, until over 30–40% of circulating volume is lost.

MANAGEMENT

When the compensating mechanisms maintaining the blood pressure have been exhausted, the blood pressure can fall dramatically. At this point, shock is advanced and the risk of imminent death is significant. Once significant blood loss has been recognized, volume replacement has begun via large-bore peripheral access, medical therapies have been used and found ineffective, and surgical intervention has been organized, other methods to more accurately assess volume status and adequacy of the circulation should be used to aid clinical assessment.

The first and simplest of these is invasive measurement of central venous pressure. A central venous catheter can be placed in any central vein, but it should be remembered that, in hypovolemia, identification of a central vein may be difficult without the use of ultrasound. The internal jugular vein is the preferred site in this situation, as the femoral vein is relatively inaccessible, and the subclavian route may have a higher risk of complications in late pregnancy and the early postpartum period, especially if inserted under urgent conditions.

The National Institute for Clinical Excellence (NICE) has recently issued guidance stating that cannulation of central veins using two-dimensional ultrasound imaging should be the preferred method, with the evidence strongest for the internal jugular route[8]. In the healthy, non-pregnant adult, the systemic venous capacity is 3–4 liters, or 75% of circulating volume. If the tone of the venous capacitance vessels did not change as volume was lost from the circulation, the central venous pressure would fall quickly and early, with early compromise of the cardiac output. However, as blood volume is lost, the tone in these venous capacitance vessels increases, moving blood centrally, and maintaining central venous pressure.

Confusion surrounding the concept of venous return can be dispelled if it is thought of in terms of right atrial pressure rather than an increased flow of blood to the right atrium. As blood is lost, the volume in the venous capacitance vessels is reduced and the tone in these vessels increases. The central venous pressure falls progressively, but to a lesser degree due to the compensatory increase in this venous tone. Figure 1 shows the relationship between venous capacitance and central venous pressure during acute blood loss and immediate replacement. As blood is lost from the circulation, the patient follows the line A to B (Figure 1). The central venous pressure falls slowly at first, then more steeply as the extent of blood loss increases. As volume is returned to the circulation, the patient will follow first the line B to C and then

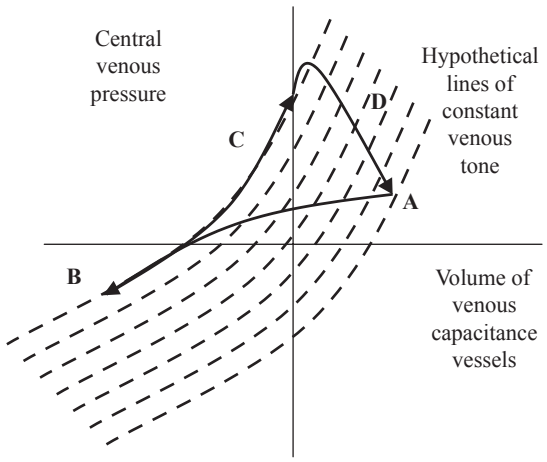

Figure 1 Central venous pressure and venous capacitance during blood loss and replacement. Modified from Bradley RD. *Studies in Acute Heart Failure*. London: Edward Arnold, 1977:11

C to D, rather than simply returning from B to A. This is due to a number of factors and is addressed in a later section in this chapter.

The ability to palpate a peripheral pulse is a good sign, but correlates poorly to any specific arterial pressure. Loss of peripheral pulses is a late preterminal sign of hypovolemic shock. Arterial pressure is most simply measured using a sphygmomanometer. This is familiar to all clinicians and uses a Riva Rocci cuff placed around the upper arm. The correct size of cuff must be chosen, because, if the arm is too large for the chosen cuff, the estimated reading will be falsely high.

Frequently, arterial blood pressure is measured non-invasively by means of an automated version of this technique. Unfortunately, such methods become inaccurate and unreliable when the blood pressure deviates significantly from normal, especially in times of poor peripheral perfusion and hypotension[9], which are the very conditions seen in marked hypovolemia due to postpartum hemorrhage. Automated non-invasive blood pressure devices tend to over-estimate hypotension and under-estimate hypertension. They can repeatedly cycle in an attempt to measure when marked hypotension is present, which can delay its early recognition. Finally, they can sometimes give a totally erroneous reading suggesting an adequate blood pressure when, in reality, the blood pressure is absent or unmeasurable in the face of marked hypovolemic shock, thereby giving a false sense of security[9].

The most reliable method of arterial blood pressure measurement under abnormal or rapidly changing conditions is by means of an intra-arterial cannula and direct measurement via a transducer. This method has the added advantage of providing easy access for blood samples for arterial blood gas analysis and other blood tests. Although such systems commonly used heparinized saline, the use of heparin is unnecessary[10], and the use of plain saline allows samples to be taken for coagulation tests without fear of contamination and erroneous results.

Hemoglobin estimates indicate the concentration of hemoglobin in the sample. The simplicity of this statement only reinforces the point that the concentration of hemoglobin following acute blood loss reflects either medical intervention or the patient's compensation to blood loss. Acute blood loss alone will not change the concentration of hemoglobin in the blood left in the system. The concentration is reduced only when the lost volume is replaced by internal fluid shifts or external fluids are added to the system that are low in hemoglobin. If left untreated, however, acute blood loss results in a fall in hemoglobin concentration after about 4–6 h due to internal compensatory fluid shifts. In contrast, intravenous administration of fluid will dilute the hemoglobin more quickly.

Further information regarding the circulation status can be gained by more invasive or complex techniques. These include the pulmonary artery catheter, pulse contour analysis, and the esophageal Doppler technique. The measurement of cardiac output by means of the thermodilution technique using a pulmonary artery catheter was first described by Bradley and Branthwaite in 1968[11] and subsequently popularized by Swann, Ganz and co-workers[12]. Despite being the gold standard for invasive assessment of cardiac output and left atrial pressure for several decades, the technique has become less favored of late amid gathering evidence that the risks may outweigh the benefits in many circumstances[13]. The benefit of the pulmonary artery catheter is that it provides reliable measurements even in the face of changing body position and is equally effective in the awake conscious patient and the sedated or anesthetized patient receiving artificial ventilation. The risks include those associated with the insertion of a large-bore cannula into a central vein, which is higher risk in the volume-deplete patient suffering massive blood loss, even with the aid of the two-dimensional ultrasound technique. The risks also relate to risks of infection, cardiac arrhythmias, pulmonary artery damage and lung injury. Review of the use of the pulmonary artery catheter in the obstetric population[14] shows that most of the experience has been in patients with pre-eclampsia and eclampsia rather than massive postpartum hemorrhage.

Fortunately, pulse contour analysis is a realistic alternative to the pulmonary artery catheter[15]. The system requires only standard peripheral arterial and central venous cannulae.

A common example of this technique uses cardiac output estimated initially and periodically thereafter by the lithium dilution technique (LiDCO Ltd., Cambridge, UK[16]). The pressure waveform is analyzed using this static cardiac output measurement as a reference to estimate a stroke volume. Changes to the pulse waveform and heart rate from this point are used to estimate stroke volume and cardiac output on a continuous display. Calibration is performed by periodic re-assessment of the cardiac output using the lithium dilution technique. Limitations relate to issues of non-linearity or aortic compliance, how closely the radial arterial pulse waveform resonance relates to the proximal aortic waveform and, therefore, stroke volume, the common problems of damped arterial waveforms, drift between static measurements of cardiac output, and problems associated with poor transmission of pulse waves in severe arrhythmias[17]. Despite these concerns, this technique can provide a continuous idea of cardiac output, systemic blood pressure and vascular resistance in any patient with central venous and peripheral arterial access and is well suited for monitoring the postpartum patient who has undergone massive hemorrhage and is undergoing resuscitation. Other pulse contour analysis systems are also commercially available that use alternative methods for measurement of the reference cardiac output, such as the PiCCO system (Pulsion Medical Systems, Munich, Germany) which employs a transpulmonary thermodilution measurement from an axillary or femoral artery.

REPLENISHING LOST VOLUME

Replacing lost circulating volume should commence as soon as significant bleeding is recognized and, ideally, before the signs of significant hypovolemia have developed. Important initial measures are to simultaneously provide supplemental oxygen, ensure multiple large-bore peripheral intravenous access, undertake an initial rapid clinical assessment and summon senior members of assistance from anesthesia, intensive care, surgical and hematology departments when these individuals are available. Each institution should have a rapid response protocol in place for the management of massive hemorrhage and postpartum hemorrhage in particular. This protocol should be familiar to all, easily accessible and followed (see Chapters 13 and 22).

The principal underlying aim of volume replacement during and following massive postpartum hemorrhage is restoration and maintenance of tissue perfusion to all body organs in order to maintain cellular function and viability. Although the initial focus is on restoration of the common clinical indicators of shock, the clinician must proceed further. Even if all conventionally used criteria resolve, shock may still be present on a cellular, tissue or organ basis[18]. Compensated shock is the term often used to describe the state where conventional hemodynamic parameters have been returned to normal, despite persisting occult tissue hypoperfusion, typically in the splanchnic bed. In spite of adequate volume replacement, patients may develop multiple organ dysfunction with its associated morbidity and mortality.

Replenishing the lost volume must take place simultaneously with control of the bleeding. Medical and surgical attempts to control bleeding must not be delayed by prolonged volume resuscitation in the face of ongoing blood loss. Volume resuscitation should be aimed at restoration of circulating blood volume as well as returning the oxygen-carrying capacity and hemostatic functions to an effective, albeit subnormal, level.

Initial volume replacement enhances right atrial filling and improves cardiac output. As shock develops with blood loss, venous tone increases as described above. Volume administration should be rapid, but titrated to the right atrial filling pressure. Initially, right atrial filling pressure may be restored by a smaller volume than that lost due to the reduced capacity in the venous capacitance vessels. Indeed, immediate rapid re-infusion of the entire volume lost may provoke fluid overload if the tone in the capacitance vessels did not decrease as rapidly. This can be appreciated from Figure 1; here, rapid volume replacement occurs along the line B to C. Central venous pressure rises despite the intravascular compartment remaining depleted. As the venous tone relaxes following resuscitation, further volume administration can occur with a central venous pressure falling toward

normal as the volume in the venous capacitance becomes replete (line C to D). Thus, volume administration should be rapid but infused in discrete volume challenges, with the effect on the right atrial filling pressure, systemic blood pressure and other hemodynamic variables being monitored. Commonly, 250–500 ml of either a crystalloid or a colloid is administered over a period of 10–20 min as the urgency dictates (a patient with life-threatening class 4 shock will receive 2–3 liters more quickly, but, even then, the principles of monitoring the hemodynamic variables during the infusion of fluid remain). Simple measures of tissue underperfusion, which may persist after apparent restoration of global hemodynamics, include the base deficit and serum lactate. Efforts to measure and enhance tissue perfusion should continue until all such parameters return to normal. More specific measures to monitor tissue perfusion, including tissue oxygen tension devices[19] and gastric tonometry[20], are not widely used.

The best fluid to use for volume expansion in hemorrhagic shock remains a matter of debate. Both crystalloid and colloid are effective, but each has advantages and disadvantages[21] (Table 3). One recent large study showed no difference in mortality in intensive care patients requiring volume expansion whether this expansion was made with saline or albumin[22]. Colloids expand the intravascular space preferentially, whereas crystalloids quickly become distributed throughout the extracellular space. Saline has the disadvantage of hyperchloremia, which causes a dilutional or hyperchloremic acidosis[23,24]. The use of crystalloids is not associated with anaphylaxis, whereas colloids such as the gelatins can produce severe life-threatening reactions, although this is less common with hydroxyethyl starch[25]. Crystalloids have minimal effect on coagulation other than a dilutional effect, although saline infusions may have a procoagulant effect[26]. Overall, crystalloids have a lower cost and lower incidence of side-effects, but the colloids have several theoretical advantages regarding tissue edema and oxygen delivery to the tissues. Despite intense debate and research interest, neither crystalloids nor colloids have been shown to be superior to one another regarding survival outcome from hemorrhagic shock.

It is essential that a protocol be available for the use of blood products in instances of massive bleeding. In the UK, the responsibility for maintaining such a protocol lies with the

Table 3 Intravenous fluids

Type of fluid	*Advantages*	*Disadvantages*
Crystalloids		
Saline	cheap; easily available; long history of use	produces a hyperchloremic acidosis; small procoagulant effect
Hartmann's	no risk of anaphylaxis; minimal direct effect on the base deficit; easily available	mildly hypotonic
5% dextrose	no place in acute expansion of the intravascular space	hypotonic; no significant expansion of the vascular space; rapid distribution to intracellular and extracellular spaces
Hypertonic saline	rapid expansion of the intravascular space in excess of the volume infused; possible beneficial effects on red cell and endothelial edema and capillary blood flow	insufficient data; uncertainty regarding possible adverse effects such as on the immune system
Colloids		
Gelatins	largely remains in the intravascular space for 2–4 h	risk of anaphylaxis; no clear survival advantage over crystalloids
4% human albumin	more physiological than gelatins; remains predominantly in the intravascular space for 12 h	expensive; no clear survival advantage over crystalloids
Hydroxyethyl starch	remains in the intravascular space for 12–24 h	risk of coagulopathy, renal injury and reticulo-endothelial accumulation

Hospital Blood Transfusion Committee, a multidisciplinary committee that all hospitals must by law ensure is in place and answerable to the hospital executive. It is unacceptable to have situations where the laboratory insists on blood samples being sent for blood count and coagulation studies before any blood products are issued; the on-call hematology consultant should be actively involved and aid with the use of blood, fresh frozen plasma, platelets, cryoprecipitate and the use of the new recombinant activated Factor VII.

The Trendelenburg position is often used in the management of the hypotensive patient, but its benefit has been questioned. The concept is to displace blood from the lower limbs centrally, to increase preload and enhance cardiac output as a temporary measure until adequate blood volume can be restored. However, there is little proof that this theoretical benefit transpires in practice. Sibbald and colleagues in 1979[27] showed that, in hypotensive patients, the Trendelenburg position did not significantly increase preload, but did increase afterload and blood pressure at the expense of cardiac output. A recent review of available data concludes that the Trendelenburg position 'is probably not a good position for resuscitation of patients who are hypotensive'[28].

The conventional approach to severe hemorrhage, where the endpoint is euvolemia with restoration of a normal blood pressure, heart rate and cardiac output, has been questioned in the out-of-hospital trauma setting[29]. Although not based on evidence from the obstetric population, the physiological rationale may still be applicable. Falling blood pressure and cardiac output, together with increased sympathetic tone and release of endogenous catecholamines, reduce the rate of blood loss. Restoration of these parameters without control of the bleeding will increase the total volume of blood loss, increasing the degree of coagulopathy, reducing oxygen-carrying capacity and ensuing multiple organ dysfunction. Low-volume fluid resuscitation for hemorrhagic shock may be a possibility[30] and the evidence suggests that volume resuscitation should be deliberately limited to the minimum required to sustain vital organ function until the bleeding has been arrested, such as by surgery[29,31].

Recently, small-volume hypertonic resuscitation has been advocated for hemorrhagic shock. The concept is that a relatively small infused volume will cause much larger expansion of the circulation by drawing water into the intravascular compartment. There is evidence that there may be beneficial effects of endothelial and red cell edema and capillary flow, but there are concerns regarding other potentially adverse effects such as that on the immune system[32]. This latter concern has not been shown to be a problem in clinical practice[33].

Maintenance of the hemoglobin concentration is essential to maintain oxygen-carrying capacity and delivery to the tissues. Titration of fluid and blood products to an exact hemoglobin level in a rapidly bleeding patient is difficult. A hemoglobin level of 7–8 g/dl appears an appropriate threshold for transfusion in the intensive-care population, with possible benefit for a higher level of 9 g/dl for those with ischemic heart disease[34]. It is logical to aim at the high end of the target range when resuscitating from hemorrhagic shock as there is a tendency to drift down. A target of 10 g/dl has been suggested as a reasonable goal in the actively bleeding patient[35].

Coagulation disorders are both predisposing factors for, and consequences of, massive postpartum hemorrhage. A bleeding diathesis from a coagulopathy, thrombocytopenia or platelet dysfunction may result from pre-existing disease, a pregnancy-acquired disorder, such as eclampsia, or treatment, such as aspirin. Massive blood loss also creates both a coagulopathy and thrombocytopenia through dilution and consumption. These issues and their management are discussed in detail in Chapters 25 and 26.

SUMMARY

Rapid assessment of the presence of occult bleeding or intravascular volume depletion is essential. The body can compensate for blood loss such that, by the time obvious clinical signs are present, a significant volume can already be lost and tissues already in a state of hypoperfusion. Normal physiological adaptations in late pregnancy that persist into the postpartum period can make recognition and quantification

of intravascular loss difficult, and can render the body less capable of withstanding massive blood loss. This can be further complicated by pregnancy-related disease such as pre-eclampsia and its treatment, and modalities such as hydralazine and magnesium.

Assessment of both the degree of loss and the response to volume replacement require clinical skills, invasive hemodynamic monitoring and the early involvement of senior clinicians. There is no one correct fluid to use. It is usual to use a combination of crystalloids or colloids and blood products to maintain a hemoglobin concentration of near 10 g/dl during the actively bleeding period (7–9 g/dl is probably safe once the active bleeding has been stopped). Coagulopathies and thrombocytopenia also need to be corrected with appropriate transfusion products and with active involvement of the hematologists. There may be a place for limited volume expansion before the bleeding has been stopped surgically to reduce the volume lost, but this must not be at the cost of demonstrable organ ischemia.

Prompt recognition, close monitoring of volume status, rapid arrest of the bleeding and adequate volume resuscitation are all required but when used together can reduce mortality from postpartum hemorrhage.

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6

BLOOD LOSS: ACCURACY OF VISUAL ESTIMATION

A. Patel, R. Walia and D. Patel

As discussed in numerous other chapters, clinical estimation of blood loss is notoriously inaccurate. The degree of inaccuracy varies greatly, with many studies demonstrating that visual estimates range from 30 to 50% of actual losses[1–3]. Of great importance, this inaccuracy increases with increasing blood loss[2]. When translated into clinical practice, underestimation may delay or deter identification and diagnosis of postpartum hemorrhage. This circumstance may result in an unplanned obstetric emergency, with catastrophic outcomes. To overcome this potential problem, multidisciplinary drills to highlight the nature of the problem may be of help, particularly in training programs.

We designed a labor ward drill to provide obstetric care teams an opportunity to assess their blood loss-assessing skills. A multi-station blood loss simulation was designed with seven stations which created opportunities to assess predetermined simulated blood losses. Grape jelly and pomegranate juice were used to simulate clots and blood. Each station had a measured amount, ranging from 50 to 4000 ml. Simulated blood quantities were placed on sanitary pads, delivery pads, basins and drapes and on the floor. This study was approved by the Institution Review Board.

A total of 49 participants completed the skills session. Participants included medical students, physician assistants, nurses, obstetric and gynecologic residents and attending staff. The results of the study are depicted in Figure 1. The findings clearly document the inaccurate estimation of blood estimation, as well as the fact that the accuracy of the estimate decreased with increasing blood volume. This was particularly true above 1000 ml. Of interest, the underbuttocks absorbent delivery pad was most deceptive for estimating. In general, underestimates were similar for liquid and clots, but the 4000 ml

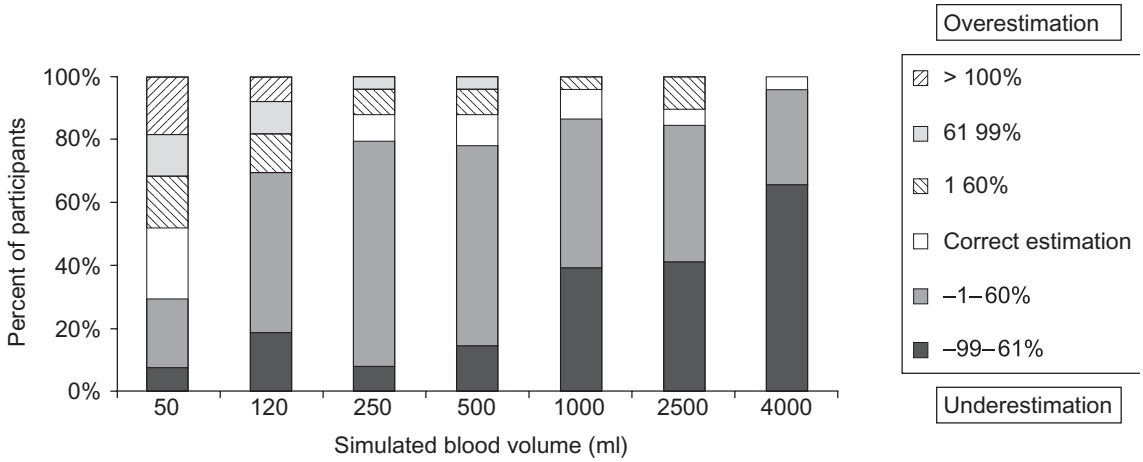

Figure 1 Accuracy of blood volume estimate

station consisted entirely of 'clots' and was most underestimated by the vast majority of participants.

This training program was enlightening for participants to understand the limitations of the visual assessment of blood loss. Repetitive interval sessions may aid individuals to increase accuracy or to develop a personal blood loss assessment coefficient to anticipate levels of underestimation. Such a coefficient would be comparable to a golf handicap and of great use to individuals who regularly are called upon to assess blood loss in a variety of situations. Future studies could expand on this experiment with larger numbers and under more varied conditions, of which the quality and quantity of atmospheric lighting is most important. This information may be informative in the ongoing education of labor and delivery room staff in drills and other attempts to simulate real-time emergency situations.

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Section II

Causation

7

DOPPLER EVALUATION OF HEMODYNAMIC CHANGES IN UTERINE BLOOD FLOW

G. Urban, P. Tortoli, S. Ricci, M. Paidas, P. Vergani and P. Patrizio

INTRODUCTION

The main uterine artery and its branches are derivatives of the hypogastric artery. At the level of the internal cervical os, the uterine artery bifurcates into the cervical and corporal branches. At the uterotubal junction, the corporal branch turns laterally and upward toward the ovary where it establish anastomoses with the ovarian artery, forming an arterial arcade that provides perfusion to the upper aspect of the uterine corpus. The blood flow takes a linear course in the hypogastric artery, then turns into a serpentine course in the uterine artery, and finally regains a linear course throughout the gestation, as the uterus gradually increases in size.

Approximately eight to ten arcuate arteries originate from each uterine branch and envelope both the anterior and the posterior walls of the uterus for about one-third of the thickness of the myometrium[1]. These arteries take a tortuous course and establish anastomoses with the corresponding arteries from the contralateral side in the midline of uterine myometrium.

The radial arteries arise from the arcuate arteries and are directed inward toward the uterine mucosa. The total number is undefined and most likely is dependent on parity and human biodiversity.

In the past, conventional Doppler techniques have been used unsuccessfully to study uterine hemodynamic patterns in an attempt to provide diagnostic clues for the management of postpartum hemorrhage. Recently, however, advances in signal acquisition and processing have allowed precise and reproducible analysis of velocity profile patterns and other variables such as wall distension and shear rate at specific sites of the uterine circulation.

Several studies have demonstrated a progressive drop in impedance in all the compartments of the uterine circulation, from the main arteries to the spiral arteries, as pregnancy advances[2–4]. The impedance of the spiral arteries decreases and blood flow velocities increase between the 5th and 7th weeks of gestation. During that period, the hemodynamic status of the uterine and arcuate arteries remains unchanged; it is only after the 8th week of gestation that a decrease in impedance and an increase in absolute flow velocities are detectable. This delay between the changes in the spiral and uterine arteries may represent the magnitude of the increase of placental volume and spiral arterial involvement, which is needed to effect appropriate and supportive uterine hemodynamics[5].

INTRAPARTUM DOPPLER VELOCIMETRY

Fleischer and colleagues[6] assessed 12 normal parturients throughout labor with a continuous wave Doppler unit to assess intrapartum changes in uterine and umbilical artery waveforms during labor. Each patient served as her own control. In the latent-phase of labor and with intact membranes, as well as in the active phase after rupture of membranes or during oxytocin stimulation, no significant changes were noted in umbilical artery systolic/diastolic (S/D) ratios before, during or after a uterine contraction. The uterine artery end-diastolic flow velocity fell progressively during uterine contractions, reaching 0 when the uterine pressure exceeded 35 mmHg. Despite intrauterine pressure of > 60 mmHg, the diastolic notch did

not appear. This study demonstrated that, at term, umbilical artery velocity waveforms do not change over a wide range of uterine pressures. Changes seen in uterine artery waveforms suggested that the end-diastolic component is primarily determined by changes in the arcuate and spiral arteries, both of which are affected during uterine contractions.

MULTIGATE SPECTRAL DOPPLER ANALYSIS

In our studies, we used a new ultrasound method to investigate blood flow, called multigate spectral Doppler analysis (MSDA), a technology that overcomes the limitations related to the use of a single sample volume[7]. With this method, 256 small sample volumes are aligned along an ultrasound scan line that intercepts the blood vessel, and the Doppler data from each sample volume are independently analyzed to produce a high-resolution flow profile. This non-standard method has been implemented in a system based on a proprietary electronic board connected to a commercial ultrasound machine (Aloka SSD1400) and a personal computer. The board, which is installed on a PCI slot of a host PC, samples the I/Q signals and processes the data in an on-board DSP to carry out the velocity profile. The profile is finally transferred in real-time to the PC to be displayed on the monitor. The hypogastric, uterine and arcuate arteries were investigated in women in labor before epidural anesthesia, after at least 1 h postpartum, and in women before pregnancy. To our knowledge, no group of investigators had previously considered flow rates in terms of the capacity to sustain a life-threatening postpartum hemorrhage.

This Doppler evaluation shows essentially how we define bidimensional Doppler or '2-DD'. Multi-sample volumes from multigate along the scan line depict a bidimensional dynamic representation of the blood flow, where the horizontal axis is the depth and the longitudinal axis is the velocity. Actually, this is the best estimation in real time of the blood flow throughout the vessels, showing an areal flow (cm^2/s) from depth (cm) × velocity (cm/s). Our experience shows that, during menses, areal flow through the arcuate artery is one-eighth (or perhaps one-tenth, depending on the anatomic variants) of the flow in the uterine artery, which is three-quarters of the flow in the hypogastric artery at the start of the menstrual cycle. This flow increases by one-third until ovulation (Figure 1) and remains constant until menstruation. By way of comparison, after conception and in early gestation, this flow increases until the end of the second trimester, after which it remains stable throughout labor, at which time the arcuate artery flow is one-fifth of the uterine, or almost double the flow before pregnancy. In the first and second stages of labor, this flow is markedly reduced, if not totally discontinued, by compressive action of the uterine contractions. During uterine contractions, the myometrial fibers also obliterate the flow in the radial arteries, reflecting the fact that they are tributaries of the arcuate arteries (see above), wherein flow stops until the end of contraction and then rises to reach a steady-state flow until the next contraction ensues. During each contraction, the placental lacunar space is compressed, thus pumping the blood to the fetal circulation throughout the umbilical vein. The compression of the radial arteries during each contraction acts as a valvular mechanism, avoiding reverse flow in the uterine circulation while directing the flow to the fetus. After delivery of the placenta, the resistance in the radial and spiral arteries decreases abruptly, being close to '0'. As a consequence, there is an open flow of blood in the uterine cavity, which is contained by the compression caused by the prolonged uterine contractions. At this stage, the arcuate and radial flow is almost absent. The absence of flow through the radial and spiral arteries facilitates the clotting mechanism in the endometrial bed.

Inefficiency of uterine contractions for whatever reason is a high-risk factor for postpartum hemorrhage. Likewise, an increase in the areal flow of the arcuate arteries, i.e. higher than one-fifth of the flow in the uterine arteries, is also a potential risk for postpartum hemorrhage. The differences of areal flow between the hypogastric, uterine and arcuate arteries, in various physiologic conditions, including postpartum, are shown in Figure 1.

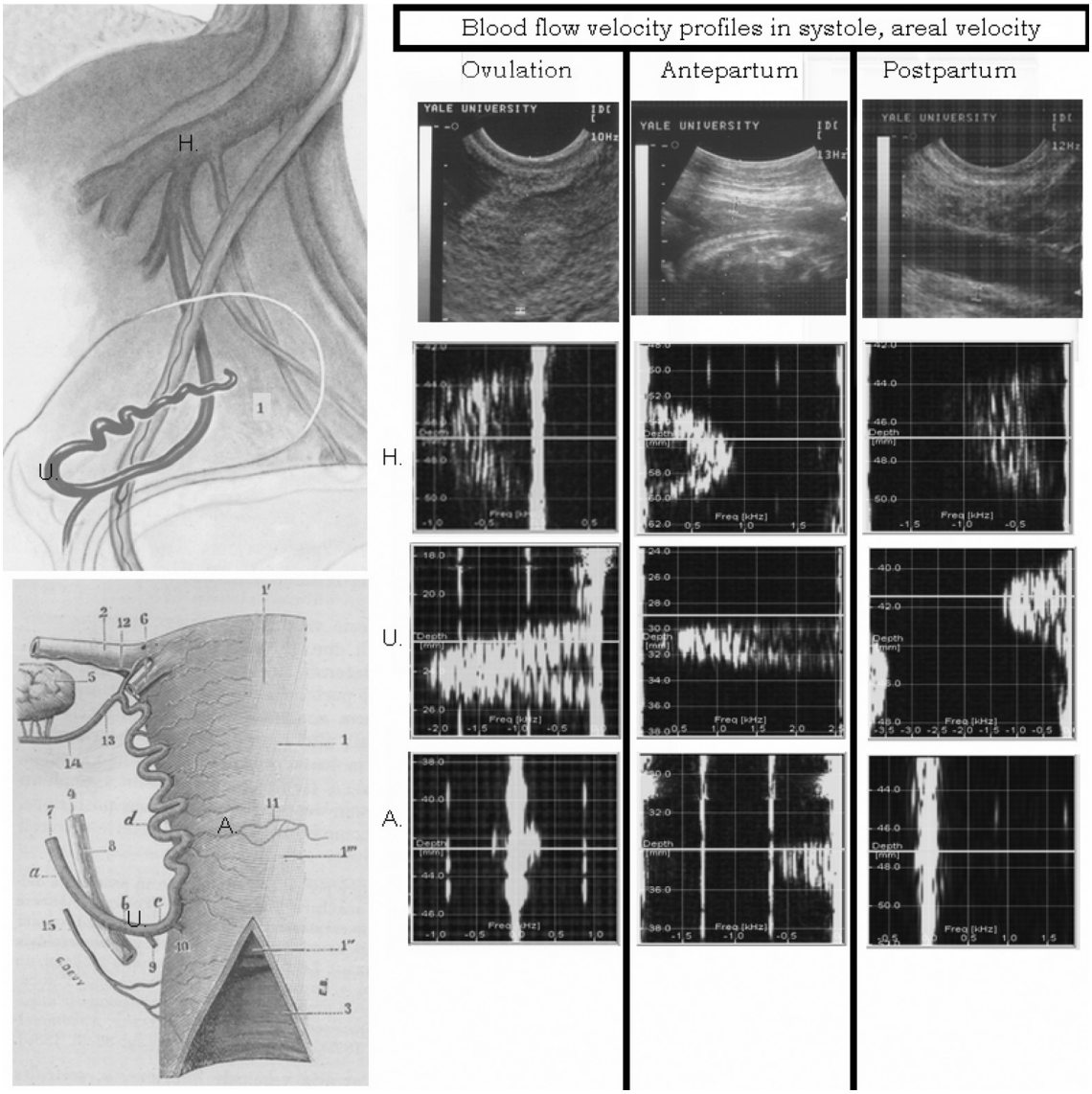

Figure 1 Multigate spectral Doppler analysis using GASP software for areal velocity in women at the ovulation phase of the normal menstrual cycle, in the antepartum phase of labor and at 1 h postpartum. In each column, the first image is the conventional bidimensional image of the area of interest during multigate acquisition, the following from top to bottom are hypogastric (H) artery velocity profile (areal flow), uterine (U) artery velocity profile (areal flow), and arcuate (A) artery velocity profile (areal flow). All images are frozen in systolic peak

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8

PATHOPHYSIOLOGY OF POSTPARTUM HEMORRHAGE AND THIRD STAGE OF LABOR

R.-U. Khan and H. El-Refaey

INTRODUCTION

The physiology of postpartum hemostasis depends primarily upon mechanical events mediated by hormones, which induce strong uterine muscular contraction. Virtually all recent studies focus on the latter, but the phenomenon cannot be understood without examining why uterine contraction stops bleeding. Broadly speaking, myometrium and decidua are arranged such that powerful muscular contractions after delivery favor hemostasis (Figure 1)[1–3]. Spiral arteries 'fan out' to create a low-resistance vascular bed in the intervillous space, which facilitates placental blood flow. This flow has been shown to decrease with muscular activity[4]. Third-stage contractions are powerful and prolonged: they act to stop placental blood flow and to separate the placenta and membranes.

PLACENTAL SEPARATION AND UTERINE ACTIVITY

Mechanical events

The biomechanical events which lead to delivery of the placenta and its membranes begin to take place even before the start of the second stage of labor. Membrane detachment starts during the first stage and slowly spreads upwards from the internal os[5].

As the trunk of the baby is delivered, the uterus muscle fibers undergo a very powerful contraction. Muscle fibers shorten, and the uterus is reduced in size and volume, a process characterized as retraction. These events are probably facilitated by the spiral arrangement of uterine muscle fibers, whereby the reduction in uterine volume leads to a reduction in placental site surface area. As the placenta is a relatively rigid and inelastic structure, the surface area of its attachment site decreases when it is tightly compressed.

According to Brandt, compression of the placenta forces placental blood back into the sinuses in the decidua basalis[6]. These sinuses become blocked by the action of strong myometrial contraction, and thus the compressed placenta attempts to force blood back into a high-resistance system. Ultimately, the sinuses become so congested that they rupture. The blood from the ruptured sinuses tears the fine septae of the spongy layer of the decidua basalis, and thus the placenta is sheared off[7]. Dieckmann and colleagues implied that this 'retroplacental hematoma' has no functional value, and a subsequent investigation suggested that it is the contraction and retraction of the uterine wall itself that cause it to rend itself apart from the placenta[8].

Ultrasonographic investigations recently corroborated that the Dieckmann theory is correct. Herman and colleagues conducted real-time ultrasonographic imaging of the third stage of labor and identified a 'detachment phase', wherein the placenta completes its separation[9]. This detachment is preceded by a 'contraction phase', in which the placental-site uterine wall undergoes thickening. However, the 'latent phase' before this thickening occurred varied between patients and was thought to determine the overall length of the third stage. Of interest, neither the latent phase nor the contraction phase was associated with ultrasound evidence of retroplacental hematoma formation.

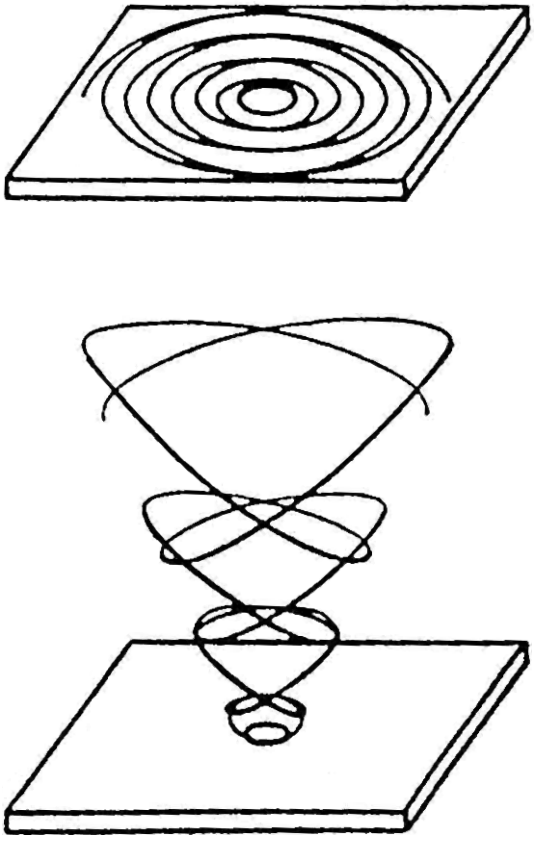

Figure 1 (a) Circular uterine muscle at rest: two sets of crossing spiral; (b) at term: stretching of the spirals (Goerttler, 1931[1]). The innermost part of the muscular layer has been described as superficially 'circular' musculature, which is in fact two sets of crossing spirals[2]. An alternative description of muscle fibers travelling in all directions has been described[3]. Both descriptions suggest that blood vessels are compressed during contraction of muscle cells

The two classical methods of placental delivery result in different bleeding patterns. In the Schultze method, separation begins in the center of the placenta (the fetal surface), and this part descends first, with the remainder following. The Matthew Duncan separation method involves detachment of the leading edge of the placenta, and the entire organ slips down and out of the uterus sideways. The latter method is much less common (20% of the total), but is supposed to result in more bleeding for two possible reasons. First, in the Schultze method, any extravasated blood is trapped within the membranes which follow the placenta and may form a retroplacental clot, whereas this blood escapes immediately in the Matthew Duncan method. Second, placental separation is slower in the Matthew Duncan method, allowing more time for bleeding[10]. As clinicians are able to neither predict nor alter the method of placental separation, the distinction between the Schultze and Matthew Duncan methods is most probably clinically irrelevant.

Control of postpartum bleeding occurs by contraction and retraction of the interlacing myometrial fibers surrounding maternal spiral arteries of the placental bed. Myometrial contraction compresses the spiral arteries and veins, thereby obliterating their lumina. It is for this reason that the myometrial fibers involved are often referred to as 'living ligatures'[10]. In addition, it is thought that some hemostasis occurs by means of direct pressure as the uterine walls are forced to firmly oppose one another as a result of myometrial contraction.

It is worth noting the physiological effect of early cord clamping, a common intervention which is part of the active management of the third stage of labor, is to retain blood in the placenta, which prevents it from being so tightly compressed by the uterus. This, in turn, reduces the amount of myometrial retraction and contraction, leading to more, not less, bleeding. However, this blood is thought to form a retroplacental clot, which speeds up the shearing off of the placenta. Ultimately, the consequent speedy delivery of placenta should lead to quicker hemostasis, but the intervention of cord clamping is a paradox in that it involves causing increased initial bleeding to lessen ultimate total bleeding.

Unfortunately, apart from the recent ultrasound studies mentioned above, there is a distinct paucity of information about the physical changes which lead to hemostasis and placental separation.

Endocrine mechanisms leading to mechanical events

Like all muscular activity, uterine contractility depends on both electrical and hormonal stimuli. 'Intrinsic' activity may be mediated by stretch receptors, although it is unclear whether

such mechanisms are neural or neurohormonal. Two classes of hormones have been implicated in third-stage uterine contractility, namely oxytocin and prostaglandins.

Oxytocin

Interest in the role of oxytocin in the third stage has been partly motivated by the long-standing experience with therapeutic oxytocin to prevent postpartum hemorrhage. Broadly speaking, oxytocin causes increased uterine contractions by acting on myometrial oxytocin receptors. However, research has failed to show a clear and simple relationship between physiological oxytocin action and third-stage events for a number of reasons. Oxytocin assays are notoriously unreliable, because the decidua synthesizes its own oxytocin. As a result, plasma levels do not reflect oxytocin concentrations at the myometrium. Moreover, plasma oxytocin levels take no account of the density of myometrial oxytocin receptors, which has been shown to participate in a complex control mechanism with oxytocin itself and other factors. Finally, oxytocinase, a plasma enzyme, denatures oxytocin before it reaches its site of action[11].

During labor, oxytocin is released in a pulsatile manner, and both the pulse frequency and duration increase[12]. Exactly what triggers the pulsatile oxytocin release is presently unclear. Ferguson speculated that uterine stretching of the cervix stimulates oxytocin release, leading to uterine contractions[13]. This phenomenon so far has not been demonstrated in humans, but there may be significant pressure changes on adjacent pelvic organs and the vagina which result in neurological stimulation.

A pulse of oxytocin does not necessarily correspond to a uterine contraction, and some women do not experience a rise in plasma oxytocin after the delivery of the baby[14]. Moreover, it is not necessary to have an oxytocin pulse in order to deliver the placenta and achieve hemostasis. Additional methods of control must be involved. Whereas it is known that myometrial oxytocin receptor density increases during pregnancy and labor, the precise controls of this up-regulation are unknown[15].

For many years, synthetic oxytocic agents have been successfully used in the third stage both to prevent and to treat postpartum hemorrhage. At the same time, however, therapeutic oxytocic agents used to augment labor are sometimes associated with uterine atony in the third stage. In this latter circumstance, the non-pulsatile administration of these agents may be leading to down-regulation of oxytocin receptors, as has been demonstrated in *in vitro* studies[15]. Despite the acknowledged therapeutic role of oxytocic agents in the third stage of labor, the true physiological role of oxytocin in the third stage remains unclear. It appears to have an inconsistent or paradoxical relationship with the third stage.

Prostaglandins

Prostaglandins are potent stimulators of myometrial contractility, acting via cyclic AMP-mediated calcium release. The therapeutic usefulness of prostaglandin agents in postpartum hemorrhage lends credence to the possibility of a physiological role for prostaglandins in the third stage of labor. The prostaglandins involved in uterine contraction are produced in decidual tissue, placental tissue and fetal membranes[16]. The uterotonic action of prostaglandins does not depend on gestation. There are many classes of prostaglandin; the two classes implicated in uterine contraction are PGE_2 and $PGF_{2\alpha}$.

Several observers have noted that large amounts of prostaglandin are released in the third stage of labor. In an elegant experiment, Noort and colleagues measured plasma levels of prostaglandin metabolites during and up to 48 h after labor[17]. $PGF_{2\alpha}$ levels reached their maximum and started to decline within 10 min after placental separation (Figure 2). The subsequent rapid decline in these levels suggested that the prostaglandins arise from either necrosis/cellular disruption at the placental site, or from the fetal membranes. The latter are known to be a major source of prostaglandins. *In vitro* experiments have shown that intrapartum amniotic fluid triggers prostaglandin synthesis in fetal membranes. The 'active agent' in the amniotic fluid remains unknown[16]; however, these observations are thought to reflect the active role of prostaglandins in securing hemostasis by way of myometrial contraction in the third stage.

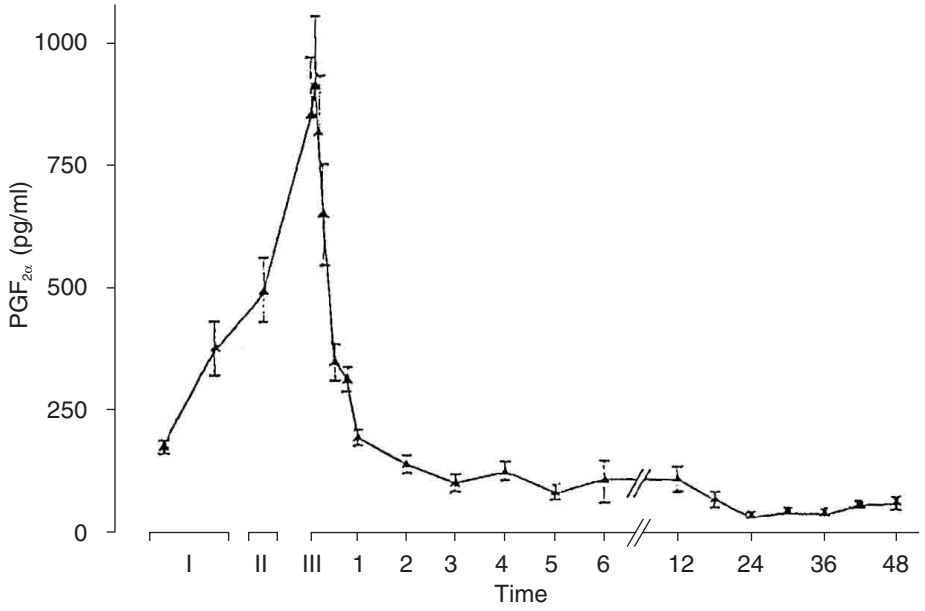

Figure 2 Plasma $PGF_{2\alpha}$ levels (pg/ml; mean ± standard equivalent of the mean). (I) In early labor and at full dilatation; (II) at delivery of the fetal head; (III) at placental separation and up to 48 h after placental separation (Noort *et al.*, 1989[17])

The interaction between prostaglandins and endogenous or therapeutic oxytocin in the third stage is not well understood. Numerous animal experiments have demonstrated interactions between prostaglandins and oxytocin at luteolysis, initiation and maintenance of pregnancy, and possibly at onset of labor[18]. However, therapeutic oxytocic agents used in the third stage do not appear to have a significant effect on prostaglandin metabolite concentrations[19]. Further studies are required to better understand from where the prostaglandins arise, and what controls their release.

In the next few years, it is likely that misoprostol, a prostaglandin E_1 analogue with uterotonic properties, will play an increasing role in the management of the third stage, as it is both cheaper and more thermostable than existing agents.

Coagulation

Many standard obstetric text books provide only the vaguest of suggestions that coagulation at the placental site represents an important hemostatic mechanism. Whilst this is certainly true, the exact pathway(s) involved are unclear. Before and after delivery, subtle changes take place in both coagulation factors and fibrinolysis agents. Plasma concentrations of clotting factors increase not only during pregnancy but also after delivery, which suggests a hypercoagulable state[20]. However, after placental separation, the fibrinolytic potential of the maternal blood also increases, and this tends to reduce the potential of blood to clot[21].

These conflicting changes are difficult to reconcile and are further complicated by changes in platelet activity before and after delivery. However, there are indications that an inflammatory response arises at the placental bed after placental delivery[22]. Such a response would promote local coagulation. This finding is important in terms of evolutionary advantage, because it allows prevention of hemorrhage at the placental site, while elsewhere (particularly in deep pelvic and leg veins) thrombi are less likely to persist, due to the increased fibrinolysis.

von Willebrand disease (factor VIII deficiency) is an important example of a coagulopathy which can result in increased risk of postpartum hemorrhage. This is especially true in the disease variant featuring factor VIIIc deficiency. In many ways, von Willebrand disease

mimics a platelet adhesion dysfunction, and indeed the only aspect of hematological hemostasis after placental delivery which can be emphasized with any certainty is the formation of platelet plugs at arterioles. Postpartum hemorrhage rates in von Willebrand's disease are in excess of 15%, and it has been suggested that this hemorrhage is largely preventable by minimizing maternal trauma at delivery and giving prophylactic treatment with desmopressin (DDAVP)[23].

In summary, the hemostatic mechanisms during and after placental separation probably involve the contraction of muscle sheaths around the spiral arteries, leading to platelet plug formation, retraction of the uterus causing mechanical occlusion of arterioles facilitating platelet plug formation, and the activation of both the clotting cascade and fibrinolysis. As of this writing, many of these events are vague assumptions rather than demonstrated fact, as third-stage physiology research has been grossly neglected. The fact that for decades effective treatments have been available for postpartum hemorrhage in the developed world has acted as a true disincentive for novel work and ideas. It is tragic that the third stage of labor, the most dangerous moment of pregnancy, is so poorly understood.

PATHOPHYSIOLOGY OF POSTPARTUM HEMORRHAGE

Although most of the physiological processes in the third stage of labor remain unclear, they broadly help to explain the etiology of atonic postpartum hemorrhage. In this section, the etiology and accompanying pathophysiology will be discussed.

Uterine atony

The most common cause of postpartum hemorrhage is uterine atony, i.e. failure of the uterus to contract. Primary postpartum hemorrhage due to uterine atony occurs when the relaxed myometrium fails to constrict these blood vessels, thereby allowing hemorrhage. Since up to one-fifth of maternal cardiac output, or 1000 ml/min, enters the uteroplacental circulation at term, postpartum hemorrhage is capable of exsanguinating the mother within a short time. Whilst uterine atony is responsible for 75–90% of primary postpartum hemorrhage, traumatic causes of primary postpartum hemorrhage (including obstetric lacerations, uterine inversion and uterine rupture) comprise about 20% of all primary postpartum hemorrhage (see Chapter 9). Significant but less common causes of postpartum hemorrhage include congenital and acquired clotting abnormalities, which comprise around 3% of the total[24]. Uterine atony is responsible for the majority of primary postpartum hemorrhage originating from the placental bed. Although the most important risk factor is a previous history of atonic postpartum hemorrhage (relative risk 3.3)[25], many other important risk factors often found in combination.

Failure of the uterus to contract may be associated with retained placenta or placental fragments, either as disrupted portions, or more rarely a succenturiate lobe. The retained material acts as a physical block against strong uterine contraction, which is needed to constrict placental bed vessels, but, in most cases, dysfunctional postpartum contraction is the primary reason for placental retention. It is more likely for the placenta to be retained in cases of atonic postpartum hemorrhage, and so the contraction failure often becomes self-perpetuating. The reasons for this contractile dysfunction are unknown. The exception is uterine fibroids, where the source of distension cannot be removed by uterine contraction, and must therefore cause the atony. However, the uterus does not even have to be distended during the third stage for contractile dysfunction to occur. Distension prior to delivery, which occurs with multiple pregnancy and polyhydramnios, also affects the ability of the uterus to contract efficiently after delivery, and is thus another risk factor for atonic postpartum hemorrhage.

When postpartum hemorrhage occurs following an antepartum hemorrhage, the scenario is particularly difficult since there have been two episodes of blood loss. A rare but serious complication of abruption is extravasation of blood into the myometrium, known as a Couvelaire uterus, which impairs the physiological uterine contraction/retraction hemostatic process. However, the relationship between the extravasation process and uterine dysfunction is

not fully understood. Chorioamnionitis has a similar effect for unknown reasons. Both antepartum hemorrhage and chorioamnionitis also impair uterine contraction during the first two stages of labor, and prolonged labor in general is a risk factor for postpartum hemorrhage. Conventional wisdom suggests that delay in the first two stages leads to uterine atony, but it is more logical to suggest that uterine dysfunction before onset of labor results in delay in all three stages, and thus causes postpartum hemorrhage. As far as we are aware, there is no ongoing research into this 'universal uterine dysfunction'.

The lower segment as an implantation site

In both placenta previa and placenta accreta, the placental bed (and thus the postpartum bleeding site) is in the lower segment. The presence of lower segment implantation makes hemorrhage and placental retention much more likely. Although existing evidence is scanty, there are indications that the etiology of pathological bleeding is inextricably linked with the anatomical and physiological limitations of the lower segment.

Placenta previa

In placenta previa, the placental site is located in an abnormally low position. Atonic postpartum hemorrhage is a recognized complication and, even if Cesarean section is performed, severe intraoperative bleeding is a significant risk[26]. The usual pharmacological methods used to stem hemorrhage are often less effective. Surgical methods, such as oversewing of bleeding sinuses and the B-Lynch suture, are sometimes also ineffective so that hysterectomy proves necessary. Hemorrhage is often not stopped unless the entire lower segment is removed; a subtotal hysterectomy is often inadequate, and many surgeons perform total abdominal hysterectomy as the operation of choice. Thus, the involvement of the lower segment makes it more likely not only that hemorrhage will occur, but also that standard treatment modalities will fail.

Authors in conventional texts often suggest that, in lower segment implantation, the muscle surrounding the placental bed is inadequate to the task of postpartum contraction/retraction, and thus hemorrhage ensues[26]. As contraction/retraction are considered essential prerequisites for both placental detachment and postpartum hemostasis, the inference is that physiological hemostasis from a lower segment placental bed is impossible. This is obviously not the case, however, as clearly not all cases of Grade IV placenta previa necessitate hysterectomy. The only possible conclusion is that there are qualitative and quantitative differences in the musculature of the lower segment in different patients. A recent literature search on this topic confirms that the nature and origin of these differences have never been investigated.

Biswas and colleagues have compared placental bed biopsy changes in placenta previa and normally implanted placenta; they have shown that previa is associated with significantly higher trophoblastic giant cell infiltration and physiological changes of the myometrial spiral arterioles[27]. This work is typical of modern obstetric research in that it concentrates on antenatal events while ignoring postpartum events. However, the findings are interesting because they suggest that the seeds of potential placenta accreta are sown in most cases of placenta previa. Nonetheless, no knowledge regarding the qualitative features of lower segment myometrium exists.

Placenta accreta

Placenta accreta is morbid adherence of placenta such that it invades the myometrium. It is rare; in 1990, the quoted incidence was around 1 in 2000 to 1 in 3500 pregnant women in North America[28]. The condition is strongly linked to lower segment implantation; it occurs in up to 15% of women with placenta previa[26]. The adherence is also associated with a deficiency of decidua in the lower segment. The most common cause of this decidual deficiency is endometrial scarring, which may be secondary to previous Cesarean section or myomectomy, previous endometritis, past history of evacuation of retained products of conception or uterine abnormalities.

Uterine surgery is a major risk factor for placenta previa and placenta accreta[29]. There is an increased tendency for placental implantation in

the vicinity of the uterine scar with secondary trophoblast invasion of the myometrium. Uterine scarring is also known to be associated with an increased risk of scar dehiscence, febrile morbidity and other factors[30]. Thus the scar is classically considered to be a 'weak area'. Scarring of muscle results in the normal tissue being replaced by fibrous tissue. Intrauterine retraction forces induced during labor tend to thin out the lower segment, and these forces stretch the scar to the point of rupture. Uterine rupture is not considered predictable[31], but is more likely with each Cesarean section. Although poorly described in the literature, our personal clinical experience suggests that, with each ensuing Cesarean section, the entire lower segment often seems to become thinner. Indeed, the lower segment may take on a translucent quality. This appearance is not limited to the scar itself. It is possible that the 'weak scar' in fact represents a generalized lower segment weakness induced by previous surgery.

Clinical experience also suggests to us that it is not enough to assume that postpartum hemorrhage is more common with lower segment implantation purely because lower segment muscle is inadequate to the task. In cases of placenta previa and placenta accreta, the lower segment looks even thinner than normal. We hypothesize that the contractile nature of lower segment muscle, which is already less than that of the upper segment, is further lowered by the presence of the placenta. This would mean that implantation itself has an adverse effect on lower segment myometrium. Furthermore, there is a body of anecdotal evidence which implies that placental size and trophoblast invasion are greater in areas of limited decidual tissue, including implantation on scars and in ectopic pregnancies. We hypothesize that trophoblast would invade readily into the poorly decidualized lower uterine segment, increasing the likelihood that placenta accreta will develop.

In terms of the previous discussion, it is unfortunate that a dramatic and remorseless rise in the Cesarean section rate is being observed throughout the developed world. This phenomenon will inevitably give rise to an increase in the complications associated with placenta previa, placenta accreta and scar rupture. The complications are particularly important because they tend to be relatively less amenable to medical treatment and sometimes necessitate radical surgical intervention, such as hysterectomy.

Whereas knowledge of the ultrastructure of placental bed musculature is lacking with regards to the upper segment, it is virtually nonexistent for the lower segment. New research into this area is urgently needed, because all non-surgical therapeutic modalities for postpartum hemorrhage involve enhancement of uterotonicity and, in the absence of sufficient myometrium, they will simply not work. We hypothesize that lower segment placentation/surgery leads to structural and thus functional changes in the muscle histology. Thus, we envisage a new, clinically important class of postpartum hemorrhage, 'lower segment postpartum hemorrhage'. This new subclass will be best managed by new protocols which address the features specific to lower segment involvement.

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9

OBSTETRIC TRAUMA

D. G. Evans and C. B-Lynch

ACUTE UTERINE INVERSION

Acute uterine inversion, defined as when the uterus is turned inside out, is a rare but serious complication of the third stage of labor. The estimated incidence is approximately 1 in 20–25 000 deliveries[1–3]. As the estimate of a later report was < 1 : 2000[4], the true incidence is unclear because some of the milder forms correct themselves spontaneously and are thus not recognized or reported.

Classification

Uterine inversion may be complete or incomplete, depending on whether the fundus has passed through the cervix[5]. When the uterine inversion occurs within the first 24 h postdelivery, it is classified as acute. Inversion occurring after the first 24 h and up to 4 weeks postpartum is classified as sub-acute, and the rare chronic inversion occurs after the 4th week postpartum.

Etiology

The expulsion of the placenta was probably intended by Nature to occur as a result of gravitational forces, with the mother in the same squatting position that is often adopted for defecation. When the third stage is conducted in the dorsal position, however, help may be necessary for placental expulsion. Accordingly, the inappropriate management of the third stage of labor is often implicated in the etiology of acute uterine inversion. Indeed, Crede's method of placental delivery with uncontrolled cord traction, referred to in most textbooks of midwifery and older textbooks of obstetrics, may indeed increase the risk of acute uterine inversion. The firmly contracted uterus is used as a piston to push the placenta out, in the same manner that a piston is used to push fluid out of the barrel of a syringe. Pressure is applied with the palm of the hand in the axis of the pelvic inlet, in a downward and backward direction with the aim of forcing the placenta out through the lower genital tract. Unfortunately, application of Crede's maneuver when the uterus is not contracted may well facilitate acute inversion. On the other hand, the Brandt Andrews maneuver, also mentioned in standard textbooks of midwifery and obstetrics, a modification of Aristotle's method of delivering the placenta by cord traction, recommends applying tension, but not traction, to the umbilical cord with one hand, whilst the other hand is placed on the abdomen gently moving the uterus upwards and backwards. Today, controlled cord traction is standard practice for the third stage of labor.

Other etiological factors include forcibly attempting to expel the placenta by using fundal pressure when the uterus is atonic, and traction on the umbilical cord in a fundally placed placenta when the uterus is relaxed. It may also be brought about by a local atony, more particularly of the fundal placental site together with active contractions of the rest of the uterus. Other etiological factors include macrosomia, polyhydramnios, multiple pregnancy, primiparity and oxytocin administration[5]. In other instances, however, the inversion occurs spontaneously from sudden increased abdominal pressure as a result of coughing, sneezing or straining.

Chronic inversion may result from an acute inversion left unrecognized or from a submucous fibroid which has prolapsed through the cervix. A placental polyp resulting from a retained cotyledon of the placenta may present in the same fashion.

Diagnosis

Symptoms are acute and pronounced. Generally, the mother is aware of something coming down and this is usually quickly followed by unanticipated profound shock. The uterus may appear at the introitus outside the vagina and the fundus is no longer palpable abdominally. In partial inversion, the fundus of the uterus may be indented and may or may not pass through the cervical os. In such instances, it is neither palpable abdominally nor visible at the vulva. Vaginal examination detects the inverted body of the uterus, and, above and encircling it, the ring of the cervix. In all instances, pain may be severe due to stretching of the infundibulopelvic ligaments and other viscera.

Shock is the outstanding sign, and may in part be neurogenic due to stretching of the viscera and in part due to hemorrhage and hypovolemia. The degree of shock is proportional to blood loss and hemorrhage is variable, depending on whether any attempt has been made to remove the placenta. Some bleeding will always be present unless the placenta is completely adherent to the uterine wall. It is important to recognize that severe hemorrhage will accompany any attempt at removing the placenta before the uterus is replaced[5,6]. This eventuality is a special risk if the birth has been attended by a traditional birth attendant (TBA) in parts of the underdeveloped world.

Management

Acute uterine inversion is a true obstetric emergency[6], and clearly one which may lead to severe postpartum hemorrhage. If present and available, a supportive team should be summoned to the delivery suite for resuscitation and protocol management (see Chapter 20). Uterotomics, if started, are to be stopped and manual replacement attempted under adequate and appropriate anesthesia followed by delivery of the placenta assisted by restart of oxytocin[7].

Elevation of the foot of the delivery table or bed may relieve the tension on the viscera and reduce the pain and shock. Immediate resuscitation with intravenous fluids is indicated via large-gauge venous access. Adequate analgesia must be instituted prior to attempting replacement, and the bladder should be catheterized. Antibiotic prophylaxis is advisable.

Any delay increases the difficulty in replacing the uterus, and the first health-care professional present should make the initial attempt at replacement. This will be aided if regional anesthetic is already in place[8]. The placenta should be left *in situ* and no attempt made to remove it. The portion of the uterus that came down last should go back first, that is, the lower segment initially and the fundus later. The hand is lubricated with hibitane cream (or other suitable antiseptic if available) and placed inside the vagina. With gentle maneuvers of the fingers around the cervical rim and simultaneous upward pressure with the palm of the hand, the uterus is gradually replaced. The employment of force is dangerous, as the thinned-out lower segment may be torn or otherwise traumatized. The vaginal vault may already have been torn in some cases. The degree of shock does not diminish until the uterus is replaced. In the majority of instances, replacement of the uterus is successful using this conservative method[9]. If replacement is successful, the placenta should be manually removed with the aid of ergometrine or an oxytocic infusion. In underdeveloped countries or in a home setting, boiled water brought to a bearable temperature can be used to soak clean towels or cloths to assist in pushing and packing the vagina. This may facilitate replacement attempts and control further blood loss. Bimanual massage of the fundus may improve contraction.

If replacement is unsuccessful, measures to relax the cervical retraction ring should be the next line of therapy. Beta mimetics or amyl nitrite inhalation can often relax the retraction ring sufficiently to allow uterine replacement[9]. A similar effect is seen with the administration of halothane anesthesia, but, unfortunately, use of this agent in sufficient doses can result in the unwanted and life-threatening complications of uterine atony, hypotension and severe hemorrhage. Halothane is no longer used for these and other reasons. A 2 g intravenous bolus of magnesium sulfate can be used in the hypotensive patient (0.25 mg of intravenous terbutaline in the stable patient) to relax the cervical contraction ring[10]. Intravenous

nitroglycerine can be tried although it is not commonly used.

Further attempts at replacement of the uterus should take place under general anesthesia in an operating theater equipped and ready to perform a laparotomy. Before resorting to a laparotomy, however, the tried and tested O'Sullivan hydrostatic technique[11] should be attempted. Here, the patient is first resuscitated to restore vital signs including adequate blood volume and pressure. The obstetric team and anesthetist are summoned.

Adequate analgesia is essential before:

(1) Attempt at repositioning without the use of uterine relaxant;

(2) If response is not imminent or sustained, an anesthetist should provide uterine relaxation to facilitate repositioning and the administration of uterotonics;

(3) General anesthesia is preferable, administered by an obstetric anesthetist. Digital repositioning should be maintained to support and establish good uterine muscle tone;

(4) 1–2 liters of saline at body temperature should be infused into the vagina through rubber tubes placed in the posterior fornix, whilst obliterating the introitus with the obstetrician's hand. As the vaginal walls distend, the fundus of the uterus rises and the inversion is usually promptly corrected. Once this is achieved, fluid is allowed to slowly escape from the vagina whilst the placement of the uterine fundus is achieved and maintained.

When O'Sullivan first described this technique, he used a douche-can and wide rubber tubing to deliver the solution. More recently, a silastic vacuum cup has been used to instil the sterile solution into the vagina[12]. Until replacement is effected, however, towels soaked in warm hypertonic saline solution and draped over the inverted uterus may reduce the edema which will inevitably occur and which further impedes replacement of the uterus. In extremely difficult cases, replacement may require mid-line laparotomy, with the patient cleansed and draped in the Lloyd Davis (frog-legged) position with a head-down (Trendelenberg) tilt. The patient is catheterized with an indwelling catheter and broad-spectrum antibiotics are administered. With the bowels packed upward and away from the uterus, the obstetric surgeon places his hands in front and back of the lower segment with the finger tips between and below the level of the inverted fundus. With progressive pressure on the fingertips of both hands which flip up simultaneously, the internal dimple is replaced progressively by the rising uterine fundus (Figure 1a–e)[13]. Uterine perfusion returns with re-establishment of uterine pulse pressure.

If this technique fails, then the mid-line abdominal incision can be extended upwards if necessary. The inverted uterus resembles a funnel; it is best to exteriorize the uterus. Instrumental upward traction is applied to the round ligaments bilaterally using Allis or ring forceps, while the assistant exerts upward pressure on the inverted parts from the vagina below. This maneuver is the Huntington technique[14,15].

Failure at this stage warrants employing the Haultain technique whereby an incision is made vertically in the posterior cervix via the abdominal route, following the dimple as a guide to relieve the constriction at this level. The assistant exerts upward pressure from the vagina to effect reduction and replacement[16].

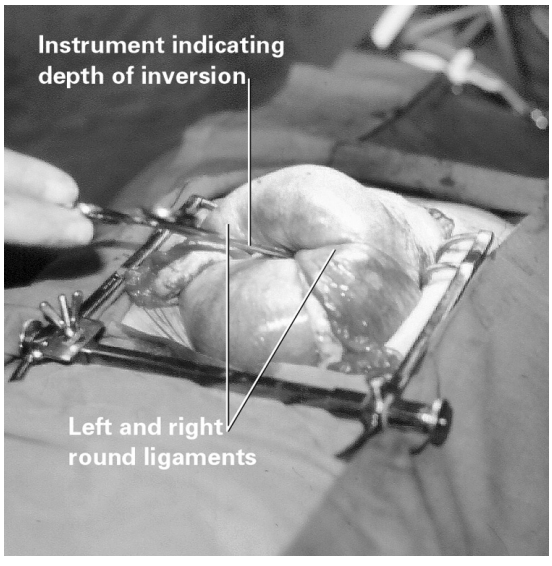

Figure 1a Acute uterine inversion

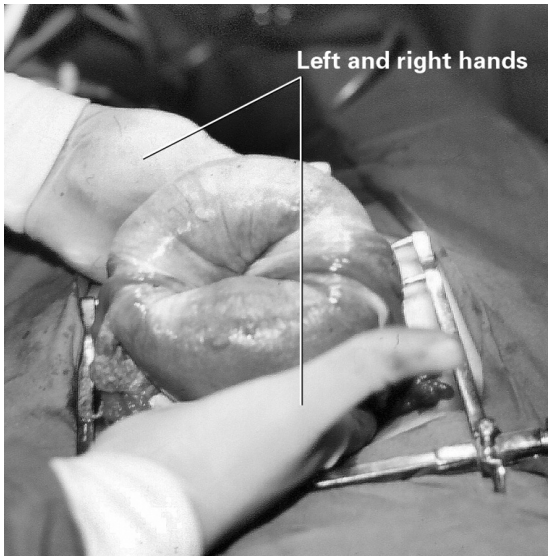

Figure 1b Acute uterine inversion. Finger tips placed below fundus of uterus to facilitate reduction

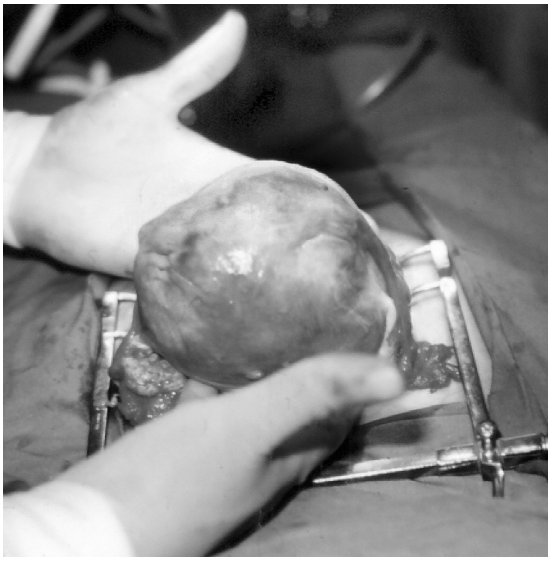

Figure 1d Acute uterine inversion. Return of vascularity

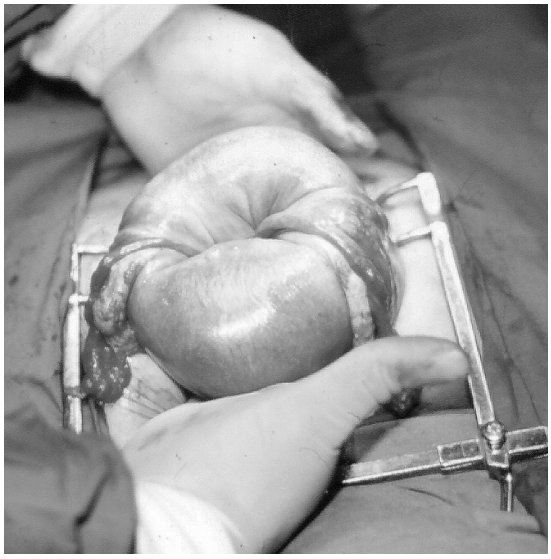

Figure 1c Acute uterine inversion. Progressive reduction with some ischemia

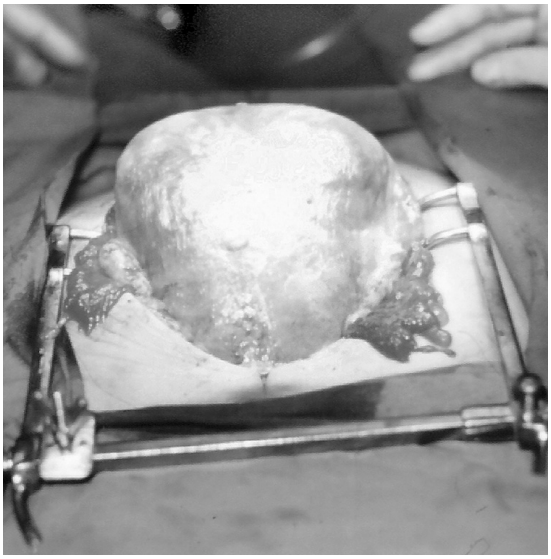

Figure 1e Acute uterine inversion. Complete reduction and revascularization with normal clinical features. (B-Lynch technique of non-instrumental reduction of acute uterine inversion at laparotomy. ©Copyright '05)

On return of the uterus to its normal position, the placenta should be removed manually from the vagina, and uterine contraction maintained abdominally by bi-manual stimulation. Ergometrine, oxytocic intravenous infusion, or mesoprostyl can be administered. The posterior uterine incision, if used, is then repaired in layers, and the abdomen closed in the usual fashion. The patient should be monitored in the intensive care or the high-dependency unit for 24 h.

A sub-acute inversion is managed in a similar manner but may resolve spontaneously as the uterus involutes[4].

In chronic inversion, the uterus involutes in its inverted position and remains in the vagina as a soft swelling, which bleeds readily to touch and shows areas of superficial ulceration. Prolonged inversion may result in conversion of the columnar epithelium of the uterine wall into a stratified squamous epithelium. Replacement of a chronic inversion can prove extremely difficult, due partly to the inevitable edema present and the friable nature of the tissues. The techniques adopted for replacing the acutely inverted uterus are no longer helpful in this chronic situation. Bed rest, elevation of the foot of the bed, antibiotic prophylaxis, and vaginal cleansing with hibitane packs may be helpful to reduce the edema and treat any infections, but it may eventually be necessary to perform a hysterectomy. If the chronic inversion is due to the presence of a fibroid or a placental polyp, initial removal of the polyp by ligating and cutting the pedicle as near to the base as possible may facilitate replacement of the inverted uterus.

RUPTURED UTERUS

Uterine rupture is a serious obstetric complication with high morbidity and mortality. In developed countries, the increasing number of Cesarean sections performed for minor degrees of disproportion, fetal distress or pre-eclampsia in primiparae is of considerable importance in calculating the long-term risks associated with Cesarean section, particularly in terms of the incidence and risk of uterine rupture. Both the short- and long-term risks are accentuated in resource-poor countries.

Uterine rupture may be complete when the tear extends into the peritoneal cavity, or incomplete when the serosa remains intact. The rupture may be spontaneous, traumatic or the result of scar dehiscence and may occur either during pregnancy, early in labor or following a prolonged labor[17].

In developed countries, the most common cause of uterine rupture is dehiscence of a previous lower segment transverse Cesarean section scar. Rupture of a classical scar is eight times more common than that of a previous lower segment incision, and is far more apt to occur before rather than during labor. Previous rupture of a scar confers a 10–20-fold increase in risk of a subsequent rupture[18,19].

Rupture of the uterus is generally sudden, accompanied by severe abdominal pain and followed by vascular collapse. In many cases, however, asymptomatic dehiscence takes place during a vaginal delivery after a previous Cesarean section, when the dehiscence is gradual and retraction of the uterus arrests hemorrhage from the wound. Because of this possibility, it is always necessary to exclude silent dehiscence by manual exploration of the uterus after delivery of the fetus when a scar is present on the uterus.

A major factor in spontaneous uterine rupture is obstructed labor, especially in the developing world when women routinely delivery without the benefit of the presence of trained health-care providers. Rupture may be due to maternal or fetal causes (generally macrosomia). Examples of maternal causes are cephalopelvic disproportion from pelvic contraction due to developmental, constitutional or nutritional causes, abnormal presentation such as shoulder presentation, breech or brow, persistent mentoposterior face presentation, transverse lie, fetal abnormality, hydrocephalus, fetal tumor, fetal ascites, conjoined twins, maternal tumors, intrinsic cervical lesions, extrinsic fibroids or tumor, locked twins, and rarely uterine misalignment such as incarcerated retroverted uterus, and pathological uterine anteversion. Additionally, grand multiparity, the use of uterotonic drugs to induce or augment labor, placenta percreta, and intrauterine manipulation have all been implicated as causes of uterine rupture[19,20].

The most common predisposing cause of rupture during pregnancy is a weak scar following a previous Cesarean section[20]. Rarely, rupture can occur following unrecognized injury to the uterus at a previous difficult delivery. It may present with sudden severe abdominal pains and collapse, or the symptoms may present gradually, when rupture is based on scar dehiscence. If the onset is gradual, diagnosis may be difficult as the abdominal pain may be slight and accompanied only by alterations in the fetal heart tracing, maternal tachycardia and minimal vaginal bleeding. This triad is then followed by patient collapse, cessation of fetal

movement and easy palpation of the fetal parts if the fetus has been expelled completely into the peritoneal cavity. If the patient is in a hospital and the catastrophe recognized at its onset, the outcome should be the safe delivery of the baby and repair of the uterus. If the patient is not in a hospital, on the other hand, the catastrophe is just that, a catastrophe of a dead child and its mother.

Uterine rupture during labor is also most commonly due to dehiscence of a previous Cesarean scar with pain over the scar, followed by sudden severe abdominal pain and collapse. In grand multiparae with a friable inelastic uterine wall, rupture may occur in early labor even where there has been no previous scar or difficult delivery, although this eventuality is not nearly as common as rupture in the previously scarred uterus. Here, however, diagnosis may be difficult initially as the presentation may be confused with a small accidental hemorrhage and therefore missed.

Rupture after a prolonged labor is commonly due to obstructed labor, with marked thinning of the lower segment and increased retraction of the upper segment resulting in the formation of a retraction or Bandl's ring. The tear begins in the lower uterine segment, may extend up to the fundus or down into the vagina, or proceed laterally into the broad ligament. If the tear is posterior, it may go through the posterior vaginal fornix into the Pouch of Douglas (colporrhexis)[20]. If the rupture is in the lower anterior segment, the bladder is stripped from its attachment to the lower segment. The peritoneum remains intact and so the rupture is characterized as incomplete. A multiparous patient in obstructed labor will continue to have tetanic contractions until the uterus ruptures, whilst a primiparous patient will usually go out of labor. Classical clinical signs of a rupture in a multiparous patient can be dramatic; abdominal pain is constant, the contractions become virtually continuous initially with only short intervals between them and later no interval between contractile forces, with the formation of a Bandl's ring followed by rupture and collapse. The contractions then usually stop[20–22], the fetus is expelled into the peritoneal cavity, the fetal parts are easily palpable and the uterus adopts an altered shape.

Rarely, the uterus may rupture during early to mid-pregnancy or during labor in patients who have had a previous cornual ectopic pregnancy. Here also, the rupture is dramatic, is located over the repair site of the ectopic and is characterized as a fundal blow-out. Sudden severe abdominal pain is experienced over the fundus of the uterus followed by collapse.

Rupture of a previously unscarred uterus is usually a catastrophic event resulting in death of the infant, extensive damage to the uterus and a very high risk of maternal death from blood loss. The damage to the uterus may be so extensive that repair is impossible and a hysterectomy is required. In developed countries, the incidence of ruptured uterus in an unscarred uterus is approximately 1 : 10 000 deliveries[22]; in the underdeveloped countries, the data are unknown. The incidence of rupture of a uterus with a previous Cesarean section scar is 1%[22,23]. A trial of labor following a previous Cesarean section increases the risk of perinatal death and rupture of the uterus compared to elective repeat Cesarean section. In one large Canadian study, a trial of labor following a previous Cesarean section was associated with an increased risk of rupture (by 0.56%) but fewer maternal deaths than in an elective section (1.6 vs. 5.6 per 100 000)[19].

In less developed countries, the incidence of uterine rupture varies from 1.4% to 25%, with 25% in Ethiopian women with obstructed labor[23]. Uterine rupture accounted for 9.3% of maternal mortality in one study from India and 6.2% in a study from South Africa[24].

A laparotomy is indicated when rupture of the uterus is suspected. The patient is anesthetized, cleansed, draped and the bladder catheterized with an indwelling catheter. A mid-line lower abdominal incision should be used as this may be extended cephalad if necessary. The fetus should be delivered expeditiously and the uterus delivered from the abdominal incision to assist in controlling the bleeding and assessing the situation while resuscitative measures are undertaken. In the series of over 1300 worldwide reported successful applications of the B-Lynch (Brace) suture, 25 cases were applied for persistent uterine atony after repair of a uterine rupture. In these cases, successful bleeding control and hemostasis were achieved (CBL

world-wide communication www.CBLynch.com)[25].

Hysterectomy may be necessary and should have been consented, if at all possible. It is not necessary to remove the ovaries merely because this is easier in a crisis. As with a Cesarean hysterectomy performed in late labor, the cervix is no longer a discrete and circumscribed solid structure, easily delineated and permitting accurate placement of vaginal clamps. In the acute situation, hemostasis and avoidance of further dissection are of paramount importance, and the removal of the distal cervix is not critical. The most difficult surgical situation occurs when the rupture is extraperitoneal into the broad ligament, with a massive hematoma distorting the anatomy and obscuring the bleeding points. Here, it may be necessary to pack the space, the end of the pack being brought out through a gap in the uterine repair[20]. A balloon catheter with light traction may be used for enhanced tamponade with or without the application of the B-Lynch (Brace) suture application[26].

Other conservative surgery may be appropriate on occasions, for example, when simple repair of the tear may be preferable to hysterectomy. With an anterior rupture, the bladder may be involved; the appearance of hematuria is almost pathognomonic. Repair is undertaken and the bladder catheterized for 2 weeks. A posterior fornix rupture (colporrhexis) is relatively easy to repair. Incomplete rupture is not usually apparent until delivery has been achieved. It will commonly declare itself by intrapartum or postpartum hemorrhage. It should always be excluded by manual exploration after delivery of the fetus. Both bladder tears and colporrhexis may be missed if not anticipated. If this is the case, bleeding may continue, to the surgeon's dismay.

BLUNT ABDOMINAL TRAUMA

The three main causes of serious blunt abdominal trauma in pregnancy are motor vehicle accidents, falls and domestic or intimate partner physical abuse. In the developed world, the most common cause of blunt abdominal trauma is motor vehicle accidents[27,28]. In the less developed countries, the incidence of domestic physical abuse or intimate partner physical abuse can be as high as 13.5%[29]. Developed countries are not immune from this problem, however, and a large review of the prevalence of abuse during pregnancy in the United States documented that between 0.9% and 20.1% of pregnant women were abused by their partners. This figure covers all forms of abuse, emotional, physical and sexual[30].

Direct abdominal trauma by punching or kicking the abdomen increases the risk of adverse outcome of the pregnancy. Adverse outcomes are more common with direct physical assaults than with motor vehicle accidents[29,30]. Partner abuse also tends to be a repetitive event, increasing the risk to the fetus[31]. In some countries, partner abuse and violence against women is accepted as a cultural norm, thus reducing the numbers of reported cases. Even in the Chinese community in Hong Kong and despite western socialization, it is not uncommon for women to submit to their husbands and endure humiliation for the sake of keeping their family together. Providing help for these pregnant women is challenging[32].

Motor vehicle accidents account for 60–75% of cases of blunt trauma. Most injuries are minor, but, in the United States, between 1300 and 3900 women each year suffer a fetal loss as a result of a motor vehicle accident[27,28]. Despite the majority of the injuries being minor, the fetus is always at risk and careful assessment must be carried out in all cases of blunt abdominal trauma resulting from motor vehicle accidents. Assessments must be frequent and repeated with special attention to conditions commonly seen after such trauma. These include abruptio placentae, preterm labor, uterine rupture, fetomaternal hemorrhage, direct fetal injury and fetal demise[33].

The pattern of injury following automobile accidents depends on the type of seat belt restraints. An unbelted driver or passenger is usually ejected from the vehicle or sustains injuries when they hit the interior of the car. The injuries are mainly to the face, head, chest, abdomen and pelvis. With shoulder and abdominal restraints, rib, sternum and clavicular fractures are common, whereas in the lap-only belted, lumbar spine and hollow viscus injuries are more frequent. Sharp objects in the

pockets of the clothing on the person can cause additional trauma; a fountain pen may perforate the lungs or heart. Even bulky outdoor overclothing represents a hazard. With thick clothing, there is a short distance between the body of the person and the restraint. On impact, the weight of the body causes acceleration forwards. The speed of contact between the person and the restraint can compound the damage sustained to the body.

During the first trimester, the uterus is well protected within the pelvis and sustains very little damage from blunt trauma. With advancing pregnancy, however, the uterus becomes an abdominal organ and therefore more susceptible to trauma. The blood supply to the pelvis is markedly increased the more advanced the pregnancy, giving rise to retroperitoneal hemorrhage which can be life-threatening. Bowel injuries are less common, as the bowel occupies the upper abdominal space later in pregnancy, is a more movable entity and is not in the direct line of the trauma.

Assessing the extent of trauma can be difficult, as clinical signs initially may be sparse. Patients should be assessed frequently to detect deterioration in their condition. The presence of bony injuries should raise suspicion of intraperitoneal hemorrhage: rib fractures are associated with liver and spleen injuries and pelvic fractures with retroperitoneal hemorrhage and injury to the genitourinary system.

Difficulty is often encountered in detecting a small amount of bleeding into the peritoneal cavity. As blood may be non-irritant, ultrasound examination may be equivocal, and CT scanning exposes the fetus to a large radioactive dose. The decision to proceed to a laparotomy may therefore be entirely based on clinical judgement.

The most common cause of fetal death in non-fatal accidents is abruptio placentae. In minor injuries, the incidence is between 1 and 5%, in contrast to major trauma where the incidence may be as high as 30%. At the time of impact, the intrauterine pressure may be as high as ten times the pressure reached at the height of a labor contraction. Blunt trauma causes the uterus to compress and then expand and the placenta shears away from the uterine wall. The degree of separation may bear no relationship to the degree of trauma; abruption may occur with very little evidence of injury to the mother. It usually, but not always, follows soon after the trauma.

Vaginal bleeding, abdominal pain, increased uterine tone, uterine tenderness, high frequency contractions, and abnormal fetal cardiotocography are the classical clinical signs of a placental abruption. In a posteriorly inserted placenta, severe backache and vaginal bleeding may be significant symptoms. The bleeding may be revealed or concealed within the uterus. If concealed, in severe cases, the uterus becomes woody hard as described by Couvelaire, blood having been extravasated into the muscular wall of the uterus. Fetal parts are impossible to feel and the patient's condition rapidly deteriorates due to hypovolemia and pain.

The management of abruptio placentae depends on the severity of the abruption, the nature of the general injuries sustained, the condition of the fetus and the duration of the pregnancy. The trauma surgeon and the obstetrician should work together in managing the patient. Establishing wide-bore intravenous access is essential. The hematologist should also be involved. A complete thrombophilia screen should be requested and cross-matched blood organized, together with fresh frozen plasma.

A preterm uncompromised fetus should be observed by continuous cardiotocography for a minimum of 6–12 h or by a Pinard stethoscope in less developed communities and, if the gestation is under 34 weeks, the mother should be given corticosteroids to mimimize the adverse effect of prematurity on lung maturation. If the fetus is previable and compromised, vaginal delivery is the safest for the mother.

In a term pregnancy with abruptio and an uncompromised fetus, vaginal delivery is an option. However, Cesarean section is advised if the fetus is compromised. If the fetus, on the other hand, has died, induction of labor and vaginal delivery are appropriate and safe for the mother.

Preterm labor following blunt abdominal trauma may be precipitated by extravasation of blood into the myometrium stimulating uterine contraction. Prostaglandin release may stimulate uterine activity. Preterm labor requiring tocolysis occurs in 10–30% of cases of blunt

abdominal trauma, but less than 1% deliver before 34 weeks. Tocolytics should be used guardedly, lest they mask the sign of abruption. Contractions following blunt abdominal trauma abate without treatment in 90% of cases. All tocolytics have side-effects which the obstetrician should be familiar with: beta mimetics induce tachycardia and may mask the early signs of abruption; non-steroidal anti-inflammatory agents affect platelet and renal function; and calcium channel blockers cause hypertension. The fetal heart rate and the uterine contractions should be continuously monitored[34].

Uterine rupture is a rare (1%) occurrence in blunt abdominal trauma; when it does occur, it is usually in association with a fractured pelvis. The site of rupture is commonly the fundus of the uterus or the site of a previous uterine scar. Fetal mortality in such cases is 100%, and maternal mortality 10%[35–38]. Diagnosis may be difficult with vague abdominal pain, uterine tenderness, but with easily palpable fetal parts, and a poor trace or absence of a fetal heart on cardiotocography. Fetal demise and maternal shock are more dramatic presentations.

If suspected, exploratory laparotomy in the presence of the trauma surgeon is indicated. Uterine repair should be undertaken only if the patient is hemodynamically stable. If not, hysterectomy should be performed. However, the risk of a rupture in a subsequent pregnancy is high, and the patient and her family should be advised this at an appropriate time.

Fetal injury occurs very infrequently following blunt abdominal trauma. Fracture of the long bones or the skull is the most common injury and occurs in approximately 1% of cases. If the fetus is distressed, immediate delivery is called for. In the preterm non-compromised fetus, delivery may be delayed, but serial monitoring is advised[39,40].

Fetomaternal hemorrhage occurs in up to 30% of cases of blunt abdominal trauma, especially if the placenta is situated anteriorly. Most fetuses will have a normal outcome, although anemia, supraventricular tachycardia and fetal demise can occur depending on the extent of the fetomaternal hemorrhage[41,42]. Victims of blunt abdominal trauma should be screened for Rhesus factor, and all Rhesus-negative mothers given Anti-D immunoglobulin to prevent sensitization. Sensitization can occur as early as the 5th week of pregnancy. A Kleihauer–Betke test is essential to assess the magnitude of the fetomaternal hemorrhage and adjust the dose of Anti-D immunoglobulin accordingly.

In all cases of blunt abdominal injuries, fetal assessment is of paramount importance. Cardiotocography is the most sensitive method of immediate fetal surveillance. Ultrasonography is only accurate in predicting 40% of cases of abruption. Uterine activity is the most sensitive indicator for predicting abruption following blunt abdominal trauma. Frequent contractions have an adverse effect on fetal outcome.

As a guideline, patients who have sustained blunt abdominal trauma, but have no abdominal tenderness, no vaginal bleeding and no contractions should be monitored 2-hourly for 6–12 hours. Patients with abdominal tenderness, vaginal bleeding and contractions should be monitored continuously[43,44].

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10

PLACENTAL ABNORMALITIES

M. K. Mehasseb and J. C. Konje

INTRODUCTION

Obstetric hemorrhage is still considered to be one of the leading causes of maternal mortality and morbidity[1–7]. Placental abnormalities are a major contributor to obstetric hemorrhage. The common abnormalities include placental abruption, placenta previa, morbidly adherent placentae (accreta, increta, percreta) and retained placenta. These abnormalities, for example, accounted for 36% of pregnancy-related deaths due to hemorrhage in one series[8].

PLACENTA PREVIA

Placenta previa is defined as partial or complete insertion of the placenta onto the lower uterine segment after fetal viability (20 weeks in developed countries and 24–28 weeks in developing countries). Four grades of placenta previa are recognized (Figure 1):

(1) Grade I: placenta is in the lower segment but its edge does not reach the internal os;

(2) Grade II: lower placental edges reach the os but do not cover it;

(3) Grade III: edge covers the os and the placenta is asymmetrical;

(4) Grade IV: placenta symmetrically covers the os.

Although this classification/grading system is the most common, others reflect the ultrasound definition of the placental site.

An alternative anatomical grading is provided below:

(1) *Total placenta previa*: where the internal cervical os is completely covered by placenta;

(2) *Partial placenta previa*: where the internal os is partially covered by placenta;

(3) *Marginal previa*: where the edge of the placenta is at the margin of the internal os but does not cover it;

(4) *Low-lying placenta*: where the placental edge does not reach but is in close proximity to the internal os.

This other classification depends on the state of the cervix at the time of examination; for example, a low-lying placenta at 2 cm dilatation may

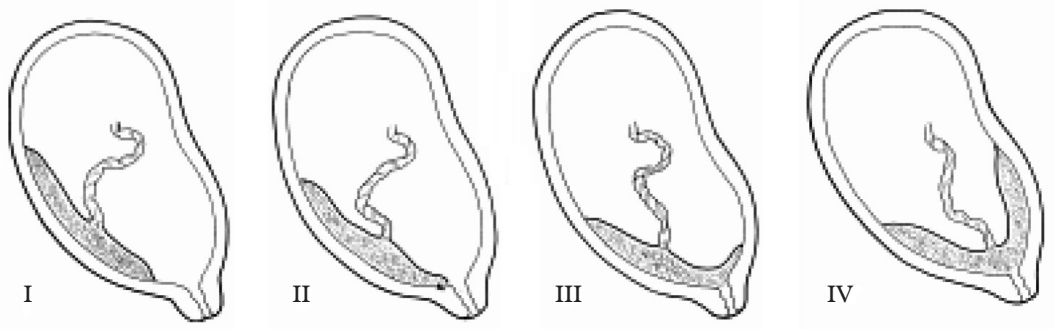

Figure 1 Grades of placenta previa: I, Encroaching on the lower segment; II, reaching the internal os; III, asymmetrically covering the internal os; IV, symmetrically covering the internal os

become a partial placenta at 8 cm dilatation. Since a digital examination is not recommended in cases of placenta previa, this alternative classification has limited clinical application.

Incidence and risk factors

The overall incidence is variable in different series, but is on average 1 in 300 deliveries[9,10]. Risk factors for placenta previa include:

(1) It is thought to be more common with advanced *maternal age*. This may, however, be a reflection of increased parity rather than age. However, a rise in incidence from 0.3% to 0.7% over a 10-year period has been attributed to a shift to an older obstetric population[11].

(2) Women of higher *parity* have a higher incidence[12].

(3) *Multifetal gestation*: secondary to an increase in the surface area occupied by the placental mass[13].

(4) The incidence increases with the number of *previous Cesarean section deliveries*[14,15]. A single Cesarean section increases the risk by 0.65%, two by 1.5%, three by 2.2% and four or more by 10%. A previous Cesarean section in association with placenta previa increases the risk of Cesarean hysterectomy almost four-fold[11].

(5) *Smoking* doubles the risk of placenta previa[13–16]. This may be attributed to placental hypertrophy secondary to carbon monoxide hypoxemia[16].

(6) Patients with *placenta previa* have 12 times the usual risk of having a recurrent previa in subsequent pregnancies.

(7) For unclear reasons, *fetal anomalies* are increased with placenta previa even after control for maternal age[9]. It is also uncertain if there is an association with intrauterine fetal growth restriction[17,18].

Diagnosis

This can either be clinical or by imaging.

Clinical

The most characteristic feature is *painless vaginal bleeding*. This is usually *recurrent* and *unprovoked* and does not commonly appear until the end of the second trimester. The first episode is usually self-limiting and is rarely so profuse as to prove fatal. However, the earlier in pregnancy the first presentation of bleeding, the more likely is the later need for early intervention. 'Fetal distress' is unusual unless the hemorrhage is severe enough to cause maternal shock.

Abdominal palpation is not diagnostic but, where the presenting part is free in late pregnancy or abnormal, placenta previa should be suspected.

Sometimes, especially with minor degrees of placenta previa, bleeding might not appear until the onset of labor. This may clinically mimic abruption (see below).

The possibility of placenta previa should always be considered in women who present with bleeding in the latter half of pregnancy. The diagnosis can seldom be made solely on a clinical basis.

There is no role for digital examination in the diagnosis unless in the operating theater as part of the double set-up with adequate preparation for proceeding to Cesarean section. Although uncommon, where imaging (see below) is easily available and reliable, it remains useful in cases where the diagnosis is in doubt and where double set-up facilities are unavailable.

Imaging

The most commonly used method of placental localization in modern obstetrics is *ultrasound scan*. It is safe, accurate and non-invasive and is the method of choice for making the diagnosis. The gestational age at which diagnosis is made significantly influences accuracy. The earlier the scan is performed, the more likely the placenta is to be found in the lower pole of the uterus. Consequently, routinely localization of the placenta at the 20–22 weeks' gestation anomaly scan poses several questions. For example, is a low-lying placenta at this stage predictive of placenta previa at the time of delivery, or does such screening reduce the adverse outcome for the

pregnancy? More importantly, should the scan be repeated at 32–34 weeks' gestation and does the asymptomatic patient have to be admitted and if so when?

About 28% of placentas in women scanned transabdominally before 24 weeks are found to be 'low' but by 24 weeks this drops to 18% and only 3% are low-lying by term[19]. Conversely, a false-negative scan for a low placenta is found in as many as 7% of cases at 20 weeks[20]. Such results are more common when the placenta is posterior, the bladder is over-filled, the fetal head obscures the margin of the placenta, or the operator fails to scan the lateral uterine wall[21]. A low-lying placenta is more common in early pregnancy because the lower segment does not exist. This apparent 'placental migration' is due to enlargement of the upper segment and formation of the lower segment, with many apparently low placentas being found to be above the lower segment. Comeau and colleagues[22] and Ruparelia and Chapman[23] have shown that the more advanced the pregnancy is, the more accurate a scan diagnosis of placenta previa will be.

Transvaginal ultrasound is not only more accurate in diagnosing placenta previa but it is more precise in defining the relationship of the lower edge of the placenta to the internal os (Figure 2). Placenta previa is diagnosed on transvaginal ultrasound scan when the placental edge is less than 3 cm from the internal os. Where the distance between the lower edge of the placenta and the internal cervical os is measured, the persistence of a low-lying placenta at a later gestation is higher. Taipale and colleagues[24], for example, observed that, if a placenta overlapped the internal os by at least 25 mm at 18–23 weeks, the positive predictive value for previa at delivery was 40% with a sensitivity of 80%. Indeed, Becker and colleagues[25] found that, when the lower edge overlapped the os by at least 25 mm at 20–23 weeks, a vaginal delivery was not possible at all at term (i.e. it had a 100% positive predictive value).

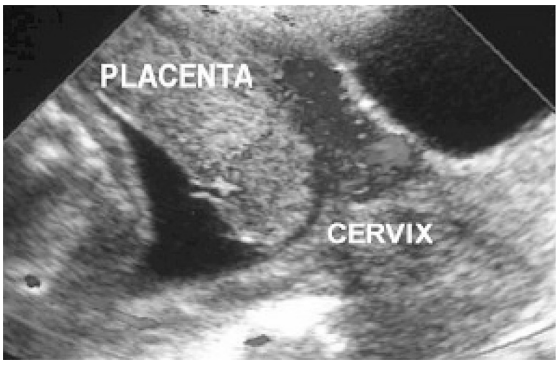

Figure 2 Transabdominal ultrasound scan with superimposed color Doppler signal showing an anterior placenta previa

Although the routine practice of localizing the placenta at the anomaly scan will no doubt continue, its limitations should be recognized and, wherever possible, transvaginal ultrasound scans should be offered to improve the accuracy of localization and also measure the distance from the os to the placental edge to help define the degree of 'low lying'.

Since there are no randomized, controlled trials of the effect of routine localization versus no localization on the mother and fetus, current practice will have to be governed by large-cohort case studies. It is, however, easy to assume that, where there is a low-lying placenta, education of patients and carers enhances the chances of a better outcome for mother and baby. Whether such patients should be routinely admitted at a later gestation is debatable. Most units do not, however, routinely admit but repeat the scans at 32–24 weeks' gestation. Dashe and colleagues[26] observed that persistence of placental previa diagnosed at 20–23 weeks occurred in 34% of cases at delivery, whereas 73% of those present at 32–35 weeks persisted at delivery. A policy of routine scanning will therefore reduce the false-positive rates but will be at the expense of increasing workload and patient anxiety. Unfortunately, none of the studies reported on the proportion of patients with low-lying placentas diagnosed at 32–34 weeks that later presented with bleeding. For units not routinely scanning for placental site at 20 weeks, scanning for placental site is only indicated with abnormal presentation, vaginal bleeding or a chance finding when ultrasound was undertaken in late pregnancy for other reasons. For such cases, a transvaginal approach is recommended as it is associated with a better diagnostic accuracy, especially with posterior placenta previa[27,28]. This approach has been shown to be safe and is well tolerated.

Transperineal sonography has been used by some investigators[29]. It allowed easy visualization of the internal os in all cases and carried a positive predictive value of 90% and a negative predictive value of 100% for placenta previa.

Magnetic resonance imaging (MRI) has been used to visualize placental abnormalities including placenta previa (Figure 3). It has the advantages of being an objective, reproducible test, minimizing the operator error. However, due to cost and logistic limitations, it is unlikely that it will replace ultrasonography for routine evaluation[30,31].

Management

Management depends on whether the patient is symptomatic or not. Asymptomatic patients (where the diagnosis is made on ultrasound scan) are managed expectantly, often as for those with mild symptoms that are non-threatening to either the mother or fetus.

Those with symptoms can be divided into four categories depending on the maternal condition, severity of hemorrhage, the gestational age and the neonatal facilities available in the unit. These categories are:

(1) Pregnancy < 37 weeks' gestation without threat to the mother;

(2) Pregnancy > 37 weeks without threat to the mother;

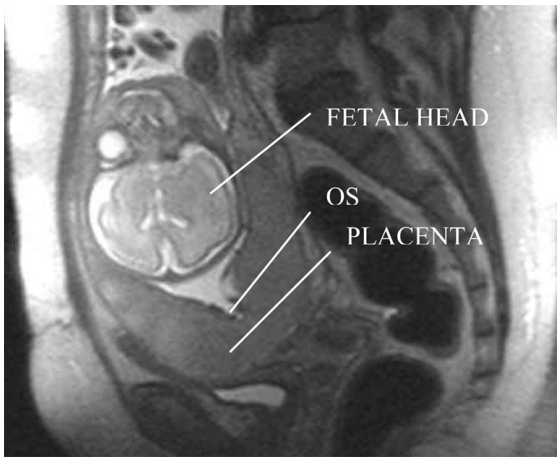

Figure 3 MRI of a grade IV placenta previa (completely covering the internal os)

(3) Severe life-threatening, non-stopping (continuing) hemorrhage < or > 37 weeks;

(4) Hemorrhage associated with uterine contractions.

The management of the third and fourth categories is immediate delivery by Cesarean section. In the presence of non-life-threatening hemorrhage after 37 weeks' gestation, a planned delivery is also advisable. This must, however, be with the recognition that such a hemorrhage could very rapidly become life-threatening. For category 1, the best approach is expectant management, although this must not be to the detriment of maternal life.

Expectant management

The perinatal mortality in placenta previa is directly related to gestational age at delivery[32–35]. Macafee[33] and Johnson and colleagues[35] introduced expectant management of placenta previa with the aim of achieving maximum fetal maturity possible while minimizing the risks to both mother and fetus, the overall objective being to reduce perinatal mortality, and, at the same time, reducing maternal mortality. This management plan was based on the assumption that most episodes of bleeding are usually small, self-limited and are not fatal to the fetus or mother in the absence of provoking trauma (e.g. intercourse, vaginal examination) or labor, and that a proportion of cases, particularly those presenting early with lesser degrees of previa, may resolve to permit vaginal delivery. More recently, an improvement in perinatal mortality attributed mainly to prolongation of pregnancy with expectant management has also been reported[36,37].

Although Macafee[33], in his regimen, advocated that the patient remained as an inpatient in a fully equipped and fully staffed maternity hospital from the time of initial diagnosis to delivery, a policy of permitting a selection of women to return home has also been advocated[38] as part of expectant management, but remains controversial. Cotton and colleagues[32] reported no difference in their perinatal and maternal mortality rates in those sent home and those managed in hospitals, whereas D'Angelo and Irwin[39] suggested keeping the mother in

hospital until delivery was justified, on the grounds that neonatal mortality and morbidity and cost of treatment were reduced. Kaunitz and colleagues[40], in a review of 355 maternities managed at home, however, reported one intrapartum death from placenta previa.

This controversy is more evident in cases of asymptomatic transvaginally diagnosed placenta previa. For this group, it is becoming increasingly acceptable to manage them at home[41,42]. In a review of 15 930 deliveries in Edinburgh, Love and Wallace[43] concluded that, while clinical outcomes were highly variable and cannot be predicted from antenatal events, the majority of cases with or without bleeding, irrespective of the degree of previa, could be managed on outpatient bases. There are no randomized, controlled trials on the different approaches to this aspect of placental previa and such evidence is urgently needed to enable rationale decision-making in clinical practice.

Although most experts will advocate immediate delivery where there is severe hemorrhage (heavy vaginal bleeding producing maternal hypovolemia), it is, however, not considered a contraindication to expectant management[43]. An aggressive approach involving admission and repeated blood transfusions improves perinatal morbidity and mortality, especially where the bleeding occurs very early in pregnancy. In one study, where approximately 20% of the women lost over 500 ml of blood, half of them were managed expectantly with a mean gain in gestation of 16.8 days[44]. Crenshaw and colleagues[34], on the other hand, managed only 43–46% of patients successfully with an aggressive expectant approach, whereas Cotton and colleagues[32], with an aggressive approach, successfully managed 66% of women expectantly.

During expectant management, preterm labor remains a problem. Brenner and colleagues[45] found that 40% of women with placenta previa had prelabor rupture of membranes, and went into spontaneous labor or other developed problems that resulted in delivery before 37 weeks' gestation. Inhibiting contractions in those with preterm labor would seem logical, but some regard antepartum hemorrhage as a contraindication to the use of tocolytics[46]. With vaginal bleeding and uterine contractions, placental abruption, which is widely regarded as a contraindication to tocolysis, cannot be excluded. In addition, placental abruption is said to coexist with placenta previa in 10% of cases, and tocolytics cause maternal tachycardia and palpitations, features that could be confused with hypovolemia. Sampson and colleagues[47] advocate the use of tocolytics in cases of placenta previa and uterine contractions after 21 weeks and cite a reduction in perinatal mortality from 126 to 41 per 1000.

Mild blood loss in placenta previa is not associated with a significantly high perinatal mortality. In contrast, significant blood loss is associated with a high perinatal loss. Liberal use of blood transfusion has been reported to nullify this effect[32]. Although there is no theoretical limit to the number of blood transfusions a patient can have, most blood banks do not have endless supplies. To optimize oxygen supply to the fetus and protect the mother against anticipated future blood loss, the ideal aim of transfusion should be to maintain a hemoglobin level of at least 10 g/dl or a hematocrit of 30%.

Despite expectant management, 20% of women with placenta previa are delivered earlier than 32 weeks. These cases account for 73% of perinatal deaths[32]. They remain a major problem and, although the use of cervical cerclage has been advocated, this is generally not used. The neonatal mortality and morbidity are reduced in this group by maternal corticosteroid administration.

Continuous hospitalization is costly and has an associated psychological effect of separation on families. In developing countries, this may be unaffordable to many families. However, the advantages include easy access to resuscitation and prompt delivery and ensuring bed rest (which anecdotally has been thought to decrease the occurrence of hemorrhage) as well as limitation of activities. With improvement in transportation facilities and ambulance services in developed countries, highly motivated women who clearly understand the necessity of restriction of activity and are within, for example, 15–30 min of the hospital perhaps may be monitored at home. This will only apply to cases of grades I–III placenta previa or asymptomatic grade IV. In all cases of expectant management, cross-matched blood (two units) must be

available at all times. However, in many hospitals this requirement is the *sine qua non* of a limitation on therapeutic options.

Method of delivery

A diagnosis of placenta previa means delivery by Cesarean section, but this is not inevitable, especially where the previa is to a minor degree. For the minor degree of placenta previa (grade I or II anterior) and an engaged fetal head, pregnancy may be allowed to continue beyond 37–38 weeks and vaginal delivery anticipated. In such patients, amniotomy followed by syntocinon can be considered.

In patients with a major grade of placenta previa (grade II posterior, grades III–IV), delivery should be by elective or emergency Cesarean section. The former is ideal since emergency delivery has a negative effect on perinatal mortality and morbidity, independent of gestational age. Cotton and colleagues[32] found that 27.7% of babies born as emergencies had anemia compared to 2.9% delivered electively.

Cesarean section for placenta previa poses several problems. It should, therefore, never be left to an inexperienced obstetrician. The Royal College of Obstetricians and Gynaecologists in the UK recommends that such Cesarean sections are performed by consultants. Although general anesthesia was preferred to regional in the past, there is an increasing tendency to using the latter especially as Frederiksen and colleagues[48] demonstrated not only its safety but a reduction in intrapartum blood loss compared to that with general anesthesia.

Procedure

Epidural analgesia is increasingly being advocated for Cesarean section (in developed countries) although Moir[49] considers placenta previa to be an absolute contraindication to an epidural. This is because epidurals, by lowering the blood pressure, may critically reduce uterine and placental perfusion. Crawford[50], however, believes that, in experienced hands, an epidural is safe. Indeed, an increasing number of anesthetists offer regional anesthesia to these patients[30,31]. Where the patient's condition is stable and there is no active bleeding, epidural or spinal anesthesia should not be regarded as contraindicated provided an experienced anesthetist is available.

The uterine incision should be a transverse lower segment incision (if possible), provided there is a lower segment. Where the lower segment is non-existent or is very vascular, some obstetricians advocate a classical or a De Lee's incision. Scott[51], however, believes that such incisions are rarely justified because of their consequences and long-term disadvantages. When difficulties are encountered with transverse lower segment incisions, these may be converted to inverted T-, J- or U-shaped incisions.

Where the placenta is anterior, two approaches are available for incising the uterus, going through the placenta or defining its edge and going through the membranes above or below the placenta. The former approach requires speed and may result in significant fetal blood loss[52]. The latter, however, may be associated with undue delay in the delivery of the fetus, more troublesome bleeding from a partially separated placenta and therefore fetal blood loss and anoxia. Myerscough[52] advises against cutting or tearing through the placenta because of the inevitable fetal blood loss that occurs as fetal vessels are torn. Because the lower segment is less muscular, contraction and retraction, which result in the occlusion of the sinuses of the placental bed, are inadequate, and intraoperative hemorrhage is therefore not uncommon[53]. Where hemostasis is difficult to achieve, bleeding sinuses could be oversewn with atraumatic sutures[51]. If this is unsuccessful, packing the uterus is possible, but the major disadvantage is that, by leaving the pack *in situ* during closure of the uterus, the bleeding may continue but remain concealed for some time as the pack is soaking through. The use of balloons with a tamponading effect on the bleeding placenta bed or intramyometrial injection of prostaglandin $F_{2\alpha}$ has been shown to be useful in such cases[52]. More recently, where the facilities are available, uterine artery embolization has been used with excellent results. The difficulty with this is planning to ensure that the facilities and the interventional radiologist are available on the labor ward during the delivery. When the bleeding remains uncontrollable,

ligation of the internal iliac artery or even hysterectomy may be necessary as the last resort (see Chapters 32 and 34).

PLACENTAL ABRUPTION

The Latin term *abruptio placentae* means '*rending asunder of the placenta*', implying and denoting a sudden accident, which is a valid clinical characteristic of most cases. It represents bleeding due to premature separation of a normally sited placenta after fetal viability. The initial event in abruption is bleeding into the decidua basalis.

Incidence and risk factors

It occurs in about 1 in 200 pregnancies[10], although higher incidences have been reported[54]. When placentas are examined routinely, the incidence is much higher at 4.5%[55] suggesting that small episodes are more common than those diagnosed clinically. Placental abruption can be revealed or concealed (Figure 4), the former occurring in 65–80% of cases. The concealed type is clinically more dangerous as it is often associated with more severe complications.

Risk factors for placental abruption include:

(1) *Parity*: more common in women of higher parity;

(2) *Age*: more common in older women but this may again be a reflection of parity rather than age;

(3) *Previous placental abruption*: this varies from 6 to 16.7% after one episode and 25% after two episodes. Up to 7% of those with abruption severe enough to result in fetal death have the same outcome in a subsequent pregnancy and 30% of all future pregnancies in women who have a placental abruption do not result in a living child[56–59].

(4) *Premature rupture of fetal membranes*: a meta-analysis of 54 studies demonstrated a three-fold increase in the risk of abruption[60] and this risk was much higher with rupture between 20 and 36 weeks' gestation and if rupture was for longer than 24 hours[61,62];

(5) *Cigarette smoking*: the incidence in smokers is almost double that in non-smokers; smokers who quit have an associated reduction in risk;

(6) *Cocaine use*: significantly increased risk compared to non-users[63];

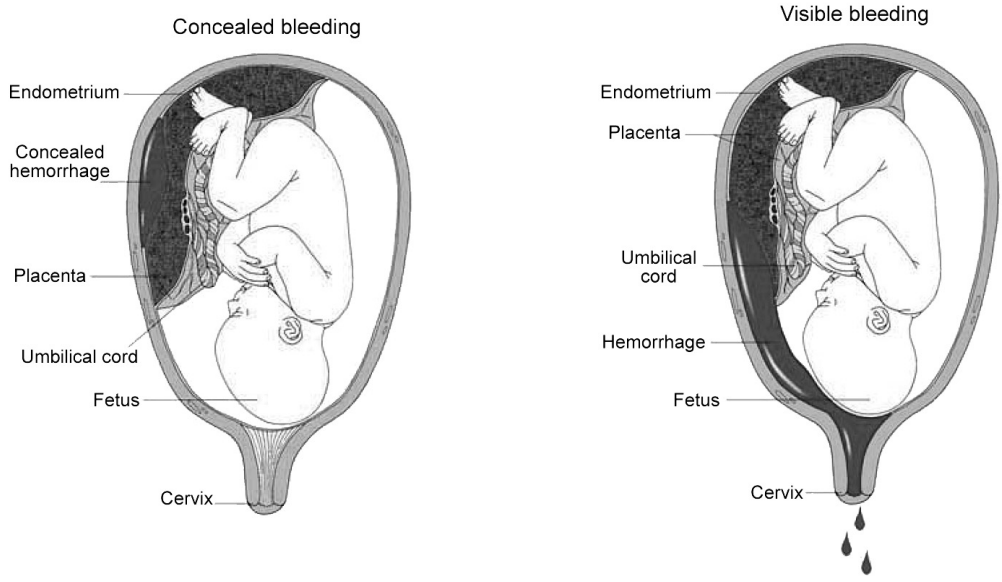

Figure 4 Concealed and revealed placental abruption

(7) *Abdominal trauma*: placental abruption complicates 1–6% of minor injuries and up to 50% of major injuries[64];

(8) *Sudden decompression of the uterus after membrane rupture*, e.g. in twin pregnancies, external cephalic version or pregnancies with polyhydramnios;

(9) Unexplained raised α-fetoprotein;

(10) Hyperhomocysteinemia and thrombophilias, especially factor V Leiden[65,66];

(11) Hypertensive disorders of pregnancy.

Diagnosis

Unlike placenta previa where ultrasound is the mainstay of diagnosis, the diagnosis of placental abruption is usually made on clinical grounds (Table 1). Ultrasonography may, however, be helpful in certain instances, for example, where there is a large retroplacental hematoma. This, however, is an uncommon finding even in severe cases. The symptoms and signs are diagnostic in moderate to severe cases. In the mild forms, the diagnosis may not be obvious until after delivery when a retroplacental clot is identified.

Placental abruption classically presents with vaginal bleeding, abdominal pain, uterine contractions and tenderness. Vaginal bleeding, however, is a symptom in no more than 70–80% of cases[28]. The bleeding which occurs after the 36th week of gestation in about 50% of cases[28] is characteristically dark and non-clotting. Because labor is the commonest factor precipitating placental separation[70], nearly 50% of patients with placental abruption are in established labor. The presence of uterine contractions may, however, be difficult to distinguish from the abdominal pain of abruption which is often unremitting. Where this distinction is possible, the contractions are characteristically very frequent with a rate often of over five in 10 min[71].

Table 1 Clinical picture of placental abruption[71]

Symptom/sign	*Frequency* (%)
Vaginal bleeding	78
Uterine tenderness or back pain	66
Fetal distress	60
Preterm labor	22
High-frequency contractions	17
Hypertonus	17
Dead fetus	15

The absence of abdominal pain does not exclude placental abruption, especially where the placenta is posteriorly sited. This is evidenced by the so-called 'unsuspected or silent abruption' referred to by Notelovitz and colleagues[72] and the higher pathological incidence of placental abruption found by Fox[55]. The presence of pain is probably indicative of extravasation of blood into the myometrium. In severe cases (grade 3), the pain is sharp, severe and sudden in onset. Some patients may, in addition, present with nausea, anxiety, thirst, restlessness and a feeling of faintness, whereas others may complain of absent or reduced fetal movements.

Some patients present with signs of shock where the blood loss is significant (tachycardia predominates; blood pressure has a poor relation with blood volume in this condition). The presence of hypertension may, however, mask true hypovolemia but an increasing abdominal girth or a rising fundal height must raise the suspicion of significant concealed hemorrhage. Typically, the uterus is 'woody hard' in severe cases where the fetus is difficult to palpate and a continuous fetal heart rate monitor or real-time ultrasonography is essential to identify the fetal heart beat. The fetus may be 'distressed' with fetal heart rate abnormalities or it may be dead. The former occurs in grades 1–2, but, in grade 3, the latter is an invariable occurrence by definition[73]. In severe cases complicated by disseminated intravascular coagulation, there may be absence of clotting in the vaginal blood loss, which is dark-colored. The incidence of coagulopathy varies from 35 to 38%[57,74] and this occurs mainly in the severe forms.

A vaginal examination reveals blood clots in the vagina, which is typically non-clotting. Serous fluid from a retroplacental clot may be confused with liquor. The cervix may be dilating since 50% of cases are in labor. If the membranes are ruptured, blood-stained liquor is usually present.

Ultrasound scan is not a sensitive method of diagnosing placental abruption but is useful in

excluding coincident placenta previa, which is present in 10% of cases. Where the retroplacental clot is large, ultrasonography identifies it as hyperechogenic or isoechogenic when compared to the placenta. Such echogenicity may therefore be misinterpreted as a thick placenta[75]. A resolving retroplacental clot appears hyperechogenic within 1 week and sonolucent within 2 weeks.

Though ultrasound scan is not an accurate diagnostic tool, it is useful in monitoring cases managed. The size of the hematoma, location and change in size over time and fetal growth are all parameters monitored by ultrasound scan. A Kliehauer–Betke test may be useful in making the diagnosis when a patient presents with abdominal pain but without vaginal bleeding or even in cases of 'unsuspected or silent abruption'.

Management

The severity of the abruption, the state of the fetus and the gestational age of the pregnancy all impinge on management which can be divided into general and specific measures. Sher and Statland[76] divided placental abruption into three degrees of severity upon which management can be based. These are shown in Table 2.

General management is similar to that for any patient presenting with bleeding (see above under placenta previa). The specific measures include immediate delivery, expectant management and management of complications.

Immediate delivery

This depends on the severity of abruption and whether the fetus is alive or dead. If the fetus is dead, vaginal delivery should be the goal after maternal resuscitation, as fetal death occurs commonly in the severe variety of placental abruption, often with coagulopathy. Once resuscitation has been initiated, the fetal membranes should be ruptured to hasten the onset of labor. This is effective in most cases but, in a few, augmentation with syntocinon may be needed. This must be administered cautiously as uterine rupture could occur from an overstimulated uterus.

Where the fetus is alive, the decision on how best to achieve delivery is not always easy. This is compounded by the fact that the outlook for the fetus is poor, not only in terms of immediate survival but also because studies have shown that as many as 15.4% of liveborn infants do not survive[77]. However, delivering by Cesarean section when the fetus is alive has been shown in non-randomized, controlled trials to have a better outcome than vaginal delivery (52% vs. 16%[78]; 20% vs. 15%[73]). Indecision and unnecessary delays in performing Cesarean sections[70] are responsible for most poor results from Cesarean section in the last quarter of pregnancy. Cesarean section must therefore be considered in all cases where the fetus is alive, particularly if there is evidence of fetal distress. However, the presence of coagulopathy adds considerable risk to the mother, and morbidity and mortality could be increased by surgery.

Once the decision is to deliver and the fetus is alive, the degree of abruption and the state of the fetus must be taken into consideration before delivering. When the abruption is severe, Cesarean section must be performed once resuscitation has commenced. Such delivery should be performed promptly, especially as most post-admission fetal deaths occur in fetuses delivered more than 2 hours after admission.

Table 2 Grading of placental abruption (Sher and Statland)[76]

Grade	*Description*
0	Asymptomatic abruption with a small retroplacental clot (< 150 ml)
1	Vaginal bleeding (150–500 ml); uterine tetany and tenderness may be present; no signs of maternal shock or fetal distress
2	Vaginal bleeding; no signs of maternal shock; signs of fetal distress
3	Vaginal bleeding; marked uterine tetany yielding a board-like consistency on palpation; persistent abdominal pain, with maternal shock and fetal demise; coagulopathy may be evident in 30% of cases

If the abruption is mild to moderate, the mode of delivery should be determined by the condition of the baby, its presentation and the state of the cervix. In the presence of abnormal fetal heart rate patterns, immediate delivery by Cesarean section is the option of choice. However, if the decision is to deliver vaginally, continuous fetal monitoring should be available to enable early identification of abnormal fetal heart rate patterns. Golditch and Boyce[79], Lunan[80] and Okonufua and Olatubosun[78] have all shown that the perinatal mortality is higher with vaginal delivery in the absence of electronic fetal monitoring. There is a place for the use of prostaglandins in the ripening of the cervix of women with mild abruption, but then the danger of inducing tetanic contractions must always be borne in mind. Where amniotomy is feasible, this often hastens delivery but, where it is not possible, syntocinon can be used, though once again maintaining vigilance for hyperstimulation.

Expectant management

This is recommended where neither the fetus nor the mother are at risk. Unfortunately, the lack of signs of fetal compromise on monitoring does not guarantee absence of deterioration in the fetal condition. With expectant management, pregnancy is prolonged in the hope of improving fetal maturity and therefore survival.

It is ideal for pregnancies less than 37 completed weeks of gestation; however, since neonatal survival is virtually guaranteed > 34–35 weeks' gestation, there is no place in persisting with such an approach for pregnancies > 34 weeks where fetal monitoring cannot be maintained. Expectant management is recommended for patients in whom vaginal bleeding is slight, abdominal pain is mild and usually localized and they are cardiovascularly stable. Once a decision has been made on conservative management, the fetal condition must be monitored closely as it may change very quickly.

Expectant management can be in the community or in the hospital; admission is not associated with a better outcome. However, where patient education and access to hospital are poor, admission may provide a safer option. It is perhaps in such communities that admission may be rejected because it is expensive or causes significant family disruptions.

During expectant management, fetal growth should be monitored by regular ultrasound scan as fetal growth restriction is a common finding in association with placental abruption. The timing of delivery depends on further vaginal bleeding, the fetal condition, gestational age and available neonatal care facilities. If the bleeding episodes are recurrent, induction at 37–38 weeks is advisable, provided there is no fetal compromise. Where the initial episode is small and self-limiting and there are no acute features of fetal compromise (e.g. abnormal cardiotocography or a biophysical profile score < 6) or chronic fetal compromise (growth restriction, oligohydramnios or abnormal umbilical artery Doppler recording), no evidence supports induction of labor. Despite this, it is nevertheless common for induction of labor at term to be advocated in such patients, using the speculative argument that some undetected damage might have occurred to the integrity and function of the placenta and, in the face of such uncertainty, delivery at term confers more advantages.

In a small proportion of cases, mild abruption may co-exist with labor. Whether abruption provoked labor, or vice-versa, is difficult to establish in these cases. The use of tocolytics in such patients is controversial, as their use in the presence of placental abruption is regarded by many as contraindicated since they may worsen the process of abruption[46]. Sholl[81], however, stated that a trial of tocolytics in the presence of mild placental abruption and labor may successfully prolong pregnancy without jeopardizing the mother and fetus. There have as yet been no large trials to confirm Sholl's statement.

Management of the complications of placental abruption

Complications of placental abruption include:

(1) *Maternal shock*: this may be disproportionate to the revealed blood loss. The type of resuscitation should therefore be determined by the clinical state of the patient. In most cases of shock, features of

disseminated intravascular coagulation must be excluded, as their presence will require additional measures to replace coagulation factors.

(2) *Disseminated intravascular coagulation* (DIC): treatment will require correction of the coagulation factor deficits, in consultation with a hematologist. Monitoring of renal function is essential as acute tubular necrosis is a recognized sequela.

(3) *Ischemic necrosis of the distal organs* (e.g. kidneys and brain): this requires adequate fluid replacement.

(4) *Postpartum hemorrhage* (secondary to DIC or Couvelaire uterus): treatment is with uterotonic drugs and other methods of managing postpartum hemorrhage.

(5) *Isoimmunization*: the administration of anti-D needs to be within 72 h but the quantity administered should be determined by Kleihauers–Betke test.

Management of cases with intrauterine fetal death

Where there is fetal death (in 20% of cases), placental detachment is usually greater than 50%, and approximately 30% of patients show evidence of coagulopathy. Such cases should therefore be classified as severe. The management should consist of the following:

Evaluation and replacement of blood loss

Blood loss > 2500 ml is common. At least 4 units of blood should be cross-matched and transfusion commenced with packed red blood cells, regardless of the initial vital signs as the initial hematocrit or hemoglobin levels may be normal due to hemoconcentration. Once resuscitation has been established, subsequent hypotension and tachycardia may then appear.

Management of coagulopathy (30% of cases)

Without evidence of excessive vaginal bleeding, no therapy is warranted even in the presence of abnormal laboratory results. Appropriate replacement of blood components and preservation of the intravascular volume are the cornerstones of treatment. Heparin has no role in the modern management of consumptive coagulopathy. The presence of coagulopathy *per se* is not an indication for Cesarean delivery but rather a strong contraindication. Also, the presence of an unfavorable cervix is not an indication for Cesarean delivery, unless the condition of the mother necessitates prompt delivery. The abdominal and uterine incisions can bleed excessively when coagulation defects persist (see Chapter 25).

Delivery

Unless there is an obstetric contraindication to vaginal delivery or hemorrhage is so brisk that it cannot be safely managed with vigorous blood transfusion, every attempt should be made to deliver these patients vaginally (without jeopardizing maternal health).

Amniotomy (artificial rupture of membranes) and syntocinon infusion should be started. The rigidity of the uterus or the presence of a high intrauterine pressure should not deter the use of syntocinon. If no rhythmic uterine contractions are superimposed on the background uterine hypertonus, then syntocinon should be started in standard doses. The benefits of achieving a vaginal delivery override the risks of using syntocinon. There is no evidence that its use is associated with enhanced passage of thromboplastin into the maternal circulation and thereby initiating or enhancing maternal consumptive coagulopathy[82]. With intrauterine fetal demise, no time limit for delivery is necessary. The maternal outcome is mainly dependent on the diligence of fluid and blood replacement rather than on the interval to delivery[83]. Where the cervix is unfavorable and maternal health is not in danger, prostaglandins may be used to induce delivery.

PLACENTA ACCRETA, INCRETA AND PERCRETA

This is a group of morbidly adherent placenta of varying severity. Such morbid adherence occurs when the implantation site is lacking a sufficient amount of decidua. Consequently, the physiological cleavage plane through the decidual

spongy layer is missing. This leads to one or more cotyledons being firmly anchored to the decidua basalis and even to the myometrium.

The term 'placenta accreta' is used to describe any placental implantation that is firmly adherent to the uterine wall. Placental villi are anchored to the myometrium due to defective decidualization. If villi invade the myometrium, the condition is called placenta increta. If the invasion goes as deep as reaching the serosal surface, this is called placenta percreta (see Chapter 8).

Although uncommon, they are associated with a significantly high maternal morbidity and sometimes mortality primarily due to hemorrhage, uterine perforation, infection and the associated surgical difficulties and complications[84].

Incidence

They occur in about 1 in 2500 deliveries. There has been a marked increase in the last 50 years, probably secondary to the increase in Cesarean section delivery rates[85].

Risk factors include implantation over the lower uterine segment overlying a previous surgical scar or excessive uterine curettage resulting in Asherman's syndrome. Placenta previa is identified in one-third of cases, and 25% of women have had a previous Cesarean delivery. Nearly one-quarter have previously undergone curettage and another quarter are grand multigravida (five or more)[86].

Diagnosis

Diagnosis is often not made until after delivery. Some patients may present with vague features which include a raised maternal serum α-fetoprotein[87] and bleeding before delivery, although this is usually a consequence of placenta previa. Uterine rupture may occur antenatally due to myometrial invasion by chorionic villi at the site of a Cesarean section scar[88].

The use of ultrasound Doppler color flow mapping improves the diagnostic sensitivity. The two most sensitive criteria are, first, a distance less than 1 mm between the uterine serosal bladder interface and the retroplacental vessels, and, second, the presence of large intraplacental lakes[89].

Preliminary work suggests that the application of three-dimensional color power Doppler ultrasound can be complementary to other techniques for antenatal imaging. It has been shown to be superior to magnetic resonance imaging in this context[90].

Management

In most cases, problems arise after delivery of the baby. Most of the complications of morbidly adherent placentas are related to the problems of delivery or failure to deliver. Management must therefore aim to minimize these complications (see Chapter 24).

Hemorrhage is the most common and this is associated with attempts to detach the placenta from the uterus. In most of these cases, unfortunately, the ultimate treatment is usually hysterectomy. Alternative approaches to management include uterine/hypogastric artery ligation or angiographic embolization. Sometimes, the percreta type might even invade the bladder base, further complicating the surgical procedure required and making the control of hemorrhage very difficult.

In cases of extensive placenta accreta (involving most of the placental surface), bleeding might be very limited until attempts at manual removal are made. At times, traction on the cord may lead to uterine inversion. Manual removal is usually not successful as the plane of cleavage between the uterus and the placenta cannot be developed. The safest treatment is usually hysterectomy. Attempts at uterine conservation include piece-meal removal of as much placental tissue as possible followed by packing of the uterine cavity, but this approach is reported to carry an unacceptably high mortality rate of 25%[86]. Another option to conserve the uterus is to leave the entire placenta *in situ* if there is no bleeding. Kayem describes a case where spontaneous resorption of the placenta occurred over 6 months following uterine artery embolization[91]. Other groups describe a similar approach, but using methotrexate. The placenta spontaneously delivered after 4 weeks[92,93].

RARE TYPES OF PLACENTAL ABNORMALITIES: SHAPE

Some anatomical variations in the shape of the placenta can give rise to serious postpartum hemorrhage. These include bipartite placentas, succenturiate lobes and placenta membranacea.

Bipartite placenta

Bipartite placenta occurs when the placenta is occasionally separated into two lobes, and the division is incomplete with vessels of fetal origin extending from one lobe to the other before ending in the umbilical cord. Its incidence is about 1 in 350 deliveries[94].

Succenturiate lobes

In this abnormal form, one or more small accessory lobes develops in the membranes at a distance from the main placenta. The succenturiate lobes usually connect to the latter with vascular connections of fetal origin. It can be considered to be like a small version of the lobate placenta. The accessory lobe may be retained in the uterus after delivery, causing serious hemorrhage. Its incidence has been reported to be as high as 5%[95].

Placenta membranacea

This type of placenta develops as a thin membrane-like structure with the whole of the fetal membranes covering the functioning villi. The diagnosis can be made with ultrasound scan. It can give rise to serious hemorrhage as an association with placenta previa or accreta. One variation is the 'ring-shaped' or 'horse-shoe' placenta where the process does not involve the whole placenta, but only a central part. This might occur in about 1 in 6000 deliveries[95].

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Section III

General preventive measures

11

ACTIVE MANAGEMENT OF THE THIRD STAGE OF LABOR

W. Prendiville and M. O'Connell

THE EVIDENCE

Traditionally, the third stage of labor is defined as that time between the delivery of the baby and delivery of the placenta. Separation of the placenta from the uterine wall results from a combination of capillary hemorrhage and uterine muscle contraction. The length of the third stage of labor, and its subsequent complications, depends on a combination of the length of time it takes for placental separation and the ability of the uterine muscle to contract.

Preventive clinical management of the third stage of labor varies from the purely expectant to an active approach, or some variation thereof. The expectant ('pure' physiological) approach involves waiting for clinical signs of placental separation (alteration of the form and size of the uterus, descent and lengthening of the umbilical cord and blood loss) and allowing the placenta to deliver either unaided using gravity or with the aid of nipple stimulation, as described in most maternity books[1,2]. In contrast, the full active approach involves administration of an oxytocic agent, early umbilical cord clamping and division and controlled cord traction for delivery of the umbilical cord[3–6].

In daily practice, the term 'active management' does not mean the same thing to all health-care professionals. Marked variation in practice is seen. A recent survey of management of the third stage of labor in 14 European countries confirmed this variation[7]. Whereas all units professed to practice active management of the third stage of labor, prophylactic uterotonics were infrequently employed in units in Austria and Denmark. Controlled cord traction was almost universally used in Ireland and the UK, but in less than 50% of units in the other 12 countries surveyed. Policies with respect to clamping and cutting the umbilical cord also varied widely, with most practitioners clamping and cutting immediately. However, this procedure was not performed in most units in Austria, Denmark, Finland, Hungary and Norway until the cord stopped pulsating[7]. [Editor's note: to add to this confusion, there is some concern that early clamping may deprive the neonate of an important amount of blood and its associated hemoglobin, a factor of great importance in many countries of the world. The components of AMTSL, as outlined in the November 2003 Joint Statement of the International Confederation of Midwives (ICM) and the International Federation of Gynecology and Obstetrics (FIGO), are administration of a uterotonic agent (oxytocin is the drug of choice), controlled cord traction, and uterine massage, after delivery of the placenta. See further discussion below.]

Given these circumstances, we reiterate this definition as the combined approach using three component interventions: (1) a prophylactic uterotonic agent; (2) early clamping and division of the umbilical cord; and (3) controlled cord traction.

UTEROTONIC AGENTS

The commonly used uterotonic agents are divided into three groups: oxytocin and oxytocin agonists, ergot alkaloids and prostaglandins.

Oxytocin

Oxytocin (Syntocinon) is a cyclic nonapeptide that is obtained by chemical synthesis. This synthetic form is identical to the natural hormone that is stored in the posterior pituitary and released into the systemic circulation in response to suckling and labor. Oxytocin

stimulates the smooth muscle of the uterus, more powerfully towards the end of pregnancy, during labor, and immediately postpartum. At these times, the oxytocin receptors in the myometrium are increased[8,9]. The oxytocin receptor is coupled via G9q proteins to phospholipase C. The resultant activation triggers release of calcium from intracellular stores and thus leads to myometrial contraction[10].

Low-dose intravenous infusion of oxytocin elicits rhythmic uterine contractions similar in frequency, force and duration to those observed during labor. Higher infusions can cause sustained uterine contractions. A transient relaxation of smooth muscle, with an associated brief episode of hypotension, flushing and reflex tachycardia, has been observed with rapidly administered intravenous bolus injections[11].

Oxytocin acts rapidly, with a latency period of less than 1 min after intravenous injection and 2–4 min after intramuscular injection. When oxytocin is administered by a continuous intravenous infusion, the uterine response begins gradually and reaches a steady state within 20–40 min. Removal of oxytocin from plasma is accomplished mainly by the liver and kidneys, with less than 1% excreted unchanged in urine. The metabolic clearance rate amounts to 20 ml/kg/min in the pregnant woman[12,13].

The prophylactic use of oxytocin in the third stage of labor has been described in a Cochrane review, where oxytocin alone was compared to no uterotonic and also compared to ergot alkaloids[14].

Oxytocin vs. no uterotonics

Seven trials including more than 3000 women were described in this comparison. Variation was noted not only in sample size and dose of oxytocin used, but also in mode of administration, with the intramuscular route being used in three trials[15–17] and the intravenous route used in the other four trials[18–21]. Those who received prophylactic oxytocin had clear benefit in terms of postpartum hemorrhage (Figures 1 and 2). Although debate surrounds the precise definition of postpartum hemorrhage, this benefit was seen whether the cut-off was taken as > 500 ml (relative risk (RR) 0.5, 95% confidence interval (CI) 0.43–0.59) or > 1000 ml (RR 0.61, 95% CI 0.44–0.87). A trend towards a decreased need for therapeutic oxytocin was also demonstrated (RR 0.50, CI 0.39–0.64) in those who received prophylactic oxytocin. A non-statistically significant trend was also seen in the need for manual removal of the placenta in the prophylactic oxytocin group (RR 1.17, 95% CI 0.79–1.73) as well as an insignificant increase in blood transfusion (RR 1.30, 95% CI 0.50–3.39).

Oxytocin vs. ergot alkaloids

Six trials including over 2800 women were described in this comparison. Variation was noted not only in sample size, dose of oxytocin used, and preparation of ergot alkaloid used, but also in the mode of administration, with the intramuscular route being used in one trial[15],

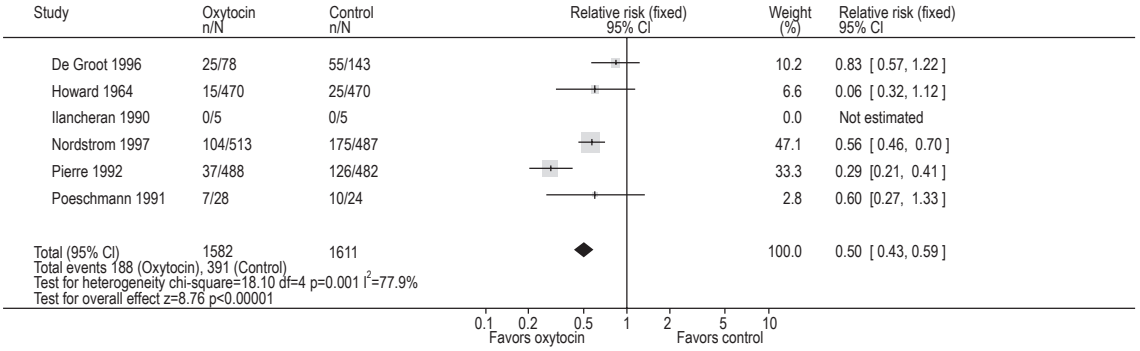

Figure 1 Comparison of oxytocin vs. no uterotonics (all trials), with outcome of postpartum hemorrhage (clinically estimated blood loss ≥ 500 ml). Cochrane review[14]

the intravenous route in four trials[18,19,22,23] and both intravenous and intramuscular routes in one trial[24].

Little differential effects were demonstrated between these two oxytocics (Figures 3 and 4). Ergometrine was associated with more manual removal of the placenta (RR 0.57, 95% CI 0.41–0.79) and a statistically insignificant tendency towards hypertension (RR 0.53, 95% CI 0.19–1.58).

Oxytocin agonists

Carbetocin appears to be the most promising of these agents in preventing postpartum hemorrhage[25]. Carbetocin is a long-acting synthetic octapepetide analogue of oxytocin, with agonist properties and similar clinical and pharmacological properties to naturally occurring oxytocin. It binds to oxytocin receptors and causes rhythmic contractions of smooth muscle of the uterus, increases the frequency of contractions and increases uterine tone. Intramuscular injections of carbetocin provide similar responses to tetanic contractions (in approximately 2 min), as does intravenous administration, but with a longer duration of activity[26]. Oxytocin agonists for the prevention of postpartum hemorrhage are currently the subject of an additional Cochrane review[27].

Syntometrine

Syntometrine is a mixture of 5 IU oxytocin (Syntocinon) and 500 μg ergometrine maleate. Ergometrine is a naturally occurring ergot alkaloid which stimulates contractions of the uterine and vascular smooth muscle. Following administration, it increases the amplitude and frequency of uterine contractions and tone and thus impedes uterine blood flow. Intense contractions are produced and are usually followed by periods of relaxation. Hemostatis is caused by contractions of the uterine wall around bleeding vessels at the placental site.

The vasoconstriction caused by ergometrine involves mainly capacitance vessels, leading to an increase in central venous pressure and blood

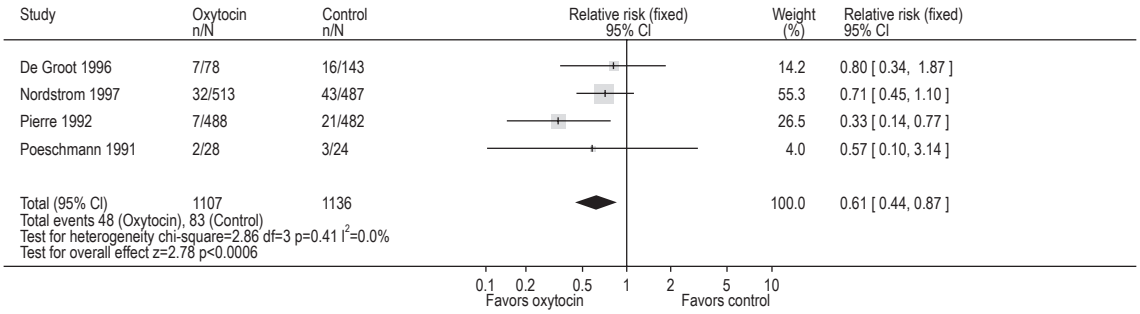

Figure 2 Comparison of oxytocin vs. no uterotonics (all trials), with outcome of severe postpartum hemorrhage (clinically estimated blood loss ≥ 1000 ml). Cochrane review[14]

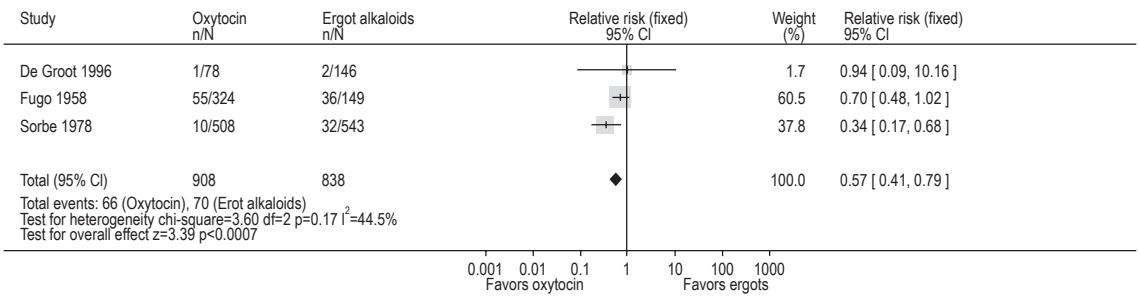

Figure 3 Comparison of oxytocin vs. ergot alkaloids (all trials), with outcome of manual removal of the placenta. Cochrane review[14]

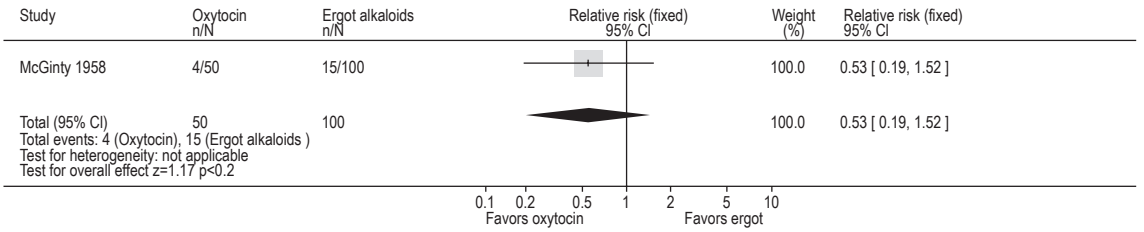

Figure 4 Comparison of oxytocin vs. ergot alkaloids (all trials), with outcome of diastolic blood pressure > 100 mmHg between delivery of the baby and discharge from the labor ward. Cochrane review[14]

pressure. Ergometrine produces arterial vasoconstriction by stimulation of the α-adrenergic and serotonin receptors and inhibition of endothelial-derived relaxation factor release. Uterine contractions are initiated within 1 min of intravenous injection and last for up to 45 min, whilst, with the intramuscular injection, contractions are initiated within 2–3 min and last for 3 h or longer[28–30].

The prophylactic use of ergometrine–oxytocin in the third stage of labor has also been the subject of a Cochrane review, where ergometrine-oxytocin was compared to oxytocin[31].

Ergometrine–oxytocin vs. oxytocin

Six trials including 9332 women were described in this comparison. Variation was noted not only in sample size but also in outcomes measured. Maternal outcomes in terms of nausea and vomiting, the need for blood transfusion and blood pressure measurements were considered in four trials[32–35]. Manual removal of the placenta was considered in two trials[33,36]. All six trials addressed the issue of postpartum hemorrhage, but much variation was seen in the quantification of the amount of blood lost[32–37].

In terms of postpartum hemorrhage, all six trials[32–37] demonstrated a significantly lower rate of postpartum hemorrhage with ergometrine–oxytocin regardless of the dose of oxytocin used (odds ratio (OR) 0.82, 95% CI 0.71–0.95). Four trials examined the effects of uterotonics on diastolic blood pressure[32–35]. Whilst there was a marked difference in the criteria used to ascertain the changes in diastolic blood pressure, a consistent picture, nevertheless, emerges demonstrating an elevation of diastolic blood pressure both with ergometrine–oxytocin and oxytocin. However, the use of ergometrine–oxytocin was associated with a greater rise in blood pressure than when using oxytocin alone (OR 2.40, 95% CI 1.58–3.64).

The incidence of nausea and/or vomiting was addressed in four trials[32–35]. In these trials, a greater incidence of these side-effects was noted with ergometrine–oxytocin use compared to oxytocin alone (vomiting: OR 4.92, 95% CI 4.03–6.00; nausea: OR 4.07, 95% CI 3.43–4.84; vomiting and nausea: OR 5.71, 95% CI 4.97–6.57). The same trials studied the incidence of need for blood transfusion and found no difference (OR 1.37, 95% CI 0.89–2.10). In the two trials that addressed the issue of manual removal of the placenta, no significant difference was shown (OR 1.03, 95% CI 0.80–1.33)[33,36].

Prophylactic use of ergot alkaloids in the third stage of labor

Ergot alkaloids are amide derivatives of the tetracyclic compound lysergic acid. There are three categories: (1) the ergotamine group: ergotamine, ergosine and isomers; (2) the regotoxine group: ergocornine, ergocristine, ergokryptine and isomers; and (3) the ergotamine and isomers.

The ergot alkaloids act as partial agonists or antagonists at adrenergic, dopaminergic and tryptaminergic receptors. All the ergot alkaloids significantly increase the motor activity of the uterus. They produce persistent contractions in the inner zone of myometrium through calcium channel mechanism and actin–myosin interaction, leading to the shearing effect on placental separation. The gravid uterus is very sensitive to

ergot alkaloids, and small doses can be administered immediately postpartum to obtain a marked uterine response. The different preparations and routes of administration have been the subject of a number of studies, both for therapeutic and prophylactic use[15,38–41]. All ergot alkaloids have qualitatively the same effect on the uterus; ergometrine is the most active and is also less toxic than ergotamine. For this reason, ergometrine and its semi-synthetic derivative methylergometrine have replaced other ergot preparations as uterine-stimulating agents in obstetrics. The injectable forms of both preparations are unstable when stored unrefrigerated and at high temperatures. The oral forms similarly deteriorate within weeks when stored in increased temperatures. Methylergometrine differs little from ergometrine in its pharmacokinetics.

Clinical trials have been conducted on the use of ergot alkaloids in the third stage of labor for prevention of postpartum hemorrhage[15,23,38]. The use of ergot alkaloids in the third stage of labor compared with no uterotonic drugs and with different routes of administration is again the subject of a Cochrane review[42].

Prostaglandins

Prostaglandins ripen the cervix by altering the extracellular ground substance, by increasing the activity of collagenase, and by increasing the elastase, glycoaminoglycans, dermatan sulfate, and hyaluronic acid levels in the cervix[43,44]. They allow for cervical smooth muscle relaxation and increase intracellular calcium, thus facilitating contraction of the myometrium.

Misoprostol is a synthetic analogue of naturally occurring prostaglandin E_1. It is rapidly absorbed following oral administration and its bioavailability exceeds 80%. Peak plasma levels are reached in 30–60 min, and it is converted to its active misoprostol acid, which has a half-life of 30–60 min. It is metabolized in the liver, and less than 1% of the active metabolite is excreted in the urine. In pregnancy, it is absorbed across the vaginal mucosa. After oral administration, the plasma concentration increases rapidly to reach a peak in 30 min and rapidly declines, whereas with vaginal administration the peak is reached in 1.5 h before steadily declining. Moreover, the area under the misoprostol concentration vs. time curve is increased, implying greater exposure time[45].

The prophylactic use of prostaglandins in the management of the third stage of labor has been the subject of a Cochrane review wherein misoprostol was compared[46] to (1) either placebo or no uterotonic; (2) conventional injectable uterotonic; or (3) injectable prostaglandin vs. injectable uterotonic.

Misoprostol vs. placebo/no uterotonic

Six trials were included in this comparison. Misoprostol 400 μg was the dose used in three of the trials[47–49]. A dose of 600 μg was used in an additional three trials[50–52]. One trial compared doses of 600 μg, and 400 μg with placebo/no uterotonic[53].

At both doses, misoprostol was either equal or less effective than placebo/no treatment for blood loss of 1000 ml or more and appeared to have a protective effect on the use of additional uterotonics, although this did not reach statistical significance. Misoprostol was, however, associated with more vomiting, shivering, and pyrexia than placebo, and this was dose-related and occurred across the trials.

Rectal misoprostol was compared to placebo in one trial[49]. No statistically significant reduction in blood loss of at least 1000 ml (RR 0.69, 95% CI 0.35–1.37) or need to use additional uterotonic agents (RR 0.70, 95% CI 0.31–1.62) was observed.

Misoprostol vs. conventional injectable uterotonics

Fourteen trials were included in this comparison[51,54–69]. The trials are heterogeneous in terms of dose of misoprostol used, route of administration and injectable uterotonic used. Overall, the risk of postpartum hemorrhage of at least 1000 ml was higher for the misoprostol group (RR 1.34, 95% CI 1.16–1.55) compared to either intravenous or intramuscular injections of oxytocin[70].

Injectable prostaglandins vs. injectable uterotonics

Seven trials compared injectable prostaglandins with conventional injectable

uterotonics[17,41,71–75]. The trials were heterogeneous, and reliable estimates of outcomes were not possible. The injectable prostaglandins were associated with less blood loss, a shorter duration of the third stage of labor, more vomiting, diarrhea and abdominal pain than conventional uterotonics. [Editor's note: Interested readers should see also Chapter 12 and Section IV, with the tables in Chapter 19.]

EARLY CORD CLAMPING AND DIVISION

The timing of umbilical cord clamping is variable[76]. In the active management of the third stage of labor, early cord clamping is generally carried out in the first 30 s after birth, regardless of the presence or absence of cord pulsations[77]. Late cord clamping constitutes expectant management, whereby clamping is deferred until cord pulsations have ceased. A precise definition of early or late cord clamping is not currently available[78].

Delayed clamping of the cord facilitates placental transfusion. This results in an increase in infant blood volume by 30% and an increase in hematocrit and hemoglobin levels, with a resultant increase in iron stores and less anemia in infancy[78–80]. However, the benefits associated with this increase in infant blood volume are short-lived, lasting no longer than 3 months[79]. In Rhesus-negative women, early clamping of the cord may increase the likelihood of feto-maternal transfusion and so exacerbate the risk of isoimmunization[78]. Early clamping of the cord has also been associated with a higher risk of respiratory distress syndrome in pre-term infants[81]. At present, evidence is insufficient to recommend early or late cord clamping, and the issue is the subject of a Cochrane review[82].

COMPARISON OF ACTIVE VERSUS EXPECTANT MANAGEMENT

As noted above, the active management of the third stage of labor consists of three interlocking interventions: a prophylactic uterotonic agent, early clamping and division of the umbilical cord, and controlled cord traction.

This management package has been compared to expectant management of the third stage of labor in a Cochrane review[83]. Five trials were included in the analysis[84–88]. Active management was routinely practiced in the first four of these trials, and both active and expectant management were practiced in the fifth trial. The oxytocics used included oxytocin alone, ergometrine alone and a combination of oxytocin and ergometrine.

The incidence of postpartum hemorrhage both at the 500 ml (RR 0.38, 95% CI 0.32–0.46) and 1000 ml (RR 0.33, 95% CI 0.21–0.51) levels was significantly decreased in the actively managed group compared to the expectantly managed group (Figures 5 and 6). More importantly, the need for blood transfusion was also significantly less in the actively managed group (RR 0.34, 95% CI 0.22–0.53), and the duration of the third stage of labor was not unexpectedly of shorter duration in the actively managed group (RR 0.15, 95% CI 0.12–0.19). A tendency toward an increase in

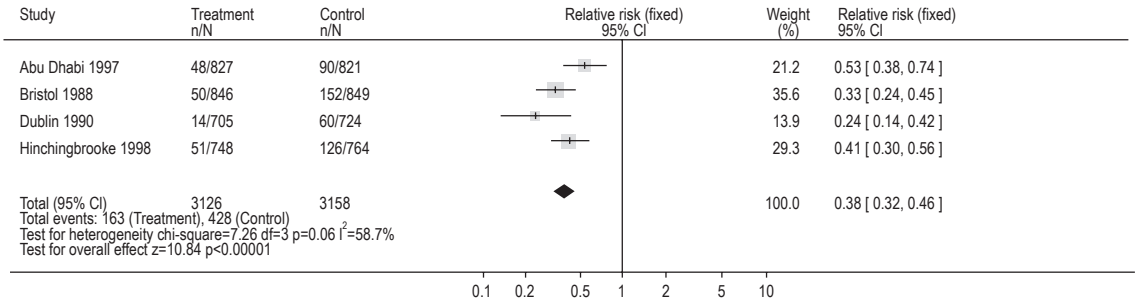

Figure 5 Comparison of active vs. expectant management (all women), with outcome of postpartum hemorrhage (clinically estimated blood loss ≥ 500 ml)[83]

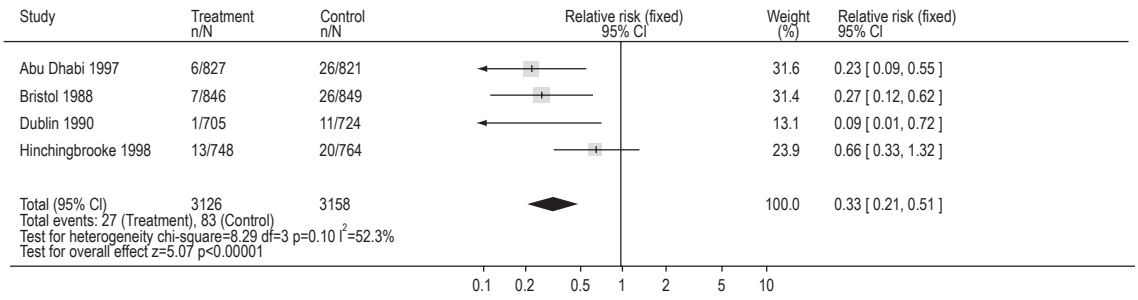

Figure 6 Comparison of active vs. expectant management (all women), with outcome of severe postpartum hemorrhage (clinically estimated blood loss ≥1000 ml)[83]

the need for manual removal of the placenta was noted in the actively managed group (RR 1.21, 95% CI 0.82–1.78), but this did not reach statistical significance. The incidences of nausea and vomiting were increased in the actively managed group (RR 1.83, 95% CI 1.51–2.23 and RR 2.19, 95% CI 1.68–2.86, respectively). However, this was only noted where ergometrine was used as the oxytocic.

Based on the data presented above, the authors conclude that active management is superior to expectant management in terms of blood loss and other serious complications of the third stage of labor, and that active management should be routine for women expecting a vaginal delivery in a maternity hospital.

[Editor's note: At the International Conference on the Prevention of Post Partum Hemorrhage held in Goa on July 12–15, 2006, there was considerable discussion on the appropriateness of this intervention to be performed in the hands of skilled birth attendants who were working in a domiciliary delivery, although it was recognized that all such individuals would not have access to an injectable uterotonic for logistic reasons.]

The European 5th Framework has funded an expert group from 14 European Union (EU) countries to address postpartum hemorrhage in the EU. The group reviewed the literature, surveyed participants with respect to current protocols and devised a consensus document[89]. This group also clarified the definition of active management of the third stage of labor. The consensus document has received wide support from a large number of international authorities and forms the basis for future comparative research and audit. It is reproduced in full as an Appendix to this chapter.

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APPENDIX: EUROPEAN CONSENSUS ON PREVENTION AND MANAGEMENT OF POSTPARTUM HEMORRHAGE

*The EUPHRATES group(**EU**ropean **P**roject on obstetric **H**aemorrhage **R**eduction: **A**ttitudes, **T**rial, and **E**arly warning **S**ystem), European Union 5th Framework*

INTRODUCTION

The EUPHRATES study comprises five parts, the second of these being 'the development of a minimal European core consensus on prevention and management of post partum hemorrhage'. This consensus is not a protocol or guideline. It represents a European consensus on what could be agreed on by all. Each maternity unit should have its own written protocol concerning prevention and treatment of postpartum hemorrhage (PPH).

Method

This consensus is based on three pillars: (a) review of literature, (b) survey of present protocols and practice, (c) consensus by experts gathered in a special board (see list of members at the end of this Appendix).

The following principle was followed. Where solid evidence was available (level of evidence = 1), a consensus process was not necessary. Consensus was necessary in two circumstances: disagreement as to the clinical relevance of an outcome measure clearly shown to be affected by an intervention (e.g. active management of third stage) and situations where action has to be taken but no high-level evidence is available (e.g. medications in presence of continuing postpartum hemorrhage).

STATEMENTS

1. General considerations

1(a) *Definition of postpartum hemorrhage in terms on milliliters lost*

Evaluation of blood loss is unreliable.

Action is often taken following maternal signs (e.g. hypotension, malaise) rather than on estimated blood loss.

Blood loss at Cesarean section is generally greater than at vaginal delivery.

Despite these three caveats, our group endorses the following classical definitions:

- ≥ 500 ml = postpartum hemorrhage
- > 1000 ml = severe postpartum hemorrhage
- ≤ 24 h = primary, or early, postpartum hemorrhage
- > 24 h = secondary, or late, postpartum hemorrhage

In regions and in groups where anemia of pregnancy is prevalent, the recognition of lesser amounts is clinically important.

1(b) *Communication*

Substandard care is often related to lack of communication within the team and between the team and other professionals. Managing difficult cases as a team may make the difference between life and death. Identified communication problems include the following:

- Failure by the first-line care providers to call senior colleagues in time
- Reluctance of senior colleagues to come, when informed of problem
- Failure by the obstetrical team to inform on time other specialists, e.g. intensive care, anesthesiology, hematology.
- In theater, failure of anesthesists and obstetricians to keep each other informed of relevant events, such as rapid blood loss, tachycardia, blood pressure support

interventions (fluid replacement and/or vasopressor use), etc.

- Failure to obtain blood, because of lack of perception by the laboratory/blood transfusion staff of the severity of the case

1(c) *Implementing local policies to ensure rapid availability of blood products at all times*

It is mandatory that appropriate blood products be available easily and rapidly in units where women deliver. Different European countries achieve this through different systems and there is no evidence that one system should prevail.

There should be a written document, detailing how this is to be implemented and including practical information such as transfusion department phone number, etc. This document should be widely disseminated.

1(d) *Audits and enquiries*

The impact of existing guidelines/consensus statements on severe maternal hemorrhage should be monitored by audit and/or confidential enquiries.

2. Prevention of postpartum hemorrhage at vaginal birth

2(a) *Active management of the third stage of labor*

- Active management of the third stage of labor is usually defined as a three-component intervention: (1) prophylactic uterotonic, (2) early (or less early) clamping of cord, and (3) controlled cord traction. Active management in the third stage of labor has been proven to be effective in reducing blood loss in all women[1]. The evidence that active routine management reduces severe maternal adverse effects (morbidity) resulting from postpartum hemorrhage is less convincing.

The full package of active management is certainly a valid (and validated) option.

- Isolated uterotonics may also be a useful option[2].

Our group concludes:

- Caregivers should be trained to be proficient in active third-stage management, and to offer it to all women.
- It is acknowledged, however, that, provided the woman and caregiver are fully informed, a decision not to use active management in some individual cases and/or settings should not be considered substandard care.

2(b) *Type, dosage, route, speed and timing of administration of prophylactic uterotonic drugs*

There is a lack of randomized trials addressing the questions of dosage, route and timing of prophylactic uterotonic drug administration, because most trials have compared the full package made up of three interventions to no intervention.

(i) *Type of drug*

- Oxytocin is the most frequently used drug for active management in Europe.
- In the United Kingdom and Ireland, Syntometrine is widely used. This is a combination of oxytocin and ergometrine. Syntometrine is more effective but is associated with more side-effects than oxytocin[3]. Syntometrine is not suitable for all women, e.g. in hypertension.
- Ergometrine has been reported in the European survey as additional prophylaxis (following the administration of oxytocin), after the placenta has been delivered in women with risk factors such as multiple pregnancy or grand multiparae. This has never been assessed in a randomized trial.
- Misoprostol is less effective than injectable uterotonics in reducing postpartum blood loss; however, its superiority over placebo as part of the active management of the third stage of labor remains uncertain[4].

Our group concludes:

- Oxytocin is the first drug of choice for all women in the third stage of labor.
- Syntometrine may be preferred by some clinicians but is contraindicated in hypertension and pre-eclampsia.

- Additional ergometrine (following the administration of oxytocin) in selected cases is considered acceptable practice.
- Misoprostol, although less effective, may be considered in situations where injectable uterotonics are not available.

(ii) *Dosage*

- Oxytocin: most trials have used intramuscular (IM) or intravenous (IV) administration of 5 or 10 IU of oxytocin. The European survey shows this dosage to be widely practiced. Particular dosages have been reported in various settings, e.g. 20 IU in 500 ml IV bolus[5] or lower doses such as 1 IU in 10 min ('turning up the drip').
- For Syntometrine, there is only one dosage: ergometrine 500 μg with oxytocin 5 units (Syntometrine® 1 ml contained in one ampoule).
- Misoprostol: most trials have used 400–600 μg when administered orally, and 400 μg per rectum.

(iii) *Route of administration*

- Oxytocin: If an IV line is *in situ*, the intravenous route is the route of choice. 'Turning up the drip' delivers low quantities, e.g. 1–2 IU (1000–2000 mU) in 10 min. If no IV line, IM administration is preferable.
- Syntometrine/Ergometrine: Intramuscular administration.
- Misoprostol can be administered orally or intrarectally.

(iv) *Speed of administration*

A case of maternal death in the 1997–1999 UK Confidential Enquiry was attributed to severe hypotension following rapid administration of 10 IU oxytocin IV. A key recommendation was made that the administration should be 'slow'. However, no definition of 'slow' is available.

(v) *Timing of administration*

A recommendation often made, among others in the Bristish National Formulary, is to administer prophylactic oxytocic therapy 'on (= just after) delivery of the anterior shoulder', and that is also the timing in use in many randomized trials. In practice, it is reported in our survey that it is usually administered after delivery of the baby. Two randomized, controlled trials[5,6] compared oxytocin given before and after the placenta had delivered, and found no benefit in providing the uterotonic as early as possible. Further research is needed.

Our group concludes:

- The best time to administer prophylactic oxytocic therapy is just after birth.
- Whether it is administered before or after cord pulsation has ceased seems relatively unimportant.

2(c) *Manual removal of the placenta*

- Should be performed without delay in presence of hemorrhage.
- No European consensus could be obtained as to when this should be performed in the absence of bleeding. Some would act after 20 min while others would wait for more than 1 hour. Evidence is lacking and further research is needed.

2(d) *Other*

Nipple stimulation or early breastfeeding have been advocated for prevention of postpartum hemorrhage, as simple and physiological, in particular in low-resource settings. The available evidence from two randomized controlled trials[7,8] is insufficient to reach a conclusion.

3. Prevention of postpartum hemorrhage at Cesarean section

- For women undergoing delivery by Cesarean section, there is an increased risk that blood transfusion may be necessary.
- It is reasonable to advise routine administration of an uterotonic drug immediately after the baby has been born by Cesarean section.
- Accurate blood loss assessment at Cesarean section is difficult. Measuring both vaginal as

well as abdominal blood loss may increase accuracy.

- For Cesarean sections that are considered to be at greater risk of hemorrhage (e.g. placenta previa, especially in the presence of uterine scar), it is recommended that a senior obstetrician be present.

4. Management of postpartum hemorrhage

4(a) *Postpartum hemorrhage after vaginal delivery*

We divided the event into three stages: (i) concern about possible excessive bleeding, (ii) early management of hemorrhage, and (iii) continuing hemorrhage.

(i) *Concern about possible excessive bleeding*

- If relevant, remove placenta
- Empty bladder, massage uterus until it is well contracted, give additional uterotonics
- Look for any obvious bleeding in episiotomy or tear, and act on findings.

(ii) *Immediate management in case of hemorrhage*

- Call for help
- Measure blood loss, blood pressure, and pulse rate, insert large gauge intravenous infusion if not yet in place and take blood samples
- Check the placenta for completeness

(iii) *If bleeding continues*

- Circulatory support as necessary with crystalloids, colloids and/or blood products
- Ensure appropriate care with sufficient staff or appropriate referral
- Administer additional uterotonic drugs (injectable prostaglandins)
- Perform bimanual compression (time awareness)
- Explore under anesthesia the genital tract for retained placenta or part thereof, or traumatic damage and act on findings.

Whether an anesthetist is available immediately and whether the woman has got an effective epidural will determine the order in which the above and the following occur.

- Keep communication open with the anesthetist and the rest of the team.

(iv) *If bleeding still not controlled*

- Circulatory support as necessary with colloids and/or blood products, and vasopressors if needed
- Ensure appropriate oxygenation
- Monitor for coagulation abnormalities
- Uterine packing or intrauterine balloon
- Uterine artery embolization

4(b) *Hemorrhage at Cesarean section*

(i) *Immediate management*

- Ensure bladder is empty.
- Explore the uterine cavity and remove the placenta and/or clots
- Massage uterus until well contracted, give additional uterotonics
- Look for and repair trauma, consider exteriorization of uterus
- Measure blood loss

(ii) *Hemorrhage not controlled*

- Continue circulatory support as necessary with colloids and/or blood products and vasopressors if needed
- Ensure appropriate oxygenation and consider mechanical ventilation when needed
- Ensure appropriate care with sufficient staff
- Additional uterotonic drugs (injectable prostaglandins)
- Appropriate surgery

4(c) *Factor VII*

Recombinant activated factor VII (NovoSeven®) may be a future option in catastrophic

hemorrhage, permitting sometimes to avoid hysterectomy. At present, NovoSeven is very expensive and its safety has not yet been adequately evaluated. Therefore, the use of this drug should be limited to units with adequate expertise and resources, and participating in ongoing registers of use.

Consensus Special Board

The Special Board was made up of experts from 14 European countries:

Austria: Mathias Klein (Obstetrician), Heinz Leipold (Obstetrician); **Belgium**: Sophie Alexander (Obstetrician, Epidemiologist), Paul Defoort (Obstetrician), Corinne Hubinont (Obstetrician), Wei hong Zhang (Epidemiologist); **Denmark**: Jens Langhoff-Roos (Obstetrician), Desiree Rosenborg (Anesthetist); **Finland**: Risto Erkkola (Obstetrician), Vedran Stefanovic (Obstetrician), Jukka Uotila (Obstetrician); **France**: Marie-Hélène Bouvier-Colle (Epidemiologist), Gérard Breart (Epidemiologist), Catherine Deneux (Epidemiologist), Thierry Harvey (Obstetrician), Frédéric Mercier (anesthetist); **Hungary**: Istvan Berbik (Obstetrician), Jeno Egyed (Obstetrician), Janos Herczeg (Obstetrician); **Ireland**: Mikael O'Connell (Obstetrician), Walter Prendiville (Obstetrician); **Italy**: Anna Maria Marconi (Obstetrician), Graziella Sacchetti (Obstetrician); **Nederlands**: Kathy Herschderfer (Midwife), Jos Van Roosmalen (Obstetrician); **Norway**: Bente Ronnes (Midwife), Babill Stray-Pedersen (Obstetrician); **Portugal**: Diogo Ayres-de-Campos (Obstetrician), Nuno Clode (Obstetrician), Teresa Rodrigues (Obstetrician); **Spain**: Enrique Barrau (Obstetrician), Vicenç Cararach (Obstetrician), Dolores Gomez (Obstetrician); **Switzerland**: Olivier Irion (Obstetrician), Carolyn Troeger (Obstetrician); **United Kingdom**: Zarko Alfirevic (Obstetrician), Peter Brocklehurst (Obstetrician, Epidemiologist), Alison MacFarlane (Epidemiologist), Jane Rogers (Midwife), Clare Winter (Midwife).

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12

MISOPROSTOL: THEORY AND PRACTICE

M. B. Bellad and S. Goudar

INTRODUCTION

Prostaglandins have revolutionalized obstetric practice. In particular, the advent of misoprostol has precipitated an enormous amount of innovative research as well as controversy. At present, misoprostol is being investigated for its role in the management of postpartum hemorrhage, induction of labor, cervical ripening and termination of pregnancy. Initially, this drug was approved by the US Food and Drug Administration (FDA) in 1988 for oral administration for the prevention and treatment of peptic ulcers associated with the use of non-steroidal anti-inflammatory drugs. Since the early 1990s, however, misoprostol has been viewed with increasing interest by obstetricians and gynecologists because of its uterotonic and cervical ripening activity. The multiple off-label uses for misoprostol underlie its description as 'one of the most important medications in obstetrical practice'[1]. Even in 2005, misoprostol was not approved by the FDA for use in pregnant women, a stand strangely and strongly supported by its manufacturer[2].

MISOPROSTOL

Misoprostol is a synthetic PGE_1 analog. Naturally occurring PGE_1 is not orally sustainable, as it is unstable in acid media and is also not suitable for parenteral use because of its rapid degradation in the blood. Misoprostol, the synthetic PGE_1 analog, is produced by bringing about an alteration in the chemical structure of the naturally occurring compound, thereby making it orally stable and clinically useful. Misoprostol is otherwise called alprostadil and its chemical formula is $C_{22}H_{38}O_5$ ((±)–methyl (13E)-11,16-dihydroxy-16-methyl-9-oxo-prost -13-enoate), as shown in Figure 1[3].

Misoprostol is manufactured as oral tablets of 200 µg scored and 100 µg unscored. It has several advantages – stability in ambient temperature, long shelf-life and low cost – that have made it a central focus of research in obstetrics and gynecology for 25 years[4]. Misoprostol is rapidly absorbed via the oral route and, although not formulated for parenteral use, can also be administered sublingually (buccally), rectally and vaginally[5–7].

Pharmacokinetics, physiology and teratogenicity profile

Misoprostol is extensively absorbed and undergoes rapid de-esterification to misoprostol acid; this compound is responsible for its clinical activity and, unlike the parent compound, it is detectable in plasma. After oral administration, the peak level of misoprostol acid is reached within 12 ± 3 min, with a terminal half-life of 20–40 min. Plasma levels of misoprostol acid vary considerably between and within studies, but mean values after single doses show a linear relationship with the dose over the range of 200–400 µg. No accumulation of misoprostol acid was noted in multiple dose studies and a

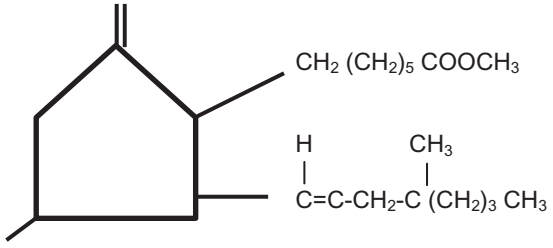

Figure 1 Chemical structure of misoprostol[3]

plasma steady state was achieved within 2 days. The bioavailability of misoprostol is decreased when administered with food or antacids[8].

Misoprostol is primarily metabolized in the liver and less than 1% of its active metabolite is excreted in the urine[9]. Patients with hepatic disease should receive decreased doses, whereas dose adjustment is not necessary for patients with renal disease who do not require dialysis. Misoprostol has no known drug interactions and does not induce the hepatic enzyme systems[9].

Pharmacokinetic studies in pregnant women show that sublingual and oral misoprostol used for first-trimester termination of pregnancy produce earlier and higher peak plasma concentrations than vaginal or rectal misoprostol, resulting in earlier, more pronounced uterine tonus (oral misoprostol 7.8 ± 3.0 min vs. vaginal misoprostol 20.9 ± 5.3 min)[6,7,10]. These findings have very recently been validated in women after delivery[11]. The effects of misoprostol on the reproductive tract are increased and gastrointestinal adverse effects are decreased when it is administered vaginally[10,12,13]. When misoprostol tablets are placed in the posterior fornix of the vagina, plasma concentrations of misoprostol acid peak in 1–2 h and then decline slowly (Figure 2)[5]. Vaginal application of misoprostol results in slower increases and lower peak plasma concentrations of misoprostol acid than does oral administration, but overall exposure to the drug is increased (indicated by the increased area under the curve in Figure 2)[5]. The peak plasma levels of misoprostol are sustained for up to 4 h after vaginal administration[5] (Figure 2).

Among women who were 9–11 weeks pregnant and given misoprostol before a surgical termination of pregnancy, intrauterine pressure began to increase an average of 8 min after oral administration and 21 min after vaginal

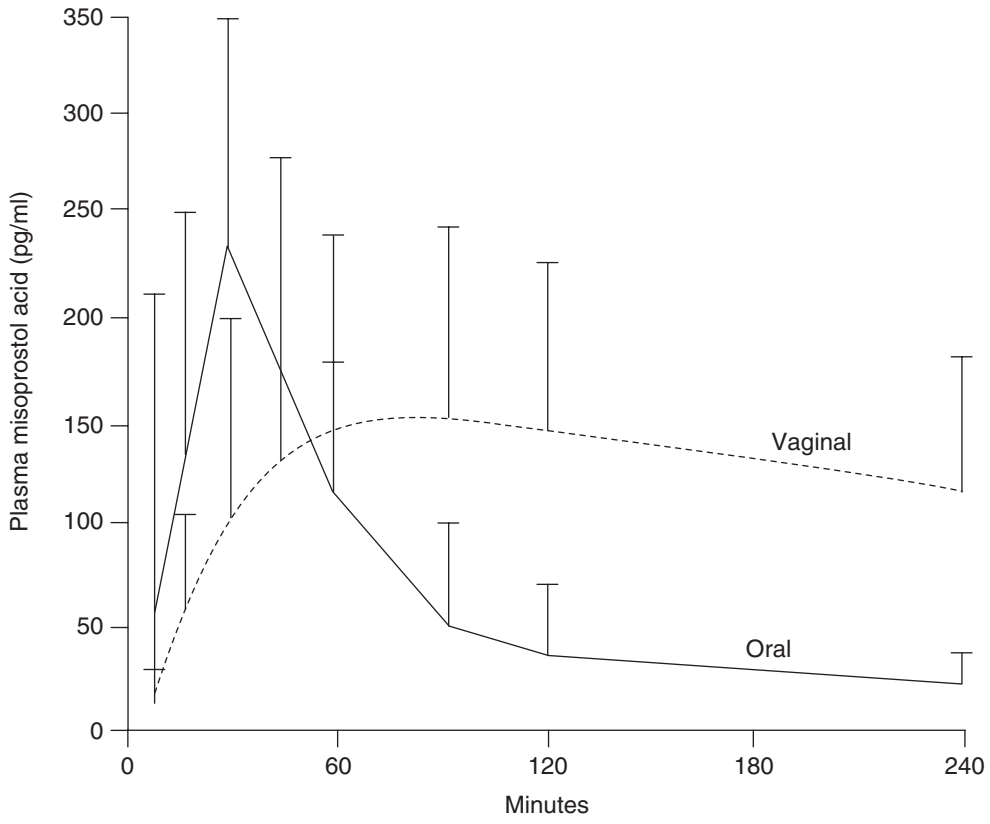

Figure 2 Mean (standard deviation) plasma concentrations of misoprostol acid after oral and vaginal administration of misoprostol in 20 women. Reprinted from Zieman M, *et al.*[5]

administration; it was maximal 25 min after oral administration and 46 min after vaginal administration, respectively. Uterine contractility initially increased and then reached a plateau 1 h after oral administration, whereas uterine contractility increased continuously for 4 h after vaginal administration. Maximal uterine contractility was significantly higher after vaginal administration[10]. The maximum serum concentration was achieved 23 min later in rectal administration and the peak levels were lower compared to oral administration of misoprostol[7] (Figure 2).

In the pharmacokinetic study by Tang and colleagues[6], the peak plasma level of misoprostol acid was highest and earliest after administration of misoprostol by the sublingual route. Misoprostol tablets dissolved in water and taken orally have also been shown to produce a faster onset and stronger uterotonic effect than either oral tablet or rectal administration[14,15]. However, there was no significant difference when misoprostol was used in the form of moistened tablets compared to dry tablets for first-trimester termination of pregnancy[16].

Adverse effects

Common side-effects of misoprostol include diarrhea and abdominal pain. Less common side-effects include headache, abdominal cramps, nausea and flatulence, chills, shivering, and fever, all of which are dose-dependent. It is interesting to note that, before its use in pregnant women, chills, shivering and fever were not commonly reported side-effects, suggesting that these are dose-dependent.

Package warnings are very clear that misoprostol is not to be taken by pregnant women, and non-pregnant women should use contraceptives while taking misoprostol and should be warned about the effects of misoprostol if taken by pregnant women. Misoprostol should also be avoided in nursing mothers because of concern over causing diarrhea in the baby[8,11].

Congenital anomalies sometimes associated with fetal death have been reported subsequent to the unsuccessful use of misoprostol for termination of pregnancy, but the drug's teratogenic mechanism has not been elucidated[17,18]. Several reports associate the use of misoprostol during the first trimester of pregnancy with skull defects, cranial nerve palsies, facial malformations (Mobius syndrome), and limb defects[19]. Misoprostol is listed as a pregnancy category X drug.

Toxic doses of misoprostol have not been determined; however, pregnant women have tolerated cumulative doses up to 2200 μg administered over a period of 12 h without

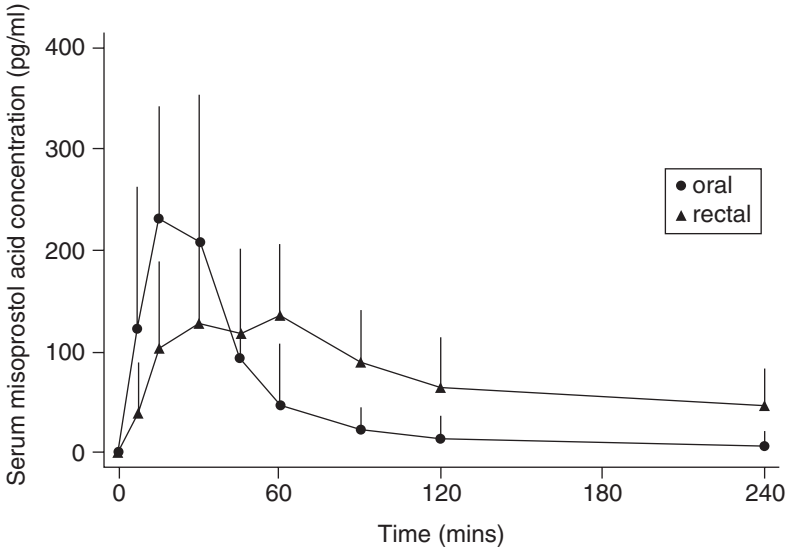

Figure 3 Mean serum concentration of misoprostol acid over time with oral and rectal administration. Error bars represent one standard deviation[7]

any serious adverse effects[20]. A dose of 6000 μg of misoprostol, taken orally to induce termination of pregnancy (with trifluoperazine), resulted in abortion, hyperthermia, rhabdomyolysis, hypoxemia and a complex acid–base disorder[21].

MISOPROSTOL IN THE FIRST TRIMESTER

For first-trimester medical termination of pregnancy, misoprostol is used most extensively in conjunction with either mifepristone or methotrexate. Both regimens are effective. In the initial studies of mifepristone and misoprostol for medical termination of pregnancy, both drugs were given orally. Only regimens of mifepristone in combination with oral misoprostol have been licensed for abortion in any country. Administration of 600 mg of oral mifeprostone followed 48 h later by 400 μg of oral misoprostol resulted in 91–97% complete abortion in women who were no more than 49 days pregnant, compared to 83–95% of women who were no more than 56 days pregnant[22–25]. Lowering the dose of mifepristone to 200 mg and increasing the dose of oral misoprostol to 600 μg increases the efficacy, with abortion rates of 96–97% among women no more than 49 days pregnant and 89–93% among women 50–63 days pregnant[26,27]. A combined regimen of mifepristone and misoprostol can result in complete abortion in 94–95% for medical abortion to women of 9–13 weeks pregnancy but is associated with high incidence of heavy bleeding[28,29]. The timing of administration of misoprostol after mifeprostone for medical termination of pregnancy ranges from 6 to 48 h. The complete abortion rates improve with one or two additional doses of misoprostol.

Vaginal administration of misoprostol was more effective and better tolerated than oral administration for the induction of first-trimester abortion[30,31]. However, some studies concluded that both oral and vaginal misoprostol were of similar efficacy. Sublingual administration of misoprostol had a success rate of 92%[32].

A single dose of intramuscular or oral methotrexate (50 mg per square meter of body-surface area) followed 5–7 days later by 800 μg of vaginal misoprostol resulted in complete abortion in 88–100% of women provided this regimen; 53–60% of women aborted within 24 h after one dose of misoprostol was administered[33–39]. If complete abortion did not occur within that interval, repeating the misoprostol dose resulted in complete termination of pregnancy in 19–32% of women within 24 h after the second dose[33,34]. The remaining 10–30% of women who aborted successfully had a delayed response, with the abortion completed over an average period of 24–28 days[33,34].

Misoprostol has also been used alone for medical termination of pregnancy, with variable efficacy. The earliest studies of misoprostol-induced termination of pregnancy in the first trimester reported complete abortion rates of 5–11% among women given a total dose of 400 μg of oral misoprostol[40,41]. Up to three 800-μg doses of vaginal misoprostol given every 48 h resulted in complete termination of pregnancy in up to 96% of women who were no more than 63 days pregnant[42]. However, in a randomized trial comparing methotrexate plus vaginal misoprostol with vaginal misoprostol alone, only 47% of the women given misoprostol alone had complete termination of pregnancy, as compared with 90% of the women given methotrexate plus misoprostol ($p < 0.001$)[43].

With regard to the use of misoprostol as a cervical-priming agent before vacuum aspiration of the uterus, numerous randomized, controlled studies have shown that misoprostol is more effective than placebo and vaginal PGE_2 in terms of the degree of cervical dilatation achieved[44,45]. As cervical priming facilitates surgical vacuum aspiration, the risks of dilatation and evacuation of the uterus are therefore minimized. These results were replicated by numerous other randomized, controlled trials involving a large number of participants. The best regimen for cervical ripening in the first trimester is 400 μg of vaginal misoprostol given 3–4 h before suction curettage[44,46,47]. In one study, misoprostol, when administered with mifeprostone for termination of early pregnancy in scarred uteri, was safe and effective, but further randomized trials are essential to confirm this[48].

Sublingual misoprostol was effective in facilitating cervical dilatation before surgical abortion, and its use significantly decreased the time

of surgical evacuation and minimized blood loss during the procedure[49,50].

MISOPROSTOL IN EARLY PREGNANCY FAILURE

Single or repeated doses of misoprostol result in complete expulsions with minimal side-effects and complications in evacuation of first-trimester missed abortions[51,52]. Vaginal misoprostol is more effective then oral administration[53]. Misoprostol is also effective in incomplete termination of pregnancy, and it is safer than the surgical method[54,55].

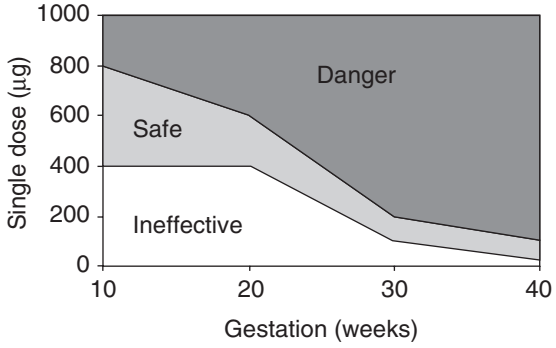

Figure 4 Safe single doses of misoprostol for producing uterine contractions at various gestations[63]

MISOPROSTOL IN THE SECOND TRIMESTER

Indications for termination of pregnancy in the second trimester include chromosomal and structural fetal abnormalities as well as social reasons. Surgical evacuation of the uterus, still being practiced in some centers, is associated with greater morbidity, mortality and complications. Intra-amniotic hypertonic saline/urea instillation, intra-amniotic PGF_2 infusion, extra-amniotic ethacridine lactate, oxytocin infusion and vaginal PGE_2 were practiced before the introduction of misoprostol.

Intravaginal misoprostol in the dose of 400 µg is effective and associated with fewer side-effects[56]. Vaginal misoprostol was found to be as effective as or more effective than PGE_2. Misoprostol was equally effective as extra-amniotic prostaglandins[57–60]. Misoprostol in the dose of 400 µg every 3 h was more effective in terms of a significantly shorter drug administration-to-abortion interval and a higher percentage of successful abortion within 48 h compared to misoprostol 400 µg every 6 h, and the incidence of side-effects was similar in both groups except for that of fever. However, the fever returned to normal within 24 h after the last dose of misoprostol[61].

Vaginal misoprostol was significantly more effective as judged by drug administration-to-abortion interval and the need to augment the therapy with oxytocin infusion when compared to oral misoprostol[62].

It is somewhat paradoxical that a greater dose (800 µg) of vaginal misoprostol is essential for abortion in the first trimester, whereas doses in the range of 25–50 µg induce labor in the third trimester. The optimal dose of vaginal misoprostol for induction of labor in the second trimester probably lies somewhere between 50 and 800 µg. Within this range, higher doses may be needed to cause termination of pregnancy early in the second trimester, whereas lower doses may be sufficient later in the second trimester. Higher and more frequent doses are associated with shorter drug administration-to-abortion interval compared to lower and less frequent doses[1,63] (Figure 4).

MISOPROSTOL IN THE THIRD TRIMESTER

Induction of labor

This is one of the common obstetric interventions primarily performed with the aim of reducing maternal and perinatal morbidity and mortality. The success of induction of labor not only lies with replication of physiological mechanisms, but also depends upon the cervical status. An unfavorable cervix presents the greatest challenge to successful induction. The development of effective, safe (to both mother and fetus) and less expensive pharmacological agents to accomplish this task has been the focus of much clinical research.

The results of the first study (1993) suggested that misoprostol is a cost-effective and safe alternative for induction of labor at term. Many later studies, including randomized trials,

not only confirmed this finding, but also have shown that misoprostol is more effective than a placebo or other prostaglandins; moreover, it is associated with a higher rate of vaginal delivery within 24 h, a shorter induction-to-delivery interval and significantly lower Cesarean section rates than pooled figures for the control groups[64–67].

Studies of different routes of misoprostol administration were conducted for induction of labor, including oral, vaginal, intracervical and sublingual[68–73]. Although all routes were successful, vaginal misoprostol is associated with a shorter induction-to-delivery interval, lower number of doses and diminished oxytocin use[68,70]. Misoprostol gel is associated with fewer uterine contraction abnormalities and longer induction-to-labor and delivery interval when compared to misoprostol tablets[71].

The safety of misoprostol is crucial, as some studies have shown a high frequency of uterine tachysystole and hyperstimulation, including some reports of uterine rupture during the induction of the labor with misoprostol[74–76]. A vaginal dose of 25 μg is often recommended as the more prudent dose, as it is associated with lower incidence of uterine hyperstimulation and it is comparable to the 50 μg dose in achieving delivery within 24 h[64,77–81]. Doses higher than 50 μg have been associated with increased risk of complications. The interval of administration of misoprostol ranges from every 3 to 6 h. It is better to use 6-h dosing intervals to avoid the possible risk of tachysystole[82]. Misoprostol is also effective as a cervical ripening agent for prelabor rupture of the membranes[83]. Oral misoprostol not only induced labor but also resulted in delivery within 24 h without increasing maternal or neonatal complications[66,84].

Misoprostol is not recommended for induction in cases of previous Cesarean section, as it is associated with higher frequency of disruption of prior uterine incision compared with use of PGE_2 or oxytocin. Misoprostol use is associated with a 5.6% rupture of uterine scars compared to 0.2% in patients attempting vaginal birth after Cesarean delivery without stimulation, as shown by meta-analysis[85]. Misoprostol use in grand multipara is not associated with adverse maternal or neonatal outcome. However, its use in such patients warrants strict vigilance[86,87]. The use of prostaglandins including misoprostol increases the uteroplacental resistance but does not affect the umbilical blood flow in a Doppler velocimetry study of umbilical, uterine and arcuate arteries immediately before and 2–3 h after the administration of vaginal misoprostol or cervical PGE_2, thus suggesting misoprostol is as safe as PGE_2 gel[88]. Available data suggest that vaginal misoprostol in a dose of 25 μg every 6 h is as safe as PGE_2 in patients with a live fetus for induction of labor.

Induction of labor after fetal death

Misoprostol is ideally suited agent for induction of labor after fetal death as there is no concern about the adverse effects of uterine hyperstimulation on the fetus. For fetal death at term, a dose as low as 50 μg every 12 h may be adequate for induction of labor, whereas higher doses are necessary in patients with fetal death in the second trimester and early in the third trimester[89,90].

THIRD STAGE OF LABOR

Postpartum hemorrhage is a major cause of maternal morbidity and mortality. It is sudden, dramatic and unpredictable. In developing countries, over 125 000 or approximately 28% of total maternal deaths are caused by postpartum hemorrhage each year. According to one estimate, the risk is approximately 1 in 1000 deliveries[91].

Based on misoprostol's uterotonic effects, this drug has been evaluated for both prevention and treatment of postpartum hemorrhage (see Chapters 4 and 16–19). The WHO misoprostol multicenter trial concluded that use of an oral tablet of 600 μg was associated with a higher risk of severe postpartum hemorrhage, the need for additional uterotonic agents, shivering and pyrexia compared with intramuscular or intravenous oxytocin[92]. However, the dose of misoprostol used in these trials varied from 400 to 600 μg (orally and rectally). Moreover, the frequency of postpartum hemorrhage (blood loss > 1000 ml) was not lower in the misoprostol group than in the control group in any of the trials. None the less, there was higher

use of oxytocin in the control groups. In many reports, misoprostol 600 μg oral or 400 μg rectal is significantly less effective than injectable uterotonics in preventing postpartum hemorrhage[92–103]. Misoprostol at the dose of 400–600 μg is associated with risk of shivering, and doses more than 400 μg also significantly increase the risk of pyrexia. At present, oral or rectal misoprostol is not as effective as conventional injectable uterotonic agents, and the high rates of shivering and fever associated with its use make it undesirable for routine use to prevent postpartum hemorrhage, especially for low-risk women. Thus, there is insufficient evidence to date to support the routine use of misoprostol when oxytocin or methylergometirne is available. There is some evidence of increased uterotonic effect with the administration of misoprostol, either by the sublingual route or as an oral solution[6,14,15]. Use of buccal misoprostol in a placebo-controlled trial to prevent hemorrhage at Cesarean delivery was not associated with a significant difference between the two groups, both in the incidence of postpartum hemorrhage and a difference in pre- and postoperative hemoglobin level. However, misoprostol reduced the need for additional uterotonic agents during Cesarean delivery[104]. In all of these studies, it is important to note that misoprostol was compared to conventional uterotonics. It is tragic but true, however, that these latter drugs are not available in many parts of the world where women deliver with no medical assistance whatsoever.

Despite the lesser efficacy of misoprostol compared with conventional injectable oxytocics and the potential to cause side-effects, several factors – ease of use, stability in field conditions, longer shelf-life, and less expense – underlie its continued evaluation as a uterotonic agent. It remains of great interest, especially for use in home deliveries by traditional birth attendants and minimally qualified nurse midwives in less developed areas where administration of injectable uterotonics may not be feasible or may not be available. Here, it offers a plausible preventive strategy in such areas for reducing maternal mortality related to postpartum hemorrhage[105–107]. The results of an ongoing National Institute of Child Health and Human Development (NICHD) sponsored Global Network for Women's and Children's Health Research randomized, placebo-controlled trial of misoprostol in home delivery settings in rural India will perhaps answer the question regarding the benefit of oral misoprostol in the prevention of postpartum hemorrhage[108] (see also Chapter 8).

Oral misoprostol in the dose 600 μg was associated with lower incidence of measured blood loss ≥ 500 ml and lower incidence of reduction in postpartum hemoglobin (reduction of hemoglobin ≥ 2 g/dl was 16.4% with misoprostol and 21.2% with ergometrine), but the difference were not statistically significant. Shivering was significantly more common with misoprostol, whereas vomiting was more common with ergometrine in a randomized, controlled trial with misoprostol 600 μg and ergometrine (0.5 mg, four tablets) in the home delivery settings of rural Gambia[109]. Rectal misoprostol has also been reported to control postpartum hemorrhage that is unresponsive to oxytocin and methylergometrine in the dose of 1000 μg[110].

Rectal misoprostol in the dose of 800 μg could be a useful first-line drug for the treatment of primary postpartum hemorrhage[111]. In a randomized, double-blind, placebo-controlled trial with sublingual misoprostol at a primary health center in Bissau, Guinea-Bissau, West Africa, the incidence of postpartum hemorrhage was not significantly different between the two groups. However, significantly fewer women in the misoprostol group experienced a blood loss of ≥ 1000 ml or ≥ 1500 ml. The decrease in hemoglobin concentration tended to be less in the misoprostol group, the mean difference between the two groups being 0.16 mmol/l (–0.01 to 0.32 mmol/l). From this study, it was concluded that sublingual misoprostol reduces the frequency of severe postpartum hemorrhage[112]. Further randomized, controlled trials are necessary to identify the best drug dose and route of administration for the treatment of postpartum hemorrhage[113], particularly when use of conventional agents is not possible. Such studies should differentiate the site of use for misoprostol. When there is no syringe to inject methergin or oxytocin or no refrigeration facility for these drugs, misoprostol may be the only viable option and should be compared to the

local standard practice (where there is no use of uterotonic agents).

OTHER USES

Misoprostol is used prior to procedures such as intrauterine insemination and hysteroscopy[114–116]. Its use in cervical pregnancy is documented with one case report; however, extreme caution is recommended with this approach and methotrexate is favored by many authorities[117].

CONCLUSION

Misoprostol is one of the most important medications in obstetric practice. As of the time of writing, its use in pregnant women remains unapproved by the US FDA, except in conjunction with mifeprostone (or, in some cases, methotrexate) for first-trimester medical termination of pregnancy. Despite this, the international literature is replete with favorable reports of off-label uses. For example, there is strong and consistent evidence to support the use of misoprostol for cervical ripening before surgical abortion in the first trimester and for induction of labor in the second and third trimesters. Whereas lower dose and strict vigilance are required for use of misoprostol for induction of labor with a live fetus, it is ideal for induction of labor in patients with intrauterine fetal death.

Misoprostol may also prevent postpartum hemorrhage when injectable uterotonic agents are either impractical or unavailable. On the other hand, misoprostol may not be the preferred uterotonic for prevention of postpartum hemorrhage where injectable oxytocics are readily available. Its use in the treatment of postpartum hemorrhage in regions of the world where the standard of care is delivery without uterotonic agents (i.e. delivery with no uterotonic medication) needs further evaluation. The oral route is associated with faster effect and with more side-effects. The other routes, such as vaginal and rectal, have sustained and longer effects with less side-effects. The sublingual and buccal routes and dose need further evaluation.

Finally, after considerable dialogues between the American College of Obstetricians and Gynecologists (ACOG) and Searle, the manufacturer of misoprostol, the FDA has approved a new label for the use of misoprostol during pregnancy. The new labeling revises the contraindications and the precaution that misoprostol should not be used in pregnant women by stating that the contraindication is only for pregnant women who are using the medication to reduce the risk of non-steroidal anti-inflammatory drugs. Misoprostol is now a legitimate part of the FDA-approved regimen for use with mifeprostone to induce abortion in early abortion and is also recognized for induction of labor[118].

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13

LABOR WARD DRILLS

M. Tipples and S. Paterson Brown

INTRODUCTION

As the leading cause of maternal mortality world-wide and a major contributor to maternal morbidity, massive obstetric hemorrhage deserves center stage in the training of midwifery and obstetric staff. That this need for training is global is highlighted by the recent increase in deaths due to obstetric hemorrhage in the UK (CEMACH[1]). Although much knowledge is gained at the bedside, practical teaching with a structured approach to this unique life-threatening emergency provides a sense of security and preparedness that cannot be obtained by reading or attending lectures.

Several well-established courses focus on practical emergency teaching, and further information is available through their websites: ALSO at www.also.org.uk, MOET at www.alsg.org.uk, and MOSES at www.bartsandthelondon.org.uk/simulationcentre/courses.asp. These courses present a structured approach to resuscitation with skills, drills and scenarios taught and applied to the seriously ill patient. As good as such courses may be, they cannot begin to train everyone in all things and there remains a need for strong local supplementation.

All functioning obstetric units should possess a multidisciplinary massive hemorrhage protocol, which should be updated and rehearsed regularly. Running these sessions as a local drill helps to test such systems in place to deal with obstetric hemorrhage and makes them particularly useful to local staff. Clinical scenario and skills training add detail and depth to this training, but efficiency in the system is an essential prerequisite to effective care. This chapter describes how various practical training techniques (drills, skills and scenarios) work and how such programs are set up locally.

GENERAL PRINCIPLES OF ADULT EDUCATION

Adult learning

Before embarking, it is worth reflecting on how adults learn and appreciating that they are not satisfied with facts alone, but also like to understand and be able to apply the knowledge they acquire. Three different processes are involved in learning, all of which can be complementary and are featured in practical teaching sessions.

Visual

This includes the learning we do through reading, but also includes what is assimilated through watching a person or people doing something practical. Being able to picture the scene and actions that were taken enables one to easily recall them when a similar situation presents itself.

Auditory

This includes learning through listening, but also includes dialogue, questions and discussion.

Kinesthetic

This involves learning through doing and includes both hands-on practice and role play. Hands-on practice is especially useful for practical skills, whereas role play encourages the learner to work logically through a sequence of events in a clinical scenario.

All three forms of learning are variably suited to different things. For example, learning to tie a knot can be visualized and explained, but one needs to do it to finally realize the skill. Of

importance, different individuals tend to gain more from one approach compared to another: some prefer watching what is going on, others benefit most from open discussion and feedback, and still others relish the challenge of being the doers in the practical teaching demonstration. Appreciating these differences and staying sensitive to the particular needs of those being taught helps keep practical teaching fun and effective while, at the same time, avoiding what can be extremely stressful for some individuals.

Practical teaching

The same preparations should be made whether teaching skills, drills or scenarios.

Knowledge

A sound knowledge base is required before practical teaching can be undertaken successfully. An initial lecture/workshop/discussion should be organized if staff are unfamiliar with practical teaching or if new material is to be taught, as this allows staff to prepare themselves. It also helps reinforce the idea that practical teaching is an opportunity to put what one knows into practice.

Environment

A suitable location should be found that is conducive to the teaching that has been planned. The layout of the room should allow those involved in the scenario to access the patient and those watching to see clearly. Heating and ventilation should be considered, but acoustics are vital and can sometimes conflict (e.g. noise from an open window). When teaching about obstetric hemorrhage, a delivery room or an operating theater makes for a very realistic environment, but it occasionally conflicts with clinical needs. To try to avoid this, one can plan impromptu teaching when the delivery suite is quiet. Such 'unannounced' teaching is good for testing how the systems are working (i.e. drills), but, as it does not allow planning in terms of who or how many people can be taught, it may be less useful when running clinical scenarios. Another alternative is to consider reducing elective surgery to facilitate training at a given time, remembering, of course, that labor ward workloads are unpredictable and a back-up teaching location needs to be available (for example, a seminar room or antenatal classroom).

Setting the tone

The instructor should give a general explanation at the beginning of the teaching session. This will establish the mood and motivate the learners by outlining the usefulness of the content. For example 'Obstetric hemorrhage is the leading cause of maternal death globally, and today we are going to run through a simulated case of placental abruption. The aim is for you to consolidate and apply your knowledge of this, which should assist you when you face a similar situation in a real emergency'. At this stage, it may be useful to place the clinical problem in the context of recent local events.

The specific objectives of the session should then be explained together with what is expected of everyone in terms of who is going to do what, and whether questions can be asked throughout, or be kept till the end. It is extremely useful to allow questioning throughout, as many people will forget if asked to wait till the end, but it can spoil the momentum of the scenario and role play. This must be judged anew in each session.

Dialogue

The actual 'doing' in practical teaching and role play works through the simulation starting from very specific instructions. Progress can vary according to what the learner does, and the instructor needs to stay alert and flexible in order to remain in control, to cover all intended teaching points and to guide the session to an appropriate conclusion.

Feedback

This is sometimes known as critique and is an essential part of the learning process as it promotes retention of important points. One form of systematic feedback, described by Pendleton and known as Pendleton's rules, comprises four

stages: the learner says what she/he did well, then what she/he could improve upon; this is followed by the trainer saying what the learner did well and then what can be improved upon. Allowing the learner to comment first gives the instructor an opportunity to assess the candidate's insight into her or his own ability and behavior. The instructor then has the opportunity to highlight both good practice and areas for improvement not already covered by the learner in order to stress and reinforce learning points to all present.

Closure

Bearing in mind that adults need to understand before they change behavior, it is crucial that questions and discussion be encouraged. A summary of the key learning points from the session should then be given, so that everyone leaves with a clear message of the most important issues.

DRILLS, SKILLS AND SCENARIOS

These three styles of teaching differ in their aims. All require and test different skills and knowledge, the features and differences of which are summarized in Table 1, together with examples of suitable teaching material.

Drills

These are practice or 'dummy' runs and are comparable to fire practices in testing the local systems. Running a drill not only allows local scrutiny (i.e. what actually happens when the alarm is put out), but also can be a very effective test of local arrangements and services and of staff knowledge of them.

Preparations for a drill

When running drills, the staff that are going to be involved should be faced with the drill in a normal clinical area, unprepared, in order to receive a realistic idea of what would happen in a true situation. Clearly, the drill should not conflict with patient care and therefore the timing will depend to some extent on existing workload. The lead clinician for the teaching session should, however, have informed the lead midwife and, in the case of an obstetric hemorrhage, the transfusion hematologist and other

Table 1 Key features and differences in skills, drills and scenario teaching

	Skill	*Drill*	*Scenario*
Definition	Acquisition of a skill	A chain of events in response to a problem	Improvised clinical role play
Aim of the teaching	Ensure correct technique	Test the local emergency system	Apply and practice clinical care in a improvised set-up
Teaching environment	Seminar room	Throughout hospital in day-to-day environment	Seminar room, operating theater or delivery room
Examples of things suitable for teaching and testing in relation to obstetric hemorrhage	Brace suture Rusch balloon Aortocaval compression CPR	Response to the emergency massive obstetric hemorrhage call	APH – abruption – placental previa PPH – atony – trauma – RPOC
Skill mix	Doctors and midwives	All delivery suite staff and laboratory staff, hematologists and porters	Multidisciplinary: obstetricians, midwives, anesthetists, pediatricians

CPR, cardiopulmonary resuscitation; APH, antepartum hemorrhage; PPH, postpartum hemorrhage; RPOC, retained products of conception

necessary individuals, such as transportation staff. This is not only as a matter of courtesy but also to plan timings in order to avoid clashes of interests. The transfusion hematologist may prepare spare serum for grouping and make empty blood bags available for the 'dummy run'.

Running the drill

Table 2 illustrates an example of an assessment sheet for a massive obstetric hemorrhage drill, suggesting things that can usefully be monitored; these include the following:

- Who responds to the initial emergency buzzer?
- Is the appropriate emergency call put out?
- How effective is the emergency bleeping system?
- Is transportation alerted and does she/he respond?
- Do transfusion staff receive any communication?
- How quickly does blood arrive at the bedside?
- How quickly is the patient transferred to the operating theater?

Table 2 Example of an assessment sheet for massive obstetric hemorrhage drill. This assessment sheet can be expanded to include the response times for individual doctors, and their reactions and actions

- Time emergency buzzer pulled
- Staff responding to the initial buzzer
- Time switchboard received emergency call
- Staff responding to the emergency bleep
- Initial treatment of ABC (airway, breathing and circulation) resuscitation instituted quickly and effectively
- Time transportation person arrives in blood transfusion
- Time blood samples received in the laboratory
- Time appropriate blood arrives at patient's bedside
- Time patient transferred to the operating theater
- When does the anesthetist/consultant/hematologist arrive?

Such analyses can help to illustrate system failures and modify local policy. The identification of problems stimulates and informs guideline development. Clarifying the roles of different staff and streamlining activity can also improve future responses and improve care. Such developments can be monitored at future drills and improvements in the system should be fed back to staff.

Having run drills for obstetric hemorrhage at Queen Charlotte's and Chelsea Hospital for many years, the following are examples of problems identified and system changes made in response.

Communication As identified in numerous confidential enquiries, problems in communication often hamper emergency responses. We found that we struggled with instructions between clinicians and blood transfusion staff regarding what was needed when: could we wait for group-compatible blood or even cross-matched blood? How long could we wait to have blood at the bedside? What clotting products did we need when? These are some examples of questions often not clarified over the 'phone'. It became obvious that this job was being delegated to someone very junior on the delivery suite and misunderstandings were common. As solutions we, first, installed a red phone in the operating theater that linked exclusively with a red phone in the transfusion laboratory. This enabled blood requirements to be discussed by the anesthetist directly with transfusion staff without them having to leave the patient to go to a phone outside the theater. Second, we identified time limits for transfusing blood at the bedside (for example, 'we need 4 units of blood within 30 minutes'), rather than discussing whether we could wait for blood to be cross-matched or not. This left the laboratory in no doubt of the clinical needs and has minimized delay in blood arriving at the bedside when needed.

The role of transportation The transportation person initially arrived in the delivery suite when a hemorrhage call was put out in order to take blood samples to the laboratory for grouping/

cross-matching, but this was deemed inefficient and delayed blood being brought to the bedside in the most urgent cases. As solutions, we, first, changed the process so that the transportation person now goes straight to the laboratory in readiness for the most urgent of needs in collecting O-negative blood. Second, the installation of a chute for samples to be sent to the laboratory has also helped in this context. If the clinical condition of the patient can wait for group-compatible blood, the transportation person stays in the transfusion laboratory until the sample has arrived by chute and has been grouped, ultimately bringing the appropriate blood to the delivery suite.

Skills

The teaching of practical skills can be useful in obstetric hemorrhage teaching sessions. The need for specific teaching often becomes apparent during the discussion and questioning when running a scenario. Things may have been mentioned which are not fully understood, and such circumstances illustrate how important it is for scenario teaching to be constructive. Staff must feel able to question about what something is or how it is done.

In obstetric hemorrhage, the following skills may be needed:

- Medical skills
  - bimanual uterine compression
  - aortic compression
  - cardiopulmonary resuscitation
- Surgical skills
  - insertion of an inflatable uterine balloon
  - insertion of a Brace suture
  - intravenous cut-down for venous access

Preparation for skills teaching

When teaching any practical skill that may be required in an emergency, it should be done slowly and calmly, giving ample time for reflection, questions and practice. The use of manikins and surgical aids works well, but one must remember to point out the differences to be expected when working *in vivo* (such as the need to keep an inflatable uterine balloon well into the cavity while inflating it, or how to deal with the tendency for the Brace suture to slip off the 'shoulders' while pulling it tight).

Running the skills teaching

This teaching process is best done in four steps:

Step 1 The instructor demonstrates the skill in silence. The skill is performed at normal speed so that the candidates appreciate their ultimate aim.

Step 2 The instructor then demonstrates the skill slowly with a commentary. Providing the commentary and breaking the technique down add understanding to the process and can highlight points of caution and safety as well as adding helpful hints.

Step 3 The learner provides the commentary, which the instructor follows while demonstrating the skill for the third time. The instructor must be careful not to assume knowledge during this process and stop in mid-flow if errors are made. This step is crucial in terms of surgical safety, as the instructor can tell what the learner understands. Any errors or omissions can be addressed immediately (this step may need to be repeated).

Step 4 Once step 3 is completed satisfactorily, the learner is allowed to perform the skill while providing a commentary under direct supervision.

Scenario teaching

These practical teaching sessions describe a clinical picture and facilitate role play to manage the problem. The aim of such teaching is to demonstrate appropriate clinical behavior. This includes clinical knowledge and how it is applied, but also how individuals work together as a team and communicate. Such interactions can be complex and are worth detailing further before illustrating massive hemorrhage scenarios.

Teamwork

The ability to work together as a team is fundamental to good clinical care. Individuals possess differing expertise and the group's dynamics

and ability to carry out specific tasks depend upon the interpersonal skills of all team members. Watching a group working together can highlight problems and help focus remedial action in terms of teamwork and occasionally individual behavior.

Every team needs a leader, and deciding who the leader is to be can sometimes be difficult. It is important to recognize that the team leader need not be the most senior person and, as the scenario develops, sometimes the leader will need to change. In any event, the leader should have appropriate knowledge and skills, be a good communicator and motivator, be able to maintain situation awareness (see the whole picture) and distribute the workload. At the same time, watching staff adapt to each other can be hugely instructive, and discussing these issues afterwards can help them understand each other, as well as individual needs and stresses.

Communication

The process of asking for and providing information, and of listening to what other people are trying to say, should be simple. It clearly is not and is repeatedly raised as a problem area in confidential mortality reports. In the Confidential Enquiry Report of 1997–1999[2], the greatest cause of substandard care in maternal deaths was failure of communication and team working between professionals. When running practical teaching sessions, communication within the team can be witnessed and discussed afterwards. Generally speaking, when dealing with any emergency, single precise commands should be addressed to specific individuals. Voices should not be raised and an air of calm control should be apparent. Unfortunately, some individuals tend to become overexcited, and noise levels can build up, which can affect everyone's behavior, as well as making it difficult to hear what is being said without resorting to shouting. Pointing out such behavioral features under stress during mock emergencies can only help to raise awareness.

Preparing for scenario teaching

When preparing for role-play, it is important to try to make things as realistic as possible.

The patient Depending on the subject to be taught, either a manikin or a live person can be used. Manikins tend to be good for collapse and cardiopulmonary resuscitation, whereas live models are better when responses are needed (for example, eclampsia). Either can suit massive obstetric hemorrhage. The advantage of a live model is that everyone usually learns a great deal with regard to how all levels of staff communicate with a patient in such emergencies

The equipment It helps to be more realistic if there is some equipment available when running clinical scenarios. This should be kept simple, but using it helps to illustrate what important features have been dealt with (e.g. lateral tilt and oxygen) and what omissions have occurred (e.g. intravenous access or urinary catheter). Table 3 is a suggested minimum equipment list for a massive hemorrhage scenario.

Running the scenario

Who should be involved? Deciding who should be involved in the role play and who is better left to watch quietly can be difficult. If the members of staff are new to scenario teaching, it is best, initially, to ask for volunteers. Lack of volunteers may be due to simple factors like being shy, but it may result from fear of ignorance

Table 3 Basic equipment list for practical obstetric hemorrhage training

Airway and breathing
• Guedel airway
• Oxygen mask with bag and tubing
• Stethoscope
Circulatory
• Wedge (to provide lateral tilt for the pelvis)
• Tape
• Two large-bore intravenous cannulae (14FG)
• 20-ml syringe
• Blood bottles for full blood count (FBC), cross-match (XM), clotting studies
• 2-liter bags of crystalloid run through giving sets
• Catheter
Specific equipment for massive obstetric hemorrhage
• Intrauterine inflatable balloon and bladder syringe

being exposed or raising issues of competency. It is for this reason that didactic teaching is needed prior to running scenario training, so that the theoretical material has already been covered. Those previously unsure of the theory behind the problem can build on their newly acquired knowledge in a practical way. Indeed, once members of staff become used to this method of teaching, more will come forward. Occasionally, someone may need to be invited to join in, but this should be done sensitively and with support.

Give people defined roles People need to be given a defined role and told what they can or cannot expect in terms of back-up. For example, 'You are the senior house officer who has just answered the emergency buzzer to this multiparous patient. She has just bled briskly following spontaneous vaginal delivery. The midwife is here, but all other staff are busy with an emergency in theater and you should not expect help for at least 10 minutes. Please carry on as you would in real life. I will give you any observations you request'.

Keeping the scenario going The patient can be primed to give certain responses, and monitors can be prepared with readings (cardiotocograph paper sticking out of a machine/blood pressure recordings on a monitor, etc.), but it is the instructor's role to keep the scenario flowing and give as much or as little information as is requested. The scenario needs to progress, however, and gentle encouragement and occasional subtle prompts can assist the learner in achieving the key treatment points. The aim of running scenarios is not to display ignorance, but to empower individuals to apply their knowledge in a logical and timely manner. Depending on the performance and ability of the candidate, the scenario can be resolved early or become more complex. This needs to have been anticipated by the instructor well in advance. If the candidate is becoming stressed, but has done all the basic key treatment points, then the scenario can resolve and the candidate can be congratulated. If the key treatment points have not been achieved, then help can be at hand in the form of a registrar or consultant arriving to help. If the learner is doing a fantastic job, then the scenario can progress and more complex features can be added.

Prompting can be difficult if it is to be done sensitively without demoralizing or embarrassing the learner, and is the real skill in making this form of teaching constructive. The examples that follow may be useful in the massive hemorrhage situation:

- Lateral tilt can be forgotten in the pregnant woman and a prompt asking whether there is 'anything else that could improve the circulation?' may jog a response;
- If there has been no apparent registering of, or response to, observations, information about tachycardia or hypotension can be repeated;
- Comment that uncross-matched blood is now available if staff have lost their train of thought and had already mentioned they would request blood but then forgotten about it;
- Providing the patient's physiological responses can intervene to slow down/speed up the action as required. For example, once intravenous fluids have been commenced, inform the candidate that the blood pressure is improving but that the bleeding is still brisk vaginally. This will encourage the candidate to move on to assess the cause for this;
- If the candidate moves away from the intravenous access without taking any bloods for laboratory investigation, the instructor may slow things down by asking if she/he would do anything else before moving on to assess the cause of the bleeding. The candidate could also be prompted with an empty syringe and blood bottles, if necessary, to make a teaching point.

Drawing things to a logical conclusion When the scenario has run its course, all people who have been involved in the role play should be congratulated and thanked for their participation, and then encouraged to engage in the feedback process as described above. Questions and discussion should then be encouraged before closure, with particular emphasis given to the key treatment points.

Examples of possible massive obstetric hemorrhage scenarios are given, together with their key treatment points in Tables 4 and 5.

SUMMARY

Setting up practical teaching locally improves local processes, builds on teamwork, aids with communication, and improves clinical knowledge and its application in the emergency situation. It is best kept simple and, because it can be stressful to those involved in role play, it must be introduced sensitively and conducted within an encouraging atmosphere. Staff need to know what style of teaching will be used, and what its aims are. Advertising the planned content of the session in advance will encourage staff to prepare and capitalize on enthusiasm and learning.

Table 4 Sample scenario for postpartum hemorrhage due to atonic uterus

Candidate information

A 34-year-old grand multipara delivered a healthy baby boy weighing 4.00 kg 40 minutes ago. She had physiological management of her third stage and the placenta was delivered 10 minutes ago. The midwife has noticed some fresh brisk vaginal bleeding and accosted you as you were walking past the delivery room.

Initial observations

Talking but very pale. Pulse 110/min, blood pressure 120/80 mmHg; large volume of blood on floor and bed.

Please proceed as you would in real life together with the midwife who called you. I will give you any observations you request. (The candidate can be obstetric or midwifery as either should be able to manage this emergency initially. If further progress to theater is needed, more senior help can arrive as requested.)

Instructor's notes/Key treatment points	*Achieved*
• Call for help and initiate the massive obstetric hemorrhage drill	
• Recognize that this is a circulatory problem: progress rapidly through airway and breathing and attach face mask for oxygen	
• Establish intravenous access • Send blood for full blood count, cross-match, coagulation, and U&Es • Commence intravenous fluids	
• Do clinical examination and diagnose uterine atony • Give uterine massage • Administer a uterotonic agent • Do a vaginal examination and evacuate clots • Check no obvious vaginal lacerations	
• Do bimanual uterine compression	
• Go through drugs cascade logically and give intravenous fluids and blood appropriately	
• Consider examination under anesthetic if patient fails to respond and consider other causes of postpartum hemorrhage	
• Knowledge of surgical techniques to control hemorrhage, i.e. Rüsch balloon, Brace suture, etc.	

Table 5 Sample scenario for postpartum hemorrhage not due to atony

Candidate information
A 24-year-old primipara is induced at 42 weeks' gestation. She is having intermittent abdominal pain when the prostaglandin is inserted. Within 1 hour, she is transferred to the delivery suite where she delivers a baby boy weighing 3.8 kg followed by the placenta.
Initial observations
Talking; pulse is 100/min, blood pressure 115/70 mmHg; steady trickle of blood vaginally. Please proceed as you would in real life and I will give you any observations you request. (This scenario is more complex – a precipitate labor with the possibility of a concealed abruption. The focus will be on distinguishing between genital tract trauma and disseminated intravascular coagulation (DIC). How this scenario will unfold will depend on the learner's experience and ability.)
Instructor's notes/Key treatment points — *Achieved*
• Call for help and institute massive hemorrhage call • Recognize circulatory problem. Move swiftly through airway and breathing. Administer face mask for oxygen
• Insert intravenous access • Send blood for full blood count, group and save, and coagulation screen • Commence intravenous fluids
• Abdominal examination to confirm uterus well contracted
• Vaginal examination to check for vaginal lacerations • Transfer to theater for analgesia and examination
• Catheterize
• Full EUA: check vagina, cervix and uterine cavity

EUA, examination under anesthetic

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14

NON-PNEUMATIC ANTI-SHOCK GARMENT

S. Miller and P. Hensleigh

INTRODUCTION

The FIGO/ICM recommendations for active management of third-stage labor, including uterotonic prophylaxis with additional uterotonic treatment when necessary, reduce the incidence of severe postpartum hemorrhage due to atony. However, at least 1% of all women still suffer intractable postpartum hemorrhage from uterine atony or other obstetric causes, such as genital lacerations, ruptured uterus, ruptured ectopic pregnancies, or placenta previa, accreta, and abruption. Multiple blood transfusions are often needed to resuscitate and stabilize these women and hemostasis may require surgical interventions. Until the time when quality comprehensive emergency obstetric care (CEOC), including surgery and/or blood transfusions, is readily available for all women, strategies and technologies for hemorrhage treatment and hypovolemic shock resuscitation are needed such that they can be readily provided and easily applied, even by persons with no medical training. Promising technologies to reduce maternal mortality include the non-pneumatic anti-shock garment (NASG) as a technology for reducing the mortality and morbidity associated with obstetric hemorrhage[1,2].

THE NON-PNEUMATIC ANTI-SHOCK GARMENT

The NASG is a simple device, proposed as the immediate first-aid treatment for reversing hypovolemic shock and decreasing blood loss secondary to obstetric hemorrhage, by application of lower body counter pressure. The NASG also has the potential to keep women alive during long transports from lower level facilities or home to the CEOC facilities for definitive therapies.

The NASG is a lightweight, relatively inexpensive (US$160.00 per garment), washable and reusable (at least 50 times), neoprene garment that resembles the lower part of a wet suit. The NASG, manufactured by the Zoex Company, received a United States Food and Drug Administration (FDA) 510(k) medical device regulations number (FDA device # K904267/A, Regulatory Class: II, January 17, 1991) (Section 510(k) Medical Device Amendment, FDA, Office of Device Evaluation, 1991) and can be exported to countries outside the United States. The NASG is designed in horizontal segments, with three segments on each leg, a segment over the pelvis, and a segment over the abdomen that contains a small, foam compression ball (see schematic in Figure 1).

Unlike the pneumatic anti-shock trousers (PAST), or medical anti-shock trousers (MAST), which preceded the NASG, there are no pumps, tubing, or gauges to add complexity and risk of malfunction. Using the three-way elasticity of neoprene and the tight grip of the Velcro fasteners, the garment can apply 30–40 mmHg of circumferential counter pressure to the lower body from the ankles up to the level of the diaphragm (see Figure 2). This amount of pressure is effective in reversing hypovolemic shock by shunting blood from the capacitance veins of the abdomen and lower extremities to the vital core organs, the heart, lungs and brain. The effect of this autotransfusion, estimated to be 500–1500 ml, is almost immediate upon application. The moderate NASG pressures are generated by manually stretching the neoprene material. Excess pressures and the resultant tissue ischemia, known complications with the pneumatic PAST, are

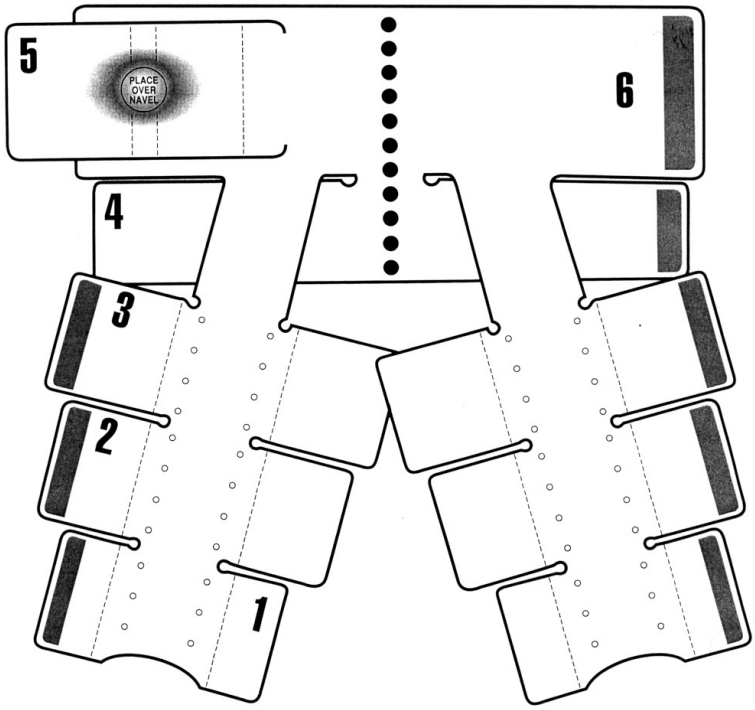

Figure 1 Schematic diagram of the non-pneumatic anti-shock garment

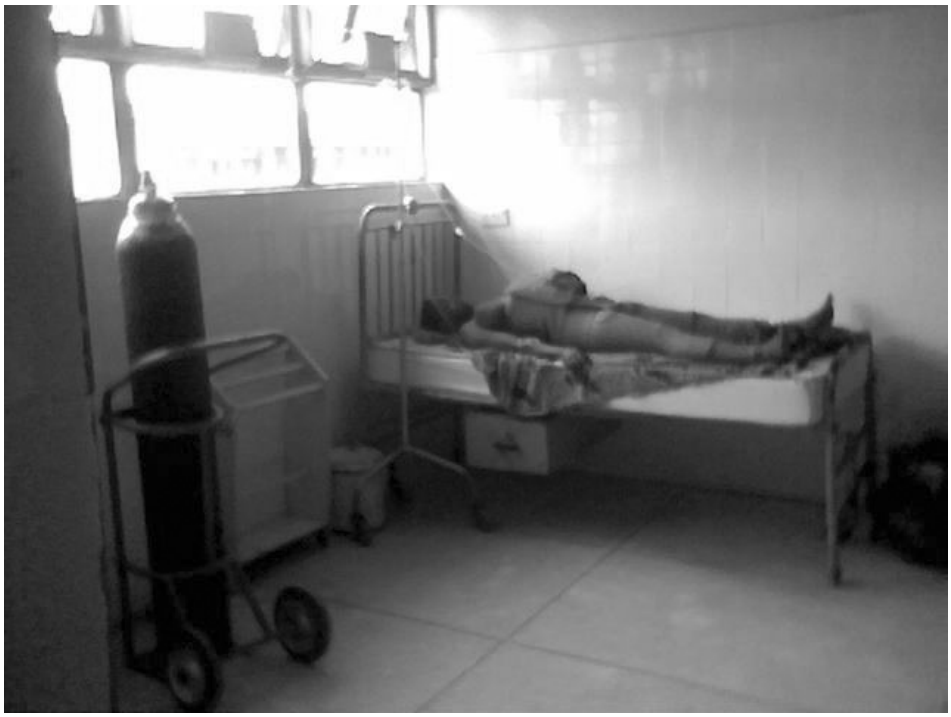

Figure 2 Patient wearing the non-pneumatic anti-shock garment in hospital

not an issue. Application of the garment requires about 2 min and, within 2–5 min after its application, most patients with severe shock regain consciousness and vital signs begin to recover. With the bleeding slowed and the blood the pressure restored, panic levels decrease, and there is time to deliberately assess the situation. Patients can remain in stable condition for hours while blood transfusions are initiated and arrangements made for surgery or other required therapies. The patient and her family can be given emotional support and prepared for transport to a referral-level facility or any required surgical procedures. If the hemorrhage is due to uterine atony, the continued infusion of uterotonics and passage of time may be all that is required for management.

DEVELOPMENT OF THE NASG

The modern NASG is a non-pneumatic refinement of the pneumatic anti-shock garment (PASG). The PASG was adapted from a device developed by George Crile, in the early 1900s before the advent of technologies to allow blood transfusions. Crile, a surgeon who wrote textbooks on blood pressure and shock, designed the first inflatable pressure suit to maintain blood pressure during surgery. This pneumatic suit underwent multiple modifications and was further refined for use as an anti-gravity suit (G-suit) for the Army Air Corps in 1942. During the Vietnam War, the G-suit was modified for resuscitating and stabilizing soldiers with traumatic injuries before and during transport. The G-suit was then modified to a half-suit, which became known as military anti-shock trousers (MAST).

The MAST/PASG has been used since the 1970s by emergency rescue squads in the United States to stabilize patients with a variety of disorders: pelvic and lower limb fractures, hypovolemic shock, septic shock, and to control intra-abdominal, pelvic, and thigh hemorrhage, as well as for gynecological and obstetric hemorrhage[3–6]. Andrea and colleagues used the MAST to stabilize women with intractable uterine bleeding while preparations were made for transcatheter emobization[7]. The PASG is included as a recommended treatment for intractable hemorrhage in the 1998 guidelines of the American College of Obstetricians and Gynecologists[8].

The PASG requires inflation and careful management of pressure levels, both to maintain adequate pressure and to prevent overinflation resulting in compartment syndromes, ischemia, and necrosis. The valves and manometers that maintain inflation are subject to leaks and malfunctions. In addition, specialized training for safe and effective use of the MAST is necessary, which makes widespread use in developing countries difficult.

EFFICACY OF THE PASG FOR TRAUMA

McSwain reviewed the physical principles responsible for the physiologic effects of lower-body counter pressure with application of the PASG[3]. Numerous studies in hypovolemic animals and humans demonstrate that the PASG increases blood pressure by decreasing the vascular volume and increasing vascular resistance within the compressed region of the body. When blood flow or arterial vascular size is measured above the device, the flow is greater and vessels are larger. In the compressed region, the radius of blood vessels is decreased, thus slowing down blood flow. In the hypovolemic model, the PASG increases venous return and the increase in preload is associated with increased cardiac output[9].

These changes in vessels and blood flow are also associated with the translocation of blood from the lower body enclosed in the device to the upper body (heart, lungs and brain), a volume which is estimated at 750–1000 ml[10]. In summary, the physiologic bases for restoration of blood pressure are: the reduced vessel size beneath the device, which produces increased systemic vascular resistance, the decreased container size, the translocation of blood to the upper body, and increased preload resulting in increased cardiac output.

Although animal studies show improved survival rates except for thoracic injuries[11,12], it is uncertain if the rapid, positive changes in vital signs and blood loss affect survival in humans. Despite widespread acceptance of the PASG for military and civilian trauma injury and reports

of small series demonstrating successful treatment of various bleeding conditions in adults and children, there are no definitive prospective randomized treatment trials to show improvement in survival. The three United States-based, prospective, alternate-day, randomized treatment trials of civilian trauma cases did not find consistent results and are confounded by inclusion of injuries to the upper body, a contra-indication to use of the PASG[13–15]. In some studies, the pH on hospital admission was lower with PASG use, intensive care unit and hospital stays were longer, and survival worse. These studies were all conducted in a metropolitan setting where high-level hospital care was available within minutes, and even the brief delay in applying the PASG may have been a detriment to the benefits of early hospital care.

Despite the lack of randomized, controlled trials supporting its use, the Committee on Trauma of the American College of Surgeons included the PASG as essential equipment for ambulances[16] and the PASG remains on the curriculum and in the textbooks for emergency medical technicians in the United States[17,18]. A position paper on the PASG by the National Association of EMS Physicians[19] cited the lack of controlled trials, but, on the basis of other reports, deemed the PASG as 'Class I usually indicated and effective for hypotension due to ruptured aortic aneurysm, but of uncertain efficacy for other emergency situations'. Its use for uncontrolled gynecologic hemorrhage, urologic hemorrhage, and ruptured ectopic pregnancy was a 'Class IIb acceptable, but uncertain efficacy, may be helpful, probably not harmful'. PASG proponents particularly recommend its use for bleeding in the abdomen, retroperitoneum, pelvis, or thighs[9]. The current recommendations in the US are that, while its effects on survival are unknown, it is probably indicated in patients with bleeding in the very areas (abdomen, retroperitoneum and pelvis) that are the bleeding sites for women with obstetric hemorrhage. Likewise, in France, use of the 'pantalon antichoc' is questioned for widespread use, but its use for post-partum hemorrhage, disseminated intravascular coagulopathies associated with pregnancy and labor, and other obstetric and gynecological bleeding is endorsed[20].

What is unknown about the PASG is what the difference in outcomes might be if the PASG (or the non-pneumatic adaptation, the NASG) were to be used in low-resource settings where there are longer transport times, slower responses at the hospital level, and longer delays in obtaining definitive therapy by blood transfusions and/or surgery.

POTENTIAL BENEFITS OF THE NASG IN LOW-RESOURCE SETTINGS

The NASG was adapted from the PASG by the National Aeronautics and Space Administration (NASA) in 1971, when the NASA/Ames Research Center developed a prototype pressure suit designed to protect hemophiliac children from bleeding into elbow and knee joints by straightening and compressing the joint until medical attention was available[21]. Both PASG and NASG provide circumferential counter pressure in the lower body, but the NASG is simpler in design, more quickly and easily applied, less expensive and avoids the risk of over-inflation and excessive pressure[22].

The NASG is particularly suited to use in low-resource settings. Lighter and more flexible than the PASG, it is more comfortable for a woman to be inside the suit for longer periods of time, something necessary in the long transport times and delayed treatment conditions of low-resource settings. As with the PASG, within minutes of being placed in the NASG, a patient's vital signs are restored and, if confused or unconscious, their sensorium generally clears[1]. Women can remain in the NASG for as long as is required to restore their circulatory volume with crystalloids and to replace blood. In prior reports of cases where blood transfusions were not readily available, this has often required 18–24 h, and, in one case, a woman remained safely in the NASG for 57 h[23]. Compared to the PASG, with pressures of 100 mmHg or more, the NASG only applies 30–40 mmHg. Higher pressures appear to be responsible for skin and muscle ischemia and adverse effects on pH as well as the occasional anterior compartment syndrome.

A second benefit of the NASG for obstetric indications is that the design of the garment permits complete perineal access so that genital

lacerations can be repaired, speculum or bimanual examinations can be performed, and manual removal of placenta or emptying of the uterus with manual vacuum aspiration or curettage can all be accomplished with the NASG in place. Thus, the source of most obstetric hemorrhages can be located and attended to while the garment maintains vital signs.

A third benefit of the NASG is that it significantly reduces further blood loss. When the NASG is applied, the external circumferential counter pressure is distributed evenly throughout the abdominal cavity and to the outside of the circulatory vessels – tamponading venous bleeding. In the event of an arterial injury, continued bleeding results from the tension in the wall of the artery keeping the defect open. However, the NASG compresses all the intra-abdominal vessels including the internal iliac and uterine arteries. This compression reduces the radius of the arteries and reduces the transmural pressure (the difference between the pressure inside the artery and the pressure outside the artery) which, in turn, reduces the tension in the arterial wall, closing the defect and reducing blood loss. Although the mean pressure applied by the NASG is only in the range of 30–40 mmHg, this low pressure, which is below arterial pressures, can still stop arterial bleeding when applied externally to the abdomen and the lower extremities[24]. Because the applied pressures could interfere with uterine blood flow, the NASG is not recommended for obstetric bleeding when the fetus is still viable, such as might be the case with placenta previa or abruption. Post-delivery, however, or when the fetus is not viable or is dead, the NASG can be used for any obstetric hemorrhage.

Another potential benefit for the use of the NASG for obstetric hemorrhage in low-resource settings is that persons with no medical background can learn to apply the garment safely with minimal training. Such training, which includes hands-on practice in application and removal of the NASG, takes approximately 1 h. Once the garment has been properly applied, patients can safely be transported and/or await definitive treatment in a more stable physical condition. This final point is critical, as the majority of maternal deaths due to obstetric hemorrhage occur in areas where skilled birth and critical care attendance are limited or absent.

The improvement in maternal morbidity and mortality can presently only be discussed as potential benefits, because there have been no definitive trials of the NASG, and there is only very limited experience with its use for obstetric hemorrhage in low-resource settings. The case series and pilot studies discussed below indicate how the NASG functions to decrease blood loss, reverse shock, and stabilize women for many hours while awaiting blood transfusions. As such, use of the NASG might contribute to decreased maternal mortality and morbidity. Experience with transport from lower-level facilities to referral centers, while theoretically beneficial, is only anecdotal at this point.

SUGGESTED PROTOCOL FOR USING THE NASG

The NASG is recommended for cases of obstetric hemorrhage meeting the American College of Surgeons' criteria for Class II hypovolemic shock: > 750 ml blood loss, pulse > 100 and blood pressure normal or slightly decreased[25]. The NASG is not recommended for use with a viable fetus, for patients with mitral stenosis, congestive heart failure, pulmonary hypertension, or in clinical conditions where there could be bleeding sites above the level of the diaphragm. Availability of the NASG does not negate the importance of preventive measures such as the active management of the third stage of labor or administration of uterotonics to treat uterine atony. The authors recommend cardiovascular resuscitation using limited crystalloid infusion with the goal of 'permissive hypovolemia'[26–30]. This means infusing 1000–1500 ml of saline rapidly followed by a slower rate of infusion, 150 ml/h, to achieve a mean arterial pressure of about 60 mmHg (blood pressure 80–50 mmHg) and urine output of 30 ml/h. Supplemental oxygen should be given until the patient is resuscitated, the hemorrhage arrested, and the circulation fully normalized.

Application of the NASG

The technique for application is for one person to stretch the neoprene panels with all their

strength and fasten them with the Velcro as tightly as possible. The lowest (ankle) segment is applied first and the abdominal segment last. If the woman experiences difficulty breathing, the abdominal panel should be loosened slightly, but not removed. However, if dyspnea continues, the NASG should be removed and the cause of the respiratory problem evaluated. A woman with normal cardiorespiratory function should experience no problems with ventilation. If there is no prompt response in terms of vital signs with placement of the NASG, the application should be checked for adequate tightness, and additional saline infusion given promptly. As soon as the patient is stable, there must be a diligent evaluation for the specific source and cause of the blood loss.

If pelvic examination or vaginal procedures are needed, the NASG should be left in place; if laparotomy is necessary, open the abdominal segment. Often there will be a drop in blood pressure when this panel is removed; this should respond to additional saline infusion.

Removal of the NASG

The NASG is left in place as long as needed to achieve hemostasis and replace red blood cell volume with transfusion of donor blood. The NASG can be removed when the hemoglobin level is > 7 or the hematocrit 20%, the pulse < 100, and the systolic pressure > 100 mmHg. Removal of the NASG begins with the lowest segment (#1) and proceeds upwards, allowing 15 min between removing each segment for redistribution of blood. If the blood pressure falls by 20 mmHg or the pulse increases by 20 beats/min after a segment is removed, replace the NASG and consider the need for more saline or blood transfusions. If there is recurrent bleeding, replace the NASG and determine the source of bleeding.

EXPERIENCES WITH THE NASG

Case series in Pakistan

Recently, examples of the potential benefits of using the NASG in cases of obstetric hemorrhage in a resource-challenged setting were documented in two published reports based on a series of 150 obstetric cases in one hospital in Silkot, Pakistan[1,23]. There was no blood bank in the hospital; if blood transfusions were necessary, they could only be obtained through direct donor transfusion. The researchers documented that patients placed in the NASG experienced rapid resuscitation from hypovolemic shock, as well as an extended period of stabilization while awaiting definitive treatment. In a combined analysis of the two reports[24], there appeared to be no adverse effects of prolonging this stabilization period, even though the average interval from diagnosis of hemorrhage to blood transfusion was 5 h 30 min, and the mean time in the NASG was more than 30 h.

Pilot studies of the NASG

Based on the successes of the case series in Pakistan, the authors and their in-country colleagues are conducting NASG pilot studies in comprehensive emergency obstetric care facilities in Nigeria (Dr Dosu Ojengbede, University of Ibadan), teaching facilities in Egypt (John Snow International), and in primary and secondary health facilities in Mexico (Population Council and IMSS-Opportunidades). These studies compare use of a standardized protocol of shock and hemorrhage care in the pre-intervention period with the same standardized protocol plus the NASG in the post-intervention phase. The primary outcome was volume of measured blood loss after initiation of treatment with or without the NASG. To obtain a relatively objective measure of blood loss, maternal bleeding after admission to the study is measured using a specially designed, closed-end, calibrated plastic blood collection drape. Prior studies of this drape indicate that it is more accurate than visual assessment in measuring postpartum blood loss[31]. Secondary outcomes include severe acute maternal morbidities (SAMMs: acute respiratory distress syndrome, cardiac deficiency, central nervous system damage, and renal failure) and need for emergency hysterectomy. The standard protocol included: active management of third-stage labor, immediate use of uterotonics for suspected postpartum uterine atony, training in limited intravenous crystalloid fluid

replacement[32,33], and, in the post-intervention, prompt application of the NASG.

Inclusion criteria were obstetric hemorrhage with shock (minimum requirements: estimated blood loss > 750 ml, systolic blood pressure < 100 mmHg and/or pulse > 100). There were a variety of obstetric hemorrhage etiologies, including postpartum hemorrhage due to atony or lacerations, ectopic pregnancies, ruptured uterus, complications of abortion, and a variety of placental pathologies. Overall, postpartum uterine atony and/or retained placenta or placental fragments accounted for 44% of all participants. Pre-intervention data were collected from May to September 2004. Post-intervention data collection has been completed in Egypt and is underway in Nigeria and Mexico.

NASG pilot study in Egypt

The study sites in Egypt comprised high-volume referral CEOC teaching facilities (El Galaa, Alexandria, Assiut, and Al Minya). All are staffed by senior obstetricians and obstetric residents with immediate access to banked donor blood and surgery. Pre-intervention data, including measured blood loss, were collected for 3 months, after which all providers were trained in the use of the NASG. The only change to the pre-intervention clinical management was the use of the NASG. Post-intervention data were collected for another 3 months.

The primary outcome was mean measured amount of blood lost after a woman entered the study. A sample size of 150 pre-intervention obstetric hemorrhage patients (no-NASGs) and 150 post-intervention obstetric hemorrhage patients (NASGs) was needed to detect a 50% difference in blood loss between the two groups with power (β) of 80% and a significance level (α) of 5%. The final study sample comprised 156 no-NASG and 204 NASG patients with obstetric hemorrhage who met the entry criteria. Diagnoses of obstetric hemorrhage covered a range of primary diagnoses with no statistically significant differences between no-NASGs and NASG patients. The three most common diagnoses were uterine atony, genital lacerations, and complications of abortion. The NASG women had a statistically significant greater loss of blood on study entry and more severe signs of shock than did the no-NASG group. Estimated blood loss at entry to the study was 1000 ml for NASG cases and 750 ml for no-NASGs ($p < 0.001$), mean systolic blood pressure for NASG cases was 88.3 mmHg vs. 97.2 mmHg for no-NASGs ($p < 0.001$), and mean diastolic blood pressure was 56.7 mmHg for NASGs vs. 60.8 mmHg for no-NASGs ($p = 0.005$). A probable reason for the NASG group's worse condition on study entry was that the clinical researchers waited until women were in deeper shock before putting on the garment, a new technology that they were not accustomed to applying.

As shown in Table 1, NASG patients had 46% less mean measured blood loss (50% less median measured blood loss) than did those patients not treated with the NASG ($p < 0.001$). NASG and no-NASG patients had similar blood loss during surgery: NASG patients lost only 32 ml more ($p = 0.748$), and NASG patients had a lower amount of estimated 'other' blood loss (spilled on floor, on gauze or towels) compared to no-NASG cases ($p = 0.209$). Patients treated with the NASG had a statistically significant lower amount of post-study entry blood loss (drape + intraoperative + 'other') compared to no-NASGs ($p < 0.001$). The NASG group received 193.3 ml more blood than those not receiving the NASG ($p = 0.034$), and the NASG group also received 225.6 ml more of intravenous fluids ($p = 0.06$). There was a non-statistically significant 84% lower incidence of severe acute maternal morbidities (SAMMs) and mortalities, which were combined as 'extreme adverse outcomes'. One patient (0.5%) had an extreme adverse outcome among the NASG patients (renal failure), whereas five patients (3.2%) died or suffered SAMMs among the no-NASG patients (odds ratio (OR) 0.15, 95% confidence interval (CI) 0.02–1.31)[34].

A greater percentage of patients in the NASG group had surgeries compared to no-NASG patients (49.0% vs. 37.8%, $p < 0.03$), perhaps due to their worse condition on study entry. The most common surgeries were Cesarean section and salpingectomy. Both groups spent

Table 1 Results from NASG Pilot study in Egypt

	No-NASG (*n* = 156) *Mean ± SD*	*NASG* (*n* = 204) *Mean ± SD*	*p Value*
Mean blood loss measured with drape (ml)	561.6 ± 447.4 (median 500)	303.5 ± 219.5 (median 250)	< 0.001[a]
Mean intraoperative blood loss (ml)[c]	394.1 ± 537.5	426.0 ± 641.2	0.748[b]
Estimated 'other' blood loss (ml)[c]	196.3 ± 333	140.2 ± 221.3	0.209 [b]
Blood loss post-entry to study (drape + intraoperative + other) (ml)	902.7 ± 696.5 (median 700)	591.3 ± 532.0 (median 450)	< 0.001[a]
Volume blood transfusion (ml)[d]	963.2 ± 668.4	1156.5 ± 707.8	0.034[b]
Volume intravenous fluids (ml)	2035.5 ± 1190.6	2261.1 ± 1033.3	0.057[b]
Extreme adverse outcomes	5 women (3.2%)	1 woman (0.5%)	OR 0.15, 95% CI 0.02–1.31

Selected variables: NASG
[a]Mann-Whitney *U* test used for comparison of groups with unequal variances; [b]from Student's *T* test; [c]for the 159 women who had operations, 59 in the no-NASG group and 100 in the NASG group; [d]for the 248 women who had blood transfusions, 95 in the no-NASG group and 153 in the NASG group

almost equal time in the hospital following admission, NASG patients a mean of 2.0 ± 1.5 days, and the no-NASGs a mean of 1.9 ± 1.6 days ($p = 0.50$). Both groups received comparable dose of oxytocin; for those with uterine atony, the mean total was 30.7 units for no-NASG and 32.0 for NASG patients.

A sub-analysis of women who entered the study with severe hemorrhage (> 1500 ml) revealed no difference in frequency by study group, no-NASGs 26.9%, NASG 31.4%, $p = 0.36$. However, the mean volume of blood lost in the drape for the NASG group was 66% less than for the no-NASGs (278.1 ± 221.5 ml NASG vs. 818.1 ± 641.3 ml no-NASG, $p < 0.001$). This was a greater mean blood loss difference by study group than among all patients (with and without severe hemorrhage at study entry). A non-statistically significant decrease was found for extreme adverse outcomes; among those who did not receive the NASG, such outcomes occurred in four patients (9.5%) and in only one NASG patient (4.6%) (OR 0.5, 95% CI 0.1–1.9).

The results among this sample of women in university teaching hospitals appear very promising. While the women with the NASG had lost more blood and had greater signs of shock, the primary outcome of measured mean blood loss was statistically significantly less. The non-statistically significant difference in extreme adverse outcomes is promising, but will require a larger sample over a longer period of time in order to demonstrate if there is a true difference in this most important outcome.

NASG pilot studies in Nigeria and Mexico

Pilot studies are currently underway at four urban acute obstetric hospitals in Nigeria and in rural primary health-care facilities (Unidades Medicales Rurales or UMRs) with long transport times to rural CEOC facilities in Mexico. The design and methodology of these studies are similar to those in the Egypt study. One difference is that, in Mexico, pre-weighed adult diapers are used to collect blood during long transports between the UMRs and the CEOC facilities where women are brought for definitive treatment. (The blood collection drapes used in the CEOC tend to slip off during the often multiple vehicle changes involved in transport from the UMRs.) The used diapers are weighed at the CEOC facilities and blood volume is calculated from the weight of the diaper; at the CEOC facilities, the diapers are then replaced

by the closed-end plastic blood collection drape. In Mexico, the number of no-NASG cases was ten and the number of NASG cases 27.

The following case history illustrates the application of the NASG in a rural Mexican community. A 25-year-old woman, gravida 2 para 1, delivered at home attended by a traditional birth attendant (TBA) who had been sensitized to the need for transport in the NASG by community outreach. When the woman began to hemorrhage from a retained placenta, the TBA arranged transport to a study UMR. The trip took over 2 h; on arrival at the UMR, it was estimated that the patient had lost more than 2000 ml blood and had a pulse of 160. The NASG was applied and the woman transported by ambulance another 2 h to a CEOC facility. Blood loss during the trip was measured at 300 ml. At the hospital, intravenous fluids were started, a manual removal of the retained placenta was performed, and two units of blood were transfused. The patient was discharged with a hemoglobin level of 8.

In contrast to the community setting in Mexico, the Nigerian study is set in urban CEOC hospitals. Before introducing the NASG protocol, data were collected for 3 months, as in the other pilots. While data are still being collected in this study, an interim analysis includes 27 no-NASG patients and 63 with NASG. The most common diagnoses are antepartum hemorrhage and postpartum hemorrhage, i.e. 12 women (44%) in the non-NASG group versus 39 (65%) in the NASG group. The estimated blood losses on study entry were similar for both groups (1258 ml vs. 1487 ml), but the NASG women had more severe symptoms of shock, with a mean blood pressure of 53/23 mmHg compared to 91/55 mmHg. The percentage with Class 3 or Class 4 shock in the NASG group was also greater, 85% vs. 22%. According to the protocol, measurements of blood loss were to be made using the same closed-end blood collection drapes used in the Egypt study. However, in some cases, this could not be accomplished and visual estimates were made of blood loss. In all cases, the amounts of blood lost and replaced were reconciled with the admission and subsequent hematocrit values. The difference in measured plus estimated blood loss after study entry was more than a liter greater in the no-NASG group, 1385 ml vs. 257 ml.

An interim analysis from the Nigeria study concerns the recovery of 33 women with severe postpartum hemorrhage[35]. This subset of women met three of the four American College of Surgeons' Class III or IV shock criteria: > 1500 ml blood loss, packed cell volume < 20%, pulse > 120, blood pressure < 80/50 mmHg, and altered mental status. During resuscitation, the vital signs were recorded every 15 min. Although not always accomplished, the protocol advised giving 1500 ml saline rapidly, followed by additional saline to achieve minimum blood pressure of 80/50 mmHg, corresponding to a mean arterial pressure of 60 mmHg.

Thirty-two women survived without morbidity; one woman expired. Among the 32 surviving women, the estimated mean blood loss upon study entry was 1471 ml and mean packed cell volume 18.9%. Mean measured and estimated blood loss with the NASG in place was 220 ml. Mean volume of blood transfused was 1442 ml and the discharge packed cell volume 23.8%. After placing the NASG, 28 of the 32 women had improvement in their vital signs by the next 15-min recording. The resuscitation interval (the time from placement of the NASG until achieving a mean arterial pressure ≥ 60 mmHg) was 52 min. The patients with more rapid intravenous saline infusion responded more rapidly; those receiving an infusion at > 1000 ml/min recovered in 24 min while those receiving < 1000 ml/min took 83 min.

Preliminary analysis: Nigeria and Egypt severe hemorrhage

A recent analysis was conducted combining the Egypt data[34] and data from six tertiary-care hospitals in Nigeria on all women (n = 263) with severe hemorrhage (estimated blood loss on admission ≥ 1000 ml, pulse > 120). There were 104 in the pre-intervention, standard-care group, and 159 treated with standard care and the NASG. There were no differences in the pre-intervention and NASG groups by country or age. There were a variety of diagnoses; the leading cause of hemorrhage was uterine atony, approximately 33%. The patients' conditions

on study entry were statistically similar in the two groups. The difference in median blood loss in the drape after treatment was statistically significantly different; those in the NASG group lost 64% less, 250 ml vs. 700 ml (median difference 490 ml, 95% CI: 350–600 ml). Neither mortality alone, $n = 7$ (6.7%) for pre-intervention vs. 3 (1.9%) for the NASG groups, nor severe morbidity, $n = 5$ (5.3%) vs. 2 (1.3%), were statistically significantly different. However, a combined severe adverse outcome variable, a combination of mortality and SAMMs, was statistically significantly different, with those in the NASG group less likely to suffer a severe adverse outcome, RR = 0.28, 95% CI 0.10–0.77[36].

CONCLUSIONS

The data from these pilot trials are promising. The Pakistan data, while only descriptive, indicate that women can remain stabilized for long periods while awaiting blood transfusion, a situation typical in low-resource settings. The Egypt study was adequately powered to demonstrate a statistically significant difference in measured blood loss for women suffering obstetric hemorrhage, with symptoms of hypovolemic shock treated with the NASG and standardized hemorrhage and shock protocol compared with women with similar diagnoses and clinical symptoms treated only with standardized hemorrhage protocols. The data from Mexico are extremely preliminary, but may indicate the utility of the garment for stabilization and transport of hemorrhaging women who deliver outside of facilities and who are not attended by skilled providers. The preliminary Nigerian data also indicate promising use in facilities to which women with severe shock are brought as a last resort.

At this time, with only these pilot studies and descriptive case series, definitive evidence for the use of the NASG for management of obstetric hemorrhage and hypovolemic shock is not available. In order to demonstrate that the NASG not only decreases blood loss and facilitates resuscitation from shock, but also decreases maternal mortality and morbidity, a much larger trial with a strong experimental design is needed. Given that, the NASG is lightweight, reusable, relatively inexpensive, and can be used at the lowest level of the health-care system; it has the potential to make a great contribution to reducing maternal mortality and morbidity from obstetric hemorrhage and hypovolemic shock if it proves efficacious in clinical trials or by strong evidence from multiple quasi-experimental trials.

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15

SPECIAL CIRCUMSTANCES: JEHOVAH'S WITNESSES, THOSE WHO REFUSE BLOOD TRANSFUSION AND/OR CONSENT

J. C. W. Marsh, M. O. Elebute and D. H. Bevan

THE JEHOVAH'S WITNESSES SOCIETY

Jehovah's Witnesses (JW) belong to the religious organization, the Watch Tower Bible and Tract Society. They number an estimated 6 million world-wide, of whom 145 000 live in the UK[1]. In Australia, a 2001 population survey showed that the 81 000 JW represented 0.4% of the population[2]. JW refuse blood transfusion with the 'primary components' of blood (see below for definition) and are prepared to die rather than be transfused. Until 2000, the church would have expelled any member who had been transfused with any prohibited component of blood. Such an individual would have been ostracized and shunned by the members of the church and their family, leading to social isolation. In 2000, rejection by the church was abandoned and it was left to the individual to revoke his own membership from the Society. Although this change in policy was seen as a relaxation of the JW policy on blood transfusion, the JW Society felt that no JW would wish to dissociate themselves[3]. In practical terms, this change may mean that some JW may, in absolute medical confidentiality, accept transfusion under certain circumstances. Regardless, under British law, any competent adult has an absolute right to refuse transfusion. Readers are directed to previously published works on this area of ethics (discussed in reference 4), whereas issues of consent in adult JW are discussed later in this review. Transfusion in children of JW is not discussed in this review. Instead, the reader is referred to recent summaries[4,5] based on guidelines from the Association of Anaesthetists of Great Britain and Ireland (2005)[6] and the Royal College of Surgeons Code of Practice (2002)[7].

BLOOD 'PRODUCTS' ACCEPTABLE FOR JW

The JW Society demands that the 'primary components' of blood must be refused. These are red and white blood cells, platelets and plasma (fresh frozen plasma). Autologous blood collection and storage for later re-infusion (pre-deposit) is not acceptable to most JW as the blood is separated from the individual for a period of time by storage. In contrast, 'fractions' of plasma or cellular components such as albumin, immunoglobulins, non-recombinant clotting factors and hemoglobin-based oxygen carriers are left to individual choice ('matters of conscience'). This circumstance highlights the importance of full discussion with each individual JW patient to elucidate what may be and what may not be acceptable to them. Regardless of their personal choice, all JW will accept crystalloids, synthetic colloids (e.g. dextrans), hydroxyethylstarch and gelatins (for example Gelofusine).

During the mid-1980s, there was enormous interest in the development of red cell substitutes, as summarized in a more recent review[8]. These were either based on perfluorocarbons or hemoglobin-based oxygen carriers which used hemoglobin from one of three sources: bovine blood, outdated units of human red cells or recombinant technology. Anecdotal reports describe their use in JW patients on a compassionate basis[9,10]. Not all JW will accept them, and their use in JW would be a matter of conscience for the individual. Disappointingly, their undesirable safety profile and lack of efficacy

have meant that today only a few products are still being tested clinically and none are licensed for human use in the USA, Europe or Canada[11,12]. Similarly, none of the platelet substitutes under consideration are available for clinical use (reviewed in reference 4). These used modified platelets, infusible platelet membranes, fibrinogen-coated albumin microspheres or semi-artificial platelet substitutes such as autologous erythrocytes or liposomes. Their derivation from blood components would provide the same restrictions of acceptability to JW as other blood components.

Recombinant products are accepted by most JW, such as granulocyte-colony stimulating factor (G-CSF) used to treat neutropenia and to mobilize peripheral blood stem cells for autologous and allogeneic transplantation. Erythropoietin (rHuEPO) has been given to many JW, although some JW refuse the Epoetin-beta preparation (NeoRecormon) because it contains a trace of albumin. In contrast, Epoetin-alfa (Eprex) does not contain any albumin as an expedient. Darbepoietin-alfa is a novel erythropoiesis-stimulating factor with two additional carbohydrate side-chains and extra sialic acid residues compared to rHuEPO, resulting in a longer half-life and increased activity *in vivo*[13]. The use of rHuEPO in JW is discussed in greater detail below. The availability of recombinant factors VIII and IX permits the treatment of JW with hemophilia A and B, respectively, and desmopressin (DDAVP) for mild von Willebrand's disease.

Recombinant coagulation factor VIIa (rFVIIa; Eptacog-alfa; Novoseven: Novo-Nordisk) is licensed for treatment of hemophilia patients with inhibitors and for congenital disorders of platelet function[14,15]. The drug is also being used (off-license) to treat life-threatening hemorrhage in non-hemophilic patients[16]. In the setting of severe thrombocytopenia, if the thrombocytopenia is due to decreased production of platelets (as in leukemia and other bone marrow failures), it is anticipated that rFVIIa would be ineffective because rFVIIa needs access to platelet surfaces to prevent bleeding. In autoimmune thrombocytopenia, however, a low platelet count is hemostatically more effective as the platelets are younger and have more membrane surface, making it more responsive to rFVIIa. However, rFVIIa is currently so expensive that cost issues may act as ethical issues, given that a single dose currently costs about £3600 in the UK. Case reports of its successful use in JW to control life-threatening bleeding in idiopathic thrombocytopenic purpura[17], and to correct the coagulopathy and bleeding in liver cirrhosis[18] both exist.

In addition to fractions of blood components outlined above, the following blood maneuvers may or may not be acceptable to JW patients as a matter of individual choice ('matters of conscience'): acute normovolemic hemodilution, intraoperative and postoperative blood salvage techniques, hemodialysis and heart bypass surgery where non-blood fluids must be used to prime the pumps[19,20].

Acute normovolemic hemodilution involves removing blood from the patient at the beginning of an operation, replacing it with crystalloid or colloid, and replacing the blood (which has been kept in direct contact with the patient) near the end of surgery. Intraoperative cell salvage is often acceptable, although postoperative collection of blood from surgical drains is not acceptable. Contamination with malignant cells, bacteria and amniotic fluid may be relative contraindications. Intraoperative cell salvage has been reported in a JW with placenta previa[21]. There were no reports of amniotic fluid embolism in 174 women during Cesarean section, but with an incidence of only 1 : 8000 to 1 : 80 000 of all deliveries, this study was too small to assess the risk adequately. Nevertheless, this maneuver, if available, may be considered for JW women with a high risk of life-threatening hemorrhage.

Organ transplantation may be acceptable to JW. Although autologous blood donation is not acceptable, there are reports of autologous and allogeneic stem cell transplantation in JW[4]. Liver and pancreatic transplantations have also been performed in JW[22,23].

THE IMPACT OF WITHHOLDING BLOOD IN JW PATIENTS

Non-obstetric patients

A series of 300 JW patients accrued from multiple centers in the USA between 1981 and 1994

and undergoing surgery with a postoperative hemoglobin (Hb) < 8 g/dl showed an inverse correlation between mortality and Hb level, with a sharp rise in mortality when the Hb fell below 5–6 g/dl[24]. There were no deaths in 99 patients with a nadir Hb between 7.1 and 8.0 g/dl, but mortality rose from 8.9% with Hb levels between 6.1 and 7.0 g/dl to 100% when the nadir Hb was 1.1–2.0 g/dl. The odds of death increased 2.5 times for each gram decrease in postoperative Hb. This study, although not in patients with postpartum hemorrhage, emphasizes the fact that mortality (and morbidity) are extremely high with very low Hb levels.

In the setting of intensive care (ICU), a trend to higher mortality was observed among 21 JW patients compared with non-JW patients treated between 1999 and 2003, although APACHE II scores, APACHE II risks of death and ICU lengths of stay were similar between the two groups[2]. Of interest, three of the 21 patients had postpartum hemorrhage; of these, one died. Just over half the patients did not receive rHuEPO. The authors comment that this was not only because of patient refusal but also because of the lack of a formal protocol for managing JW patients which left the use of rHuEPO to the discretion of individual physicians. As in the previous study, no JW patient with an Hb level of < 2 g/dl survived.

A single-center study of 85 JW patients undergoing neurosurgery reported that JW patients had longer hospital stay and longer operation times, but less blood loss perioperatively[25]. The authors suggest that longer operation times may have been due to more careful and slower surgical technique. Cell salvage was used in 47% of JW compared with 4% of non-JW. There was no report of the use of rHuEPO in their patients. A similar outcome compared with non-JW patients was noted despite performing potentially hemorrhagic spinal and intracranial cerebrovascular procedures.

The treatment of hematological disorders such as leukemia in JW patients poses extreme problems because red cell and platelet transfusions are critical to support the cytopenias, which are due not only to the bone marrow failure associated with the leukemia but also due to the chemotherapy[4,26]. In most instances of acute myeloid leukemia, modified chemotherapy regimens have been used to try to reduce the risk of death from anemia or bleeding, but at the expense of either failure to achieve complete remission or early relapse of the leukemia. An exception is acute promyelocytic leukemia where the use of all-trans retinoic acid (ATRA) and arsenic trioxide can induce remissions as single agents without causing major myelosuppression[27,28]. The treatment of acute lymphoid leukemia is somewhat more successful in JW patients as the drugs are not so myelosuppressive as those used in acute myeloid leukemia.

Obstetric patients

The outcome of 332 JW women who had 391 deliveries during the period 1988–1999 was reported from Mount Sinai Hospital in New York[29]. All women were offered rHuEPO after 28 weeks if the hematocrit level was < 36%, but most refused because the drug contained albumin. Obstetric hemorrhage occurred in 24 (6%) of patients, two of whom died. The mortality rate was 521/100 000 live births, which represented a 44-fold increase compared with maternal deaths from all causes in the general obstetric population at that institution during the same time interval. In addition to the two fatal cases of postpartum hemorrhage, a third JW patient with massive postpartum hemorrhage survived; this patient chose, before the delivery, to accept blood products.

The off-label use of rFVIIa has been found effective in several reported cases of peripartum hemorrhage unresponsive to all conventional measures. These reports included women with disseminated intravascular coagulation (DIC), eclampsia or HELPP syndrome, previously considered relative contraindications to rFVIIa use. The use of rFVIIa in peripartum bleeding in the JW context has not been specifically reported, but, as a recombinant non-blood-derived hemostatic agent, it is acceptable to JW and should therefore be strongly considered in life- or function-threatening bleeding. The recommended dose is 90–100 μg/kg, rounded up to the nearest number of vials, given as an intravenous bolus. The use of rFVIIa in obstetric hemorrhage is discussed in more detail elsewhere in this book.

Published case reports of JW obstetric patients merit further discussion. Kalu and colleagues reported a triplet pregnancy in a JW woman[30]. The prophylactic antenatal use of rHuEPO at 28 weeks (600 IU/kg intravenously on three occasions over 2 weeks), along with oral iron supplementation, produced a rise in the Hb level from 11.1 to 13.2 g/dl. The patient had an uncomplicated elective Cesarean section with 500 ml estimated blood loss and Hb level of 12.2 g/dl on day 2. The authors highlighted the need for further studies to establish the safety and optimal dose of rHuEPO in pregnancy, the target Hb level and the optimal route for iron administration (see below). De Souza and colleagues report the antenatal use of rHuEPO at a dose of 50 IU/kg twice weekly from 29 weeks in a JW woman, resulting in an increase in the Hb level from 10.9 to 13.3 6 weeks later[21]. At 34 weeks, antenatal hemorrhage necessitated Cesarean section with intraoperative cell salvage. Maternal postoperative Hb level was 12.0 g/dl and recovery uneventful, despite a theoretical risk of amniotic fluid embolism (as discussed earlier). The use of rHuEPO in pregnancy is not contraindicated, as there is no evidence of harm in pregnancy. An additional advantage is that it is secreted in breast milk and stimulates erythropoiesis in premature infants when breast-fed[31]. A case in the USA reported a pregnant JW patient with placental abruption and intrauterine death at 31 weeks who developed DIC after vaginal delivery[32]. Her Hb level fell from 11.8 to 2.9 g/dl. The patient agreed to have rHuEPO and also a polymerized human Hb solution (PolyHeme) which resulted in a rise of her Hb level to 4.5 g/dl and clinical stabilization. The problems associated with the clinical development of red cell substitutes are discussed earlier.

MANAGEMENT OF ELECTIVE SURGERY

Consent and planning

The management of JW patients undergoing elective surgery has helped further the development of 'bloodless surgery' for the general population[19,20]. Important practical maneuvers include acute normovolemic hemodilution, intraoperative cell salvage, the preoperative use of rHuEPO and use of antifibrinolytic agents such as aprotonin and tranexamic acid to prevent blood loss, as well as meticulous surgical hemostasis. A major issue to address preoperatively in JW is their management of unexpected life-threatening blood loss. Before any elective surgery, it is vital that there is a formal planning meeting with the patient, involving the surgeon and anesthetist who will be performing the surgery, along with input from the hematological team. The latter member could be either a consultant hematologist or a transfusion nurse specialist who is an official member of the hospital transfusion team (see above). The main aims of this meeting are to (1) ensure the patient is fully informed of the risks of bleeding and (2) establish and document the extent of the patient's consent in terms of exactly what blood products/maneuvers are acceptable and what are not acceptable for that individual patient. Below are described the current guidelines used at our hospital (protocol of St George's Hospital, London, 2006) and updated from our previously published guidelines[4].

Guidelines for consent to elective surgery in JW patients

Early warning system

The fact that a JW patient requires an elective operation must be ascertained and communicated to the 'JW ad hoc team' (see below) at least 2 weeks (10 working days) before the operation date. Notification of less than 2 weeks before planned surgery may lead to cancellation.

The JW ad hoc team

This consists of the consultant surgeon and consultant anesthetist (key participants) and the consultant hematologist or transfusion nurse specialist (facilitator). The consultant anesthetist is self-identified as prepared to accede to the JW patient's beliefs and wishes (a list is held by the Anesthetic Office). All three consultants must have sufficient time and, ideally, concurrent time, for the preoperative meeting. This meeting is then arranged with the JW patient. If

this meeting cannot be accomplished by three working days before surgery, or if key participants (including the JW patient) cannot attend the meeting, then surgery should be cancelled.

Format of the preoperative meeting

This is flexible, but should contain the following. The patient is assured that the meeting is to formulate a plan for surgery that complies with her wishes and beliefs, and that no attempt will be made to frighten her or place her under duress. She should be asked if she has consulted the written advice of the JW Transfusion Committee on permissible products for infusion, and if she differs from the view of the JW Transfusion Committee in any respect. The duration of the meeting should be set at a maximum of 45 min except in unusual circumstances. All comments, questions and answers must be documented.

The surgeon outlines the proposed operation, describes possible complications that may result in bleeding, and reminds the patient of the ever-present risk of bleeding with any surgery. This description and its understanding by the patient are also documented. The anesthetist outlines techniques used to avoid transfusion of blood. The patient's informed consent to these matters is obtained and documented. The anesthetist asks what actions are and are not sanctioned by the patient if she is unconscious or otherwise unable to communicate and dying of unexpected blood loss, and this too is documented.

The hematologist (or transfusion nurse specialist) asks the JW patient which therapeutic agents are acceptable to infuse to support blood volume and/or hemostatic function in the event of bleeding. The written or spoken advice of the JW Transfusion Committee to the patient may be helpful at this stage (see below). The answer to this question is documented. If clinically appropriate and timely, the hematologist explains the technique of preoperative Hb enhancement using rHuEPO. If the patient accepts this therapy, clinical assessment and rHuEPO therapy (if appropriate) is arranged on the Hematology Day Unit.

At the end of the discussion, the JW patient and her supporter(s) should be asked if they have any further questions or concerns. The clinical team then agree (or disagree) with the patient to go forward with the operation on the terms agreed upon, and this commitment is documented. If the patient has made an Advance Directive, it should be read and a copy placed in the notes.

On occasion, these guidelines are difficult to achieve, as it may not always be possible for all interested parties to meet simultaneously. In this situation, the transfusion nurse specialist/hematologist and the patient can meet with the surgeon and anesthetist separately, using a single checklist form to document discussions (and results of investigations) for both consultations.

In most instances, JW patients will insist on being accompanied by either a relative or associate who is also a JW. Under such circumstances, it may then be difficult to know for certain whether peer pressure has prevented the patient from making her own decisions. Although the Association of Anesthetists of Great Britain and Ireland (AAGBI) issued guidelines in 2005[6] and state that 'it is very important to take the opportunity to see the patient without relatives or members of the local community', the patient may insist on their presence at this meeting. The patient should be offered private consultation, but, if it is declined, one has to accept her desire, as well as her written or verbal consent, as a true indication of her will.

Preoperative assessment

The patient should be seen by a hematologist to review her medical history for bleeding episodes, hypertension, previous anemia and any drug history for medications that may exacerbate bleeding, such as aspirin, non-steroidal anti-inflammatory drugs and warfarin. The presence of infection, inflammation or malignancy predicts a poor response to rHuEPO. Any evidence of anemia should be thoroughly investigated and treated preoperatively. The following investigations are recommended: full blood count, coagulation screen, serum B12, folate and ferritin, serum urea and creatinine, electrolytes and liver function.

Other practical issues

Rationalizing the frequency and volume of blood sampling is important to reduce blood loss postoperatively. The use of pediatric blood sample tubes is recommended. Postoperative folic acid should be considered when reduced oral intake is anticipated, and folinic acid used when oral intake is not possible. Iron supplementation should be used if there is postoperative bleeding. If the patient is unable to take oral iron or if rHuEPO is being used, then intravenous iron infusions, such as iron sucrose (Venofer), can be given safely. There is some evidence that intravenous iron may be more efficacious than oral iron generally when rHuEPO is used preoperatively[33] and when used in dialysis patients[34], but some centers use oral iron supplementation and only reserve intravenous iron if there is a poor response on the basis of iron studies.

Erythropoietin (rHuEPO) administration

In critically ill patients, one randomized study showed that rHuEPO significantly increased Hb levels and reduced blood transfusion requirements, although it had no impact on clinical outcome or mortality[35]. rHuEPO is effective in boosting the Hb level in individuals undergoing autologous blood donation (although this maneuver is unacceptable to JW patients). For some JW, it can be used pre- and postoperatively, or in the ante- or postnatal period. High doses are needed compared with chronic kidney disease patients. The current UK licensed dose for Eprex (Epoetin-alfa) is 600 U/kg weekly for 3 weeks and on the day of surgery. An alternative regimen is 300 U/kg given for 15 days, starting 10 days before surgery. From a practical point of view, having started on a program of rHuEPO preoperatively, it is important to ensure the date of surgery. In the event of cancellation of surgery, rHuEPO would need to be continued to avoid a fall in Hb level when it is discontinued.

Management of life-threatening bleeding in an unconscious adult JW patient

The most difficult aspect in the management of JW is when faced with an unconscious patient who is at immediate risk of dying from blood loss, whether in ICU or the Accident and Emergency department, and the relatives inform the medical team that the patient is a JW and produce an Advance Directive signed by the patient confirming his/her wish not to be transfused, even if their death is imminent from massive bleeding. A Canadian case found a doctor liable for assault when a blood product was transfused to an unconscious JW. In contrast, a British case was upheld because the patient's refusal was open to doubt, as it was potentially subject to influence by co-religionists (cases discussed in reference 4). There must be the following certainties: (1) that the patient is a committed JW, (2) they have independently and freely decided to refuse transfusion, and (3) they had considered this to the point of death at the time of making their Advance Directive. The Association of Anaesthetists of Great Britain and Ireland advise in their guidelines that, 'In the management of an unconscious patient whose status as a JW may be unknown, the doctor caring for the patient will be expected to perform to the best of his ability, and this may include the administration of blood transfusion'[6]. However, this guideline only applies when the JW status is unclear and/or the relatives/associates cannot produce an Advance Directive. The reader is also referred to The Royal College of Surgeons Code of Practice, 2002, for further discussion on this issue[7].

Described below are the current guidelines used at St George's Hospital, which were drawn up with the help of our Trust solicitors[4].

Guidelines for life-threatening bleeding in an unconscious adult JW

(1) Any documentary evidence, for example, an Advocate Directive (living will), stating that the patient will not accept blood transfusion even in the event of life-threatening bleeding, should be requested from relatives or associates of the patient and examined, if time permits.

(2) A copy should be put in the case notes and its contents respected.

(3) The doctor (who should be of Consultant status), if time permits, should discuss with

the patient's relatives the implications of withholding blood.

(4) The doctor should act in the best interests of the patient and will be expected to perform to the best of his/her ability, which may involve giving blood if steps 1, 2 and 3 are impossible.

(5) A clear and signed entry of the steps taken should be written in the patient's case notes.

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Section IV

Special preventive measures: misoprostol in action

'With the emerging evidence on the use of various routes of administration of misoprostol, particularly in the non-hospital setting, it is becoming clear that this drug should be available at the community level in the hands of trained personnel, especially where oxytocin, Uniject and other uterotonics are not present or practical for use.'

The Working Group of the Goa International Conference on the Prevention of Post Partum Hemorrhage, July 15, 2006, Goa, India

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16

MISOPROSTOL IN PRACTICE

M. Potts

Prior to the availability of misoprostol, it was impossible to carry any significant element of emergency obstetric care into homes where women deliver without a skilled birth attendant. As a low-cost, easy-to-administer, powerful uterotonic with an excellent safety profile and long shelf-life, misoprostol has a revolutionary potential to reduce death and morbidity from postpartum hemorrhage in precisely those situations where it is most common – delivery at home without a skilled birth attendant.

In a placebo-controlled, community-based trial in India, administration of 600 µg misoprostol orally immediately after delivery significantly reduced postpartum hemorrhage (see Addendum). Research in Indonesia, Nepal and elsewhere is showing that community volunteers with minimal training can teach illiterate women to self-administer misoprostol effectively and responsibly[1] (see Chapter 19). A 1000 µg rectal dose of misoprostol can be used to treat postpartum hemorrhage, in situations where an appropriate technology exists to diagnose blood loss (such as blood-soaked sarong or 'kanga'), and where births are attended by traditional birth attendants (TBAs). In Tanzania, illiterate TBAs, with a brief training, used misoprostol to bring about a highly significant reduction in the number of women who needed to be referred to hospital or receive intravenous treatment[2].

Although these measures may seem revolutionary at first glance, they should be viewed as an essential step towards a long-term strategy where all women can be delivered by a certified midwife or physician practicing active management of the third stage of labor. Over the past half-century, countries such as Sri Lanka and Thailand have brought maternal mortality to low levels by ensuring over 90% of deliveries are attended by a skilled person able to use an oxytocic, and ultimately all countries should follow such a path.

Unfortunately, rapid population growth, economic collapse and the spread of HIV/AIDS in some African countries and the endless recruitment of skilled health professions from developing to developed countries will make the road to providing comprehensive obstetric care long and slow. During this interval, widespread access to misoprostol and the education to use it safely during home births have the potential to make a significant contribution – perhaps even the single most important contribution – to reducing the global burden of deaths from postpartum hemorrhage. The only other practical intervention with the potential to reduce postpartum hemorrhage in low-resource settings is realistic access to family planning, as all women who wish to limit childbearing are at risk of postpartum hemorrhage, and the older,

higher-parity women, who have the greatest unmet need for family planning, are at even higher risk.

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Editors' Addendum

The Editors wish to bring the reader's attention to the paper referred to by Professor Potts on page 156. This paper has been published in the October 7, 2006 issue of *The Lancet*. To the Editors' knowledge, this is the largest placebo-controlled study of misoprostol for the prevention of postpartum hemorrhage, and the results showed that misoprostol significantly reduced the rate of postpartum hemorrhage in the patients who were administered this agent in comparison to the patients who received the placebo control. The full title of the paper and all authors are:

R. J. Derman[1], B. S. Kodkany[2], S. S. Goudar[2], S. E. Geller[3], V. A. Naik[2], M. B. Bellad[2], S. S. Patted[2], A. Patel[4], S. A. Edlavitch[1], T. Hartwell[5], H. Chakraborty[5], N. Moss[6]. Oral misoprostol in preventing postpartum hemorrhage in a community setting.

[1]University of Missouri-Kansas City School of Medicine; [2]Jawaharlal Nehru Medical College, Belgaum, Karnataka, India; [3]University of Illinois, Chicago College of Medicine, USA; [4]John H. Stroger Jr. Hospital of Cook County, USA; [5]Statistics and Epidemiology, RTI International; [6]National Institute of Child Health and Human Development.

17

MANAGEMENT OF POSTPARTUM HEMORRHAGE AT THE COMMUNITY LEVEL

N. Prata

The ability to manage postpartum hemorrhage at the community level is an essential element in any program to decrease maternal mortality from postpartum hemorrhage[1], as most of the deliveries in developing countries occur at home without the presence of a skilled birth attendant[2].

The efficacy, safety, and importance of misoprostol use for postpartum hemorrhage management are well established for hospital-based settings[3]. However, misoprostol's most significant impact will probably be at the household level, where most deliveries occur. Some studies have tested such technology in home births, and all of them produced encouraging results. During one intervention trial in rural Kigoma, Tanzania, Prata and colleagues demonstrated that traditional birth attendants (TBAs), who assist in most home deliveries, were able to diagnose postpartum hemorrhage and effectively and safely administer 1000 μg of rectal misoprostol to control postpartum hemorrhage[4]. Blood loss measurement was standardized by employing the traditional blood collection tool used by women in the region – the local garment that is colloquially referred to as a 'kanga'[5]. This study also showed that the ability to manage postpartum hemorrhage in home births resulted

Table 1 Controlling postpartum hemorrhage (PPH) with a 1000 μg of misoprostol (intervention) in home births, Kigoma, Tanzania

	Intervention		*Non-intervention*		*Odds ratio*	
Main outcomes of the study	*n*	%	*n*	%	(95% CI)	
PPH (blood loss ≥ 500 ml)	111	24.5	73	18.5	1.3	(1.0–1.7)
Referrals	8	1.8	75	19.0	0.1	(0.0–0.2)
Additional interventions among PPH cases	*n* = 111		*n* = 73			
Type of additional interventions[a]	1[b]	0.9	69[c]	94.5		
Intravenous fluids	1	0.9	25	34.3		
Blood transfusion	1	0.9	16	21.9		
Manual removal of placenta	0	0.0	17	23.3		
Repair of tears	0	0.0	4	5.5		
Hysterectomy	0	0.0	1	1.4		
Other medical interventions[d]	0	0.0	7	9.6		

[a]Number of cases do not add up to total referred, some women had more than one intervention; [b]hospital records not available for one patient; three patients did not need additional interventions; another three were referred for other reasons than PPH; [c]hospital records not available for four patients; four patients did not need additional interventions; two cases referred for other reasons than PPH; [d]medical interventions included: Amoxyl tablets, methergin, and misoprostol.

Source: Prata N, *et al.* Controlling postpartum hemorrhage after home births in Tanzania. *Int J Gynaecol Obstet* 2005;90:51–5

in important reductions in the number of referrals and the need for additional interventions, key factors in resource-poor settings (Table 1).This is particularly helpful in rural areas.

In settings where culturally appropriate methods of measuring blood loss after delivery are difficult to devise, all women could be administered a prophylactic dose of 600 µg misoprostol after delivery of the baby. Its safety and efficacy in the hands of TBAs were shown in a randomized, controlled trial in the Gambia[6]. In addition, in places where, for cultural or other reasons, women deliver at home alone or in the presence of a family member, self-administration of a prophylactic dose of misoprostol, distributed during pregnancy by trained community health-care workers, are both viable options that can produce promising results, as was shown in other studies in Indonesia, Nepal, and Afghanistan.

It will be many decades before all women in low-resource settings can receive skilled attention at delivery in their homes. In the meantime, misoprostol has the potential to make a significant difference in reducing maternal mortality. It should be made available for use in all settings including home births, and particularly in those where it must be self-administered.

References

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3. Villar J, Gulmezoglu AM, Hofmeyr GJ, Forna F. Systematic review of randomized controlled trials of misoprostol to prevent postpartum hemorrhage. *Obstet Gynecol* 2002;100:1301–12
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5. Prata N, Mbaruku G, Campbell M. Using the Kanga to measure postpartum blood loss. *Int J Gynaecol Obstet* 2005;89:49–50
6. Walraven G, Blum J, Dampha Y, *et al*. Misoprostol in the management of the third stage of labour in the home delivery setting in rural Gambia: a randomised controlled trial. *Br J Obstet Gynaecol* 2005;112:1277–83

18

ORAL MISOPROSTOL FOR PREVENTION OF POSTPARTUM HEMORRHAGE BY PARAMEDICAL WORKERS IN INDIA (AN ICMR TASK FORCE STUDY)

N. Chandhiok

Paramedical workers conduct deliveries in the rural areas of India where active management of the third stage of labor is not routinely practised and uterotonic agents are only provided for the management of postpartum bleeding. A multi-site, cluster-randomized, feasibility study was carried out to determine if paramedical workers from rural Peripheral Health Centers (PHCs) could actively manage the third stage of labor using oral misoprostol to prevent postpartum hemorrhage. Six hundred women each received either active management of the third stage of labor with 600 μg of oral misoprostol (intervention) or the current government guidelines for prevention of postpartum hemorrhage (controls). The primary outcome was blood loss after delivery and this was measured using a calibrated blood collection drape.

Baseline characteristics were comparable in both groups and over 70% of women had

Table 1 Outcome of intervention. Figures in parentheses are percentages

	Intervention	*Comparison*			
	Tablet misoprostol (*n* = 600)	*Injection methergine* (*n* = 531)	*Tablet methergine* (*n* = 58)	*None*† (*n* = 11)	*Total* (*n* = 600)
Duration of third stage of labor (min) (mean ± SD)	7.9 ± 4.2	11.1 ± 4.1***	9.6 ± 5.0**	5.9 ± 2.4	10.9 ± 4.3***
Blood loss (ml)					
Mean ± SD	139.7 ± 100.4	211.8 ± 80.6***	211.6 ± 83.0***	171.8 ± 178.3	211.0 ± 83.4***
Median	100	200***	200***	100	200***
Q1–Q3	90–150	150–250	150–280	100–160	150–250
Range	25–1300	30–750	25–415	100–700	25–750
Postpartum hemorrhage	4 (0.7)	4 (0.8)^{NS}	–	1 (9.1)	5 (0.8)^{NS}
Additional measures					
Uterotonics	4	2	–	1	3
Intravenous fluids	4	2	–	1	3
Blood transfusion	1	–	–	–	–
Referred to higher level of health facility for PPH	2 (0.3)	1 (0.2)		1 (0.2)	2 (0.3)

***$p < 0.001$; **$p < 0.01$ when compared with the intervention; †group was not compared with intervention due to small sample

^{NS}, not significant; PPH, postpartum hemorrhage

moderate anemia. The paramedical workers were able to provide the intervention according to the guidelines in almost all deliveries (99%). There was a significant reduction in the duration of the third stage of labor (7.9 ± 4.2 vs. 10.9 ± 4.3 min, $p < 0.001$), and the measured blood loss after delivery in the intervention group (139.7 ± 100.4 ml vs. 211.0 ± 83.4 ml, $p < 0.001$). This magnitude of reduction is significant for a country such as India where 80% of the women are anemic at the time of delivery and any reduction in blood loss is considered highly beneficial. The overall incidence of postpartum hemorrhage observed in the study was extremely low (< 1% in both groups), and the study size was not adequate to address the reduction in postpartum hemorrhage at such low incidence (Table 1).

As most deliveries in rural areas take place at home, there is a need to extend this study for all domiciliary deliveries.

ACKNOWLEDGEMENT

This communication is based on the following previously published article at the Editor's request: Chandhiok N, Dhillon BS, Datey S, Mathur A, Saxena NC. Oral misoprostol for prevention of postpartum hemorrhage by paramedical workers in India. *Int J Gynaecol Obstet* 2006;92:170–5

19

OVERVIEW OF MISOPROSTOL STUDIES IN POSTPARTUM HEMORRHAGE

A. Hemmerling

INTRODUCTION

These tables of peer-reviewed misoprostol studies were compiled to provide the reader with comprehensive references to the use of misoprostol in practice since 1997, for both prevention and treatment of postpartum hemorrhage. The tables include both randomized and non-randomized trials, and they represent a diversity of situations. Table 1 provides an overview of 32 studies in the prevention of postpartum hemorrhage (including dosage and route of administration). Table 2 gives an overview of seven studies in the treatment of postpartum hemorrhage (including dosage and route of administration).

Table 1 Misoprostol for prevention

Authors	*Institutions*	*Study title*	*Journal*	*n*	*Participants in misoprostol group*	*Dosage of misoprostol*	*Route of administration*	*Participants in control group(s)*	*Control agent(s)*
Prata N, Hamza S, Gypson R, *et al.*	Bixby Program in Population, Family Planning and Maternal Health, School of Public Health, University of California, Berkeley, USA	Misoprostol and active management of the third stage of labor	*Int J Gynaecol Obstet* 2006 Jul 6 [epub ahead of print]	2532	1189	600 µg	oral	1343	current AMTSL practices
Nellore V, Mittal S, Dadhwal V	Dept. of Obstetrics and Gynecology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India	Rectal misoprostol vs. 15-methyl prostaglandin $F_{2\alpha}$ for the prevention of PPH	*Int J Gynaecol Obstet* 2006; 94:45–6	120	60	400 µg	rectal	60	125 µg 15-methyl prostaglandin $F_{2\alpha}$ i.m.
Chandhiok N, Dhillon BS, Datey S, *et al.*	Division of Reproductive Health and Nutrition, Indian Council of Medical Research, New Delhi, India	Oral misoprostol for prevention of PPH by paramedical workers in India	*Int J Gynaecol Obstet* 2006; 92:170–5	1200	600	600 µg	oral	600	current government guidelines for PPH prevention
Zachariah ES, Naidu M, Seshadri L	Dept. of Obstetrics and Gynecology, Christian Medical College Hospital Vellore, India	Oral misoprostol in the third stage of labor	*Int J Gynaecol Obstet* 2006; 92:23–6	2023	730	400 µg	oral	[1] 617 [2] 676	[1] 10 IU oxytocin i.m. [2] 2 mg ergometrine i.v.
Garg P, Batra S, Gandhi G	Maulana Azad Medical College and Lok Nayak Hospital, Delhi, India	Oral misoprostol vs. injectable methylergometrine in management of the third stage of labor	*Int J Gynaecol Obstet* 2005; 91:160–1	200	100	600 µg	oral	100	0.2 mg methylergometrine i.v.
Ozkaya O, Sezik M, Kaya H, *et al.*	Dept. of Obstetrics and Gynecology, School of Medicine, Suleyman Demirel University, Turkey	Placebo-controlled randomized comparison of vaginal with rectal misoprostol in the prevention of PPH	*J Obstet Gynaecol Res* 2005;31: 389–93	150	[1] 50 [2] 50	400 µg	[1] rectal [2] oral	50	placebo
Hoj L, Cardoso P, Nielsen BB, *et al.*	Dept. of Obstetrics and Gynecology, Aarhus University Hospital, Denmark	Effect of sublingual misoprostol on severe PPH in a primary health center in Guinea-Bissau: randomized double-blind clinical trial	*BMJ* 2005; 331:723	661	330	600 µg	sublingual	331	placebo

Continued

Table 1 *Continued*

Authors	*Institutions*	*Study title*	*Journal*	*n*	*Participants in misoprostol group*	*Dosage of misoprostol*	*Route of administration*	*Participants in control group(s)*	*Control agent(s)*
Walraven G, Blum J, Dampha Y, *et al.*	Farafenni Field Station, Medical Research Council Laboratories, Farafenni, Gambia	Misoprostol in the management of the third stage of labor in the home delivery setting in rural Gambia: a randomized controlled trial	*BJOG* 2005; 112:1277–83	1229	630	600 µg	oral	599	2 mg ergometrine oral
Vimala N, Mittal S, Kumar S, *et al.*	Dept. of Obstetrics and Gynecology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India	Sublingual misoprostol versus methylergometrine for active management of the third stage of labor	*Int J Gynaecol Obstet* 2004; 87:1–5	120	60	400 µg	sublingual	60	0.2 mg methylergometrine i.v.
Lam H, Tang OS, Lee CP, *et al.*	Dept. of Obstetrics and Gynecology, Queen Mary Hospital, Hong Kong SAR, China	A pilot-randomized comparison of sublingual misoprostol with syntometrine on the blood loss in third stage of labor	*Acta Obstet Gynecol Scand* 2004;83: 647–50	60	30	600 µg	sublingual	30	1 ml syntometrine i.v. (5 IU syntocinone and 0.5 mg ergometrine maleate)
Caliskan E, Dilbaz B, Meydanli MM, *et al.*	SSK Maternity and Women's Health Teaching Hospital, Ankara, Turkey	Oral misoprostol for the third stage of labor: a randomized controlled trial	*Obstet Gynecol* 2003;101: 921–8	1574	388	600 µg	oral	[1] 404 [2] 384 [3] 398	[1] 600 µg misoprostol plus 10 IU oxytocin i.v. [2] 10 IU oxytocin i.v. [3] 10 IU oxytocin i.v. plus 0.2 mg methylergonovine maleate
Oboro VO, Tabowei TO	Maternity Unit, Zonal General Hospital, Kwale, Delta State, Nigeria	A randomized controlled trial of misoprostol vs. oxytocin in the active management of the third stage of labor	*Obstet Gynecol* 2003;23: 13–16	496	247	600 µg	oral	249	10 IU oxytocin i.m.
Lumbiganon P, Villar J, Piaggio G, *et al.*	Dept. of Obstetrics and Gynecology, Faculty of Medicine, Khon Kaen University, Thailand	Side-effects of oral misoprostol during the first 24 h after administration in the third stage of labor	*BJOG* 2002;109: 1222–6	1686	843	600 µg	oral	843	10 IU oxytocin i.m. or i.v.

Quiroga Diaz R, Esparaza Arechiga M, Batiza Resendiz V, *et al.*	Hospital de Ginecologia y Obstetricia de Monterrey, N. L. Mexico	Vaginal misoprostol in the prevention of PPH	*Ginecol Obstet Mex* 2002;70: 572–5	400	208	800 µg	vaginal	192	current AMTSL practices
Caliskan E, Meydanli MM, Dilbaz B, *et al.*	Social Security Council: Maternity and Women's Health Teaching Hospital, Kucukesat, Ankara, Turkey	Is rectal misoprostol really effective in the treatment of third stage of labor? A randomized controlled trial	*Am J Obstet Gynecol* 2002; 187:1038–45	1606	396	600 µg	rectal	[1] 401 [2] 407 [3] 402	[1] 10 IU oxytocin i.v. plus 600 µg misoprostol rectal [2] 10 IU oxytocin i.v. [3] 10 IU oxytocin i.v. plus 1 ml methylergometrine i.m.
Karkanis SG, Caloia D, Salenieks ME, *et al.*	University of Toronto, Toronto, Canada	Randomized controlled trial of rectal misoprostol vs. oxytocin in third stage management	*J Obstet Gynaecol Can* 2002;24: 149–54	214	110	400 µg	rectal	113	5 IU oxytocin i.v. or 10 IU oxytocin i.m.
Kundodyiwa TW, Majoko F, Rusakaniko S	Dept. of Obstetrics and Gynecology, University of Zimbabwe, Harare, Zimbabwe	Misoprostol vs. oxytocin in the third stage of labor	*Int J Gynaecol Obstet* 2001; 75:235–41	499	243	400 µg	oral	256	10 IU oxytocin i.m.
Benchimol M, Gondry J, Mention JE, *et al.*	Centre de Gynecologie Obstetrique, Amiens, France	Role of misoprostol in the delivery outcome	*J Gynecol Obstet Biol Reprod (Paris)* 2001;30: 576–83	600	200	600 µg	oral	[1] 200 [2] 200	[1] 2.5 IU oxytocin i.v. [2] placebo
Gerstenfeld TS, Wing DA	Women's and Children's Hospital, Dept. of Obstetrics and Gynecology, University of Southern California Keck School of Medicine, Los Angeles, USA	Rectal misoprostol vs. intravenous oxytocin for the prevention of PPH after vaginal delivery	*Am J Obstet Gynecol* 2001; 185:878–82	325	159	400 µg	rectal	166	20 IU oxytocin i.v.
Gulmezoglu AM, Villar J, Ngoc NT, *et al.*	WHO Collaborative Group to Evaluate Misoprostol in the Management of the Third Stage of Labour	WHO multicenter randomized trial of misoprostol in the management of the third stage of labor	*Lancet* 2001; 358:689–95	18 530	9264	600 µg	oral	9266	10 IU oxytocin i.m. or i.v.

Continued

Table 1 *Continued*

Authors	*Institutions*	*Study title*	*Journal*	*n*	*Participants in misoprostol group*	*Dosage of misoprostol*	*Route of administration*	*Participants in control group(s)*	*Control agent(s)*
Hofmeyr GJ, Nikodem VC, de Jager M, *et al.*	Dept. of Obstetrics and Gynecology, Coronation Hospital and Effective Care Research Unit, University of the Witwatersrand, Johannesburg, South Africa	Side-effects of oral misoprostol in the third stage of labor – a randomized placebo-controlled trial	*S Afr Med J* 2001;91: 432–5	600	300	600 μg	oral	300	placebo
Bugalho A, Daniel A, Faundes A, *et al.*	Maternity of the Hospital Central de Maputo, Maputo, Mozambique	Misoprostol for prevention of PPH	*Int J Gynaecol Obstet* 2001; 73:1–6	663	324	400 μg	rectal	339	10 IU oxytocin i.m.
Ng PS, Chan AS, Sin WK, *et al.*	Dept. of Obstetrics and Gynecology, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories	A multicenter randomized controlled trial of oral misoprostol and i.m syntometrine in the management of the third stage of labor	*Hum Reprod* 2001;16: 31–5	2058	1026	600 μg	oral	1032	1 ml syntometrine i.v. (5 IU syntocinone and 0.5 mg ergometrine maleate 0.5 mg)
Walley RL, Wilson JB, Crane JM, *et al.*	Dept. of Obstetrics and Gynaecology, St John's, Memorial University of Newfoundland, Canada	A double-blind placebo controlled randomized trial of misoprostol and oxytocin in the management of the third stage of labor	*BJOG* 2000; 107:1111–15	401	203	400 μg	oral	198	10 IU oxytocin i.m.
El-Refaey H, Nooh R, O'Brien P, *et al.*	Dept. of Obstetrics and Gynaecology, University College Hospital, London, UK	The misoprostol third stage of labor study: a randomized controlled comparison between orally administered misoprostol and standard management	*BJOG* 2000; 107:1104–10	1000	501	500 μg	oral	499	standard oxytocic regimens (10 IU oxytocin or 0.5 mg ergometrine or 1 ml syntometrine)
Cook CM, Spurrett B, Murray H	Dept. of Obstetrics and Gynaecology, University of Sydney at Nepean Hospital Penrith, New South Wales, Australia	A randomized clinical trial comparing oral misoprostol with synthetic oxytocin or syntometrine in the third stage of labor	*Aust N Z J Obstet Gynaecol* 1999;39: 414–19	863	424	400 μg	oral	439	standard oxytocic regimens (10 IU oxytocin i.m. or 1 ml syntometrine i.m.)

Amant F, Spitz B, Timmerman D, *et al.*	Dept. of Obstetrics and Gynaecology, University Hospitals Leuven, Belgium	Misoprostol compared with methylergometrine for the prevention of PPH: a double-blind randomized trial	*Br J Obstet Gynaecol* 1999;106: 1066–70	200	100	600 µg	oral	100	0.2 mg methylergometrine i.v.
Surbek DV, Fehr PM, Hosli I, *et al.*	Dept. of Obstetrics and Gynecology, University of Basel, Switzerland	Oral misoprostol for the third stage of labor: a randomized placebo-controlled trial	*Obstet Gynecol* 1999;94: 255–8	65	31	600 µg	oral	34	placebo
Bamigboye AA, Hofmeyr GJ, Merrell DA	Dept. of Obstetrics and Gynecology, Coronation Hospital, and University of the Witwatersrand, Johannesburg, South Africa	Rectal misoprostol in the prevention of PPH: a placebo-controlled trial	*Am J Obstet Gynecol* 1998; 179:1043–6	546	271	400 µg	rectal	275	placebo
Hofmeyr GJ, Nikodem VC, de Jager M, *et al.*	Dept. of Obstetrics and Gynaecology, Coronation Hospital and University of the Witwatersrand, Johannesburg, South Africa	A randomized placebo controlled trial of oral misoprostol in the third stage of labor	*Br J Obstet Gynaecol* 1998;105: 971–5	500	250	400 µg	oral	250	placebo
Bamigboye AA, Merrell DA, Hofmeyr GJ, *et al.*	Dept. of Obstetrics and Gynecology, Natalspruit Hospital and the University of the Witwatersrand, Johannesburg, South Africa	Randomized comparison of rectal misoprostol with syntometrine for management of third stage of labor	*Acta Obstet Gynecol Scand* 1998;77: 178–81	491	241	400 µg	rectal	250	1 ml syntometrine i.m. (5 IU syntocinone and 0.5 mg ergometrine maleate 0.5 mg)
El-Refaey H, O'Brien P, Morafa W, *et al.*	Dept. of Obstetrics and Gynaecology, University College Hospital, London, UK	Use of oral misoprostol in the prevention of PPH	*BJOG* 1997; 104:336–9	237	237	600 µg	oral	0	–

PPH, postpartum hemorrhage

Table 2 Misoprostol for treatment

Authors	*Institutions*	*Study title*	*Journal*	*n*	*Participants in misoprostol group*	*Dosage of misoprostol*	*Route of administration*	*Participants in control group(s)*	*Control agent(s)*
Prata N, Mbaruku G, Campbell M, *et al.*	Bixby Population Program, School of Public Health, University of California, Berkeley, USA	Controlling PPH after home births in Tanzania	*Int J Gynaecol Obstet* 2005; 90:51–5	849	454	1000 µg	rectal	395	current practices
Walraven G, Dampha Y, Bittave B, *et al.*	Reproductive Health Programme, Medical Research Council Laboratories, Farafenni, The Gambia, South Africa	Misoprostol in the treatment of PPH in addition to routine management: a placebo randomized controlled trial	*BJOG* 2004; 111:1014–17	160	79	600 µg	200 µg oral and 400 µg sublingual	81	placebo
Hofmeyr GJ, Ferreira S, Nikodem VC, *et al.*	Effective Care Research Unit, University of Witwatersrand and Fort Hare, and East London Hospital Complex, East London, South Africa	Misoprostol for treating PPH: a randomized controlled trial [ISRCTN72263357]	*BMC Pregnancy Childbirth* 2004;4:16	238	117	1000 µg	200 µg oral and 400 µg sublingual and 400 µg rectal	121	placebo
Shojai R, Desbriere R, Dhifallah S, *et al.*	Service de gynecologie-obstetrique, CHU Nord, Marseille, France	[Rectal misoprostol for PPH]	*Gynecol Obstet Fertil* 2004; 32:703–7	41	41	1000 µg	rectal	0	–
Lokugamage AU, Sullivan KR, Niculescu I, *et al.*	Dept. of Obstetrics & Gynaecology, Royal Free and University College London School, London, UK	A randomized study comparing rectally administered misoprostol versus Syntometrine combined with an oxytocin infusion for the cessation of primary PPH	*Acta Obstet Gynecol Scand* 2001;80: 835–9	64	32	800 µg	rectal	32	1 ml syntometrine i.m. (5 IU syntocinone and 0.5 mg ergometrine maleate) plus 10 IU oxytocin i.v.
Abdel-Aleem H, El-Nashar I, Abdel-Aleem A	Dept. of Obstetrics & Gynecology, Faculty of Medicine, Assiut University, Assiut, Egypt	Management of severe PPH with misoprostol	*Int J Gynaecol Obstet* 2001; 72:75–6	18	18	600 µg or 1000 µg	rectal	0	–
O'Brien P, El-Refaey H, Gordon A, *et al.*	Dept. of Obstetrics and Gynaecology, University College Hospital, London, UK	Rectally administered misoprostol for the treatment of PPH unresponsive to oxytocin and ergometrine: a descriptive study	*Obstet Gynecol* 1998;92: 212–14	14	14	1000 µg	rectal	0	–

PPH, postpartum hemorrhage

Section V

Hospital preparation

20

RESUSCITATION

M. J. Cowen

INTRODUCTION

The key feature of all resuscitation efforts is the early recognition and management of hypovolemic shock with an overall objective of restoring the circulating blood volume to maintain normal tissue perfusion and oxygenation.

The reason for the high mortality associated with obstetric hemorrhage is simple, i.e. the delayed recognition of hypovolemia and failure to provide adequate volume resuscitation. Common problems include the failure to recognize risk factors, frequent under-estimation of the degree of blood loss, and failure to involve key personnel early enough. These problems can be operational even in developed nations, such as the UK and the US[1–3].

GENERAL CONSIDERATIONS

All resuscitation strategies include two principal objectives:

(1) Achievement of hemostasis by arresting the source of bleeding by whatever means necessary, including surgical intervention with or without anesthesia;

(2) Restoration of an adequate circulating blood volume by maintaining a normal blood pressure and urine output (> 30 ml/h in adults) (0.5 ml/kg/h).

The early recognition of problems followed by an immediate response is of paramount importance, as mobilization of the key personnel and equipment takes time. It is not possible for one individual to do all the necessary work and there is no place for acting solo in isolation. Key players must include senior obstetricians, midwives, anesthetists, hematologists and laboratory staff in the blood bank, all of whom must be alerted at an early stage, as any undue delay or failures of communication at the initial stage will invariably result in a poor outcome. In particular, the prompt involvement of experienced senior anesthetists is mandatory along with intensive care back-up facilities (see Chapters 13 and 22).

The most important first step is to secure good venous access whilst veins are still available and before shut-down occurs, preferably by two large-bore cannulae, i.e. 14 gauge (flow rate 315 ml/min) or 16 gauge (210 ml/min). The importance of cannula size and flow rate cannot be overstated, and all too often very small cannulae are inserted with poor flow rates (e.g. 20 gauge cannula flow rate = 65 ml/min) with disastrous results. In those circumstances where veins are collapsed, however, a small cannula is better than nothing.

The use of a cannula and fluid infusion are the mainstay of treatment. Most of the other activities required, including monitoring and laboratory sampling, whilst important are not actually treatment. It is easy in the busyness of the emergency scene to be distracted by these peripheral activities at the expense of treatment, i.e. intravenous fluid therapy, and it is important for the team leader to keep a sense of perspective if there is to be a good outcome.

The second most important step is to send an urgent blood sample to the laboratory for baseline readings of full blood count, including hemoglobin, hematocrit and platelet count, plus clotting tests, including prothrombin time (PT), activated partial thromboplastin time (APTT) and fibrinogen levels as a baseline. A biochemical profile and blood gas analysis are also useful, especially to measure the level of acidosis and base deficit. Because of the often rapid changes occurring, it is essential throughout the episode

to keep close liaison with hematologists and the blood transfusion laboratory.

Observations, monitoring and readings must be kept continuously, preferably by a team member or midwife solely dedicated to this activity. The most useful parameter of all is the trend recorded on the basic TPR observation chart, with particular attention to pulse rate, blood pressure and urine output, because these will provide the overall picture at a glance.

In severe cases, a central line, preferably multi-lumen, inserted in the neck, subclavian or femoral zones is invaluable, not only for monitoring of central venous pressure as a guide to hypovolemia and as an assist in determining infusion requirements, but also as a good venous access for rapid infusion especially when peripheral veins are not available or collapse. In most instances, this is not a first priority, especially considering that routine labor ward personnel may not have the skill to perform this safely.

Insertion of an arterial line is useful to monitor blood gases, acidosis, and base deficit, and also to serve as a direct dynamic blood pressure monitor in the intensive care situation. This too is not, however, a priority in the immediate management, although it will be useful later, especially in severe cases. Not all patients require blood and, in deciding which fluid to use, the hazards and risks of blood transfusion warrant an initial attempt to correct hypovolemia using crystalloid or colloid solutions.

Having said this, many patients will require rapid infusion. Proper equipment must be readily available and include a rapid infuser pump and/or pressure infusion bags, and preferably an individual team member dedicated to this activity. It is also important for all fluids to be warmed since the rapid infusion of cold fluids will create hypothermia and increase the chances of disseminated intravascular coagulation and clotting failure.

THE RECOGNITION OF HYPOVOLEMIA

The loss of circulating blood volume results in the signs of tachycardia, hypotension and oliguria. The most dangerous feature of postpartum hemorrhage is that there may be little apparent fall in blood pressure until a very late stage. This is because most patients are often young and previously fit and their cardiovascular system will compensate until a very late stage when it suddenly crashes and decompensates.

Table 1 shows a useful staging of schemes to assess the degree of obstetric hemorrhage.

In cases of severe shock, blood transfusion will normally be required if 30–40% of blood volume is lost, whilst, if over 40% blood volume is lost, the situation is immediately life-threatening[4].

TRANSFUSION CONSIDERATIONS

Blood transfusions are not without risk and it is essential that they are restricted to those in real need. Because of the known risks, which include incompatibility reactions, and infectious disease transmission, an initial attempt to correct hypovolemia should be made by using crystalloid solutions (e.g. normal saline, Ringers lactate) or colloids (gelatins, starches).

No absolute parameters can help one to decide when to start transfusing blood but clinical commonsense indicates that blood should be strongly considered after 2 liters of crystalloid and 1 liter colloid have been given if the cardiovascular system remains unstable with continued bleeding.

Blood will invariably be required if > 40% blood volume is lost, which correlates in a 70 kg adult to approximately 2.5 liters measured blood loss.

More precise arbiters are the measurement of hemoglobin and hematocrit decrease, results of which can be available almost immediately using rapid I-stat analyzers. The long-standing practice tradition that suggested that ideally the hemoglobin should be maintained at a level of 10 g/dl has changed, with rising awareness of infection risks from donated blood products, and this has led to a re-evaluation of requirements[5–7]. Recent work shows that healthy patients can tolerate a hemoglobin concentration as low as 7 g/dl[8]. Oxygen delivery will still be maintained as long as the patient is normovolemic. More recently, the American Society of Anesthesiologists Taskforce on Blood

Table 1 Staging scheme for assessment of obstetric hemorrhage

Severity of shock	*Findings*	*% blood loss*
None	None	< 15–20%
Mild	Tachycardia (< 100 bpm) Mild hypotension Peripheral vasoconstriction	20–25%
Moderate	Tachycardia (100–120 bpm) Hypotension (systolic blood pressure 80–100 mmHg) Restlessness Oliguria	25–35%
Severe	Tachycardia (> 120 bpm) Hypotension (systolic blood pressure < 60 mmHg) Altered consciousness Anuria	> 35%

From Gonik B. Intensive care monitoring of the critically ill patient. In Creasy RK, Resnik R, eds. *Maternal-Fetal Medicine*, 3rd edn. Philadelphia: WB Saunders, 1994:865–90

Component Therapy concluded that transfusion is rarely indicated when the hemoglobin level is > 10 g/dl, but almost always indicated when it is < 6 g/dl[9]. It therefore seems reasonable to conclude that transfusion should be commenced in most obstetric patients after a postpartum hemorrhage if the hemoglobin level falls below 7 g/dl[10], but that may be difficult to assess in real time under emergency situations.

In these circumstances, it is useful to have an agreed Action Plan posted in the labor and delivery ward, as published guidelines on transfusion practice are not easily referred to in the emergency situation[11–13]. As an example, Table 2 is an example of current practice which is in use at the author's hospital (taken from a national guideline[14] with local modifications[15]).

ADDITIONAL CONSIDERATIONS FOR BLOOD PRODUCTS

Additional discussion is provided in Chapter 25.

Red cells

If blood is required instantly, it may be necessary to use the emergency supply of Group O Rh(D)-negative uncross-matched stock, but preferable to wait 5–10 min for type-specific blood, or in appropriate cases for 20–30 min for fully cross-matched blood. In general, one unit of red cells increases the hemoglobin by approximately 1.5 g/dl and the hematocrit by 5% in a 70 kg woman. In the dynamic bleeding situation, however, it is appropriate to calculate transfusion requirements so as to restore the hemoglobin to approximately 10 g/dl, albeit using blood conservatively.

Platelets

Platelets should be transfused only to prevent or correct bleeding associated with a decrease in platelet count or abnormality of platelet function as they are difficult to store and in short supply[16].

Fresh frozen plasma

Fresh frozen plasma (FFP) maintains the viability of all clotting factors. The only clear indication for FFP is the replacement of coagulation factors in clotting disorders[17]. FFP should be given if the PT and APTT exceed 1.5 times the control level in the presence of continuous bleeding. In situations with massive bleeding, however, it may be necessary to give FFP even before clotting results are available. The dose required is 12–15 ml/kg or normally 4 units for

Table 2 Acute massive blood loss: a template guideline

Immediate actions	*Key points*	*Other considerations*
• Arrest bleeding	• Early surgical or obstetric intervention • Upper G/I tract procedures • Interventional radiology	
• Contact key personnel	• Most appropriate surgical team • Duty anesthetist • Blood bank	
• Restore circulating volume N.B. In patients with major vessel or cardiac injury, it may be appropriate to restrict volume replacement after discussion with surgical team	• Insert wide-bore peripheral cannulae • Give adequate volumes of crystalloid/blood • Aim to maintain normal blood pressure and urine output > 30 ml/h in adults (or 0.5 ml/kg/h)	• Blood loss is often underestimated • Refer to local guidelines for the resuscitation of trauma patients and for red cell transfusion • Monitor CVP if hemodynamically unstable
• Request laboratory investigations	• FBC, PT, APTT, fibrinogen; blood bank sample, biochemical profile, blood gases • Repeat FBC, PT, APTT, fibrinogen every 4 h, or after one-third blood volume replacement, or after infusion of FFP	• Take samples at earliest opportunity as results may be affected by colloid infusion • Misidentification is most common transfusion risk • May need to give FFP & platelets before the FBC and coagulation results available
• Request suitable red cells N.B. All red cells are now leukocyte-depleted. The volume is provided on each pack, and is in the range of 190–360 ml	• *Blood needed immediately* – use 'Emergency stock' group O Rh (D)-negative • *Blood needed in 5–10 min* – type-specific will be made available to maintain O Rh (D)-negative stocks • *Blood needed in 30 min or longer* – fully cross-matched blood will be provided	• Contact blood transfusion laboratory or oncall BMS and provide relevant details • Collect sample for group and cross-match before using emergency stock • Blood warmer indicated if large volumes are transfused rapidly
• Consider the use of platelets	• Anticipate platelet count < 50×10^9/l after > 2 liters blood loss with continued bleeding • Dose: 10 ml/kg body weight for a neonate or small child, otherwise one 'adult therapeutic dose' (one pack)	• Target platelet count:- > 100×10^9/l for multiple/CNS trauma > 50×10^9/l for other situations • Consider early use of platelets if clinical situation indicates continued excessive blood loss despite the count
• Consider the use of FFP	• Anticipate coagulation factor deficiency after > 2 liters blood loss with continued bleeding • Aim for PT & APTT < 1.5 × mean control • Allow for 20-min thawing time • Dose: 12–15 ml/kg body wt = 1 liter or 4 units for an adult	• PT/APTT > 1.5 × mean control correlates with increased surgical bleeding • May need to use FFP before laboratory results available: take sample for PT, APTT, fibrinogen before FFP transfused

continued

Table 2 *Continued*

Immediate actions	*Key points*	*Other considerations*
• Consider the use of cryoprecipitate	• To replace fibrinogen & FVIII • Aim for fibrinogen > 1.0 g/l • Allow for 20-min thawing time • Dose: 10 packs or 1 pack/10 kg in children	• Fibrinogen < 0.5 strongly associated with microvascular bleeding
• Suspect DIC	• Treat underlying cause if possible	• Shock, hypothermia, acidosis, risk of DIC • Mortality if DIC is high

For abbreviations, see text

an adult, and the objective should be to aim for a PT and APTT less than 1.5 control level. FFP requires a thawing time of 20 min, and hence early anticipation of a potential requirement is helpful.

Cryoprecipitate

It is appropriate to administer cryoprecipitate which contains fibrinogen and factor VIII when there is evidence of a consumptive coagulopathy with a fibrinogen level less than 0.5 g/l. The normal dose is 10 units. As with FFP, cryoprecipitate needs thawing time. The aim is to restore the fibrinogen level to > 1.0 g/l.

Coagulopathy

Coagulopathy can develop rapidly in an obstetric patient. Confirmatory laboratory tests are required for precise diagnosis, but in the clinical setting of postpartum hemorrhage the presence of microvascular bleeding is a good clinical indicator[18,19]. Absence of clotting with continued bleeding strongly suggest a coagulopathy. Hemostasis is normally adequate when clotting factors are greater than 30% of normal[18–21]. If bleeding continues in the presence of clotting factors > 30% normal and a PT and APTT less than 1.5 times control level, it is unlikely that low coagulation levels are responsible[18,19].

Disseminated intravascular coagulopathy

Disseminated intravascular coagulopathy (DIC) represents the most deadly form of coagulopathy wherein a vicious cycle consumes clotting factors and platelets rapidly. DIC can develop dramatically in obstetric patients, especially in association with placental abruption and amniotic fluid embolism. It also occurs suddenly after massive bleeding with shock, acidosis and hypothermia. This latter risk emphasizes the importance of warming all infused fluids whenever possible. DIC carries a high mortality and, once established, can be difficult to reverse. Patients with prolonged hypovolemia are particularly at risk. The diagnosis can be made by frequent estimation of platelets, fibrinogen, PT and APTT. Treatment consists of administering platelets, FFP and cryoprecipitate sooner rather than later.

Complications of blood transfusion

Increasing awareness of the risks of transfusion has led to diminished use of blood and blood products in recent years. Complications can occur because of incompatibility, storage problems, and transmission of infection.

The most common cause of a transfusion-related death is incompatibility leading to a hemolytic reaction[22]. Most of such deaths are due to misidentification and are entirely preventable, emphasizing the importance of safe systems for cross-checking all blood products.

Storage problems include hyperkalemia, as potassium levels rise in stored blood which, if given rapidly and repeatedly, can give rise to hyperkalemia, especially in an acidotic, hypothermic patient. Similarly, hypothermia can increase if large volumes of cold stored blood are given rapidly without a blood warmer.

The transmission of infection is arguably the most feared complication especially in terms of HIV, hepatitis B and C and cytomegalovirus (CMV). Estimated HIV transmission risks vary widely from 1 in 200 000 to 1 in 2 000 000 transfusions[23]. But the most common transmission is of viral hepatitis, although this is decreasing with improved screening. Currently, the incidence is 1 per 103 000 units of blood transfused[23]. CMV is carried in asymptomatic donors in the neutrophil. CMV infection can be prevented by using CMV-negative blood or by eliminating neutrophils from donor blood[24].

Alternatives to transfusion

Three alternative methods of autologous transfusion are presently available: preoperative donation antepartum, perioperative cell salvage, and hemodilution. Rarely, if ever, are these feasible in the unexpected massive postpartum hemorrhage, but they nevertheless merit consideration especially when treating patients who are adherent to the Jehovan Witness belief.

Antepartum donation may be considered for high-risk patients and for those with rare blood types, but it is recommended that, before donation, the hemoglobin should not be less than 11 g/l and the hematocrit 33%[25–27]. However, many obstetric patients may not be able to donate more than one unit of blood, whereas most patients requiring blood after postpartum hemorrhage require considerably more than one unit and thus would need homologous blood. Furthermore, such patients are difficult to predict. Accordingly, preoperative donation may not be beneficial or even cost-effective taking into account the low frequency of blood transfusion even in high-risk patients and the difficulty of predicting these in advance[27].

Perioperative blood salvage is a technique of scavenging blood lost during an operation, washing it and then transfusing the scavenged red cells[28]. Of concern is that washing may not adequately remove amniotic fluid and fetal debris which, when re-transfused, may precipitate the anaphylactoid amniotic fluid embolism response. Blood salvage may nevertheless be appropriate in cases of massive obstetric hemorrhage when blood bank resources are limited. Where the technique is available, it should also be considered for Jehovah Witness patients (see Chapter 15 for full discussion of perioperative salvage).

In the technique of hemodilution, 500–1000 ml blood may be collected and reinfused later; however, overall experience in massive postpartum hemorrhage is limited[29,30].

ANESTHETIC CONSIDERATIONS

Postpartum hemorrhage is the most frequent reason for emergency surgery and anesthesia in the postpartum period. The principal causes include uterine atony, trauma, retained placenta and uterine inversion, all of which are discussed in detail in other parts of this book. A large proportion of these will require anesthesia as part of the therapy to arrest the hemorrhage.

The choice of anesthetic will be dictated by circumstances, the degree of blood loss and the urgency of the situation. A general anaesthetic is preferable in most instances of significant postpartum hemorrhage with hypovolemia. The problem in using a regional block is that unrecognized hypovolemia in combination tends to aggravate hypotension and increase maternal morbidity and mortality. However, if a patient is already receiving a regional block (spinal or epidural), bleeding is controlled and the cardiovascular system stable, it may be appropriate to continue with a regional technique. If instability occurs in such circumstances, early conversion to a general anesthetic is indicated.

Crucial items for the safe conduct of an anaesthetic include the involvement of experienced senior/consultant anesthetists and additional helpers, pre-sited two wide-bore cannulae, knowledge of hemoglobin/hematocrit levels, rapid infusion devices and fluid warmers, immediate availability of crystalloid and colloid infusions and, as soon as possible, blood and blood products especially FFP, and, finally, available equipment for central venous access and direct arterial line monitoring.

A suitable general anesthetic technique includes pre-oxygenation and rapid sequence induction with cricoid pressure using either thiopentone in reduced dose (e.g. 4 mg/kg) or ketamine (1 mg/kg) or etomidate (0.2 mg/kg), followed by intubation after suxamethonium. Maintenance agents will include further muscle

relaxants (e.g. rocuronium 0.6 mg/kg) with nitrous oxide, oxygen and either a very low concentration of volatile anesthetic (e.g. isoflorane) to combat awareness, or possibly opiates such as fentanyl, alfentanil or remifentanil.

In some circumstances, e.g. uterine inversion where intensive relaxation is required, an additional volatile agent may be helpful. Equipotent doses of all volatile halogenated agents produce similar degrees of uterine relaxation[31,32]. Other alternatives include use of nitroglycerine given intravenously[33,34].

CARDIOPULMONARY RESUSCITATION

The prognosis is poor in the event of cardiac arrest in a patient with severe hypovolemia after a postpartum hemorrhage because of hypoxemia and rapidly accelerating acidosis. Nevertheless, most patients are young and previously fit, as no attempts should be spared to resuscitate.

Cardiac arrest will present with sudden loss of consciousness, absent major pulses and absent respiration. Response needs to be immediate to have any chance of success and should follow the agreed Cardiac Arrest Procedure along conventional lines in three phases, e.g. UK Resuscitation Guidelines as in Figures 1 and 2.

(1) Basic life support – the ABC system. This includes Airway control, Breathing support and Circulatory support.

(2) Advanced life support. This includes intubation and ventilation, continued circulatory support often with epinephrine (adrenaline), defibrillation and ECG monitoring, drugs and fluids, and management of complex arrhythmias.

(3) Prolonged life support, including all intensive care systems.

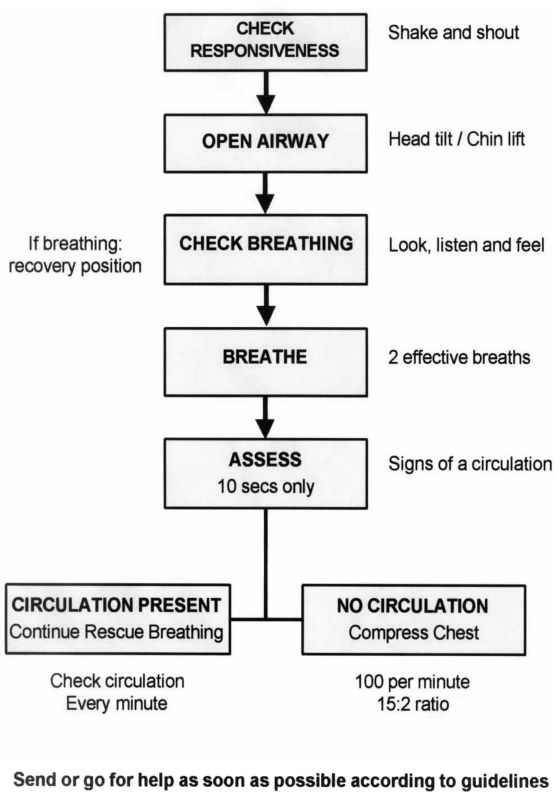

Figure 1 Adult basic life support (Resuscitation Council, UK)

Three items are of crucial importance:

(1) External cardiac massage must be commenced without delay if there are no palpable major pulses;

(2) Adrenaline 1 mg given every 3 min will frequently be required;

(3) Given that the root cause of the arrest is hypovolemia, vigorous attempts to restore a circulatory blood volume must be continued throughout the cardiopulmonary resuscitation process if there is to be any chance of success.

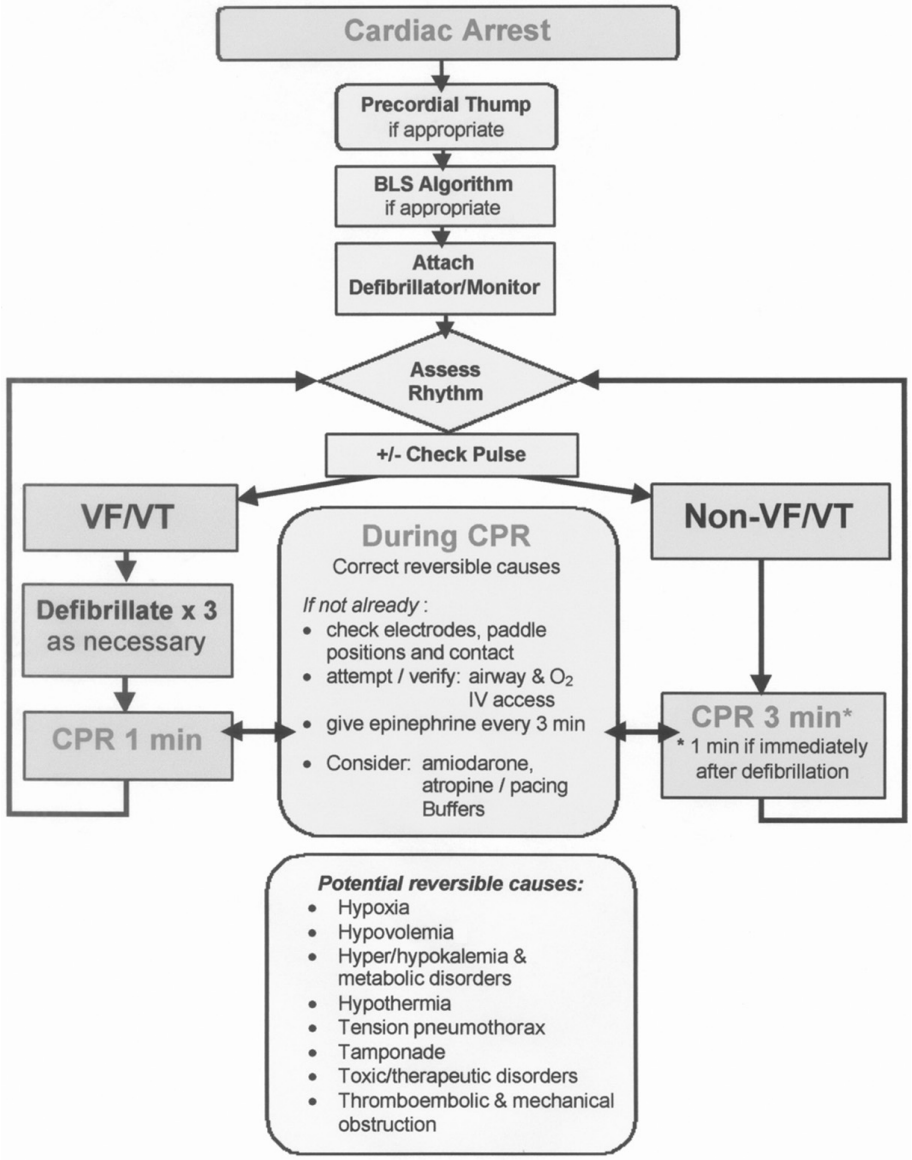

Figure 2 Advanced life support algorithm for the management of cardiac arrest in adults (Resuscitation Council UK). BLS, basic life support; VF, ventricular fibrillation; VT, ventricular tachycardia; CPR, cardiopulmonary resuscitation; ETT, endotracheal tube

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21

EQUIPMENT TRAY FOR POSTPARTUM HEMORRHAGE

T. F. Baskett

Primary postpartum hemorrhage is most often due to uterine atony which usually responds to the appropriate application of oxytocic drugs. In a minority of cases, however, the atonic uterus will not contract with any uterotonic agents, particularly in cases of prolonged and augmented labor with an exhausted and infected uterus. In these instances, a variety of surgical techniques may be necessary, including uterine tamponade with packing[1] or balloon devices[2–4], uterine compression sutures[5–8], major vessel ligation[9,10], and hysterectomy, all of which are discussed in detail in other chapters of this book. In addition to uterine atony unresponsive to oxytocic agents, numerous other causes of postpartum hemorrhage may require surgical intervention with more equipment than is available in the standard vaginal delivery or Cesarean section packs. These include high vaginal or cervical lacerations with poor exposure, placenta previa and/or placenta accreta at the time of Cesarean section, and uterine rupture. In most obstetric units, and for the individual obstetrician and nursing personnel who work there, the additional equipment and instruments for these surgical techniques are rarely used. Thus, when they are needed they may not be readily available and valuable time will be lost searching for them. For these reasons, every obstetric unit should have a readily available, sterile 'obstetric hemorrhage equipment tray' upon which is placed all the necessary material for surgical management of postpartum hemorrhage.

Experience with one such equipment tray in a large Canadian unit has shown it is used in about 1 in 250 Cesarean deliveries and 1 in 1000 vaginal deliveries[11]. The most common surgical techniques that called for use of the tray were uterine compression sutures, uterine tamponade, uterine and ovarian artery ligation, and suture of cervical and/or vaginal lacerations[11]. The most common predisposing causes of its use were placenta previa, with or without partial accreta, and uterine atony refractory to oxytocic agents[11].

The contents of an obstetric hemorrhage tray are shown in Table 1. As individual obstetric units undoubtedly have a varying availability of supplies, local conditions may modify these contents. Three vaginal retractors are necessary for access to and exposure of high vaginal and or cervical lacerations. Heaney or Breisky–Navratil

Table 1 Contents of obstetric hemorrhage equipment tray

Access/exposure
- Three vaginal retractors (Heaney, Breisky–Navratil)
- Four sponge forceps

Eyed needles
- straight 10 cm
- curved 70–80 mm, blunt point

Sutures
- No. 1 polyglactin (vicryl)
- O and No. 2 chromic catgut with curved needle
- Ethiguard curved, blunt point monocryl

Uterine/vaginal tamponade
- Vaginal packs
- Kerlix gauze roll
- Uterine balloon (depending on local availability): Sengstaken–Blakemore, Rüsch urological balloon, Bakri balloon, surgical glove and catheter, condom and catheter

Diagrams (Figures 1–4)
Pages with diagrams and instructions:
- Uterine and ovarian artery ligation
- Uterine compression suture techniques: B-Lynch, square and vertical

vaginal retractors are suitable for this purpose. Four sponge forceps are useful to identify and compress cervical lacerations, to provide compression to the edges of extensive vaginal lacerations or to uterine edges at the time of laparotomy for uterine rupture. Standard packaged suture material often contains needles that are too small for the placement of uterine compression sutures. Thus, a pair of eyed needles, preferably blunt point, one straight Keith 10 cm and one 70–80 mm curved, are advisable. A number of standard sutures should also be included: No. 1 polyglactin (vicryl) has a small needle but the vicryl can be cut off and inserted into the eyed needles. For the full B-Lynch compression suture, two of the standard suture lengths of vicryl may need to be tied together. If available, Ethiguard monocryl on a curved blunt point needle is ideal for the B-Lynch compression suture. The standard O and No. 2 chromic needles are suitable for uterine and ovarian artery ligation. For the vertical uterine compression sutures and square uterine compression sutures, the straight 10-cm needle threaded with No. 1 vicryl is appropriate.

Material and equipment for uterine and vaginal tamponade should be provided. For vaginal tamponade, which may be necessary to prevent hematoma formation following the suture of extensive vaginal lacerations, standard vaginal packing should suffice, although it may be necessary to tie more than one of these packs together. For packing the uterine cavity, standard vaginal packing tied together can be adequate, but the ideal is a kerlix gauze roll which has a thicker six-ply gauze than the four-ply of the usual vaginal pack. In recent years, balloon tamponade has also been used for uterine atony unresponsive to oxytocic drugs following vaginal delivery. A variety of balloon devices have been used, including the Sengstaken-Blakemore tube[2], the Rüsch urological balloon[4] and the Bakri balloon[3] – the latter is commercially available (see Chapters 28 and 29). Others have improvised, for example using a surgical glove tied at the wrist around a plain urethral catheter which, when filled with water or saline, will mould to the contour of the uterus[11]. A condom has also been adapted for this purpose[12]. Depending on local availability, one or more of these balloon tamponade kits should be provided on the tray.

Because uterine compression sutures will rarely be used by an individual obstetrician and the technique may be forgotten, it is useful to have diagrams, which can be easily sterilized and included in the tray or placed on a wall chart under glass (Figures 1–4)[11].

For postpartum hemorrhage due to uterine atony refractory to oxytocic agents, or secondary to trauma of the genital tract, the rapid application of surgical techniques for hemostasis is essential to reduce the need for blood transfusion, with its inherent potential morbidity. Often hysterectomy is the final definitive treatment and may be necessary as a life-saving

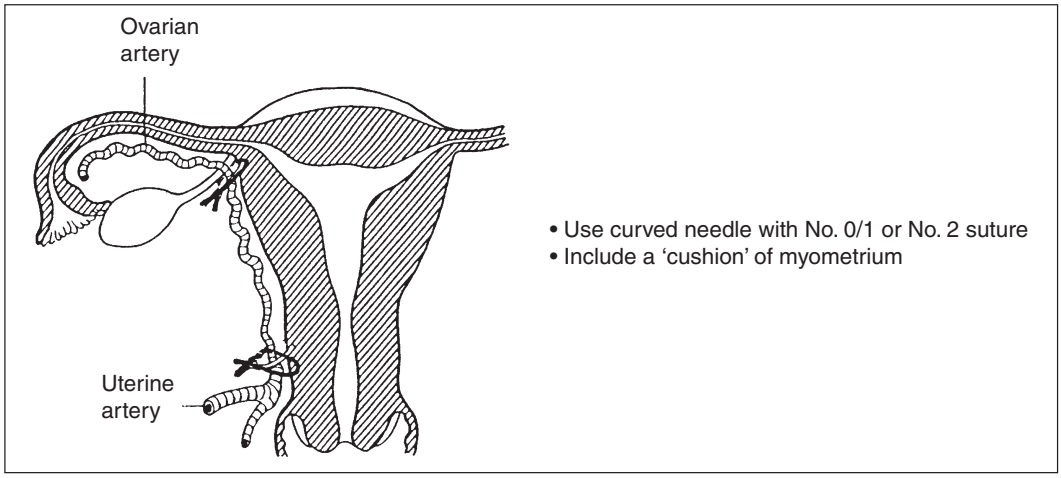
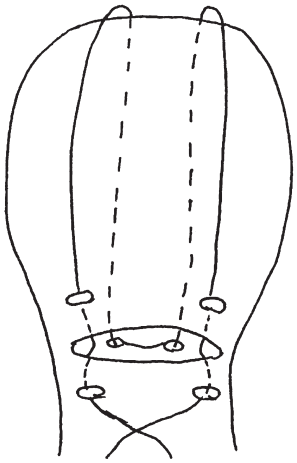
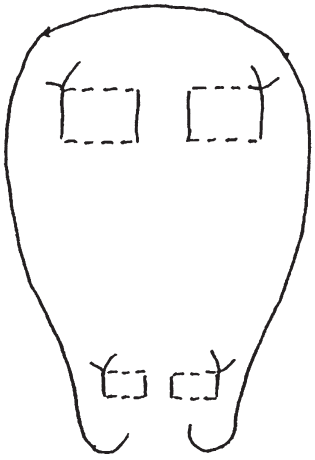


Figure 1 Uterine and ovarian artery ligation



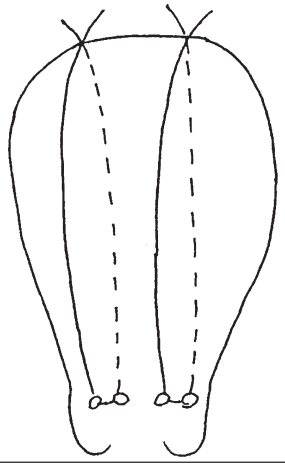
- For use with lower segment Cesarean incision
- Use large curved needle with No. 1 or No. 2 suture
- Can use large 3/8 circle curved cutting needle for same technique without Cesarean incision
- Or use Ethiguard curved blunt point monocryl
- Check that compression sutures have worked by observing blood loss p.v. before closing the abdomen

Figure 2 Uterine compression sutures: B-Lynch technique



- Suture through and through with straight 10-cm Keith needle
- Multiple square sutures may be used to cover the whole body of the uterus; may be useful for placenta previa (make sure to leave a drainage portal)
- Sub-endomyometrial injections of 1–2 ml of dilute vasopressin (5 units in 20 ml saline) may reduce local bleeding in the lower uterine segment
- Check that compression sutures have worked by observing blood loss p.v. before closing the abdomen

Figure 3 Uterine compression sutures: square



- Alternative to the B-Lynch technique if no lower segment Cesarean incision
- May be placed without opening the uterus using straight 10-cm Keith needle
- Ensure downward bladder retraction
- Two to four vertical sutures may be placed
- Check that compression sutures have worked by observing blood loss p.v. before closing the abdomen

Figure 4 Uterine compression sutures: vertical

maneuver. However, hysterectomy was avoided in all instances in one hospital using an obstetric hemorrhage tray on nine occasions in 1 year[11]. Thus, if the instruments and equipment are readily available for the rapid application of alternative surgical methods, then one is less likely to have resort to hysterectomy with its attendant morbidity and fertility-ending implications.

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22

BUILDING HOSPITAL SYSTEMS FOR MANAGING MAJOR OBSTETRIC HEMORRHAGE

D. W. Skupski, G. S. Eglinton, I. P. Lowenwirt and F. I. Weinbaum

INTRODUCTION

Maternal death from major obstetric hemorrhage is a leading killer of women world-wide, as most of the chapters in this book amply demonstrate. Attention to this topic is not glamorous, unfortunately, but few topics can be more important in improving the health of reproductive-aged women throughout the world. This chapter demonstrates a proven, in-hospital approach to decreasing morbidity and mortality of women with major obstetric hemorrhage[1]. The program hinges on building, developing and improving existing hospital systems that are necessary for the care of such women.

BACKGROUND

In the United States, the need for Cesarean hysterectomy as well as the incidence of major obstetric hemorrhage have both increased in recent years[2–4], most likely due to the known increase in Cesarean and repeat Cesarean delivery with their respective increases in placenta previa and accreta, especially in patients undergoing repeat Cesarean delivery[2–4]. In the setting of intractable obstetric hemorrhage, emergency peripartum hysterectomy is used as a life-saving procedure. According to one recent article, the incidence of emergency peripartum hysterectomy is approximately 2.5/1000 deliveries[3] and hemorrhage associated with uterine atony is the most frequent indication, followed by placenta accreta[5]. Apart from whether or not hysterectomy need be performed, maternal death is a known complication of major obstetric hemorrhage[6].

TACKLING THE PROBLEM OF MAJOR OBSTETRIC HEMORRHAGE

Recently developed programs to improve outcomes for women with major obstetric hemorrhage have focused on at least two important factors: first, the initial response to the hemorrhage, and, second, the prevention of hemorrhage in those patients who can be identified as being at high risk for it. This latter effort is in recognition of the fact that two of the three most common causes of hemorrhage cannot be identified in advance. These are uterine atony and/or placenta previa and placenta accreta[4]. In contrast, only placenta previa is reliably able to be diagnosed in advance.

Any program aimed at improving outcomes from major obstetric hemorrhage must also consider the interface of individuals and departments that may not traditionally be thought of as important in the process of caring for women with obstetric hemorrhage. The remainder of this chapter describes the details of these hospital systems and, in particular, how they have recently been revised with good effect in a major New York teaching hospital.

IMPORTANCE OF COMMUNICATION AND EDUCATION

Two extremely important and overarching processes must be initially addressed in order for any program aimed at improving outcomes to be successful: communication and education. It cannot be over-emphasized that clear channels of communication must be developed between all the people and departments that are involved in caring for women with major obstetric hemorrhage. This includes the immediate and

coordinated communications that are inevitably necessary for any rapid response team to work at maximum capacity. This communication must be far more comprehensive than just the members of the obstetric department and may need to include members of the emergency department, anesthesiology, the labor and delivery suite, nursing administration, the operating rooms, and the blood bank, to name just a few.

Basic education is equally important, and it is imprudent to believe that attending or house staff will know (a priori) all the component parts of the program based on their past experience and training. All care providers who evaluate these patients and institute therapy must possess the requisite knowledge of the pathophysiology of hemorrhagic shock in order to identify the presence and assess the severity of this problem, and to begin the process of initial treatment. It cannot be over-emphasized to all levels of staff that the diagnosis is not always as easy as training manuals might suggest. The involvement of departmental leaders who are experienced with the management of obstetric hemorrhage and available on a 24/7/365 basis is key. When they become primary stakeholders in the educational process, training for less experienced care providers should be developed and be repeated on a regular basis. Training such as this should be thought of as a continuous process – something that has to be repeated to every new rotation of house staff and attending consultants.

EVENTS AT NYHQ

The New York Hospital Medical Center of Queens (NYHQ) is an acute care 480-bed hospital in Flushing, New York, affiliated with the Weill Medical College of Cornell University, and the New York Presbyterian Hospital. The hospital serves an urban community of great ethnic diversity who are insured by both commercial and governmental payers; the hospital is designated for the highest level (Level III) of Neonatal Intensive and Maternal Care, and also has the highest designation for a Trauma Center (Level I). Separate critical care units are dedicated to Surgical, Medical and Cardiac services.

Two maternal deaths due to major obstetric hemorrhage occurred in recent years, one in the year 2000 and one in the year 2001. This circumstance prompted the creation of a patient safety team that worked to improve the hospital systems at NYHQ for caring for women at risk for, or suffering from, major obstetric hemorrhage. This patient safety team chose as its mission and was successful in the creation of an improved management scheme (clinical pathway) for the identification and management of major obstetric hemorrhage, with the express intent of reducing maternal deaths due to this cause.

Patient safety teams

Beginning in 2001, a multidisciplinary patient safety team was established that included individuals from the medical divisions of Obstetric Anesthesiology, Maternal Fetal Medicine, Neonatology and the Blood Bank, as well as the hospital departments of Nursing, Communication and Administration. Over the course of 6–12 months, meeting usually every week for 1–2 h, the newly created patient safety team evaluated the totality of the medical center's care of the two women who died from major obstetric hemorrhage, considered both the proximate and systems-related causes of these unfortunate outcomes, discussed possible recommended changes in the management, and decided on how best to change the systems at NYHQ that were then present for the care of women who might find themselves in similar circumstances.

Objective of our study

In order to assess the impact of the proposed changes in hospital systems on the outcomes of our patients, we began to carefully record a variety of pertinent outcomes prospectively from that point forward, and looked back retrospectively to record the same outcomes for the 2 years in which the deaths had occurred. The committee was of the opinion that the accurate recording of outcomes was essential to demonstrate any effect of changes in management over time. Specifically, we hypothesized that the changes we implemented in our hospital systems would lead to improved outcomes for women with major obstetric hemorrhage.

Methods

A multifaceted approach included the following:

(1) We formed an obstetric rapid response team (Team Blue), modeled it after the cardiac arrest team, and included quarterly mock drills on all shifts for various emergency clinical scenarios.

(2) We developed clinical pathways – guidelines and protocols – specifically designed to provide for early diagnosis of patients at risk for major obstetric hemorrhage and for streamlined care in emergency situations.

(3) In response to a marked increase in the volume of gynecologic emergency cases and births at NYHQ, we separated the in-house obstetric and gynecologic responsibilities to allow the in-house obstetrician to focus on obstetric emergencies without fear of neglecting gynecological emergencies.

(4) We revised the duties of the 24-h in-house staff (consultant) obstetrician to include continuous and frequent monitoring of all patients on the Labor and Delivery unit. This monitoring included those patients who had private obstetricians who might not be present on a continuous basis.

(5) We empowered all obstetric care providers (including physician assistants, nurses, resident physicians and the in-house attending physician) to immediately involve senior members of the Department whenever there was disagreement with or concern about the management scheme (particularly when there was a possible delay in recognition of the severity of hemorrhage). A senior member of the Department was then required to discuss the issue immediately with the attending physician to avoid delay.

(6) Through weekly didactic sessions, we educated all of our staff to recognize the severity of hemorrhage described in the Advanced Trauma Life Support Manual of the American College of Surgeons[7], and disseminated information regarding the new protocols for patient care. The attending, nursing and ancillary staffs were all informed regarding the intent of the changes (i.e. to improve patient safety) and the importance of early diagnosis of major hemorrhage.

(7) We established the role of the existing Trauma Team (with the full agreement of the Director of the Trauma Division) to specifically respond and assist in cases of severe obstetric hemorrhage, because the Trauma Team was the most experienced in resuscitation of patients with hemorrhagic shock within our institution. The Trauma Team includes surgical house officers working under the direction of the surgical trauma attending physician. These team members are expert in the placement of large-bore intravenous lines (by venous cut-down if necessary), are knowledgeable about the physiology of volume resuscitation, assist in obtaining adequate amounts of blood products for massive blood replacement, and also are most experienced in inserting intraluminal lines directly into the major vessels for monitoring and obtaining requisite samples.

The creation of new protocols and guidelines

The following protocols and guidelines were created to enhance the reception and perpetuation of the new activities.

- We prepared for major hemorrhage in patients with known placenta previa (Figure 1). This preparation included antenatal consultation with Maternal Fetal Medicine, Obstetric Anesthesiology and senior gynecologic surgeons; liberal use of ultrasound to identify placenta accreta in patients with prior uterine surgery and/or placenta previa. When such patients were identified, they received twice-weekly type and screen to allow for more rapid availability of blood products if major hemorrhage occurred. Amniocentesis was performed for fetal lung maturity at 36 weeks of gestation followed by planned Cesarean delivery if the fetal lungs were shown to be mature.
- We prepared for major hemorrhage in patients in whom we suspected placenta

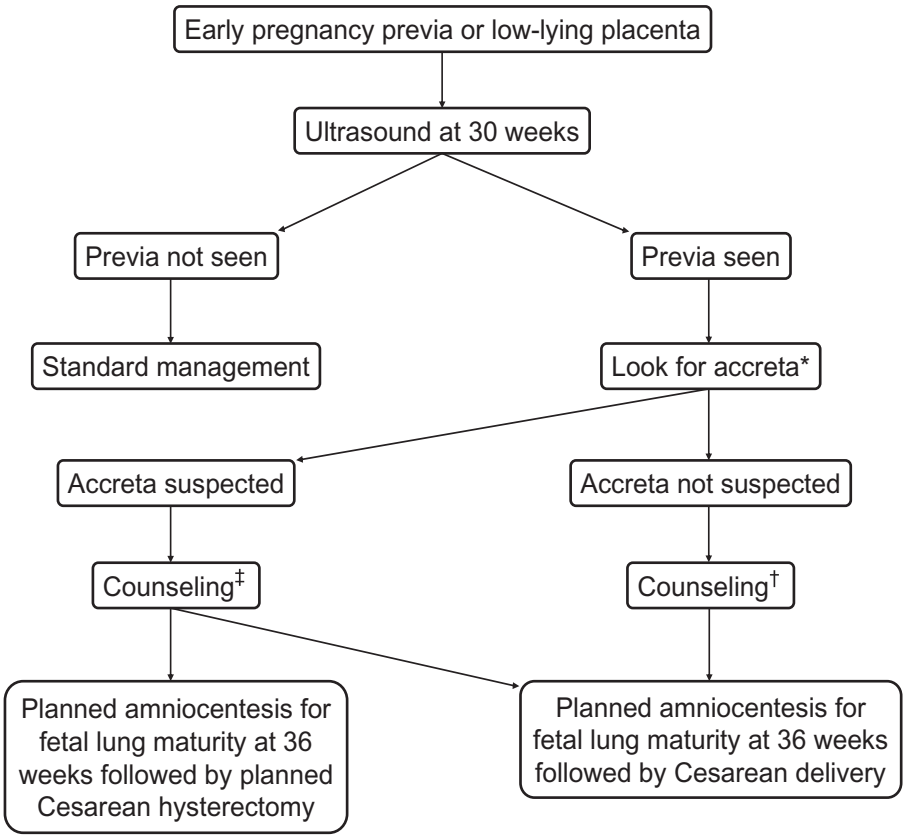

Figure 1 Proposed management scheme for patients at risk for major obstetric hemorrhage. CD, Cesarean delivery. *Suspicion for accreta is markedly increased with prior CD and anterior placenta; †includes bed rest, pelvic rest, preparation for CD, serial CBC, consider erythropoeitin, iron and vitamin supplements and serial autologous blood donation; ‡includes the counseling above and a recommendation for Cesarean hysterectomy. Low parity may decrease the strength of the recommendation if future child-bearing is desired

accreta (Figure 1). This included autologous blood donation as often as every week for a period of 4–5 weeks before the planned Cesarean delivery; erythropoietin, iron and vitamin therapy in an effort to boost red blood cell production; consultation with interventional radiology in which we would consider placement of ports preoperatively, so that embolization of major pelvic blood vessels could occur rapidly in the event of substantial hemorrhage during the operation; judicious placement of additional intravenous lines and a 7.5 French internal jugular cordis for invasive monitoring and volume replacement; intraoperative monitoring with an arterial line and central venous pressure; and transfer to the surgical intensive care unit as needed. In addition, we used the Cell Saver, but only after delivery of the fetus and after copious peritoneal irrigation had been performed[4]. Weekly autologous blood donation not only was used to prevent introduction of blood-borne infection with transfusion but also contributed to resolving any potential shortage of blood in our area.

- We obtained consultation with the Trauma Team as necessary.
- For patients with suspected placenta accreta, we discussed the likely decreased maternal mortality of planned Cesarean hysterectomy[8]. Planned Cesarean hysterectomy was then performed for those who agreed.

- For patients with suspected placenta accreta, Cesarean delivery and Cesarean hysterectomy were scheduled in the main operating room under the direction of senior gynecologic surgeons (Figure 1), because staff and facilities of the main operating room are better equipped to perform hysterectomy than is the case with the Labor and Delivery suite. This procedural change also avoided the problem of consuming staff and resources on Labor and Delivery that were considered necessary for the care of other patients.

Table 1 shows the hospital systems involved, along with an assessment of the impact on improving outcomes in women with major obstetric hemorrhage and the relative amount of work involved in the change.

In addition to the changes in systems detailed above, data on obstetric volume, mode of delivery, occurrence of major obstetric hemorrhage and outcomes important in identifying improvements were collected from 2000 to 2005. Cases were identified prospectively for the entire patient cohort (2000–2005). Demographic and outcome data on each patient were recorded retrospectively during the time period of January 2000 to May 2001 and prospectively beginning in June 2001.

The data collection program also involves monitoring by senior Departmental leaders who receive reports on a daily basis from care providers regarding all cases of major obstetric hemorrhage. These cases were highlighted and included in the database as they occurred. Outcomes analyzed included maternal deaths, lowest documented maternal pH, lowest documented maternal temperature, and the occurrence of coagulopathy.

Our definition of major obstetric hemorrhage included one or more of the following: estimated blood loss = 1500 ml, need for blood transfusion, need for uterine packing, performance of uterine artery ligation, and performance of Cesarean hysterectomy. Admittedly, this definition is different from that of postpartum hemorrhage that has been detailed in other chapters of this volume. Accordingly, the rate of major obstetric hemorrhage by our definition was expected to be lower than the known incidence of postpartum hemorrhage. Data were compared between the 2 years before

Table 1 Impact of hospital system changes on the outcomes of women with major obstetric hemorrhage

Specific change	*Impact*	*Amount of work*
Administrative		
Patient safety team	critical	extensive
Trauma Team involvement	minor	moderate
Departmental		
Obstetric rapid response team	critical	extensive
Development of clinical pathways or guidelines	major	moderate
Dissemination of clinical pathways or guidelines	major	moderate
Separation of in-house obstetrician and gynecologist	minor	moderate
Culture change to proactive attending physician	major	moderate
Care provider empowerment	major	moderate
Didactic teaching about physiology and treatment of hemorrhagic shock	major	moderate
Clinical pathways or guidelines		
Antenatal management of known placenta previa	major	moderate
Preparation for hemorrhage in suspected placenta accreta	minor	moderate
Counseling about planned Cesarean hysterectomy	minor	minimal
Scheduled Cesarean delivery for previa and accreta in the main operating room	minor	minimal
Nursing		
Culture change to team participation	major	extensive
Empowerment of nurses	major	moderate

Table 2 Major obstetric hemorrhage in the period 2000–2005

Year	*Births*	*Total Cesarean births*⋆	*Repeat Cesarean births*†	*Cases of major obstetric hemorrhage*‡	*Cesarean hysterectomy*§	*Mortality*
2000	2705	516	217	3	1	1
2001	3106	801	287	8	5	1
2002	3323	903	332	8	5	0
2003	3395	932	326	14	4	0
2004	3648	1053	374	18	5	0
2005 (8 months)	2546	759	275	12	4	0
Total	18 723	4964	1811	63	24	2

⋆2000–2001 compared to 2002–2005, $p < 0.0001$; †2000–2001 compared to 2002–2005, $p = 0.002$; ‡2000–2001 compared to 2002–2005, $p = 0.02$; §rate of Cesarean hysterectomy as a function of the total number of major obstetric hemorrhage cases 2000–2001 compared to 2002–2005, $p = 0.37$

and the 3 years after the systemic changes were implemented, 2000–2001 vs. 2002–2005.

Results

During each successive year of the study, the following important changes occurred simultaneously: increasing obstetric volume, increasing rate of Cesarean delivery, an increasing rate of repeat Cesarean delivery, and an increasing number of cases of major obstetric hemorrhage (Table 2). The increases in Cesarean delivery, repeat Cesarean delivery, and cases of major obstetric hemorrhage all were significant between the time periods of 2000–2001 vs. 2002–2005, but no difference was shown in the rate of Cesarean hysterectomy (Table 2).

Clinical characteristics, measures of severity of hemorrhage and outcomes are shown in Table 3. The patient groups from the two time periods (2000–2001 vs. 2002–2005) were similar in demographics as measured by age, parity and incidence of prior Cesarean delivery. The severities of obstetric hemorrhage also appeared to be similar between the time periods. The severity measures were APACHE II scores[9], occurrence of placenta accreta and amount of estimated blood loss (Table 3).

The major result of the combined effort was that maternal deaths were significantly reduced in the time period following the systemic changes ($p = 0.036$). This was supported by the additional findings of significant differences in lowest pH ($p = 0.004$) and lowest temperature ($p < 0.0001$). There also was a trend toward less coagulopathy ($p = 0.09$). These diverse findings were very important, because it is known that a triad of physiologic derangements occurs in hemorrhagic shock that can lead to death. This triad comprises acidemia, hypothermia and coagulopathy. Its presence helps to confirm that our major finding of reduced maternal death is not a statistical chance event, and also argues that our response to the event of a major obstetric hemorrhage became better as time passed and as care providers became more experienced and knowledgeable.

The two time periods were also analyzed according to other characteristics, such as need for Cesarean hysterectomy, volume of transfusion, operative time, need for intubation for greater than 24 h, and number of hours intubated (Table 3). No significant differences were present in these measures in the periods 2000–2001 vs. 2002–2005. The incidence of peripartum hysterectomy was 1.3/1000 (24/18 723) during the entire study period (2000–2005). Placenta accreta with prior Cesarean delivery accounted for 14/24 (58.3%) cases of Cesarean hysterectomy, and we suspected accreta in seven cases and confirmed it in four cases at delivery. The operative characteristics, morbidity and mortality of patients undergoing peripartum hysterectomy are shown in Table 4. The numbers here are different from Table 3, because Table 3 shows all patients

Table 3 Major obstetric hemorrhage: comparison of demographics, measures of severity and outcomes

	2000–2001 (*n* = 12)	*2002–2005* (*n* = 49)	*p Value*
Demographics			
Age, mean (SD)	36.5 (6.0)	34.2 (5.9)	0.23
Parity, median (range)	1 (0–3)	1 (0–5)	0.70
Prior Cesarean delivery, *n* (%)	6 (50.0)	32 (65.3)	0.33
Severity measures			
Occurrence of placenta accreta, *n* (%)	4 (33.3)	11 (22.4)	0.46
APACHE score, median (range)	11.5 (7–31)	10 (6–18)	0.07
Estimated blood loss, mean (SD)	2725 (1289)	2429 (1214)	0.46
Outcomes			
Maternal death, *n* (%)	2 (16.7)	0 (0.0)	0.036*
Lowest pH, median (range)	7.23 (6.8–7.39)	7.34 (7.08–7.44)	0.004*
Lowest temperature (°C), median (range)	35.2 (30.2–35.8)	36.1 (35.2–37.8)	< 0.0001*
Coagulopathy, *n* (%)	7 (58.3)	15 (30.6)	0.09
Cesarean hysterectomy, *n* (%)	6 (50.0)	18 (36.7)	0.51
Volume of transfusion, mean (SD)	1313 (1029)	1194 (1547)	0.80
Operative time, mean (SD)	185 (91)	184 (79)	0.99
Intubation > 24 h, *n* (%)	7 (58.3)	16 (32.7)	0.18

*Significant difference

during the entire study period and the data in Table 4 is confined to those patients who underwent Cesarean hysterectomy. Interestingly, a significant difference was also present in the lowest pH in patients undergoing Cesarean hysterectomy between the time periods of 2000–2001 vs. 2002–2005. We think this underscores that our response to women with hemorrhagic shock from blood loss improved over the course of time.

Deciphering the data

The response to major obstetric hemorrhage must be multifaceted and rapid in order to be successful. A quality assurance committee would be the traditional departmental or institutional response to a poor outcome such as a maternal death from hemorrhage, and, after this peer review, specific physician education would occur regarding the components of early identification and 'best' treatment, as determined by departmental leaders. However, this traditional response ignores the lessons learned from the Institute of Medicine report regarding errors that lead to morbidity and mortality during hospital stays[10]. When clinical judgment fails and hemorrhagic shock is not recognized or when a patient presents in an advanced state of hemorrhagic shock, a need to improve hospital systems to provide a safety net for patients is as important as is the education of a specific physician or group of physicians after an adverse outcome.

Our findings indicate that there were significant improvements in outcomes after we introduced systemic changes at our institution, including improvements in maternal deaths, lowest pH and lowest temperature. There were no difference in measures of severity of obstetric hemorrhage and significant increases in the number of cases of major obstetric hemorrhage between the study time periods, leading us to the conclusion that this improvement in outcomes is a true finding. When comparing the time periods before and after the systemic changes, the significant differences in lowest temperature and in lowest pH (Table 3) suggest that the team's response to massive hemorrhage improved after system-wide interventions. The reduction in maternal mortality, however, cannot be considered a robust observation, because this observation is hospital-based and may not be replicated in a population-based sample.

Table 4 Peripartum hysterectomy in the period 2000–2005. Incidence: 24/18 723 (1.3/1000). All data are number of cases unless otherwise designated

	2000–2001[†]	*2002–2005*[‡]	*Total*[§]
Etiology			
Placenta accreta	4	10	14
Placenta accreta with prior CD	4	10	14
Uterine atony	2	6	8
Morbidity			
Cystotomy	1	1	2
Pulmonary embolus	1	0	1
Coagulopathy	5	8	13
Acute tubular necrosis	0	0	0
ARDS	0	0	0
Myocardial infarction	0	0	0
Pneumonia	0	0	0
Mortality			
Placenta percreta	1	0	1
Other characteristics			
Operative time (min), mean (SD)	259 (52.3)	250 (66.6)	252 (62.4)
EBL (ml), median (range)	3500 (2500–5200)	3000 (1000–7000)	3250 (1000–7000)
Transfusion total volume (ml), mean (SD)	2125 (847.8)	2292 (2076.4)	2250 (1829.9)
FFP/platelets given (*n*)	5	10	15
Lowest pH, mean (SD)	7.15* (0.17)	7.27* (0.07)	7.24 (0.12)
Intubated	5	12	17
Intubated > 24 h	3	3	6
Days to discharge, median (range)	6 (4–7)	4 (3–11)	5 (3–11)
Anesthetic management			
Regional anesthesia only	1	3	4
Conversion to general	2	12	14
General anesthesia only	3	3	6

[†]2000–2001 hysterectomy $n = 6$, total births $n = 5811$; [‡]2002–2005 hysterectomy $n = 18$, total births $n = 12\,912$; [§]2000–2005 (total) hysterectomy $n = 24$, total births n = 18 723; *significant difference $p = 0.02$

CD, Cesarean delivery; ARDS, adult respiratory distress syndrome; SD, standard deviation; EBL, estimated blood loss; FFP, fresh frozen plasma

This caveat in no way diminishes the value of our findings in terms of their broad applicability in other hospitals throughout this and other countries.

The process of implementing the systemic changes required considerable effort by many individuals and was very time-intensive. The patient safety team met numerous times and deliberated on the specifics of our response. These efforts included repeated education of care providers on the diagnosis and management of hypovolemic shock. It is of considerable interest that the entire staff accepted these additional time expenditures as part of their ongoing self-education and were proud of the outcome and the results (Table 1).

This study design does not allow a determination of which of several interventions may have accounted for improvements in outcome. We strongly believe that the data presented in this chapter support the conclusion that a well-reasoned, carefully constructed and multifaceted program focusing on patient safety can improve outcomes, although we cannot

attribute any specific improvement to any specific change that we instituted. We also strongly believe that our experience demonstrates that focusing on the problem of obstetric hemorrhage by the medical and administrative departments in a given hospital can and does lead to improved outcomes. The effort involved is substantial, but rewarding.

FINAL COMMENTS

The risk of placenta previa with or without accreta in patients with multiple Cesarean deliveries is difficult to quantitate[11]. However, recently published prospective data[12,13] corroborate previously published retrospective data on the substantial risk of accreta associated with previa and prior Cesarean[14]. Placenta previa is a detectable condition, allowing for a preventive clinical pathway such as that developed in Figure 1 to be implemented. We believe that the preparation that takes place after the early identification of patients at risk is an important component in the ability to improve outcomes for our program.

When confronted with adverse outcomes, principles of quality improvement require that 'systems' thinking take place. It is tempting to attempt to correct the proximate cause (e.g. an individual physician's lack of attention to detail or suboptimal clinical judgment on an individual case) without addressing the 'systems'. We believe these data support the clear need for a systemic response and hope they are useful to others faced with the task of improving safety in obstetric suites. The specific series of changes in systems at our institution was uniquely adapted to the circumstances we encountered. It is possible that these changes may not be as important nor as easily achievable in other areas of the world. However, in any institution's response to major obstetric hemorrhage, it is important to keep in mind the numerous and potentially changing nature of obstacles to system changes and the need to put together a multidisciplinary response to overcome these obstacles. Though this is a challenging task, the result of improvements in outcomes for women with obstetric hemorrhage remains rewarding and, most importantly, achievable.

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Section VI

Therapy for non-atonic conditions

23

BLEEDING FROM THE LOWER GENITAL TRACT

A. Duncan and C. von Widekind

INTRODUCTION

In the first comprehensive English Language textbook on the subject, William Smellie, in his 1752 *Treatise on the Theory and Practise of Midwifery*[1], correctly identifies the atonic uterus as a major cause of postpartum hemorrhage with his statement '*This dangerous efflux is occasioned by every thing that hinders the emptied uterus from contracting*'. Although he refers to vaginal packing with *Tow or linen rags* (dipped in astringents such as oxycrate, red tart wine, alum or Sacchar-saturni), he does not specifically refer to bleeding from the lower genital tract. Because this omission was repeated in subsequent years by many standard textbooks and reviews of postpartum hemorrhage, it is not surprising that the present evidence base is poor, and a 2005 MESH search in PubMed of the National Library USA combining the terms 'Postpartum hemorrhage' AND 'Lacerations' OR 'Rupture' NOT 'Uterine rupture' came up with only 28 publications.

Maternal deaths specifically from lower genital tract bleeding as the cause of postpartum hemorrhage are rare in the developed world. The 2000–2002 United Kingdom Confidential Enquiries[2] reported only one death from this cause. World-wide, no accurate figures exist, but it is likely that the numbers are significant, particularly where there is significant co-morbidity and a poorly resourced maternity infrastructure[3].

CLASSIFICATION

Possible sources of bleeding from the lower genital tract include:

(1) Cervical tears;

(2) Vaginal tears (above and below the levator ani muscle, see Figure 1);

(3) Vulva and perineal tears;

(4) Episiotomies.

With the exception of cervical tears without vaginal extension, all of the above can lead to paravaginal hematomas, which in turn can be divided into those above and below the levator ani muscle (Figure 1). Infralevator hematomas include those of the vulva, perineum, paravaginal space and ischiorectal fossa. Supralevator bleeding is more dangerous, as it is more difficult to identify and control the source of bleeding, and blood loss into the retroperitoneal space can be massive.

INCIDENCE

In the UK, postpartum hemorrhage of more than 500 ml occurs in between 5 and 17% of all deliveries and postpartum hemorrhage of more than 1000 ml in 1.3% of deliveries.

Cervical tears

Minor cervical tears are common and are likely to remain undetected. However, bleeding which occurs despite a well-contracted uterus and which does not appear to be arising from the vagina or perineum is an indication for examining the cervix. Numerous cases have been described of women dying from hemorrhage due to a cervical tear, following operative vaginal delivery.

Postpartum hematoma

Because there is no agreed definition, there is no consensus as to the incidence. After

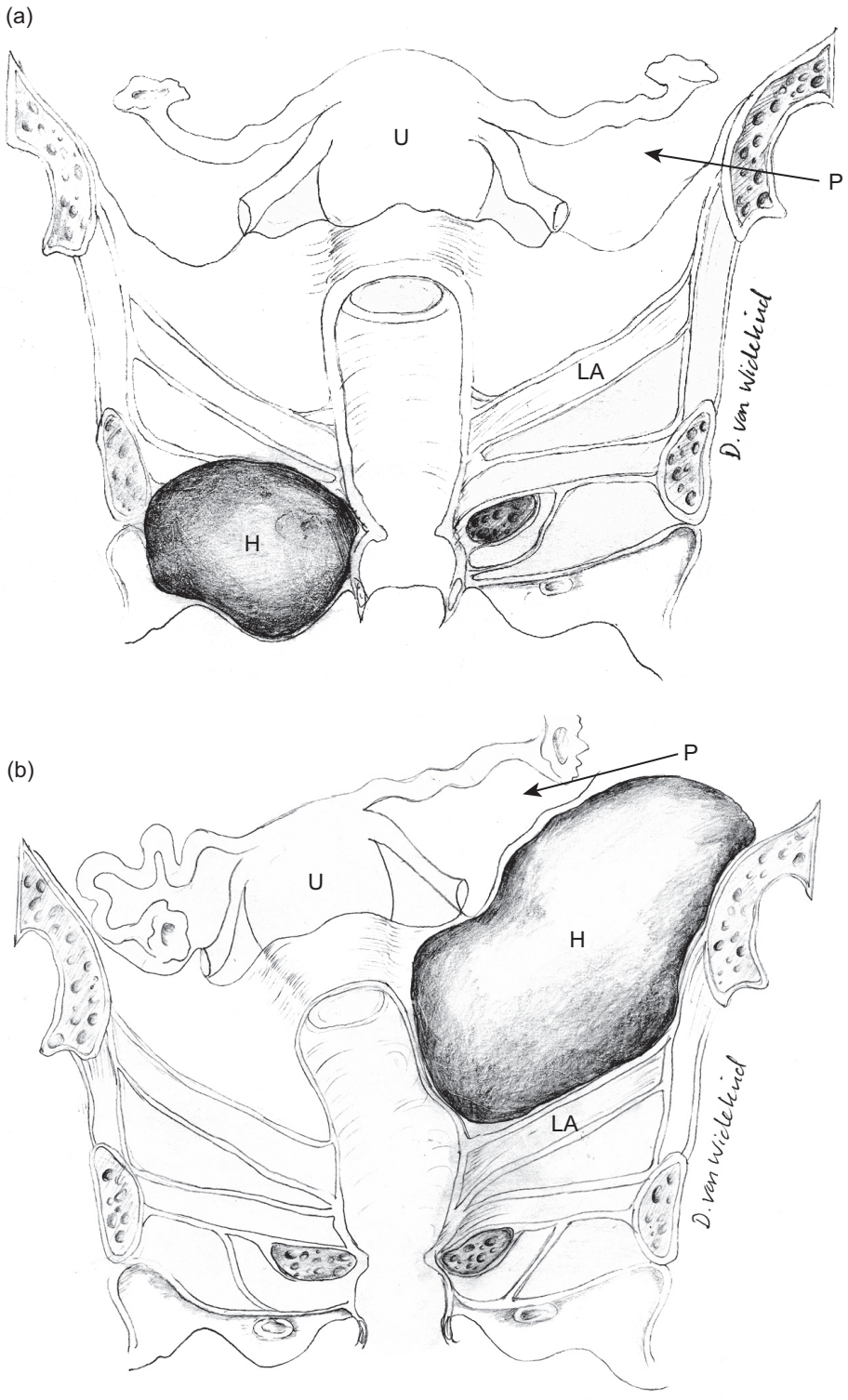


Figure 1 Paravaginal hematomas. (a) The hematoma lies beneath the levator ani muscle; (b) the hematoma lies above the levator ani and is spreading upwards into the broad ligament. H, hematoma; LA, levator ani, U, uterus; P, pelvic peritoneal reflection

spontaneous delivery, up to 50% of parturients develop a minor self-limiting infralevator/vulva hematoma[5]. In contrast, the formation of a significant postpartum hematoma is an uncommon but serious complication after delivery, with the reported incidence of around 1 in 500–700 deliveries[6]. Major pelvic (supralevator) hematomas are rare, with widely varying reported incidence of between 1 in 500 and 1 in 20 000[7].

Episiotomy

An episiotomy can bleed heavily, and, although there are no data on the incidence of hemorrhage from this cause alone, observational studies suggest that the relative risk of postpartum hemorrhage is increased four to five times if an episiotomy is performed[8].

RISK FACTORS

The major causes of postpartum hemorrhage are uterine atony, retained placental fragments, morbid adherence of the placenta and lower genital tract lacerations. Data from the North West Thames District of the UK (Table 1) reviewed the obstetric factors associated with a blood loss of more than 1000 ml and apportioned a relative risk to each factor[4]. Of these, assisted delivery (forceps or vacuum extraction), prolonged labor, maternal obesity (and associated large baby) and episiotomy were most relevant to the risks of lower genital tract hemorrhage. It is worth noting that episiotomy, with a relative risk of 5, carried the same weight as a cause of postpartum hemorrhage as did multiple pregnancy and retained placenta. Rotational forceps are a particular risk factor for spiral vaginal tears[9].

Coagulation disorders, if present, are likely to significantly increase the risk of lower genital tract hemorrhage and hematoma and therefore should always be corrected where possible. If vaginal lacerations require repair in this situation, the threshold for the use of a vaginal pack should be low.

Table 1 Risk factors for postpartum hemorrhage and approximate increase in risk[4]

Antenatal	*Relative risk*	*Intrapartum*	*Relative risk*
Placenta previa	13	Emergency Cesarean section	9
Obesity	2	Assisted delivery	2
		Prolonged labor (> 12 h)	2
		Placental abruption	13
		Multiple pregnancy	5
		Retained placenta	5
		Elective Cesarean section	4
		Mediolateral episiotomy	5
		Pyrexia in labor	2

PREVENTION

The three main areas in which risk can be reduced all require a proactive approach:

(1) Antenatal co-morbidities such as anemia and diabetes should be treated so that women entering labor are as healthy as possible.

(2) A consistent proactive approach is required in both the first and second stages of labor. Active monitoring (partogram) and early intervention are essential where progress is inadequate or cephalic-pelvic disproportion is diagnosed. Coagulation defects (including iatrogenic defects due to anticoagulation) should be corrected where possible (see Chapter 25).

(3) Postpartum, the early identification of excessive blood loss and a proactive approach to resuscitation/fluid replacement as well as identification of the source of bleeding and stopping it, are vital.

Because operative delivery and episiotomy are both significant risk factors for postpartum hemorrhage from the lower genital tract, efforts to reduce the incidence of both are likely to reduce the risk of hemorrhage. Where operative vaginal delivery is required, however, then a proper technique as described in standard textbooks[10] will reduce the risk of vaginal and cervical tears.

DIAGNOSIS

Careful and well-documented observation after delivery is imperative as the seriousness of

concealed or persistent low-grade blood loss can be underestimated.

Bleeding, especially after instrumental vaginal delivery, that occurs despite a well-contracted uterus and that does not appear to be arising from the lower vagina or perineum is an indication for examination of the upper vagina and cervix. The characteristic feature of bleeding from upper vaginal and cervical tears is a steady loss of fresh red blood.

Exclusion of upper vaginal and cervical tears requires examination in the lithotomy position with good relaxation, good light and proper assistance[7]. A tagged vaginal tampon to absorb blood loss from the uterine cavity and the use of flat-bladed vaginal retractors will assist in visualizing the vaginal walls.

The cervix should always be examined where there is continuing bleeding despite a well-contracted uterus and also after use of all rotational forceps, which are associated with a significant increase in the risk of upper vaginal and cervical tears[11]. The method for doing this is to grasp the anterior lip with one ring forceps and to place a second ring forceps at the 2-o'clock position, followed by progressively 'leap-frogging' the forceps ahead of one another until the entire circumference has been inspected.

TREATMENT

Hemorrhage from the lower genital tract should always be suspected when there is ongoing bleeding despite a well-contracted uterus. Generally, high vaginal or cervical tears require repair under regional anesthesia in theater.

The Scottish Obstetrics Guidelines and Audit Project (SOGAP) group provides detailed guidelines on the management of postpartum hemorrhage[12]. A summary of the ORDER protocol as described by Bonnar[13] is shown in Table 2, with additional boxes relating to hemorrhage from the lower genital tract.

Perineal tear repair

The technique has been well described elsewhere[14]. The principles include ensuring that the first suture is inserted above the apex of the tear or episiotomy incision, use of a continuous polyglactin/polyglycolic acid suture on a taper-cut needle, obliteration of dead spaces and taking care that sutures are not inserted too tightly. If dead spaces cannot be closed securely, then a vaginal pack should be inserted.

Vaginal tear repair

The technique for repair of superficial vaginal tears is similar to that of perineal repair, as described above. Use an absorbable, continuous interlocking stitch, which must start and finish beyond the apices of the laceration, and should where possible reach the full depth of the tear in order to reduce the risk of subsequent hematoma formation.

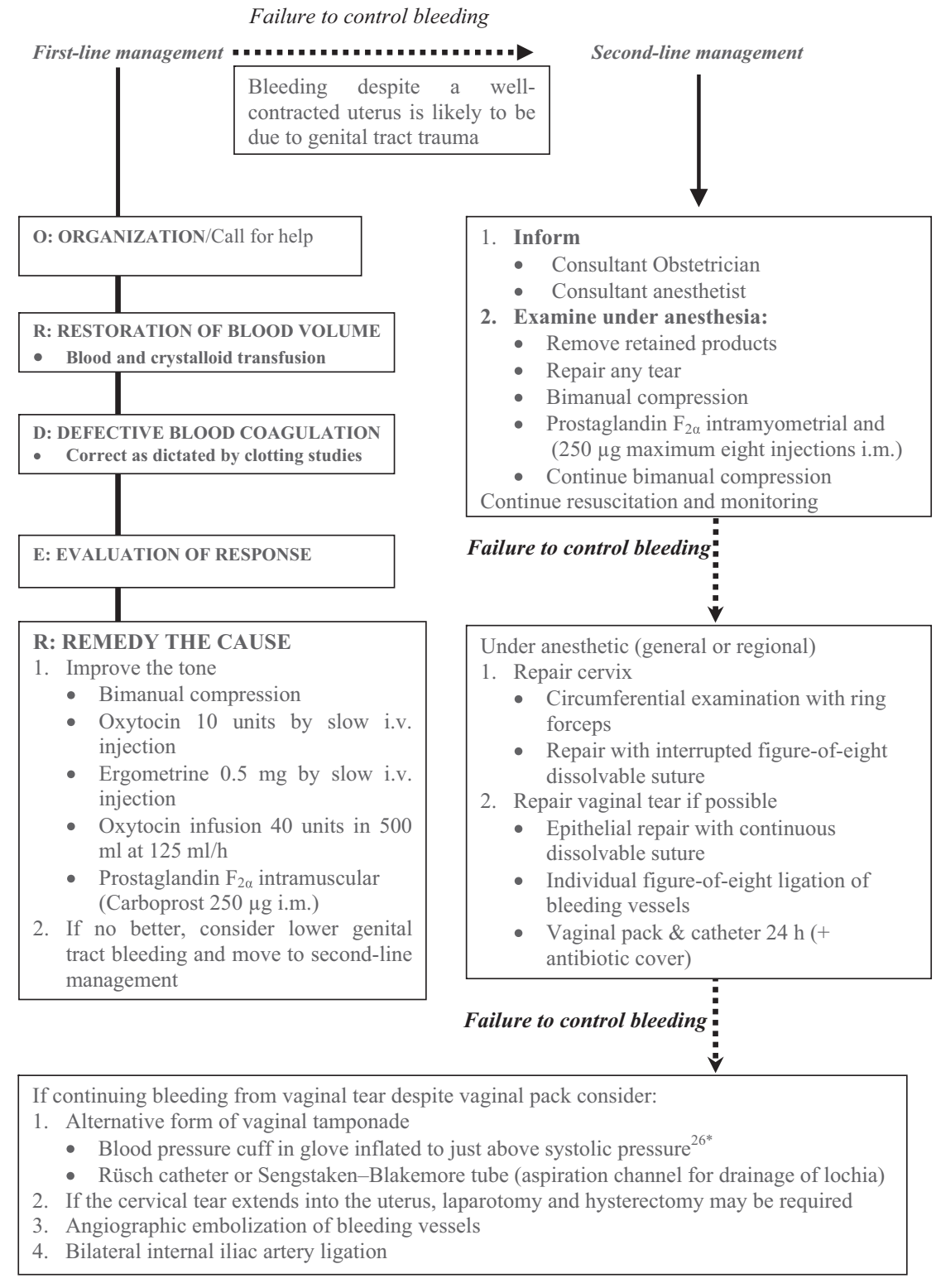
For deeper tears, an attempt should be made to identify the bleeding vessel and ligate it. If there is any significant dead space or if the vagina is too friable to accept suturing, then packing is indicated (see below), because access to deeper tears is usually difficult in an inadequately anesthetized patient. Thus, repair of such lacerations should be done in theater with adequate anesthesia.

Lacerations high in the vaginal vault and those extending up from the cervix may involve the uterus or be the cause of broad ligament or retroperitoneal hematomas. The proximity of the ureters to the lateral vaginal fornices, and the base of the bladder to the anterior fornix, must be kept in mind when any extensive repair is undertaken in these areas. Poorly placed stitches can lead to genitourinary fistulas. Vaginal packing for at least 24 h is always wise under these conditions.

Vaginal packing using gauze is the most common method to achieve vaginal tamponade. As with uterine packing, the technique of vaginal packing involves ribbon gauze inserted uniformly side-to-side, front-to-back and top-to-bottom. Vaginal packing using thrombin-soaked packs, as described for uterine packing, can also be considered[15], especially where closure of all lacerations has not been possible.

Because of the risk that the raw vaginal surface will bleed on removal of the pack, povidone iodine-soaked double lengths of 4.5×48 inch packs can be inserted inside sterile plastic drapes (this has been well described for the management of uterine hemorrhage, but the

Table 2 Management of major postpartum hemorrhage (blood loss > 1000 ml or clinical shock) (see reference 13)



principle is the same for vaginal packing) to allow for easy removal[16]. Generally, packs are left in place for 24–36 h before removal[17]. A urinary Foley catheter and broad-spectrum antibiotic cover should be given where packs are used. Balloon tamponade using Rüsch catheters[18] or Blakemore-Sengstaken[19] tubes, as described for treatment of uterine bleeding (see Chapters 28 and 29), can also be used.

Pinborg and colleagues[20] described the successful use of the blood pressure cuff in two patients to control intractable vaginal bleeding following evacuation of vaginal hematoma that developed after spontaneous vaginal delivery. A blood pressure cuff was inserted into a sterile glove, which in turn was inserted into the vagina and the pressure then gradually increased to 120 mmHg, 10 mmHg above the systolic pressure, to stop the bleeding. Eight hours later, the pressure of the cuff was reduced by 10 mmHg/h and the cuff then taken out after 32 h. Both patients made an uneventful recovery.

Cervical tear

Any cervical tear extending above the internal os warrants laparotomy. Small, non-bleeding lacerations of the cervix do not need to be sutured. Any bleeding cervical tear, and certainly any tear longer than 2 cm, however, should be sutured by using an absorbable suture on a tapered (rather than a cutting) needle. A suitable method for suturing is shown in Figure 2.

Both edges of the most caudal part of the laceration are grasped with a ring forceps and then sutured with an interrupted or figure-of-eight stitch. This is then held with a hemostat to bring down into view the next part of the tear, which is sutured in the same way, and so on until the apex is secured. The laceration should be observed for a few minutes after suturing, to ensure adequate hemostasis. The ring forceps can be replaced and left on for some time if oozing persists.

Cervical and vaginal vault lacerations that continue to ooze despite treatment as detailed above or those that are associated with hematomas may be amenable to selective arterial embolization (see below).

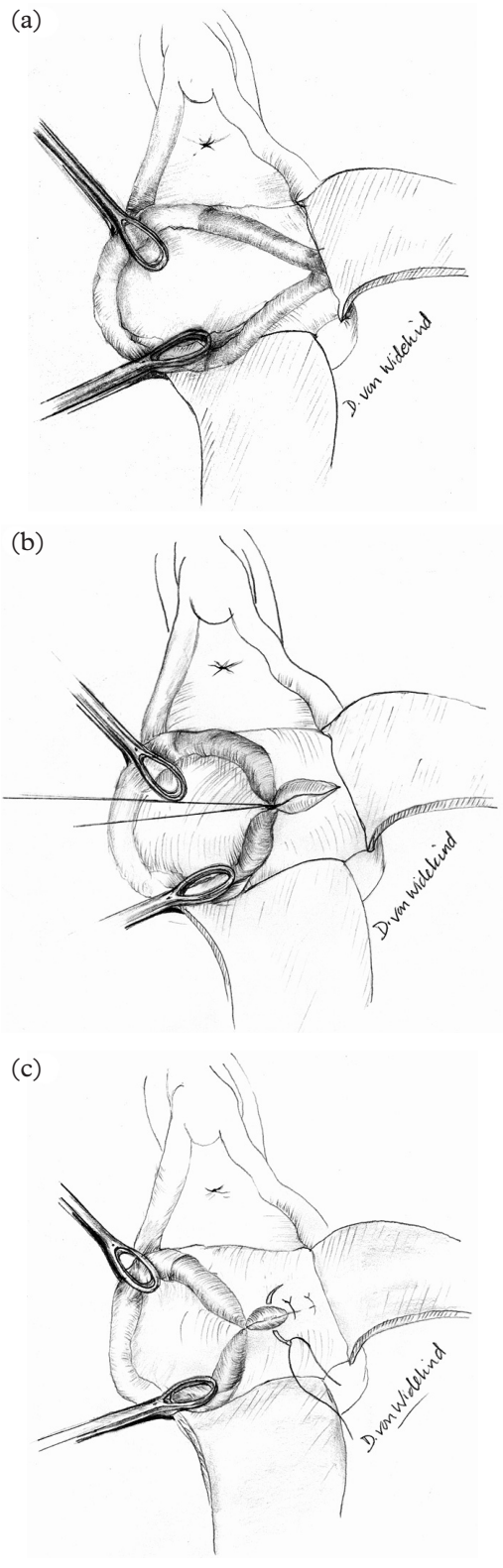


Figure 2 (a)–(c) Suturing cervical tear

Hematoma management

The literature on the management of paragenital hematomas is limited and no randomized studies of the efficacy of various treatments exist[21].

Infralevator hematomas

As always, initial management consists of resuscitation measures and analgesia followed by a period of observation. For hematomas that are less than 5 cm and not expanding, conservative treatment with ice packs, pressure dressing and analgesia is recommended[22]. The visible skin margin of the hematomas should be marked to help establish whether it is expanding. For hematomas that are expanding or more than 5 cm in size, surgical intervention is recommended. Where possible, the surgical incision should be made via the vagina to minimize visible scarring. Distinct bleeding points should be under-run with figure-of-eight dissolvable sutures. The presence of any residual bleeding or a hematoma cavity is an indication for insertion of a drain, a vaginal pack and a Foley catheter, all of which should be left in place for at least 24 h. Usually, however, no distinct bleeding point can be seen, in which case a drain and pack should be inserted[10].

Supralevator hematomas

Approximately 50% of broad ligament hematomas present early with symptoms of lower abdominal pain, hemorrhage and in severe cases, shock. The other 50% present after 24 h. Broad ligament and retroperitoneal hematomas are initially managed expectantly if the patient is stable and the lesions are not expanding[23]. Ultrasound, CT scanning and MRI may all be used to assess the size and progress of these hematomas. Close observation, intravenous fluid resuscitation, blood transfusion, vaginal packing or balloon/blood pressure cuff tamponade and antibiotics are commenced as appropriate, but, if it is not possible to maintain a stable hemodynamic state, then active intervention is indicated, with options including the following:

(1) *Laparotomy ± total abdominal hysterectomy* This is indicated where there is any possibility that a supralevator/broad ligament hematoma is due to a ruptured uterus or where a cervical tear appears to have extended up into the uterus. At laparotomy, if there is continuing bleeding from the upper vagina, then the anterior division of the internal iliac artery should be ligated in continuity, which will reduce the pulse pressure to the distal internal iliac artery branches (that supply the uterus and vagina) by 85% and the blood flow by about 50%[24] (see Chapters 32 and 34). A further vaginal pack should be inserted.

(2) *Selective arterial embolization* Where there is continuing expansion of a supralevator hematoma without extension into the cervix or uterus, selective arterial embolization is seen as the treatment of choice[25] over internal iliac artery ligation, which in itself has an uncertain chance of success[26] and involves imposing a laparotomy on an already unstable patient. The blood supply to the upper vagina is from a rich anastomotic network of vessels, arising mainly from branches of the anterior trunk of the internal iliac artery (vaginal, uterine, middle rectal arteries) and the internal pudendal artery, which is the most inferior branch of the posterior trunk of the internal iliac artery. The technique of selective arterial embolization investigates these vessels by preliminary transfemoral arteriography, followed by embolization using Gelfoam (gelatin) pledglets. Pelage and colleagues[25] reported a series of 35 patients who underwent this procedure for unanticipated postpartum hemorrhage. Bleeding was controlled in all but one, who required hysterectomy 5 days later for re-bleeding. All women who had successful embolization resumed menstruation. The procedure, however, is not without risk and deaths have been reported due to sepsis and multiple organ failure[27] (see Chapter 44).

SUMMARY

In summary, bleeding from the lower genital tract should always be considered as a possible cause of primary postpartum hemorrhage where there is continuing bleeding despite a

well-contracted uterus. Primary repair of vaginal or cervical tears with full-thickness sutures using a dissolving suture on a taper-cut needle, followed by insertion of a vaginal pack and catheter for at least 24 h will stem most bleeding. Urgent resort to laparotomy is necessary if there is a cervical tear extending beyond the internal cervical os up into the uterus, or if bleeding fails to settle despite an attempt at vaginal tamponade. Internal iliac artery ligation or selective arterial embolization should be considered where there is continuing expansion of a supralevator hematoma or upper vaginal bleeding despite the above measures. As always, regular assessments, clear documentation, a proactive approach and early intervention are vital to obtain a good outcome.

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24

ADHERENT PLACENTA: NEW MANAGEMENT OPTIONS

G. Kayem, T. Schmitz, V. Tsatsaris, F. Goffinet and D. Cabrol

INTRODUCTION

Placenta accreta occurs when a defect of the decidua basalis results in abnormally invasive placental implantation[1]. It is often diagnosed only after delivery when manual removal of the placenta has failed. Attempting forcible manual removal of a placenta accreta can easily lead to dramatic hemorrhage that may result in hysterectomy. Thus, placenta accreta and especially placenta percreta reportedly result in a maternal mortality rate of 7%, and cause intra- and postoperative morbidity associated with massive blood transfusions, infection, ureteral damage, and fistula formation[2]. Its incidence, along with the Cesarean section rate, has increased 10-fold over the past 50 years[3]. With a frequency of approximately 1 per 1000 deliveries, this disorder has become more common in today's medical practice[4].

DIAGNOSIS OF PLACENTA ACCRETA

In practice, placenta accreta is diagnosed according to clinical or histological criteria as follows[5]. If suspected before labor, prenatal diagnosis of placenta accreta is confirmed by the failure of its gentle attempted removal during the third stage of labor. If not suspected before delivery, placenta accreta can be diagnosed if manual removal of the placenta is partially or totally impossible and no cleavage plane exists between part or the entire placenta and the uterus; a heavy bleeding occurs from the implantation site after forced placental removal.

After a hysterectomy performed because of postpartum hemorrhage, placenta accreta is shown by histologic confirmation of accreta on the hysterectomy specimen.

MANAGEMENT OF ADHERENT PLACENTA

The classical approach most often recommended in cases of placenta accreta is extirpative[4]. If risk factors and prenatal imaging both strongly suggest this diagnosis, a Cesarean hysterectomy is generally planned, especially for patients who do not wish continued fertility. If the placenta accreta is discovered after delivery, the placenta is removed as soon as possible to empty the uterine cavity. In most cases, however, this forced placental delivery induces massive hemorrhage and leads to hysterectomy.

When the diagnosis of adherent placenta is not suspected before labor and a postpartum hemorrhage is obviously related to attempting forcible removal of a placenta accreta, several options are possible, dependent on the patient's wishes and the cervical situation.

If there is no wish for continued fertility or if the hemodynamic status is unstable, a hysterectomy must be performed. Otherwise, an attempt can be made to preserve the uterus using surgical (ligating hypogastric arteries) or radiological (embolization of the uterine arteries) techniques (see Chapters 30 and 32). Other methods have been published in case reports describing uterine packing, oversewing the placental bed, prostaglandin administration, direct aortic compression and argon beam coagulation in order to decrease blood loss[6]. More recently, a simple method using parallel sagittal ligatures of the lower segment has been described; it is particularly useful if the hemorrhage is located to the lower segment[7]. Other similar methods, more complex to perform, have also been described, but seem to be associated with serious side-effects (uteropyosis, synechia)[8–10].

We believe these methods can be used only when the diagnosis of adherent placenta has been made after attempting forcible removal and in case of severe hemorrhage.

An alternative therapeutic approach to the placenta is conservative rather than extirpative. Some cases of successful conservative management of placenta accreta have previously been reported[11–15].

Conservative strategy was initiated in our center in 1997 and followed the successful conservative management of one case of placenta accreta, by leaving the placenta in place[16]. Since this date, our protocol is to manage most cases of placenta accreta conservatively, leaving *in situ* each placenta that adheres either partially or totally to the myometrium. We evaluated this management by a historical consecutive study to compare the impact of conservative and extirpative strategies for placenta accreta on maternal morbidity and mortality[17].

Two consecutive periods, A and B, were compared. During period A (January 1993 to June 1997), our written protocol called for the systematic manual removal of the placenta, to leave the uterine cavity empty. In period B (July 1997 to December 2002), we changed our policy by leaving the placenta *in situ*. The following outcomes over the two periods were compared: need for blood transfusion, hysterectomy, intensive care unit admission, duration of stay in intensive care unit, and postpartum endometritis. Thirty-three cases of placenta accreta were observed among 31 921 deliveries (1.03/1000). During period B, there was a reduction in the hysterectomy rate (from 11 (84.6%) to 3 (15%); $p < 0.001$), the mean number of red blood cells transfused (3230 ± 2170 ml vs. 1560 ± 1646 ml; $p < 0.01$), and disseminated intravascular coagulation (5 (38.5%) vs. 1 (5.0%); $p = 0.02$), compared with period A. There were three cases of sepsis in period B and none in period A ($p = 0.26$). One hysterectomy was required at day 26, because of sepsis and hemorrhage, after a conservative management of an entire placenta accreta. Two women with conservative management have subsequently had successful pregnancies.

DESCRIPTION OF CONSERVATIVE MANAGEMENT

Depending on how the placenta accreta is discovered, two different types of conservative treatment can be used.

(1) When discovered during the third stage of labor, removal of the placenta is not forced; the conservative treatment leaves the placenta, in part or entirely, in the uterus when the patient's hemodynamic status is stable and no septic risk is present.

(2) When the placenta accreta is strongly suspected before delivery (based on history and ultrasound and/or magnetic resonance imaging suggestive of the diagnosis), the case is discussed at the daily obstetric staff meeting and conservative treatment is proposed to the patient. In this case, management includes the following steps (Figure 1). The precise position of the placenta is determined by ultrasound. A Cesarean section is planned, with the abdominal incision at the infraumbilical midline, enlarged above the umbilicus if necessary, and a vertical uterine incision at a distance from the placental insertion. After extraction of the infant, delivery of the placenta is attempted prudently, with an intravenous injection of 5 IU oxytocin and moderate cord traction. If this fails, the placenta is considered to be 'accreta'. The cord is cut at the placental insertion and the placenta left in the uterine cavity; the uterine incision is closed. Prophylactic antibiotic therapy (amoxicillin and clavulanic acid) is administered for 10 days.

FOLLOW-UP AFTER CONSERVATIVE MANAGEMENT

During the postpartum period, all patients are seen weekly until complete resorption of the placenta. Ultrasonography and clinical examination are performed to detect hemorrhage, pain or clinical signs of infection. To improve clinical follow-up and to help choose antibiotic therapy in cases of endometritis with or without sepsis, C-reactive protein and blood counts are

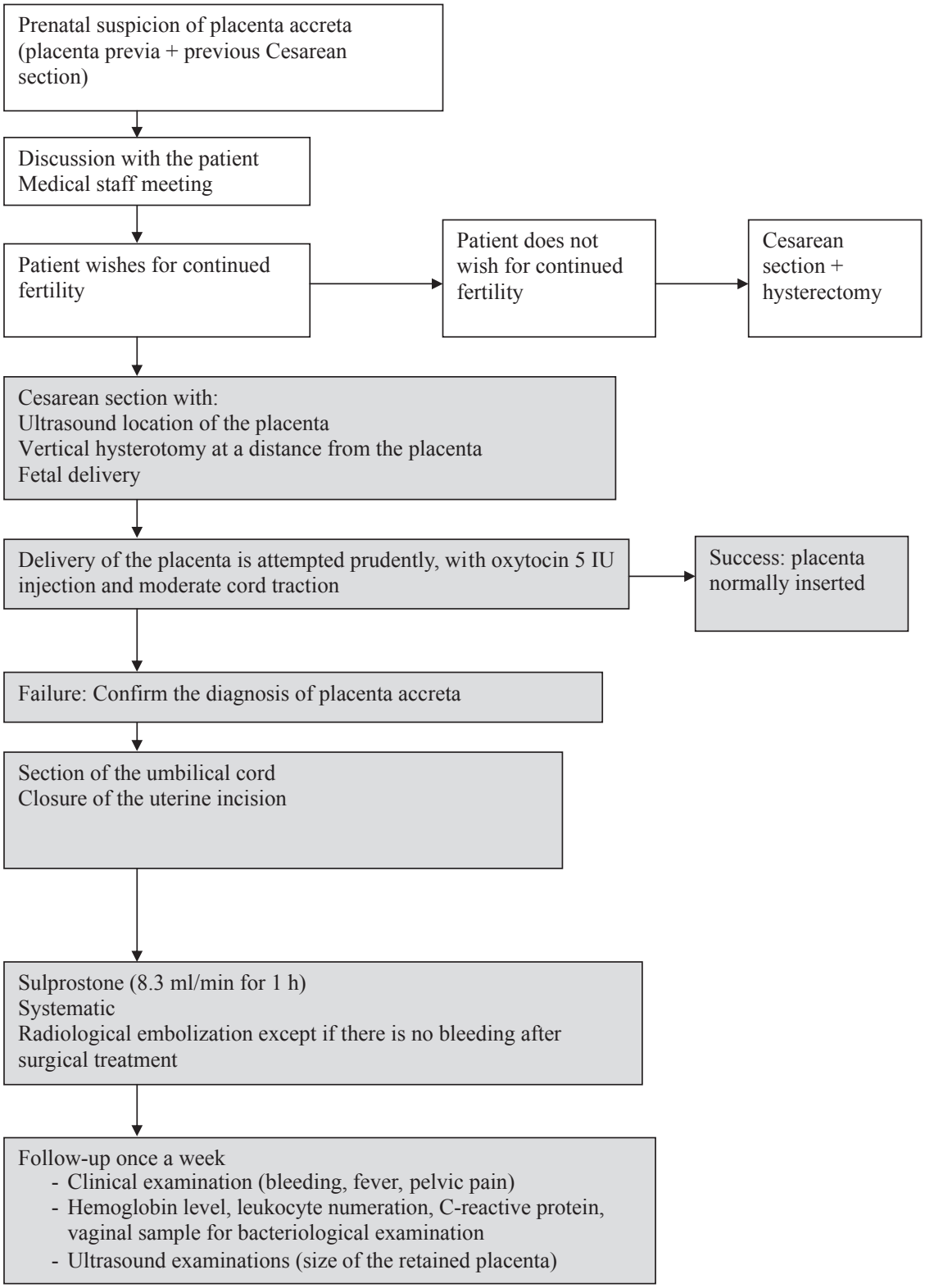

Figure 1 Conservative management of placenta accreta that is strongly suspected before delivery

assayed and vaginal samples are taken for bacteriological study.

OPTIMAL ADJUVANT THERAPY IN CONSERVATIVE MANAGEMENT

Methotrexate, uterine artery embolization and sulprostone are three adjuvant treatments described in several case reports involving conservative treatment[14,18–21]. The outcome when the placenta is left in place after methotrexate administration varies widely; it ranges from expulsion at 7 days to progressive resorption in roughly 6 months[14,18–20]. We do not use methotrexate at all. Similarly, only a few reports describe the outcome after embolization and leaving the placenta *in situ*[22]. In our practice, we perform, almost systematically, embolization of uterine arteries to diminish or prevent a postpartum hemorrhage. Sulprostone is a well-known uterotonic agent utilized in case of postpartum hemorrhage. It can be used to prevent or treat immediate abnormal postpartum bleeding. Data do not currently prove the benefit of adding this therapy to conservative treatment; however, its utilization may contribute to the prevention of major postpartum bleeding in the 2 or 3 days after delivery.

PRENATAL IDENTIFICATION OF PLACENTA ACCRETA FOR CONSERVATIVE MANAGEMENT

Prenatal identification of placenta accreta would facilitate the choices about management of delivery and allow the appropriate precautions (reinforcement of obstetric, anesthetic and radiology teams, blood transfusion readiness). However, the sensitivity and specificity of transvaginal or transabdominal ultrasound and magnetic resonance imaging vary from 33% to 95% in different studies; they depend greatly on placenta location[23–26]. For these reasons, imaging should be considered only when placenta accreta is suspected for clinical reasons (mainly placenta previa associated with previous Cesarean section). Moreover, systematic attempts at a careful and gentle intraoperative delivery of the placenta (intravenous injection of 5 IU oxytocin and moderate contraction), even when placenta accreta is strongly suspected before labor, should be preferable to confirm the diagnosis.

COMPLICATIONS OF CONSERVATIVE MANAGEMENT

Conservative management is a strategy that must be applied with discretion. Complications are possible and include sepsis and hemorrhage with failure of conservative management[21,27]. In case of secondary hemorrhage and/or sepsis following a conservative management, hysterectomy may become necessary. At present, the number of patients managed with this strategy is too low for an adequate evaluation of the risk of rare severe maternal morbidity or mortality. Accordingly, this type of management is presently appropriate only when rigorous monitoring can follow, in centers with adequate equipment and resources[26].

Ideally, these complications should be discussed prenatally with the patient to give her complete information about the different therapeutic strategies (extirpative or conservative). Given the difficulties mentioned above for prenatal diagnosis, this discussion is rarely possible. Accordingly, one possible option is to preserve maternal fertility and to diminish the risk of hemorrhage when placenta accreta is discovered during delivery.

FERTILITY AFTER CONSERVATIVE MANAGEMENT AND RISK OF RECURRENCE

In our experience, seven patients managed conservatively were contacted from 1–5 years afterwards, whereas ten were lost to long-term follow-up. Of these seven, one had another successful pregnancy 2 years later and another had two consecutive successful pregnancies, both complicated by placenta accreta, located at the same place, and treated conservatively again. The others chose, for various personal reasons, not to become pregnant again. None sought subsequent treatment for sterility.

The possibility of recurrence should thus be discussed with the woman when deciding on the initial conservative management. Moreover, in any subsequent pregnancies following a conservative management, the risk of placenta

accreta should be monitored carefully by appropriate investigations, particularly if the placenta is located in the same site as before.

CONCLUSIONS

Conservative management of placenta accreta appears to be a safe alternative to extirpative management. However, it must be applied cautiously and should be proposed only in centers with adequate resources, and the capability of securing a strict follow-up in order to detect and treat subsequent complications.

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25

ACQUIRED AND CONGENITAL HEMOSTATIC DISORDERS IN PREGNANCY AND THE PUERPERIUM

R. V. Ganchev and C. A. Ludlam

During normal pregnancy, a series of progressive changes in hemostasis occur that are overall procoagulant and help prevent excessive bleeding at the time of delivery. The concentrations of coagulation factors V, VII, VIII, IX, X, XII and von Willebrand factor (vWF) rise significantly (Table 1) and are accompanied by a pronounced increase in fibrinogen levels (up to two-fold from non-pregnant levels). Factor XIII levels tend to decrease in late pregnancy after an initial increase in the beginning of pregnancy. Markers of coagulation activation such as prothrombin fragments (PF1+2), thrombin–antithrombin complexes (TAT) and D-dimer are increased, while a decrease in physiological anticoagulants is manifested by a significant reduction in protein S activity and acquired activated protein C (APC) resistance. Fibrinolysis is inhibited not only by the rise in endothelium-derived plasminogen activator inhibitor-1 (PAI-1) but also by placenta-derived PAI-2. Microparticles derived from maternal endothelial cells and platelets, and from placental trophoblasts may contribute to the procoagulant effect[1]. Although concentrations of soluble tissue factor (TF) remain constant during normal pregnancy[2], monocyte TF activity and expression are lower when compared with those in non-pregnant women, possibly acting to counterbalance the procoagulant changes[3,4]. Local hemostasis at the placental trophoblast level is characterized by increased TF expression and low expression of tissue factor pathway inhibitor (TFPI)[1]. Approximately 4 weeks' post-delivery, the hemostatic system returns to that of the non-pregnant state[5].

Although the overall balance shifts towards hypercoagulability, occasionally medical conditions coincident with pregnancy and complications of pregnancy itself put excessive demands on maternal physiology and may result in a bleeding tendency. This chapter describes acquired and congenital hemostatic disorders that may lead to hemorrhagic complications in the obstetric patient.

Table 1 Coagulation system changes in normal pregnancy

	Increased	*Decreased*	*No change*
Systemic changes			
Procoagulant factors	I, V, VII, VIII, IX, X, XII	XIII	PC, AT
Anticoagulant factors	soluble TM	PS	
Adhesive proteins	vWF		
Fibrinolytic proteins	PAI-1, PAI-2	t-PA	soluble TF
Tissue factor (TF)		monocyte TF	
Microparticles (MP)	MP		
Local placental changes	TF	TFPI	

TM, thrombomodulin; PS, protein S; PC, protein C; AT, antithrombin; vWF, von Willebrand factor; PAI, plasminogen activator inhibitor; t-PA, tissue plasminogen activator; TFPI, tissue factor pathway inhibitor. Adapted from Brenner B. Haemostatic changes in pregnancy. *Thromb Res* 2004;114:409–14

ACQUIRED DISORDERS OF HEMOSTASIS

Thrombocytopenia

Thrombocytopenia is the most common hemostatic abnormality and may complicate up to 10% of all pregnancies. The normal platelet count ranges from 150 to 400×10^9/l, and thrombocytopenia is defined as a count of less than 150×10^9/l. The platelet count may decline by approximately 10% during normal pregnancy[6]. Spontaneous bleeding is unusual unless the count has fallen to below 30×10^9/l, but surgical bleeding or postpartum hemorrhage may occur as a consequence of platelets less than 50×10^9/l. Thrombocytopenia in pregnancy may result from variety of causes (Table 2). The timing of onset of these disorders during pregnancy and their clinical manifestations often overlap, making the identification of individual causes of thrombocytopenia sometimes problematic.

It is important to consider spurious thrombocytopenia as a possible cause of decreased platelet count before embarking on extensive investigations or treatment. This is a laboratory artefact due to EDTA-induced platelet aggregation *in vitro* and can be diagnosed by visual inspection of the blood film, when platelet changes are readily visible.

Gestational thrombocytopenia

Gestational, or incidental, thrombocytopenia (GT) is the most common cause of thrombocytopenia in pregnancy, affecting 5% of all pregnant women and accounting for more than 75% of cases of pregnancy-associated thrombocytopenia[7,8]. It presents as a mild to moderate thrombocytopenia ($100–150 \times 10^9$/l), which is detected incidentally often for the first time during the third trimester of pregnancy. The platelet count returns to normal within 7 days of delivery. GT is the physiologic thrombocytopenia that accompanies normal pregnancy and is thought to be due to hemodilution and/or accelerated platelet clearance[7,8]. It is an entirely benign condition, which is not associated with maternal hemorrhage or fetal or neonatal thrombocytopenia. It is, however, necessary to monitor the platelet count during pregnancy and, if it falls below 100×10^9/l, the diagnosis must be reviewed. Rare cases, subsequently confirmed as GT, have had counts as low as 50×10^9/l[9]. Epidural anesthesia is considered safe if the maternal platelet count is greater than 80×10^9/l. Delivery should proceed according to obstetric indications and the cord platelet count should be checked. GT is difficult to distinguish from idiopathic thrombocytopenic purpura, when thrombocytopenia is identified for the first time during pregnancy and no previous counts have been documented.

Idiopathic thrombocytopenic purpura

Idiopathic thrombocytopenic purpura (ITP) accounts for one to five cases of thrombocytopenia per 10 000 pregnancies[10] and 5% of cases of pregnancy-associated thrombocytopenia[7]; it

Table 2 Causes of pregnancy-associated thrombocytopenia

Pregnancy-specific	*Not pregnancy-specific*
Gestational (incidental) thrombocytopenia	Idiopathic thrombocytopenic purpura (ITP)
Pre-eclampsia	Thrombotic thrombocytopenic purpura (TTP)
HELLP syndrome (hemolysis, elevated liver enzymes and low platelets)	Hemolytic uremic syndrome (HUS)
	Systemic lupus erythematosus
Acute fatty liver of pregnancy (AFLP)	Viral infection (HIV, CMV, EBV)
	Antiphospholipid antibodies
	Consumptive coagulopathy
	Drug-induced thrombocytopenia
	Type 2B von Willebrand disease
	Congenital

From McCrae KR. Thrombocytopenia in pregnancy: differential diagnosis, pathogenesis and management. *Blood Rev* 2003;17:7–14

is the most common cause of significant thrombocytopenia in the first trimester. ITP is characterized by premature clearance of platelets by antiplatelet antibodies and consequent increased production of platelets by the bone marrow. The most common presentation is the finding of an asymptomatic thrombocytopenia on a routine blood count, when the distinction from GT may be difficult. Patients occasionally present for the first time with severe thrombocytopenia in pregnancy, and women with previously diagnosed ITP often experience an exacerbation in pregnancy[11]. Symptomatic patients present with minor bruises or petechiae, bleeding from mucosal surfaces, or rarely fatal intracranial bleeding.

As in the non-pregnant patient, ITP is a diagnosis of exclusion with thrombocytopenia and normal or increased megakaryocytes in the bone marrow in the absence of other causes. There is no confirmatory laboratory test, and documentation of a low platelet count outside pregnancy is invaluable. Practically, however, in the absence of a platelet count prior to pregnancy, significant thrombocytopenia ($< 100 \times 10^9$/l) in the first trimester, with a declining platelet count as gestation progresses, is most consistent with ITP. In contrast, mild thrombocytopenia developing in the second or the third trimester and not associated with hypertension or proteinuria most likely represents GT[12]. Bone marrow examination is unnecessary unless there is suspicion of leukemia, lymphoma or malignant infiltration.

The decision to treat a pregnant woman with ITP is based on assessment of the risk of significant maternal hemorrhage. The count usually falls as pregnancy progresses, with a nadir in the third trimester[11], and active treatment may have to be instituted to ensure a safe platelet count at the time of delivery. The incidence of antepartum hemorrhage is not increased in maternal ITP, but there is a small increased risk of postpartum hemorrhagic complications, not from the placental bed but from surgical incisions such as episiotomies and from soft-tissue lacerations[13].

Asymptomatic patients with platelet counts $> 20 \times 10^9$/l do not require treatment until delivery is imminent but should be carefully monitored. Platelet counts of $> 50 \times 10^9$/l are regarded as safe for normal vaginal delivery, and those $> 80 \times 10^9$/l are safe for Cesarean section, spinal or epidural anesthesia[14].

The major treatment options for maternal ITP are corticosteroids or intravenous immunoglobulin (IVIg). There is no evidence, however, that either of these treatment modalities administered to the mother affects the platelet count in the fetus or neonate. If the duration of treatment is likely to be short, i.e. starting in the third trimester, corticosteroids are an effective option. An initial dose of 1 mg/kg prednisolone (based on pregnancy weight) is recommended[11,14], which can be subsequently tapered. In addition to their toxicities in non-pregnant individuals, such as osteoporosis and weight gain, corticosteroids increase the incidence of pregnancy-induced hypertension and gestational diabetes, and may promote premature rupture of the fetal membranes.

Concerns about potential adverse maternal effects of steroids have led some to use IVIg as a first-line therapy in pregnancy[15,16]. Others reserve this treatment for patients in whom steroid therapy is likely to be prolonged or in whom an unacceptably high maintenance dose is required (> 7.5 mg prednisolone daily). The conventional dose of IVIg is 0.4 g/kg/day for 5 days, although 1 g/kg/day for 2 days has been used successfully and may be more convenient[11]. A persistent and predictable response is obtained in 80% of the cases. The response to therapy usually occurs within 24 h (more rapid than with steroids) and is maintained for 2–3 weeks. After an initial response, repeat single infusions can be used to prevent hemorrhagic symptoms and ensure an adequate platelet count for delivery.

Therapeutic options for those women with severely symptomatic ITP refractory to oral steroids or IVIg include high-dose intravenous methylprednisolone (1.0 g), perhaps combined with IVIg, or azathioprine[14], but these should only be considered after careful assessment of the potential risks. Splenectomy is now rarely performed in pregnancy. It remains an option if all other attempts to increase the platelet count fail and is best performed in the second trimester.

The offspring of mothers with ITP may also develop thrombocytopenia, as a result of the

transplacental passage of maternal antiplatelet IgG[7,12]. The incidence of severe neonatal thrombocytopenia ($< 50 \times 10^9$/l) has been reported between 9 and 15%, with intracranial hemorrhage occurring in 0–1.5% of infants[17]. Due to the inability of maternal clinical characteristics to predict neonatal thrombocytopenia, antenatal (cordocentesis) and perinatal (fetal scalp blood sampling) procedures for determination of fetal platelet count have been considered in the past. Cordocentesis carries a mortality of 1–2%, however, whereas scalp blood sampling is associated with artefactually low results and risk of significant hemorrhage. For these reasons, both procedures are now largely abandoned in the management of ITP in pregnancy. The most reliable predictor of fetal thrombocytopenia is a history of thrombocytopenia at delivery in a prior sibling[18].

In view of the very low risk of serious neonatal hemorrhage, it is now agreed that the mode of delivery in ITP should be determined by purely obstetric indications[11,14]. If the maternal platelet count remains low at the time of delivery, despite optimal antenatal management, platelet transfusion may be required to treat maternal bleeding. Mothers with thrombocytopenia are unlikely to bleed from the uterine cavity after the third stage of labor, provided that there are no retained products of conception. However, bleeding may occur from surgical wounds, episiotomies or perineal tears. Non-steroidal anti-inflammatory drugs should be avoided for postpartum analgesia. ITP should not exclude women from consideration for peripartum thrombosis prophylaxis. Prophylactic doses of low-molecular weight heparin are generally safe if the platelet count is greater than 50×10^9/l. Following delivery, a cord blood platelet count should be determined in all cases. Since the neonatal platelet count may decline for 4–5 days after delivery[11], daily monitoring is indicated. Infants should be closely observed and treatment is rarely required. In those with clinical hemorrhage or platelet count $< 20 \times 10^9$/l, treatment with IVIg produces a rapid response. Life-threatening hemorrhage should be managed with platelet transfusion combined with IVIg[11].

Secondary autoimmune thrombocytopenia

Antiphospholipid syndrome

The diagnosis of primary antiphospholipid syndrome requires the coexistence of clinical manifestations (either vascular thrombosis or pregnancy morbidity) with laboratory evidence of reproducible antiphospholipid antibodies (either lupus anticoagulant or anticardiolipin antibody)[19]. Primary antiphospholipid syndrome is associated with autoimmune thrombocytopenia in 20–40% of cases[20]. Thrombocytopenia is rarely severe and usually does not require treatment. If treatment is necessary, management options during pregnancy are similar to those for primary ITP. However, primary antiphospholipid syndrome is associated with recurrent spontaneous abortions before 10 weeks of gestation, and women with the condition are at risk of intrauterine fetal growth restriction or death, pre-eclampsia and maternal thrombosis[19,21].

A combination of low-dose aspirin and low-dose subcutaneous heparin is helpful in preventing recurrent spontaneous abortions in antiphospholipid syndrome[22]. Antenatal and postnatal thrombosis prophylaxis is indicated in women with antiphospholipid syndrome and a history of thrombosis[23]. Moderate thrombocytopenia should not alter decisions about antiplatelet or antithrombotic therapy in antiphospholipid syndrome[20].

Systemic lupus erythematosus

Immune platelet destruction may occur in systemic lupus erythematosus (SLE) because of antiplatelet antibodies or immune complexes, but thrombocytopenia is seldom severe; less than 5% of cases have platelet count $< 30 \times 10^9$/l during the course of the disease[13]. Thrombocytopenia is often the first presenting feature and may precede any other manifestations of the condition by months or years. It is difficult to document any special effect of pregnancy on SLE; the general consensus is that pregnancy does not affect the long-term prognosis of SLE, but that pregnancy itself may be associated with more flare-ups, particularly in the puerperium[24]. The management of isolated

thrombocytopenia associated with SLE in pregnancy is governed by the principles outlined for ITP. Women with SLE are also at risk for pre-eclampsia which may be complicated by thrombocytopenia.

HIV-associated thrombocytopenia

HIV-related thrombocytopenia can be caused by increased platelet destruction by antiplatelet antibodies or immune complexes, commonly during early-onset HIV. In advanced disease, drugs and infection may lead to marrow dysfunction that results in thrombocytopenia. In one series of HIV-positive women, approximately 3% were thrombocytopenic and, in most cases, thrombocytopenia was believed to be directly related to HIV infection[25]. Slightly fewer than half of the thrombocytopenic women had a platelet count $< 50 \times 10^9$/l, and 20% had hemorrhagic complications[25].

Treatment with antiretroviral therapy tends to improve the defective thrombopoiesis and increase the platelet count in HIV-positive patients, but some antiretroviral drugs may also cause thrombocytopenia. When immune destruction is believed to be a significant component of thrombocytopenia, IVIg may be required to treat hemorrhagic symptoms or to increase the platelet count before delivery in thrombocytopenic HIV-positive women[25]. Corticosteroids are also effective but may be associated with increased risk of further immunosuppression and infection. Thrombotic thrombocytopenic purpura is found more frequently in HIV-infected patients and should be treated accordingly. Cesarean delivery reduces the risk of transmission of HIV from mother to fetus.

Drug-induced thrombocytopenia

Drug-induced thrombocytopenia may be caused by immune- or non-immune-mediated platelet destruction or suppression of platelet production. Both are uncommon in pregnancy, but drug-induced causes should be considered and excluded. Drugs which are commonly associated with thrombocytopenia are shown in Table 3.

A unique form of drug-induced thrombocytopenia is heparin-induced thrombocytopenia (HIT). It occurs in 1–5% of patients receiving unfractionated heparin but is considerably less common in patients treated with low-molecular weight heparins. HIT is caused by an antibody directed against the heparin–platelet factor 4 complex, which can induce platelet activation and aggregation *in vivo*. Unlike other thrombocytopenias, HIT is complicated by arterial and/or venous thrombosis which may be life-threatening. Laboratory tests are available to confirm the diagnosis. HIT has been reported in pregnancy[26,27], although it may be less common in pregnant than in non-pregnant individuals[28]. Fetal thrombocytopenia does not occur because heparin does not cross the placenta. Heparin should be withdrawn immediately on clinical suspicion of HIT. If ongoing anticoagulation is urgently required, the heparinoid danaparoid may be used in most patients. Danaparoid has been used successfully to treat HIT in pregnancy[27]. Hirudin is an alternative in non-pregnant patients, but experience is limited in

Table 3 Drugs causing thrombocytopenia

A. *Immune mediated*
Acetaminophen
Aminosalicylic acid
Amiodarone
Amphotericin B
Cimetidine
Diclofenac
Gold/gold salts
Levamisole
Methyldopa
Quinine and quinidine
Ranitidine
Sulfasalazine
Vancomycin
B. *Unique antibody-mediated process*
Heparin
C. *Suppression of platelet production*
Anagrelide
Valproic acid
D. *Suppression of all hematopoietic cells*
Chemotherapeutic agents

Adapted from George JN, Raskob GE, Shah SR, *et al*. Drug-induced thrombocytopenia: a systematic review of published case reports. *Ann Intern Med* 1998;129:886–90

pregnancy and its use is not recommended unless there is no suitable alternative[29]. Platelet transfusion should be avoided in patients with HIT. Because HIT is potentially life-threatening, all women must have a platelet count before treatment with heparin begins. The count must be repeated on day 4 of first exposure to heparin or day 1 of repeat exposure and then at least weekly for the first 3 weeks.

Thrombocytopenia with microangiopathy

Several syndromes are associated with thrombocytopenia as a result of platelet activation, red cell fragmentation, and a variable degree of hemolysis (microangiopathic hemolytic anemia, MAHA). Some syndromes are unique to obstetric practice. The differential diagnosis is particularly pertinent for obstetricians and is important because management options differ. The differential diagnosis is summarized in Table 4.

Pre-eclampsia and HELLP syndrome

Pre-eclampsia affects approximately 6% of all pregnancies, most often those of primigravidas less than 20 or greater than 30 years of age[7]. The criteria for the condition include hypertension and proteinuria > 300 mg/24 h developing after 20 weeks of gestation[6]. Although the clinical manifestations of pre-eclampsia generally do not become evident until the third trimester, the lesions underlying this disorder occur early in pregnancy and involve deficient remodelling of the maternal uterine vasculature by placental trophoblast cells[30,31]. Thrombocytopenia develops in approximately 50% of patients, with the severity usually proportional to the severity of the pre-eclampsia. Occasionally, the onset of thrombocytopenia precedes other manifestations of pre-eclampsia[7]. Current understanding of the pathogenesis of thrombocytopenia in pre-eclampsia is that it is due to excessive platelet activation, adhesion of platelets to damaged or activated endothelium, and/or clearance of IgG-coated platelets by the reticuloendothelial system[7].

Activation of the coagulation cascade occurs in most patients with pre-eclampsia; however, screening coagulation tests such as activated partial thromboplastin time (APTT), prothrombin time (PT) and fibrinogen are usually normal. Regardless, more sensitive markers of hemostatic activity such as D-dimer and TAT complexes are often elevated. In severe pre-eclampsia, the activation of coagulation results in consumption of clotting factors and therefore prolongation of the clotting test times and a fall in plasma fibrinogen.

Table 4 Differentiation of pregnancy-associated microangiopathies

Diagnosis	*TTP*	*HUS*	*HELLP*	*Pre-eclampsia*	*AFLP*
Time of onset	2nd trimester	postpartum	3rd trimester	3rd trimester	3rd trimester
Hemolysis	+++	++	++	+	+
Thrombocytopenia	+++	++	++	++	+/±
Coagulopathy	-	-	±	±	+++
Liver disease	±	±	+++	±	+++
Renal disease	±	+++	+	+	±
Hypertension	rare	±	±	+++	±
CNS disease	+++	±	±	±	+
Effect of delivery on disease	none	none	recovery	recovery	recovery
Management	early plasma exchange	supportive ± plasma exchange	supportive consider plasma exchange if persists	supportive plasma exchange rarely required	supportive

TTP, thrombotic thrombocytopenic purpura; HUS, hemolytic uremic syndrome; HELLP, hemolysis, elevated liver enzymes, and low platelets; AFLP, acute fatty liver of pregnancy.
Adapted from Horn EH. Thrombocytopenia and bleeding disorders. In James DK, Steer PJ, Weiner CP, Gonik B, eds. *High-Risk Pregnancy: Management Options*, 3rd edn, Elsevier, 2006:901–24

The HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome is often considered to be a variant of pre-eclampsia and is the most common cause of severe liver disease in pregnant women[32]. Criteria for the HELLP syndrome include microangiopathic hemolytic anemia, aspartate aminotransferase (AST) > 70 U/l and thrombocytopenia, with a platelet count $< 100 \times 10^9$/l[33]. Patients may present with severe epigastric and right upper quadrant pain, which need not be accompanied by hypertension and proteinuria. Exacerbation of HELLP syndrome may occur postpartum and there is a recurrence risk of approximately 3% in subsequent pregnancies. The syndrome occasionally presents postpartum, usually within 48 h, but rarely as late as 6 days after delivery. Despite their similarities, HELLP is associated with significantly greater maternal and fetal morbidity and mortality than pre-eclampsia[7].

Management of pre-eclampsia/HELLP syndrome is supportive and should be focused on stabilizing the patient medically prior to early delivery of the fetus. Platelet transfusions may be needed if bleeding occurs or if thrombocytopenia is severe and Cesarean delivery is planned, though the survival time of transfused platelets in patients with pre-eclampsia is diminished[6]. If required, the consumptive coagulopathy resulting from pre-eclampsia should be treated with fresh frozen plasma (FFP). Consumptive coagulopathy severe enough to result in depletion of fibrinogen is uncommon in these disorders, but, if severe hypofibrinogenemia is present, plasma fibrinogen levels can be raised with cryoprecipitate. In most cases, the clinical manifestations of pre-eclampsia resolve within several days after delivery, although the platelet count may decline for additional 24–48 h[34]. If severe thrombocytopenia, hemolysis or organ dysfunction persists after delivery, plasma exchange may be considered[35], but the diagnosis should also be reviewed.

Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome

Thrombotic thrombocytopenia (TTP) and hemolytic uremic syndrome (HUS) share the central features of microangiopathic hemolytic anemia and thrombocytopenia. Though neither disease occurs exclusively during pregnancy, the incidence of both is increased in this setting, and up to 10% of all cases of TTP occur in pregnant patients[6].

TTP is defined by a pentad of symptoms that include MAHA, thrombocytopenia, neurological abnormalities, fever, and renal dysfunction, although the complete pentad is present at the time of diagnosis in less than 40% of patients[34]. The clinical manifestations of HUS are similar. Neurological abnormalities are particularly a feature of patients with TTP; renal dysfunction is more severe in patients with HUS. Congenital or acquired deficiency of a specific von Willebrand factor-cleaving protease, ADAMTS 13, and the consequent increased level of high-molecular weight multimers of vWF play a central role in the pathogenesis of TTP. Interestingly, levels of ADAMTS 13 decrease during normal pregnancy, perhaps accounting, at least in part, for the predisposition to development of thrombotic microangiopathy in this setting[36].

TTP and HUS may be difficult to discern from one another, as well as from other pregnancy-associated microangiopathies such as pre-eclampsia or the HELLP syndrome. The extent of microangiopathic hemolysis is generally more severe in TTP or HUS than in pre-eclampsia or HELLP, and the former disorders are not associated with hypertension. The time of onset of these disorders is also helpful in differentiating between them. TTP usually presents in the second trimester, HUS in the postpartum period and pre-eclampsia and the HELLP syndrome almost exclusively in the third trimester[7,34,37]. Plasma antithrombin levels are normal in TTP and HUS and reduced in pre-eclampsia and HELLP[34]. Another feature distinguishing these disorders is their response to delivery. Whereas pre-eclampsia and the HELLP syndrome usually improve following delivery, the courses of TTP and HUS do not. Hence, pregnancy termination should not be considered therapeutic in patients with TTP or HUS[38]. However, TTP responds equally well to plasma exchange in pregnant and non-pregnant patients with > 75% of patients achieving remission[6]. Plasma exchange should be instituted as soon as possible after the diagnosis of TTP. Daily plasma exchange should continue until at least 48 h after complete remission is obtained.

Repeated plasma exchange cycles are usually maintained until delivery. Management of HUS is supportive and includes renal dialysis and red cell transfusion. Plasma exchange has no proven benefit in the treatment of HUS.

The placental ischemia and increased incidence of premature delivery that complicate pregnancies in patients with TTP and HUS may lead to poor fetal outcomes, but these are markedly improved by good management of these conditions.

Acute fatty liver of pregnancy

Acute fatty liver of pregnancy affects one of every 5000–10 000 pregnancies and is most common in primagravidas during the third trimester[39]. The cause of the condition is unknown in the majority of instances, but some patients may have a long-chain 3-hydroxy-acyl CoA dehydrogenase (LCHAD) deficiency[40].

Patients present with overt signs of hepatic damage and may have hemorrhagic manifestations, perhaps the result of decreased synthesis of clotting factors and consumptive coagulopathy. Evidence for consumptive coagulopathy is provided by thrombocytopenia, prolonged APTT and PT and by decrease in fibrinogen and antithrombin levels.

AFLP is most aptly viewed as part of the pregnancy-associated microangiopathies; up to 50% of patients with AFLP may also meet criteria for pre-eclampsia. The extent of microangiopathic hemolysis and thrombocytopenia is generally mild compared to that observed in HELLP, TTP, or HUS[41].

Delivery is the most important aspect of management, as it starts the reversal of the pathological process. Coagulation defects are managed supportively with fresh frozen plasma, cryoprecipitate and platelet concentrates. In these patients, normalization of hemostatic abnormalities may not occur for up to 10 days after delivery. Fetal mortality in this disorder approaches 15%, though maternal mortality occurs in less than 5% of cases[39].

CONSUMPTIVE COAGULOPATHY

Consumptive coagulopathy (disseminated intravascular coagulation) is an acquired clinicopathologic syndrome, characterized by activation of the coagulation system, and resulting in widespread intravascular deposition of fibrin-rich thrombi. Consumption of clotting factors usually leads to a bleeding diathesis, although a small percentage of affected individuals may go on to develop widespread thrombosis with peripheral organ ischemia. Some degree of consumptive coagulopathy accompanies most forms of obstetric hemorrhage; however, the greater risk of coagulopathy usually arises from consumption of clotting factors and platelets as a result of massive obstetric hemorrhage. The combination of massive hemorrhage and coagulation failure is recognized as one of the most serious complications in pregnancy.

Obstetric consumptive coagulopathy is usually acute in onset (except as an uncommon late complication of retained dead fetus) and can be caused by a variety of disease processes. It is triggered by several mechanisms including release of TF into the circulation, endothelial damage to small vessels and production of procoagulant phospholipids in response to intravascular hemolysis[42] (Table 5). Blood loss

Table 5 Mechanism of consumptive coagulopathy in pregnancy

A. *Injury to vascular endothelium*
Pre-eclampsia
Hypovolemic shock
Septicemic shock
B. *Release of tissue factor (TF)*
Placental abruption
Amniotic fluid embolism
Retained dead fetus
Placenta accreta
Acute fatty liver
C. *Production of procoagulant*
Fetomaternal hemorrhage
Phospholipids
Incompatible blood transfusion
Septicemia
Intravascular hemolysis

From Anthony J. Major obstetric hemorrhage and disseminated intravascular coagulation. In James DK, Steer PJ, Weiner CP, Gonik B, eds. *High-Risk Pregnancy: Management Options*, 3rd edn. Elsevier, 2006:1606–23

itself with transfusion and volume replacement may also trigger consumptive coagulopathy. With obstetric complications associated with coagulation failure, there may be interaction of several mechanisms.

These triggers lead to the generation of thrombin, cause defects in inhibitors of coagulation and suppress fibrinolysis. Thrombin promotes platelet activation and aggregates form, which occlude the microvasculature and result in thrombocytopenia. Thrombin becomes bound to antithrombin (AT) and thrombomodulin, and these proteins are soon consumed. Following binding to thrombomodulin, thrombin activates the anticoagulant protein C, which also becomes depleted, predisposing to microvascular thrombosis. In consumptive coagulopathy secondary to sepsis, increased levels of C4b-binding protein result in the binding of more free protein S, and therefore render it unavailable to be a cofactor of the anticoagulant protein C. PAI-1 is increased out of proportion to the level of tissue plasminogen activator (tPA), resulting in depressed fibrinolysis. Fibrin is formed, but its removal is impaired, leading to thrombosis of small and middle-size vessels. The passage of erythrocytes through partially occluded vessels leads to red cell fragmentation and microangiopathic hemolytic anemia.

Placental abruption is the most common cause of obstetric consumptive coagulopathy (60% of cases; 5% of all abruptions), but the syndrome is uncommon unless the abruption is severe enough to cause fetal death. Initially, increased intrauterine pressure forces TF-rich decidual fragments into the maternal circulation. However, in severe abruption, hypovolemic shock, large volume transfusion and high levels of fibrin degradation products (FDPs) that act as anticoagulants themselves exacerbate the situation. Retained dead fetus may cause chronic consumptive coagulopathy by release of TF from the dead fetus into the maternal circulation, but generally only if the fetus is at least 20 weeks' size and the period of death is more than 4 weeks. Amniotic fluid embolism occurs during labor, Cesarean section or within a short time of delivery. Amniotic fluid is rich in TF and may enter uterine veins when there has been a tear in the uterine wall. The condition may lead to maternal death as a result of severe pulmonary hypertension following embolization of the pulmonary vessels by fetal squames. If the mother survives this acute event, there may be an anaphylactoid reaction to the presence of the fetal tissues in the maternal circulation associated with cardiovascular collapse, pulmonary edema and the development of consumptive coagulopathy. Sepsis causes consumptive coagulopathy via the release of proinflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin 1 (IL-1) and IL-6, which may trigger TF expression by monocytes and endothelial cells[43]. Severe pre-eclampsia with intense vasospasm and resulting ischemia causes endothelial injury and expression of TF.

Acute consumptive coagulopathy in pregnancy presents almost invariably with bleeding – either as a genital tract bleeding from the placental site or bleeding from the wound after Cesarean section. There may be excessive bleeding from venepuncture sites.

Laboratory investigations are essential to establish the diagnosis of consumptive coagulopathy. The characteristic changes are a low or falling platelet count and a prolongation of the APTT and PT. Fibrinogen level falls with the progression of the coagulopathy; the normal range in late pregnancy is 4–6 g/l which is significantly higher than the non-pregnant range, 2–4 g/l; coagulation fails at levels < 1 g/l. FDPs are increased, reflecting the excessive deposition of fibrin and enhanced fibrinolysis. The D-dimer is the most commonly used parameter to assess FDP levels, as it is specific for fibrin breakdown. Normal D-dimer levels are under 200 ng/ml, but often exceed 2000 ng/ml in cases of consumptive coagulopathy. The blood film may show evidence of microangiopathic hemolysis with fragmentation of red cells.

The basic principles in treatment of consumptive coagulopathy are removal of the precipitating cause if possible, correction of aggravating factors, and replacement of missing coagulation factors and platelets. Correction of aggravating factors such as shock and hypoxia is important. This includes red cell transfusion if necessary and oxygen administration. Intravenous antibiotics should be given if sepsis is suspected. Replacement of clotting factors is most effectively done with fresh frozen plasma.

If there is severe hypofibrinogenemia, cryoprecipitate may be required. Platelets should be maintained $> 50 \times 10^9$/l in the presence of active bleeding by the administration of blood group-compatible platelets. Any etiological condition should be promptly treated; it often requires delivery of the fetus. Heparin use often leads to excessive bleeding and therefore does not usually have a role in obstetric consumptive coagulopathy except in the cases of a retained dead fetus. Similarly, antifibrinolytic drugs (tranexamic acid, aprotinin) are not helpful and are usually contraindicated because they inhibit the removal of deposited fibrin by fibrinolysis.

The usual regimen, when there is coagulation failure in obstetric practice, includes administration of FFP, platelets and cryoprecipitate. FFP contains fibrinogen and all coagulation factors. Each unit is approximately 250 ml and the usual requirement is 4–6 units. Platelet concentrates are used to increment platelet count. A unit of platelets is approximately 60 ml in volume; it should raise the platelet count by 5000×10^9/l and the usual dose is five packs. Cryoprecipitate is enriched in fibrinogen, factor VIII and vWF and is particularly useful for the treatment of hypofibrinogenemia. Ten bags (each 30 ml) of cryoprecipitate should increase the fibrinogen level by 1 g/l. One 250 ml unit of FFP contains a similar amount of fibrinogen (500 mg) as one 30 ml bag of cryoprecipitate (435 mg).

The D-dimer, platelet count and fibrinogen level are clinically useful tests in monitoring replacement therapy if the patient is bleeding. The aim should be to achieve a platelet count $> 50 \times 10^9$/l, a fibrinogen level > 1.0 g/l and significant shortening of the APTT and PT to approach their normal values.

Although recombinant activated factor VII (rFVIIa) is not licensed for use in pregnancy, it has been used in obstetric patients with consumptive coagulopathy and severe bleeding not responsive to other treatment options[44,45] (see Chapter 26). Consumptive coagulopathy is not a contraindication to the use of rFVIIa if massive bleeding is occurring. However, caution should be used in patients with major consumptive coagulopathy because there are occasional reports of thrombosis and consumptive coagulopathy after the use of rFVIIa[46].

Recombinant activated protein C (raPC) has been successfully used in sepsis-related obstetric consumptive coagulopathy at a dose of 24 μg/kg/h in a 96-h infusion[47,48]. Caution is needed in patients with severe thrombocytopenia ($< 30 \times 10^9$/l) because of the increased incidence of intracerebral hemorrhage associated with its use; monitoring of the platelet count and transfusion of platelets as necessary are important considerations. In addition to acting as an anticoagulant, raPC has direct anti-inflammatory and anti-apoptotic properties[49]. This may explain in part why the other endogenous anticoagulants (antithrombin and tissue factor pathway inhibitor) used in severe sepsis have not shown such good efficacy.

The treatment of such underlying conditions such as abruptio placentae, uterine rupture and fetal death require immediate obstetric attention. Usually, there has been extensive hemorrhage and red cell transfusion is needed in addition to correction of the coagulation failure.

FACTOR VIII INHIBITORS

Acquired hemophilia is due to the development of an autoantibody to factor VIII (FVIII). The estimated incidence is approximately 1 per 1 000 000 per annum. Most cases occur in healthy individuals without discernible risk factors, but the condition is associated with autoimmune conditions such as rheumatoid arthritis and SLE, inflammatory bowel disease, multiple sclerosis and malignancies. In up to 11% of cases, the associated factor is a recent or ongoing pregnancy[50].

Acquired hemophilia may occur in relation to any pregnancy, but the risk appears to be greatest after the first delivery. Onset is usually at term or within 3 months postpartum, but may only become evident 12 months post-delivery[51]. Clinical manifestations do not necessarily correlate with inhibitor levels and can range from spontaneous bruising to life-threatening hemorrhage. FVIII inhibitors may cross the placenta and persist in the neonate for up to 3 months, but neonatal complications are rare[51]. Spontaneous resolution occurs in almost 100% of women first diagnosed in the postpartum period after 30 months[50].

Basic coagulation studies in acquired hemophilia demonstrate a prolonged APPT with a normal PT and thrombin time (TT). If plasma from the patient is mixed with normal plasma, the APPT remains prolonged due to the inhibitor antibody neutralizing the FVIII in the normal plasma. FVIII inhibitors must be differentiated from a lupus inhibitor by specific tests because the clinical implications are profoundly different. Quantification of FVIII inhibitor is by the Bethesda assay, and checking this level may help in determining the choice of therapy and monitoring the progress of the patient.

Treatment is aimed at control of bleeding and accelerating the elimination of inhibitors. Hematological measures to minimize blood loss aim to compensate for the loss of FVIII. Choice of product to attempt to normalize hemostasis depends on various considerations, including the severity of bleeding, availability of clotting factor concentrates, inhibitor level and cross-reactivity of inhibitor to porcine FVIII. Human FVIII may be effective if the titer of inhibitor is low, i.e. less than 10 Bethesda units. At higher levels, use of porcine FVIII which may not cross-react with the inhibitor, and recombinant FVIIa or prothrombin complex concentrate (PCC) becomes necessary[52].

Inhibiting the production of the inhibitor is the second management aim. Prednisolone at dose of 1 mg/kg is associated with a loss of inhibitor in 50% of patients with acquired hemophilia[52]. Other immunosuppressives should be considered if there is no response to steroids. Addition of cyclophosphamide (2.0–3.0 mg/kg) should be considered at 3 weeks if there is no decline in the inhibitor titer, or earlier if there is continued bleeding. Other methods to reduce inhibitor levels include azathioprine, plasma exchange or infusion of IVIg.

ANTICOAGULANT THERAPY DURING PREGNANCY AND THE PERIPARTUM PERIOD

Anticoagulant therapy is indicated during pregnancy in the following cases:

(1) Prevention and treatment of venous thromboembolism (VTE);

(2) Prevention and treatment of systemic embolism in patients with mechanical heart valve prostheses;

(3) Prevention of pregnancy complications in women with antiphospholipid syndrome (APS) or other thrombophilia and prior pregnancy complications.

The anticoagulants currently available for the prevention and treatment of VTE and arterial thromboembolism include heparin and heparin-like compounds (unfractionated heparin (UFH), low-molecular weight heparin (LMWH), and heparinoids) and coumarin derivatives, e.g. warfarin. The 'direct' thrombin inhibitors, such as hirudin, cross the placenta and have therefore not yet been evaluated during pregnancy[53].

Heparins are the anticoagulant of choice during pregnancy for situations in which their efficacy is established. Neither UFH, LMWH nor heparinoids cross the placenta[54]. Heparins are not associated with any known teratogenic risk, and the fetus is not anticoagulated as a result of maternal heparin use. LMWHs have potential advantages over UFH during pregnancy because they have a longer plasma half-life and a more predictable dose-response than UFH, with the potential for once-daily administration. In addition, LMWHs are associated with a lower risk of HIT and osteoporosis than UFH.

Coumarin derivatives such as warfarin cross the placenta and have the potential to cause teratogenicity as well as anticoagulate the fetus predisposing to bleeding *in utero*. It is probable that oral anticoagulants are safe during the first 6 weeks of gestation, but there is an approximately 5% risk of developmental abnormalities of fetal cartilage and bone if they are taken between 6 and 12 weeks' gestation[55]. The risk of warfarin embryopathy is dose-dependent, with an increased risk when the daily warfarin dose exceeds 5 mg[56]. Fetal intracranial bleeds *in utero* are a well-established complication after exposure to these drugs during any trimester. In general, coumarins should not be used for the prevention or treatment of VTE in pregnancy, but they remain the anticoagulants of choice for the management of pregnant women with mechanical heart valve prostheses. Because of

the hemorrhagic risk to both mother and fetus, warfarin should be avoided beyond 36 weeks gestation.

LMWHs are currently widely used for the prevention and treatment of gestational VTE. In our institution, women on prophylactic doses of LMWH are advised to have the dose of the LMWH tailed off at the end of pregnancy and omit their dose if labor is suspected. Women on a therapeutic dose of LMWH are admitted in advance of planned induction to be converted to the therapeutic dose of intravenous UFH. They should omit LMWH on the day of admission and should be started on UFH, aiming for an APTT ratio of 1.5–2.0. UFH should be reduced to 500 IU/h when contractions start, aiming for an APTT ratio < 1.5 and should be stopped at the second stage of labor or earlier if it appears that a Cesarean section may be required. In the latter case, protamine sulfate may be needed for reversal of UFH if the APTT ratio remains > 1.5. Postpartum, the heparin infusion can be restarted 4 h post-delivery at 500 IU/h, providing there is no bleeding. Patients are restarted on a therapeutic dose of LMWH 2–3 days after delivery. Warfarin can be started 4–5 days postpartum, and LMWH should be continued until an international normalized ratio (INR) of 2.0 or greater is reached on two consecutive days. Breastfeeding is safe on UFH, LMWH and warfarin.

Epidural anesthesia is generally safe in women following discontinuation of UFH, providing their coagulation screen is normal and their platelet count is $> 80 \times 10^9$/l. It remains unclear what period of time should elapse between the last dose of LMWH and insertion or removal of an epidural or spinal catheter, or how long the time interval should be until the next dose. In practice, it is reasonable to allow at least 12 h to elapse after a prophylactic dose of LMWH before inserting an epidural or spinal catheter, but a delay up to 24 h may be necessary in patients on therapeutic doses of LMWH. At least 2 h should elapse after insertion of the catheter before LMWH is given again. If there have been difficulties with the procedure, then it is prudent to delay prior to giving further prophylaxis.

Pregnant women with prosthetic heart valves pose a problem because of the lack of reliable data regarding the efficacy and safety of antithrombotic therapy during pregnancy. However, it appears reasonable to adopt one of the following three approaches:

(1) Oral anticoagulants throughout pregnancy;

(2) Replacing oral anticoagulants with UFH from weeks 6 to 12;

(3) UFH throughout pregnancy.

In the first two regimens, heparin is usually substituted for the oral anticoagulant close to term. The use of LMWH for anticoagulation in patients with artificial heart valves is still debatable.

As Walker[57] has so succinctly stated, decisions about the most appropriate anticoagulant regimen during pregnancy for women with mechanical heart valve prostheses must be made on an individual patient basis after careful counseling, and should be based as far as possible on the relative risks of the various thromboprophylaxis regimens and on whether the patient is perceived to be at higher or lower thromboembolic risk.

Women with the older type of mechanical prostheses (e.g. Starr-Edwards or Bjork-Shiley), women with a prosthesis in the mitral position, women with multiple prosthetic valves and women with atrial fibrillation may be regarded as being at high thromboembolic risk. Women with newer and less thrombogenic valves (e.g. St Jude's or Duromedics), particularly if they are in the aortic position and providing they are in normal sinus rhythm, may be regarded as being at lower thromboembolic risk.

With the information currently available, it would be prudent to advise women in the high-thromboembolic-risk category to use an oral anticoagulant with an INR target of 3.5 throughout pregnancy, although some may choose to substitute adjusted doses of heparin between 6 and 12 weeks' gestation. Warfarin should be avoided close to term and UFH or LMWH substituted. However, if labor commences in a woman on warfarin, intravenous vitamin K or fresh frozen plasma can be used to reverse its effect.

On the basis of one report that the risk of fetal complications with warfarin appears to be dose-related[56], women with mechanical heart

valves in the lower thromboembolic risk category may feel reassured about the relatively low risk to their fetus if they use warfarin throughout pregnancy, or with substitution of UFH or LMWH from weeks 6 to 12 if their daily warfarin requirement does not exceed 5 mg. Women in this category requiring higher daily doses of warfarin may wish to minimize the risk of fetal complication, and be prepared to rely on adjusted doses of UFH and LMWH, but they must be made aware that there is less good evidence to support the use of these latter regimens. In general, women with bioprosthetic valves do not require anticoagulation, but anticoagulation may be necessary for other indications.

Clear recommendations for heparin use during labor and delivery in women with artificial heart valves are not available. Intravenous UFH at therapeutic doses may be administered until 6 h before delivery. If the UFH is to be reversed, it is usually sufficient to stop the infusion (as the half-life of the UFH is approximately 1 h). If more rapid reversal is necessary, protamine sulfate is used. One mg of protamine sulfate neutralizes 100 IU of heparin if the latter has been given within the previous 30 min. Protamine sulfate should be given slowly at 5 mg/min, with a maximum single dose of 50 mg. Protamine sulfate is much less effective in reversal of LMWH.

Warfarin is initiated in the postpartum period in patients with mechanical valves. Anticoagulation with intravenous UFH while awaiting therapeutic levels of warfarin is probably not warranted. The risk of bleeding, particularly after Cesarean section, exceeds the risk of thrombotic complications[58]. Subcutaneous UFH in prophylactic doses (5000–7500 units twice daily) may be given.

CONGENITAL DISORDERS OF HEMOSTASIS

Congenital platelet disorders

Bernard–Soulier syndrome is a rare autosomal recessive platelet disorder due to a variety of mutations in membrane glycoproteins Ib, IX and V. Patients usually present early in life with spontaneous bruising, epistaxis or bleeding after minor trauma; menorrhagia is a common presentation. Laboratory findings include thrombocytopenia, large platelets, prolonged bleeding time and poor platelet aggregation *in vitro* to ristocetin.

Eleven cases of Bernard–Soulier syndrome in pregnant women have been described to date[59]. Most have been diagnosed prior to pregnancy, and postpartum hemorrhage has been more common than antepartum bleeding[60]. Management of bleeding in Bernard–Soulier syndrome in pregnancy is debatable; single-donor platelet transfusions (preferably HLA-matched), desmopressin (DDAVP) and antifibrinolytic agents have been successfully used[60].

Glanzmann's thrombasthenia is due to a spectrum of mutations in platelet membrane GP IIb/IIIa, resulting in failure to bind fibrinogen. It is characterized by excessive menstrual blood loss, bleeding from mucous membranes, and major hemorrhage following trauma or surgery. The platelet count is normal, but clot retraction is greatly impaired and agents such as adenosine diphosphate (ADP), epinephrine and collagen fail to induce platelet aggregation. Patients with this condition are at increased risk of primary postpartum hemorrhage. Single-donor platelets (again, HLA-matched if possible) and recombinant activated FVII have been used to control bleeding during the peripartum and the postpartum period[61].

The May-Hegglin anomaly is a rare autosomal dominant condition with thrombocytopenia and giant platelets. Platelet count varies between 40 and 80×10^9/l, but platelet function appears normal. Excess hemorrhage is uncommon, but patients may need a platelet transfusion to achieve hemostasis at delivery[62].

von Willebrand disease

von Willebrand disease (vWD) is the most common of the inherited bleeding disorders, found in approximately 1% of the general population without ethnic variations. It is caused by a reduced plasma concentration of structurally normal von Willebrand factor (vWF) or the presence of a structurally abnormal molecule with reduced activity. vWF is the carrier protein in plasma for FVIII, and it also acts as a bridge

between platelets and subendothelial collagen fibers.

vWF is synthesized in endothelial cells as a polypeptide of 2813 amino acids, which undergoes initial dimerization and then multimerization up to a multimer with a molecular weight of 20 000 kDa. High-molecular weight (HMW) multimers are functionally more effective in promoting platelet adhesion and aggregation. The vWF protein is released into the plasma, and is also stored in Weibel–Palade bodies in the endothelial cells. vWF is also synthesized in megakaryocytes, stored in the platelet α-granules and, on activation, secreted by the platelet release reaction. This allows accumulation of vWF at the site of vascular injury where it can promote further platelet adhesion and thus hemostasis. The mature vWF protein possesses a number of specific binding sites, which represent its different activities (Figure 1). Circulating HMW multimers are cleaved by a protease, known as ADAMTS 13, which is lacking in patients with the rare congenital thrombotic thrombocytopenic purpura.

vWD is subclassified into six categories (Table 6), which correspond to distinct pathophysiological mechanisms and are important in determining therapy. Of all the categories, about approximately 70–80% of patients have type 1 disease.

The condition commonly presents as a mild to moderate bleeding disorder, typically with easy bruising or bleeding from mucosal surfaces. The most frequent problem found in the non-pregnant female is menorrhagia, which may be quite severe. Patients with mild abnormalities may be asymptomatic, with the diagnosis made only after significant hemostatic challenges such as operations and trauma.

Laboratory tests in patients with vWD show prolonged bleeding time and may show a prolonged APTT. More definitive diagnostic tests depend on the finding of reduced vWF activity measured by ristocetin cofactor activity

Table 6 Classification of von Willebrand disease (VWD)

Type 1	Partial quantitative deficiency of apparently normal vWF
Type 2	Qualitative deficiency of vWF
Type 2A	Qualitative variants with decreased HMW multimers
Type 2B	Qualitative variants with increased affinity for platelet GP Ib
Type 2M	Qualitative variants with normal HMW multimers appearance
Type 2N	Qualitative variants with markedly decreased affinity for factor VIII
Type 3	Virtually complete deficiency of vWF

VWF, von Willebrand factor; HMW multimers, high-molecular weight multimers
Adapted from Sadler JE. *Thromb Haemost* 1994;71:520–5

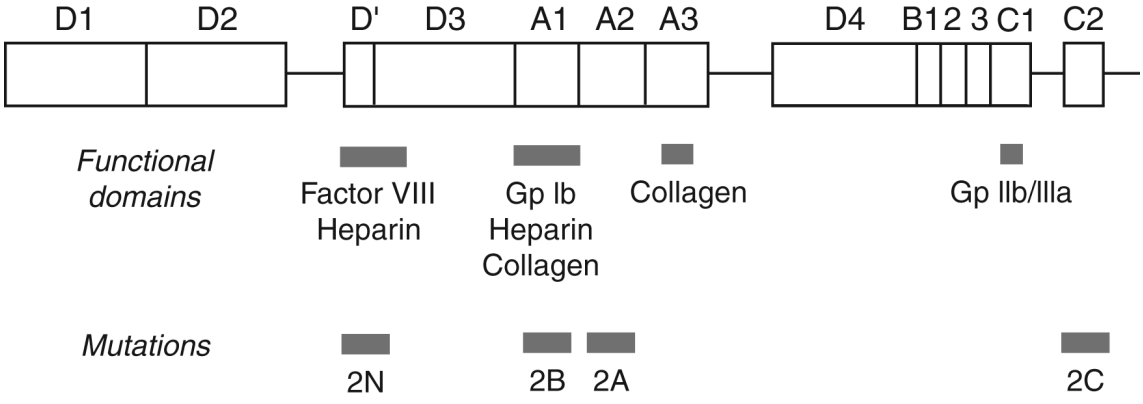

Figure 1 The von Willebrand factor. The protein consists of a series of domains with different binding sites for factor VIII, heparin, collagen and platelet glycoprotein (Gp) Ib and IIb/IIIa. The sites of gene mutations giving rise to different subtypes of VWD are marked. From Green D, Ludlam CA. VWD in bleeding disorders. *Health Press* 2004, pp. 63–69

(vWF:RCo) and collagen-binding assay (vWF:CB), accompanied by variable reductions in vWF antigen (vWF:Ag) and FVIII. Several further tests that aid in classification include analysis of ristocetin-induced platelet aggregation (RIPA), vWF multimer and assay of FVIII binding to vWF[63]. The diagnosis may not be straightforward, as one or more of the activities of FVIII and vWF may be borderline and even normal. It is often necessary to repeat the estimations on at least three occasions. Stress, physical exercise, recent surgery and pregnancy all increase plasma vWF levels and FVIII levels, and diagnosis may be difficult in these circumstances[64]. When investigating patients with borderline results, it should be taken into account that FVIII and vWF levels are 15–20% lower in individuals with blood group O compared to individuals with blood group A[64].

The aim of therapy for vWD is to correct the impaired primary hemostasis and impaired coagulation. Treatment choice depends on the severity and the type of disease, and on the clinical setting. Treatment options usually include DDAVP and vWF-containing blood products[65].

DDAVP, a synthetic vasopressin analogue, releases vWF from endothelial stores; there is also an increase in the plasma FVIII level. It is usually given by slow intravenous infusion of 0.3 μg/kg over 20 min, which can be repeated every 4–6 h on two or three occasions. The drug can also be given subcutaneously or as a nasal spray. Side-effects include hypotension, facial flushing, fluid retention for up to 24 h and consequent hyponatremia. DDAVP can safely be used during pregnancy[66] and after delivery. It is effective in securing in many situations in type 1 vWD with a 3–5-fold increase in the plasma vWF and FVIII levels. It is of no therapeutic benefit in type 3 vWD because of the very low basal levels of vWF and FVIII. The response in types 2 is less predictable. DDAVP is contraindicated in patients with type 2B because it may exacerbate the coexisting thrombocytopenia. Patients should have a test of DDAVP (if possible when not pregnant) to see if it is effective in their individual case.

Plasma-derived vWF concentrates are necessary in patients who do not respond adequately to DDAVP or in whom it is contraindicated. The loading dose is 40–60 IU/kg, and this can be followed by repeat doses every 12–24 h to maintain vWF activity (vWF:RCoF) > 50%. All currently available concentrates are derived from plasma. As at least one viral inactivation step is included in their manufacture, they are unlikely to transmit hepatitis or HIV, but there is still a risk of parvovirus infection.

von Willebrand disease and pregnancy

von Willebrand disease is the most common congenital hemostatic disorder in pregnancy. In a normal pregnancy, both FVIII and vWF levels progressively increase (Figure 2)[67]. vWF starts to rise as early as the 6th week and by the third trimester may have increased three- to fourfold. FVIII and vWF levels also increase in most women with vWD, which may explain the frequent improvement in minor bleeding manifestations during pregnancy. The hemostatic response to pregnancy depends on both the type and severity of disease. Most women with type 1 vWD have an increase in FVIII and vWF levels into the normal non-pregnant range, which may mask the diagnosis during pregnancy. However, levels may remain low in severe cases. FVIII and vWF antigen levels often increase in pregnant women with type 2 vWD with minimal or no increase in vWF activity levels. In type 2B vWD, the increase in the abnormal vWF can cause progressive and severe thrombocytopenia, but intervention is not usually required. Most women with type 3 vWD have no improvement in FVIII or vWF levels during pregnancy[68].

After delivery, FVIII and vWF in normal women fall slowly to baseline levels over a period of 4–6 weeks. However, the postpartum decline of these factors may be rapid and significant in women with vWD[68]. As the individual hemostatic response to pregnancy is variable, vWF and FVIII levels should be monitored during pregnancy and 3–4 weeks after delivery.

Antepartum hemorrhage is uncommon in women with vWD, but may occur after spontaneous miscarriage or elective termination, occasionally as the initial presentation of vWD. Women with vWD are at substantial risk for secondary postpartum hemorrhage, especially 3–5 days after delivery. vWD may also exacerbate bleeding due to other obstetric causes, such

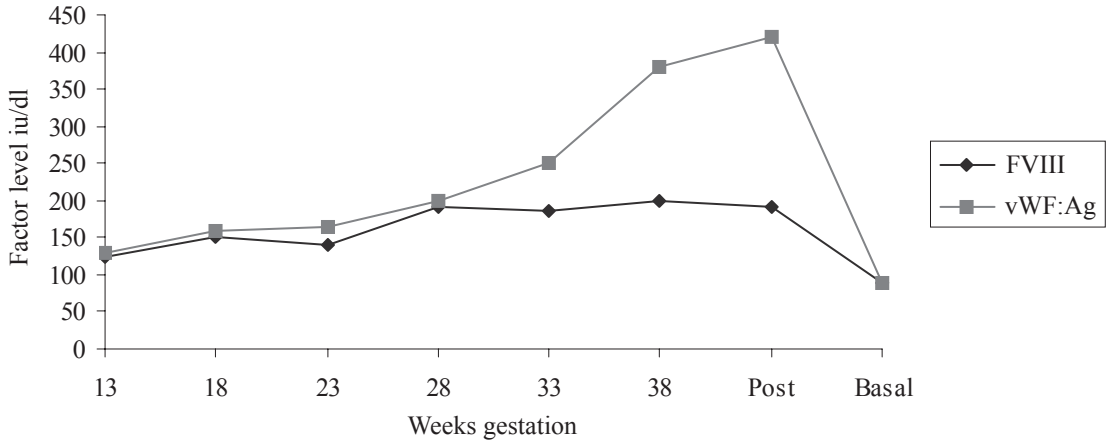

Figure 2 Levels of factor VIII and vWF in normal pregnancy. From Giangrande PL. Management of pregnancy in carriers of haemophilia. *Haemophilia* 1998;4:779–84

as uterine atony or a trauma to the birth canal. Other pregnancy-associated reasons for bleeding in women with vWD include extensive bruising and hematomas at intramuscular injection, episiotomy and surgical wound sites.

For patients whose vWD profile has normalized in pregnancy, no specific hemostatic support is required. Regional analgesia may proceed in these patients after discussion with an obstetric anesthetist. Although neonatal bleeding is rare, ventouse delivery and high-cavity forceps should be avoided. Careful and prompt repair of episiotomy wounds or perineal tears is advisable.

For patients whose vWF activity (vWF:RCo) has not normalized, decisions about regional analgesia should be individualized[69]. Hemostatic supportive therapy with DDAVP or vWF concentrate should be given to cover delivery or Cesarean section if the FVIII level is less than 50% or if vWF:RCo has not normalized[66]. Because of the high incidence of secondary postpartum hemorrhage in patients with vWD, efforts should be made to ensure that placenta is complete upon expulsion or removal.

After delivery, all patients should be closely observed for postpartum hemorrhage and uncorrected hemostatic defects treated. In responsive patients, DDAVP is the treatment of choice to prevent and treat mild to moderate postpartum bleeding[70]. FVIII and vWF:RCo should be checked a few days postpartum because they may fall rapidly after delivery. FVIII and vWF:RCo should be maintained in the normal range for at least 3–7 days after Cesarean section. It is difficult and unnecessary to diagnose vWD in the neonate, except when type 3 vWD is suspected. Generally, diagnosis can be postponed until later in childhood.

HEMOPHILIAS

Hemophilias A and B are the most common severe congenital bleeding disorders associated with reduced or absent coagulation FVIII and FIX, respectively. The incidence of hemophilia A is around 1 in 10 000 live male births. Hemophilia B is about five times less common than hemophilia A. The genes for both conditions are located on the X-chromosome; they are therefore sex-linked disorders that almost exclusively affect males. Clinically, the hemophilias have an identical presentation and can only be distinguished by measuring plasma levels of the specific clotting factors. The clinical severity is directly related to plasma concentrations of FVIII/FIX. Individuals with levels of below 1% of normal have severe hemophilia and the most frequent bleeds. Females in families with a history of hemophilia may be obligate, potential or sporadic carriers, depending on the details of the pedigree[71]. An obligate carrier is a woman whose father has hemophilia, or a woman who has family history of hemophilia and who has given birth to a hemophiliac son, or a woman who has more than one child with hemophilia.

A potential carrier of hemophilia is a woman who has a maternal relative with the disorder. A woman with one affected child and no family history may be a sporadic carrier[71]. Female carriers of hemophilia may have reduced FVIII/IX levels because of random inactivation of the X-chromosome (lyonization). If the FVIII/IX level is less than 50%, abnormal bleeding may occur after trauma or surgery.

There are two main risks for a female carrier of hemophilia in pregnancy. First, women with a low FVIII/IX level may be at risk of bleeding after delivery or during invasive procedures in the first trimester. Second, there is a 50% chance of each son inheriting hemophilia and 50% of her daughters being carriers.

As discussed earlier, the levels of FVIII and vWF rise during normal pregnancy (Figure 2). The increase is particularly marked during the third trimester, when levels of FVIII may rise to double that of the normal baseline value. Similarly, the vast majority of carriers of hemophilia A will have increased their FVIII production to within the normal range by late gestation; factor replacement therapy is thus only rarely required during pregnancy in carriers of hemophilia A. By contrast, the level of FIX does not increase significantly during pregnancy, and thus a woman with a low initial baseline FIX is more likely to require replacement to control bleeding complications during delivery.

All women who are obligate or potential carriers of hemophilia should be offered genetic testing and counseling. In particular, they should have their carrier status determined to allow for the optimal management of their pregnancies. Genetic testing should be offered when the individual is able to understand the issues concerned (usually at age of 13–15 years) and after having given informed consent[72]. In many individuals in the UK with hemophilia A and B, the causative mutation has been identified. If the mutation within the family is known, it is straightforward to screen the potential carrier. If, on the other hand, the mutation is not known, then linkage analysis using informative genetic polymorphisms may be possible. If neither of these approaches is suitable, then direct mutation detection may be possible by sequencing the FVIII/FIX gene.

Coagulation studies should also be carried out to identify carriers with low FVIII/FIX levels. Phenotypic data may be helpful in assessing the statistical risk of carrriership if molecular diagnosis is not possible. However, normal levels of FVIII/FIX do not exclude carriership[72]. Women who have low levels of FVIII may have a useful hemostatic response to DDAVP. To establish whether this response is occurring, a trial of intravenous DDAVP can be attempted, with measurement of the response in FVIII levels over the next 24 h.

Once carriership has been established, women should be offered prepregnancy counseling to provide them with the information necessary to make informed reproductive choices. A new technique of preimplantation diagnosis is potentially useful for carriers of hemophilia who, after counseling, do not wish to contemplate bringing up a hemophilic child, but would not consider termination. Following *in vitro* fertilization (IVF) treatment, it is possible to remove a single embryonic cell at the 8–16-cell stage and carry out genetic diagnosis. Female or unaffected male embryos can then be transferred into the uterus. In the UK, each such test requires a license from the Human Fertilization and Embryology Authority.

If prenatal diagnosis is requested, testing is usually carried out by chorionic villus sampling (CVS) at 11–12 weeks' gestation; DNA extracted from fetal cells is analyzed. The principal advantage of this procedure is that it may be applied during the first trimester, so that, if termination of the pregnancy is required, this is easier to carry out. The main adverse event related to CVS is miscarriage, which is estimated at about 1–2%. Fetal cells are karyotyped so that the fetal sex is established. If the fetus is female, no further tests are done. If the fetus is male, additional tests are conducted to establish whether the affected gene has been inherited. Cells for karyotyping and as a source of DNA can also be obtained from amniotic fluid (amniocentesis) after 15 weeks' gestation; here, the miscarriage rate is about 0.5–1%. Fetoscopy to allow for fetal blood sampling is rarely performed; it can only be performed after about 16 weeks' gestation and has a substantial risk of fetal death (1–6%). The use of prenatal diagnosis is decreasing in developed countries. As

hemophilia care improves, more couples are willing to contemplate bringing up a child with hemophilia[67]. When prenatal diagnosis has not been carried out but there is a risk that the child may have hemophilia, fetal sex should be diagnosed by ultrasonography[67]. This information is necessary for the obstetrician even if the parents do not wish to know the sex of the infant.

Factor VIII/IX levels in female carriers of hemophilia should be monitored regularly in pregnancy. It is particularly important to measure coagulation factor levels toward the end of the third trimester (34–36 weeks) to plan management of delivery[67]. If maternal FVIII/FIX levels remain low at 34–36 weeks in hemophilia carriers, treatment is necessary for delivery[67]. A FVIII/FIX plasma level of 40% is safe for vaginal delivery, and a level of 50% or greater is safe for Cesarean section. Epidural anesthesia may be used if coagulation defects have been corrected[67]. Recombinant FVIII/FIX or DDAVP (for carriers of hemophilia A only) should be used. Plasma-derived factor concentrate products, including those subjected to dual-inactivation processes, have the potential to transmit non-lipid coated viruses, e.g. parvovirus, and should not be used. Infection of the fetus with parvovirus may result in hydrops fetalis and fetal death.

If the fetus is a known hemophiliac, is male and of unknown hemophilia status, or is of unknown sex, care should be taken to avoid traumatic vaginal delivery. Routine Cesarean delivery is unnecessary[67], but should be carried out if obstetric complications are anticipated.

Most bleeding problems in carriers of hemophilia occur postpartum. Replacement therapy should be given immediately after delivery to mothers with uncorrected hemostatic defect. Treatment options at this stage are the same as those during labor and delivery. Supportive therapy to maintain hemostasis should be continued for 3–4 days after vaginal delivery and for 5–10 days after Cesarean section[73].

In the infant, intramuscular injections should be avoided until hemophilia has been excluded. Cord blood should be obtained for FVIII/FIX assays[74]. Routine administration of coagulation factor concentrates to neonates with hemophilia is unnecessary if delivery has been atraumatic and there are no clinical signs of hemorrhage[74].

RARE COAGULATION DISORDERS

Fibrinogen deficiency

The hypo- and dysfibrinogenemias comprise a collection of disorders that are usually dominantly inherited and associated with both bleeding and venous thrombotic manifestations. Women are at risk of recurrent miscarriage, and both antenatal and postnatal hemorrhage. In hypofibrinogenemia, both antigenic and functional fibrinogen levels are reduced. The diagnosis of dysfibrinogenemia is made by demonstrating a prolonged TT with a normal antigenic fibrinogen level.

Prophylaxis with fibrinogen concentrates improves pregnancy outcome and prevents antepartum and postpartum hemorrhage in women with hypo- and dysfibrinogenemia. Cryoprecipitate is a good source of fibrinogen but should not usually be used, as it is not virally inactivated. Its use may be considered in an emergency situation if no other alternatives are available. The half-life of infused fibrinogen is 3–5 days, and treatment is unlikely to be needed more often than on alternate days. Levels above 1.5 g/l are required toward the end of pregnancy and at the time of delivery[75].

Factor VII deficiency

Congenital FVII deficiency is the most common of the rare inherited coagulation disorders with an estimated prevalence of 1 in 500 000. It is inherited in an autosomal recessive manner and its frequency is significantly increased in countries where there are consanguineous marriages. FVII levels are usually less than 10% in homozygotes and around 50% in heterozygotes. Although there is a poor correlation between FVII levels and bleeding risk, hemorrhages occur in patients with factor VII levels below 10–15%[76]. Individuals with a moderate FVII deficiency often bleed from the mucous membranes, and epistaxis, bleeding gums and menorrhagia are common. In severe FVII deficiency (FVII level < 2%), bleeding into the central nervous system very early in life leads to a high morbidity and mortality. Congenital FVII deficiency is usually suspected when an isolated prolongation of the PT is found in a patient

without liver disease, and a normal APTT and fibrinogen level.

The FVII level may increase up to four-fold during normal pregnancy[76]. However, it is unknown whether FVII levels increase to the same degree in pregnant women with congenital FVII deficiency as they do in normal pregnancy[77]. FVII deficiency during pregnancy is a risk factor for postpartum hemorrhage. Bleeding may occur from the placental implantation site, episiotomies, lacerations to the birth canal, or surgical trauma occurring with Cesarean delivery[78].

Recombinant activated FVII (rFVIIa) has been approved in the European Union for use in congenital FVII deficiency[79]. In places where this product is not available, fresh frozen plasma, prothrombin complex concentrates (PCCs) or plasma-derived FVII concentrate may be used. Because the patient may potentially need a Cesarean delivery and because perineal trauma cannot be anticipated, prophylaxis is usually recommended at the time of delivery[78]. Recombinant FVIIa has been given as an initial bolus injection of 20–50 μg/kg, followed by further boluses of 10–35 μg/kg every 4–6 hours to cover vaginal delivery or Cesarean section in patients with congenital FVII deficiency[78,80]. It has also been used as an initial bolus injection of 13 μg/kg with subsequent continuous infusion at 1.7–3.3 μg/kg/h for 4 days[76] (see Chapter 26).

Factor X deficiency

Congenital FX deficiency is an autosomal recessive disorder. The prevalence of the severe (homozygous) form is 1 : 1 000 000 in the general population and is much higher in countries where consanguineous marriages are more common. The prevalence of heterozygous FX deficiency is about 1 : 500, but individuals are usually clinically asymptomatic. Severe FX deficiency (FX level < 1%) is associated with a significant risk of intracranial hemorrhage in the first weeks of life and umbilical stump bleeding. The most frequent symptom is epistaxis, which is seen with all severities of deficiency. Menorrhagia occurs in half of the women. Severe arthropathy may occur as a result of recurrent joint bleeds. Mild deficiency is defined by FX levels of 6–10%; these individuals are often diagnosed incidentally but may experience easy bruising or menorrhagia. The diagnosis of FX deficiency is suspected following the finding of a prolonged APTT and PT and is confirmed by measuring plasma FX levels.

Thirteen pregnancies in eight patients with isolated FX deficiency have been reported in the literature[81]. The complications described include spontaneous abortions, placental abruptions, premature births and postpartum hemorrhage. FX levels increase during pregnancy and antenatal replacement therapy is not usually needed. However, women with severe FX deficiency and a history of adverse outcome in pregnancy may benefit from aggressive replacement therapy[75]. As the half-life of FX is 24–40 h, a single daily infusion is usually adequate. FX levels of 10–20% are generally sufficient for hemostasis[75] and are required at the time of delivery.

FX is present in intermediate-purity FIX concentrates (prothrombin complex concentrates, PCCs). FX levels should be monitored as caution is required because of the prothrombotic properties of these concentrates. Fresh frozen plasma may be an alternative when prothrombin complex concentrates are not available.

Combined deficiencies of the vitamin K-dependent factors II, VII, IX and X

Congenital combined deficiency of factors II, VII, IX and X is an autosomal recessive bleeding disorder. It is caused by deficiency of enzymes associated with vitamin K metabolism (e.g. γ-glutamyl carboxylase) as a result of homozygous genetic mutations. Mucocutaneous and postoperative related bleeding have been reported. Severe cases may present with intracranial hemorrhage or umbilical cord bleeding in infancy. Some individuals have associated skeletal abnormalities (probably related to abnormalities in bone vitamin K-dependent proteins such as osteocalcin). Severe bleeding is usually associated with activities of the vitamin K-dependent factors of < 5%. Affected individuals show prolongation of the APTT and PT associated with variable reductions in the specific activities of factors II, VII, IX and X.

The clinical picture and response to vitamin K is variable, some responding to low-dose oral vitamin K but others are non-responsive even to high-dose intravenous replacement. In those individuals who are non-responsive to vitamin K, prothrombin complex concentrates are the product of choice.

There is a single report of a pregnancy progressing to term in an individual with severe congenital vitamin K-dependent clotting factor deficiency managed with oral vitamin K 15 mg daily throughout pregnancy. Bleeding from an episiotomy wound in this case required fresh frozen plasma[82].

Factor XI deficiency

FXI deficiency is an autosomally inherited condition, which is particularly common in Ashkenazi Jews in whom heterozygote frequency is 8%. Overall, the prevalence of severe deficiency is approximately 1 : 1 000 000 but partial deficiency is much more common. FXI deficiency is unlike most of the other rare coagulation disorders in that heterozygotes may have a significant bleeding tendency that is poorly predicted by the FXI level. Spontaneous bleeding is extremely rare, even in those with undetectable FXI levels. Bleeding is provoked by injury or surgery, particularly in areas of high fibrinolytic activity (e.g. genitourinary tract). Menorrhagia is common, and women with FXI deficiency may be diagnosed as a consequence of this. FXI deficiency rarely results in bleeding during pregnancy, but women with severe or partial deficiency may suffer postpartum bleeding[75].

The APTT is usually prolonged and diagnosis is confirmed by finding a low FXI level. The deficiency is classified as severe if the FXI level is less than 15% and partial at 15–70%; the lower limit of the normal range is 70%. There is controversy about changes in FXI levels during normal pregnancy, some studies demonstrating an increase and others a decrease[83]. Changes in FXI levels in women with FXI deficiency have been inconsistent during pregnancy[84]. It is therefore recommended that FXI levels should be checked at the initial visit, and during the third trimester in FXI-deficient women.

In women with partial FXI deficiency and no bleeding history but previous hemostatic challenge, treatment is not usually required during vaginal delivery. In women with partial deficiency and significant bleeding history or no previous hemostatic challenges, tranexamic acid is often used for 3 days, with the first dose being administered during labor. Tranexamic acid is also used to manage prolonged mild intermittent secondary postpartum hemorrhage which is a common presentation of FXI-deficient patients[84]. FXI concentrate is needed for severely deficient women to cover vaginal delivery and also for Cesarean section. The aim is to maintain the FXI level > 50% during labor and for 3–4 days after vaginal delivery and 7 days after Cesarean section. FXI concentrate is potentially thrombogenic; the single dose should not exceed 30 IU/kg with the aim of raising FXI level to no greater than 70%[84]. Concurrent use of tranexamic acid or other antifibrinolytic drugs with FXI concentrate should be avoided. Fresh frozen plasma can be used, but, in patients with severe deficiency, it is difficult to produce a sufficient rise (to more than 30%) without the risk of fluid overload[75]. Recombinant FVIIa has been used successfully to manage adult patients with FXI deficiency undergoing surgery, although it is not licensed for this indication[75].

Factor XIII deficiency

Congenital FXIII (fibrin stabilizing factor) deficiency is an autosomal recessive disorder. It is characterized by features of delayed and impaired wound healing with bleeding occurring 24–36 h after surgery or trauma. Umbilical bleeding in the first few weeks of life is very suggestive of the disorder. Soft tissue bleeds are more common than hemarthroses, which usually only occur after trauma. Spontaneous intracranial bleeds are a characteristic feature. Spontaneous abortions occur in early pregnancy because FXIII is required for successful implantation. Women with FXIII deficiency are also at increased risk of postnatal bleeding[75]. The severity of the bleeding state varies markedly between individuals with apparently similar FXIII plasma levels. The routine tests (APTT and PT) are normal and the FXIII level has to be specifically requested of the laboratory.

FXIII has a half-life of 7–10 days and therefore only needs to be given at 4–6-weekly intervals to maintain a level > 3% which is necessary to prevent spontaneous intracranial bleeds. Up to 50% of severely (FXIII level < 1%) affected women may miscarry without appropriate FXIII treatment[75]. All severely affected individuals should be started on monthly infusions of plasma–derived FXIII concentrate from the time of diagnosis to prevent intracranial bleeds and these should be continued during pregnancy[75]. FXIII levels fall throughout pregnancy and should be monitored, aiming to keep the trough level > 3%.

FXIII deficiency may also cause life-threatening hemorrhage in the neonate with levels < 3%. The disorder can be diagnosed from cord or peripheral blood samples. Treatment of an acute bleeding episode is with FXIII concentrate at a dose of 20 IU/kg[75].

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26

THE USE OF RECOMBINANT FACTOR VIIa

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INTRODUCTION

As described in detail in other chapters of this volume, conditions with excessive bleeding, as are seen with uterine rupture, placenta accreta, abruption and uterine atony, often require intensive resuscitation with blood components and coagulation factors. In such circumstances, blood transfusion may be life-saving, but on occasion involves exposing the patient to additional risks. Over the years, numerous efforts have been put forward to reduce these risks. One of the most spectacular is discussed in this chapter.

Recombinant activated factor VII (rFVIIa) (NovoSeven®; Novo Nordisk A/S, Bagsvaerd, Denmark) was developed for the treatment of spontaneous and/or surgical bleeding episodes in patients with hemophilia A or B with formation of allo-antibodies to FVIII or FIX after replacement therapy[1–3]. rFVIIa is currently licensed for this indication in most countries world-wide. The US Food and Drug Administration (FDA) licensed rFVIIa on March 25, 1999 for bleeding episodes in patients with hemophilia A or B and inhibitors to FVIII or FIX. The FDA approved use of rFVIIa in 2005 for additional indications such as surgical procedures in patients with hemophilia A or B and inhibitors, and treatment of bleeding episodes in patients with factor VII deficiency[4]. In Europe, it is also approved for use in bleeding episodes in patients with acquired hemophilia due to auto-antibodies against endogenous FVIII or FIX, surgical procedures in this group of patients, and Glanzmann's thrombasthenia.

Beyond its currently recognized indications, rFVIIa has been effectively used 'off label' on an empirical basis as a general hemostatic agent in a wide range of conditions associated with acute, uncontrolled, or otherwise profound bleeding, and in other clinical circumstances associated with excessive bleeding in patients without pre-existent coagulation defects[5,6]. Indeed, the early descriptions of the benefits of rFVIIa in trauma patients[7–9] were bolstered by a compassionate use study, which suggested that rFVIIa administration could reverse massive bleeding, and thus significantly decrease transfusion requirements observed in critically ill, multi-transfused trauma patients[10,11]. Recently, rFVIIa was approved for the treatment of hemorrhage associated with congenital factor VII deficiency[12,13] and Glanzmann's thrombasthenia[14,15].

PECULIARITIES OF OBSTETRIC HEMORRHAGE

Patients who develop massive, life-threatening postpartum hemorrhage often have a combination of 'coagulopathic' diffuse bleeding in addition to 'surgical bleeding'. Whereas bleeding from larger vessels may be controlled by surgeons using a variety of operations (see Chapters 30–32), the ability to control diffuse bleeding is limited and, in many cases, not feasible. Thus administration of hemostatic drugs that can control the coagulopathic component of blood loss may reduce mortality and morbidity in such patients. Clinical experience presently suggests that rFVIIa is a safe and effective hemostatic measure in severe obstetric hemorrhage, both as a adjunctive treatment to surgical hemostasis as well as a 'salvage' or 'rescue' therapy where postpartum hemorrhage is refractory to current pharmaceutical and 'uterus sparing' surgical techniques. The 'evidence' behind the preceding statement comes from three sources:

(1) Studies on its mechanism of action;

(2) Accumulating reports in the literature; and

(3) Data from clinical studies.

All suggest that rFVIIa has the potential to function as a 'universal hemostatic agent'[16] across a range of indications characterized by impaired thrombin generation in non-hemophilic patients, many of whom are critically ill and refractory to other hemostatic treatment options.

The usual manner for treating postpartum hemorrhage includes, first, non-invasive/non-surgical methods, including administration of crystalloid solutions and/or red blood cells, uterine massage, uterotonic medications (oxytocin, ergotamine, prostaglandins), and, second, invasive/surgical methods, e.g. ligation of uterine vessels, ligation of iliac arteries, angiographic embolism of uterine/iliac arteries, or the B-Lynch method. Unfortunately, the overall effectiveness of such procedures to arrest hemorrhage and prevent the need for emergency hysterectomy is estimated to be only about 50%[17,18]. Moreover, comparatively few centers world-wide have access to the physical equipment or surgical manpower resources necessary to conduct all the aforementioned procedures

COAGULATION FACTOR VII: THE HUMAN PROTEIN AND RECOMBINANT PRODUCT

Structure of the human FVII (hFVII)

Human factor VII (eptacog alpha) is a serine protease (molecular weight 50 kDa) composed of 406 amino acid residues, belonging to the group of vitamin K-dependent coagulation glycoproteins. The primary site of FVII synthesis in humans is the liver. Factor VII is composed of four discrete domains: a γ-carboxyglutamic acid (Gla)-containing domain, two epidermal growth factor (EGF)-like domains, and a serine protease domain. All appear to be involved, to different extents, in an optimal interaction with tissue factor (TF). The Gla domain of factor VII is also essential for activation of factor X and other macromolecular substrates. The activation of factor VII to factor VIIa involves the hydrolysis of a single peptide bond between Arg152 and Ile153. The result is a two-chain molecule consisting of a light chain of 152 amino acid residues and a heavy chain of 254 amino acid residues held together by a single disulfide bond[19,20] (Figures 1 and 2).

Production of rFVIIa using recombinant DNA technique

The development of rFVIIa was undertaken to alleviate the problems associated with the use of plasma-derived factor VIIa, such as limited supply and possible viral contamination. Multiple steps were involved in the development of this recombinant protein. First, the human gene for factor VII, located on chromosome 13, comprising eight exons (coding regions), was isolated from the liver gene library. After standard amplification procedures used to generate multiple copies of the hFVII gene, it was transfected into a baby hamster kidney cell line. A master cell bank of the transfected cell line that secretes factor VII in a single-chain form into the culture medium was then established. During the last steps, proteolytic conversion by autocatalysis to the active two-chain form (rFVIIa) takes place in a chromatographic purification process, which was shown to remove exogenous viruses. No human serum or other proteins are used in the production of rFVIIa (see Chapter 15). The protein backbone is identical with human purified factor VIIa. The final product (rFVIIa), despite minor differences in carbohydrate composition, is structurally similar to plasma-derived factor VIIa. The activity of rFVIIa is similar to that of natural factor VIIa present in the body[21,22] (see Table 1).

Human activated factor VII (hFVIIa) or recombinant activated factor VII (rFVIIa) is a naturally occurring initiator of hemostasis that is vital to the coagulation process, as it combines with tissue factor (TF) at the site of blood vessel damage in a natural way, stimulates thrombin generation, permits stable fibrin clot formation, and thereby the cessation of bleeding.

PHARMACOKINETIC STUDIES OF rFVIIa IN HUMANS

The pharmacokinetics of single-bolus doses of rFVIIa have been studied in various adult populations: patients with hemophilia, patients

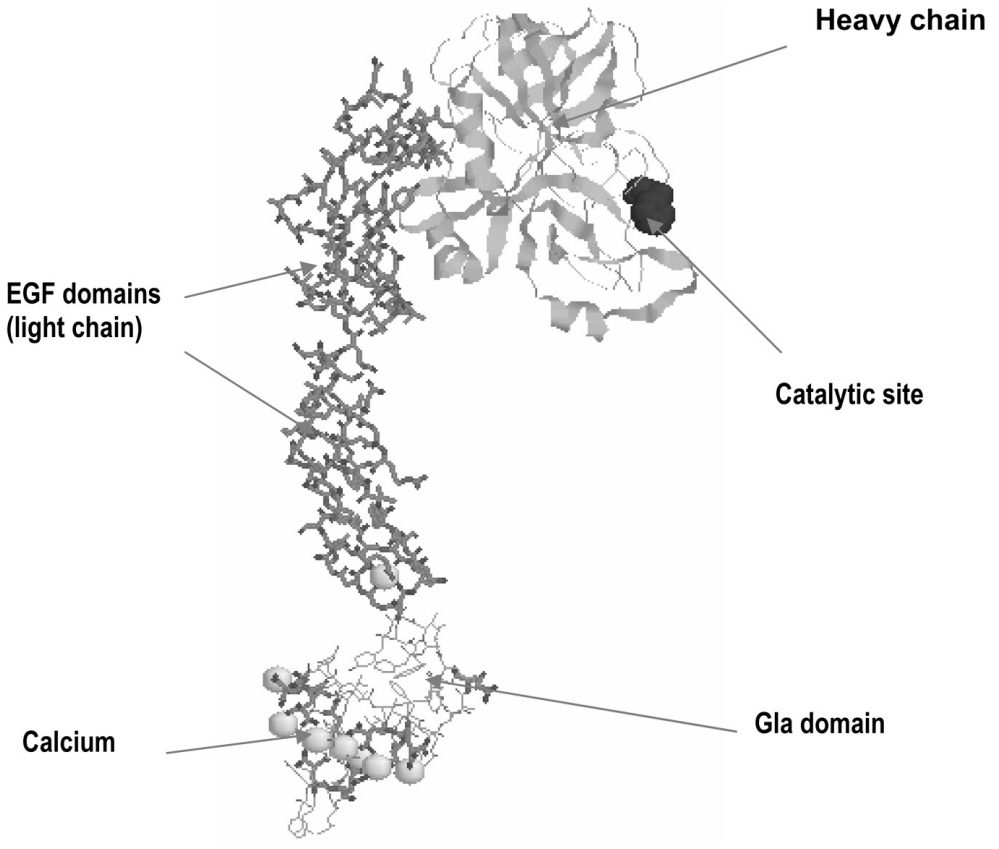

Figure 1 Three-dimensional molecular structure of factor VII. Reproduced with permission from Novo Nordisk

with cirrhosis, and healthy volunteers. The pharmacokinetic parameter values of rFVIIa after bolus administration were similar. The elimination half-life ($t_{1/2}$) ranged from 2.45 to 2.72 h and clearance (CL) ranged from 32.8 to 34.9 ml/h.kg[23]. Lindley and colleagues investigated the single-dose pharmacokinetics of rFVIIa, evaluated in three dose levels (17.5, 35.0, 70 μg/kg) in hemophilic A/B patients with inhibitors. The results of these investigations demonstrate that the mean $t_{1/2}$ of recombinant factor VIIa is independent of dose level[24].

Pharmacokinetic evaluations suggest the elimination of rFVIIa follows linear kinetics with a faster clearance rate and shorter $t_{1/2}$ when rFVIIa is administered for bleeding episodes (medians: 2.70 and 2.41 h, respectively) compared to non-bleeding indications (medians: 3.44 and 2.89 h, respectively). Therefore, the duration of action may by shorter when rFVIIa is used to control bleeding episodes. The average percentage of the preparation found in plasma was significantly lower after administration of rFVIIa in a dose of 70 μg/kg (42.7%) compared to doses of 17.5 μg/kg (50.1%) or 35 μg/kg (49.0%) ($p = 0.0067$). Additional doses for specific patient populations are warranted however[23,24]. An increased elimination rate and lower recovery of rFVIIa during bleeding may be related to consumption through complex formation with TF exposed at the site of vessel damage and on the phospholipids exposed on the activated platelet surface. The volume of distribution at steady state (V_{ss}), is two to three times that of plasma and similar to the half-life of recombinant factor VIIa[24].

MECHANISM OF HEMOSTATIC ACTION OF rFVIIa (see Figure 3)

Recombinant factor VIIa induces hemostasis at the site of injury. The mechanism of action

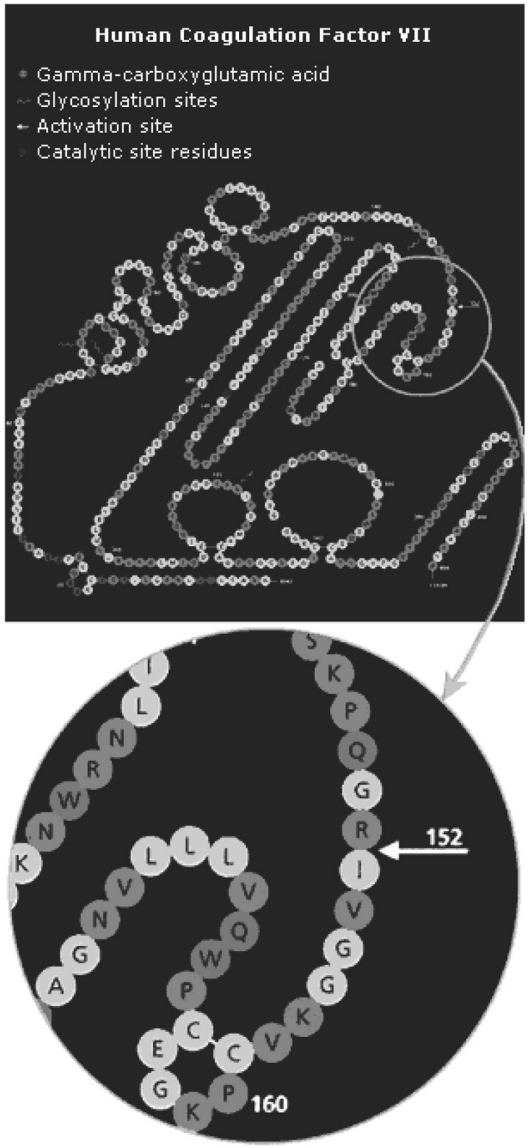

Figure 2 The active two-chain enzyme factor VIIa, is generated by specific cleavage AT Arg 152. Reproduced with permission from Novo Nordisk

includes the binding of factor VIIa to the exposed tissue factor-dependent pathway and, independently of tissue factor, activation of factor X directly on the surface of activated platelets localized to the site of injury[25,26].

The formation of the TF/FVIIa or TF/rFVIIa complex at the site of injury is necessary to initiate hemostasis. TF is a membrane-bound glycoprotein, which normally is expressed on cells in the subendothelium and is only exposed following injury. Tissue injury disrupts the endothelial cell barrier that normally separates TF-bearing cells from the circulating blood. Once exposed to the blood, TF serves as a high-affinity receptor for FVIIa. FVIIa is found in the circulation, comprising about 1% of the total circulating FVII protein mass in the plasma. It is endowed with very weak enzymatic activity, which only becomes fully realized upon binding to its cofactor, TF, at a site of vascular injury[25,26]. Factor VIIa alone shows very little proteolytic activity, only attaining its full enzymatic potential when complexed to TF.

Table 1 Recombinant vs. plasma-derived FVIIa[21]

Amino acid sequence	identical
Amino acid composition	identical
Gamma-carboxylation	identical
Peptide map	identical
Biological activity	identical
Carbohydrate composition	similar

In studies using TF incorporated into lipid vesicles, van't Veer and colleagues demonstrated that zymogen FVII acts as an inhibitor of FVIIa:TF-initiated thrombin generation. The addition of FVIIa at a concentration of 10 nmol/l in hemophilic conditions overcomes this inhibition and results in a thrombin generation equivalent to normal. These data suggest that the therapeutic effect of rFVIIa is due in part to its ability to overcome the inhibitory effect of physiologic FVII on FVIIa:TF-initiated thrombin generation[27].

However, if TF is no longer available or exposed to the clotting factors in the bloodstream, e.g. when a platelet plug covers the TF-containing subendothelial space, or when TF activity is inhibited by TFPI (tissue factor pathway inhibitor), then rFVIIa-mediated large-scale thrombin generation could take place on the activated platelet surface independently of TF[28].

The initial formation of a TF/FVIIa or TF/rFVIIa complex allows activation of FIX and FX, and is crucial in generating the initial conversion of small amounts of prothrombin into thrombin (on the TF-bearing cells), which is essential to the amplification and propagation phase of coagulation. FXa cannot move to the platelet surface because of the presence of

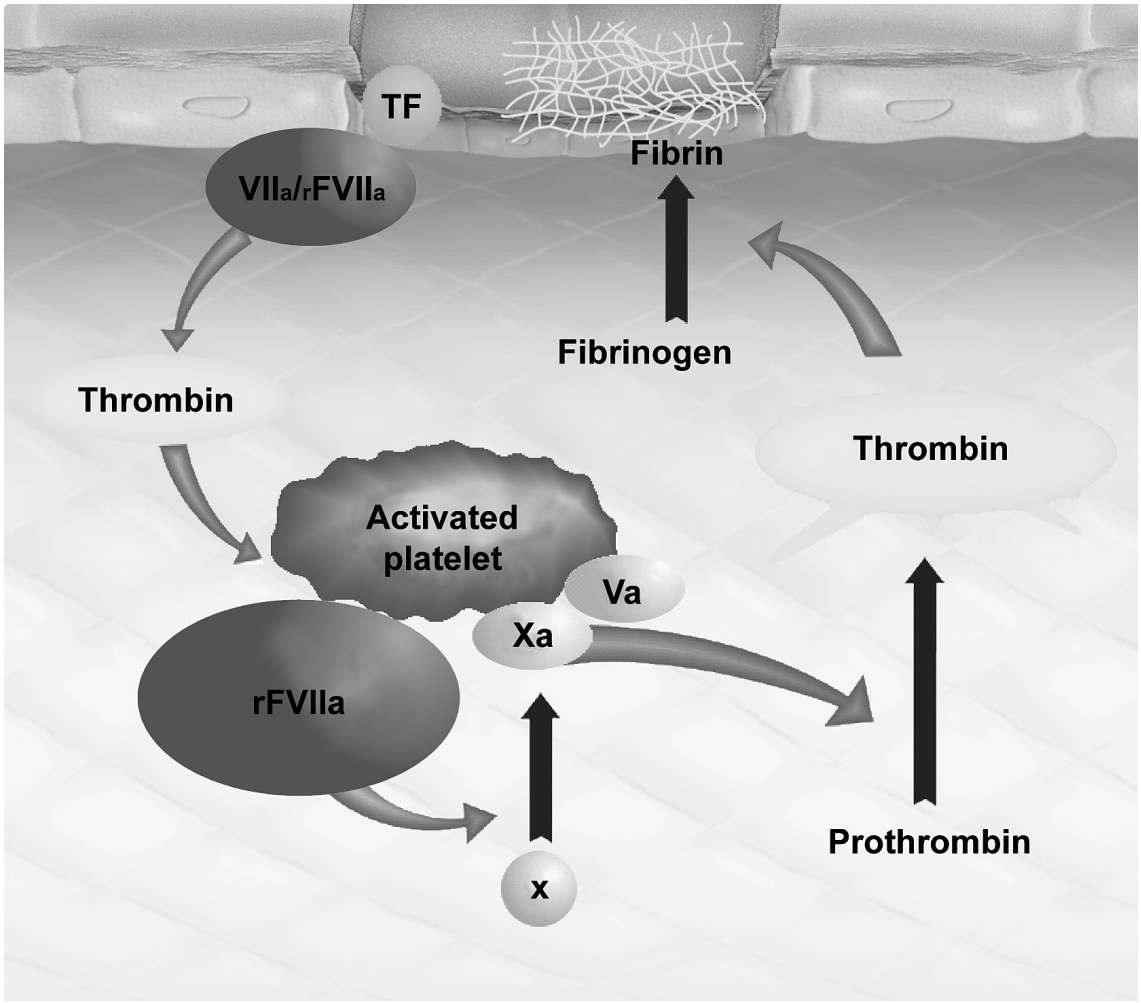

Figure 3 Mode of action of Eptacog alfa (activated) (with permission Novo Nordisk). (1) Tissue factor (TF)/FVIIa, or TF/rFVIIa interaction, is necessary to initiatiate hemostasis. (2) At pharmacological concentrations, rFVIIa directly activates FX on the surface of locally activated platelets.This activation will initiate the 'thrombin burst' independently of FVIII and FIX. This step is independent of TF. (3) The thrombin burst leads to the formation of a stable clot

normal plasma inhibitors, but instead remains on the TF-bearing cell and activates a small amount of thrombin. Thrombin leads to the activation of platelets and FV and FVIII at the site of injury.

This small amount of thrombin is not sufficient for fibrinogen cleavage, but is critical for hemostasis, as it can activate platelets, activate and release FVIII from von Willebrand factor (vWF) or activate platelet and plasma FV, and FXI. FIXa moves to the platelet surface, where it forms a complex with FVIIIa and activates FX on the platelet surface. The activated platelets provide for further thrombin generation. Platelet-surface FXa is relatively protected from normal plasma inhibitors and can complex with platelet-surface FVa, where it activates thrombin in quantities sufficient to provide for fibrinogen cleavage.

FIXa, FVIIIa and FVa bind efficiently to the surface of the activated platelet and further activation of FX into FXa occurs via the complex between FIXa and FVIIIa. During amplification, FXa complexes with FVa to generate thrombin and subsequently activate FV, FVIII and platelets.

At pharmacological concentrations (supra-physiological doses), rFVIIa also directly activates FX on the surface of locally activated platelets, helping to generate thrombin and fibrin (platelet-dependent TF-independent pathways). rFVIIa does not bind to resting platelets. Instead, the effect of high-dose rFVIIa (which only activates FX on activated platelets) is localized to the sites of vessel injury where TF is exposed and platelets are activated[29,30]. This results in the conversion of prothrombin into large amounts of thrombin. The full thrombin burst mediated by FXa in complex with FVa is necessary for the formation of a fully stabilized and solid fibrin hemostatic plug.

rFVIIa works by producing a stable fibrin clot directly at the site of vascular injury, both dependently and independently of TF. This reaction provides an extremely strong activation of thrombin at the site of tissue damage, leading to the formation of a stable fibrin network. Administration of rFVIIa might result in formation of a more stable hemostatic plug by a variety of mechanisms, including enhancement of activation of thrombin activatable fibrinolysis inhibitor[31], improvement of the physical properties of the fibrin clot, enhancement of platelet activation[32], and possibly enhancement of FXIII activation.

Lisman and colleagues observed that the enhanced thrombin generation from FVIIa not only accelerates clot formation, but also inhibits fibrinolysis by activation of thrombin activatable fibrinolytic inhibitor (TAFI) in factor VIII-deficient plasma[28]. rFVIIa binding to thrombin-activated platelets provides extra thrombin and thus ensures both full activation of TAFI and FXIII, and the formation of a dense fibrin structure. The full thrombin burst generated converts fibrinogen into a firm plug that is resistant to premature lysis, thereby facilitating full hemostasis.

MONITORING THE CLINICAL EFFECT OF rFVIIa

Currently, there is no good and/or satisfactory laboratory method for monitoring the clinical effectiveness of rFVIIa. Administration of rFVIIa results in shortening of the prothrombin time (PT) and the activated partial thromboplastin time (APTT). The PT generally shortens to around 7–8 s except in FV- or FX-deficient plasma, suggesting that patients completely deficient in FV and/or FX will not benefit from therapy with this product[33]. PT may not adequately reflect coagulation function. The APTT shortening is due to the direct activation of FX by circulating FVIIa on the phospholipids used in the partial thromboplastin time test. Data indicate that clinical improvement during rFVIIa treatment is associated with a shortening of APTT of 15–20 s[33]. Post-rFVIIa coagulation parameters normalize as early as 20 min after infusion. Thus, the shortening of these two screening tests of coagulation does not necessarily reflect clinical effectiveness, which is judged subjectively.

Coagulopathy is usually easy to recognize by the clinical assessment of ongoing bleeding, physical examination and observation of oozing from cut surfaces, intravascular catheter sites or mucus membranes. The initial evaluation during hemorrhage includes the PT, APTT, thrombin time (TT) and fibrinogen concentration, antithrombin and platelet count. In the interpretation of these tests, it is important to know the normal range and to be aware of the sensitivity of the screening tests for each coagulation factor, as these vary from laboratory to laboratory. In addition, assays of clotting parameters may provide different results with different reagents, although these parameters do not show a direct correlation to the level of hemostasis achieved. Finally, it is important to remember that laboratory coagulation parameters may be used as an adjunct to the clinical evaluation of hemostasis for monitoring the effectiveness and treatment schedule of rFVIIa[34].

Clotting parameters obtained prior to rFVIIa administration are often outside the normal range, perhaps indicating the development of dilutional or consumption coagulopathy in these patients. Post rFVIIa, clotting parameters improve, but do not normalize, and thus cannot be used as predictors of rFVIIa efficacy.

Laboratory monitoring of the efficacy of rFVIIa treatment is helpful. The effect on PT is particularly marked, but this does not always translate to clinically improved blood

coagulation. Similarly, measurement of the level of FVII in plasma does not correlate with clinical efficacy. Study of the effects of rFVIIa on monitoring plasma FVIIa levels demonstrates a linear relationship between the concentration of FVIIa and FVII:C (functional clotting ability), but the therapeutic concentration range for FVIIa has not yet been established. The use of plasma VIIa levels is controversial, and is not an assay that is widely available.

Levels of functional fibrinogen and antithrombin do not change during repeated injections of rFVIIa for the treatment of hemorrhage. The minimal changes that occur postoperatively are not greater than those seen with patients who do not have coagulation disorders. Nonetheless, it is still advisable to monitor patients at risk of systemic activation.

Telgt and colleagues showed that low concentration of rFVIIa, in the absence of TF, can activate FX as assayed by the PT[33,35]. Higher concentration of rFVIIa had no additional effect on the PT. At rFVIIa doses well below the clinically therapeutic dose, a maximum shortening of the PT occurs. Thus, at doses in the clinically therapeutic range, no further effect on the PT is observed. This suggests that, at concentrations typical for clinical use, tests based on the PT are not useful for monitoring the effect of rFVIIa. Telgt and colleagues, in an experimental study, observed that rFVIIa effectively reduced PT and APTT in normal and deficient (FVIII, FIX, FXI, FXII) plasma. This reduction of both parameters (PT and APTT) has been attributed to the ability of rFVIIa to directly activate FX, even in the absence of TF[34,35].

The best available indicator of rFVIIa efficacy is the arrest of hemorrhage judged by visual evidence, hemodynamic stabilization and reduced demand for blood components[36]. There is currently no satisfactory laboratory test to monitor the clinical effectiveness of rFVIIa.

SAFETY OF rFVIIa

The complex coagulopathy and high complication rates seen in patients with intractable postpartum hemorrhage, together with the understanding of the localized mechanism of action of rFVIIa, and the low risk of thromboembolic complications following administration of the drug both in animal models and in clinical use, all suggest that rFVIIa is a useful adjunctive therapy for control of severe postpartum hemorrhage. Recombinant FVIIa is a manufactured product, does not contain any human plasma components, and therefore is free from viral contamination. Neither albumin nor any other human protein is used in its manufacturing process. This means that there is no risk of transmission of human viruses or prions. Strict quality control standards are applied to the fermentation process as well as the subsequent extensive purification measures. Genetic recombination eliminates the dependency on donors and allows for the production of unlimited amounts of the medication[20].

Safety analyses demonstrate that rFVIIa is associated with very few treatment-related adverse events and is very well tolerated. Thus, experience with recombinant factor VIIa in several thousand patients has shown that the incidence of non-serious adverse events is 13% and serious adverse events are less than 1%[37].

Aledort calculated that the risk of rFVIIa-related thrombosis is 25 per 10^5 infusions[38]. Despite the mechanism of action, use of rFVIIa in DIC and sepsis remains controversial. Several reports suggest that rFVIIa may be used safely in such situations, without induction of thrombotic complications or when conventional replacement therapy with fresh frozen plasma and red blood cell concentrates fails to provide a hemostatic response. Non-serious side-effects are rarely seen during treatment with recombinant factor VIIa; the most common being pain at the infusion site, fever, headache, vomiting, changes in the blood pressure and skin-related hypersensitivity reactions. Adverse events have not been related to dose.

OUR EXPERIENCE

Between 2000 and 2006 in the Department of Gynecology and Obstetrics, University of Medical Sciences, Poznań we used rFVIIa in almost 45 cases of postpartum hemorrhage[39–46]. According to data gathered from other areas of Poland, we estimate that it has been used in approximately 100 cases of postpartum hemorrhage.

The data presented below concern our first 18 patients in whom rFVIIa was used. Detailed information is presented in Tables 2–5. Our patient data were obtained when we were using a study protocol and were prepared to use the drug. This was not always the case in other centers (see Table 6).

Table 2 Clinical details of patients with severe, recurring and uncontrollable bleeding post-delivery

	Number of patients
Number of postpartum hemorrhages	18
Cause of bleeding/complications	
Uterine atony	8
Genital tract trauma	1
Disseminated intravascular coagulation	8
Shock	18
Reoperations before rFVIIa administration	7
Obstetric hysterectomy*	2

*In six cases, hysterectomy was not performed. rFVIIa was administered after the decision to operate was made due to uncontrolled, life-threatening bleeding. After its administration, the bleeding stopped and the operation was not necessary. In two women, hysterectomy was performed in another hospital, before the patients were transported to our department

Table 3 Blood loss before and after rFVIIa administration

Blood loss	*Median (range)* (ml)
Before rFVIIa	3000 (1800–6800)
After rFVIIa	0.00 (0–350)

Table 4 Transfusion needed before and after rFVIIa administration

	Before rFVIIa		*After rFVIIa*	
	Median (range)	*U/P*	*Median (range)*	*U/P*
Red blood cell (IU)	6 (3–13)	6	4 (0–9)	3
Fresh frozen plasma (IU)	4 (1–8)	4	2 (0–9)	2

U/P, units per patient

Recombinant FVIIa was administered intravenously at doses of 16.6–48 μg/kg. In most cases, single administration of rFVIIa was sufficient. However, in severe coagulopathy coexisting with postpartum hemorrhage or prolonged periods of treatment (transfusions, complications of shock) and recurrent bleeding, a second dose similar to the initial dose was necessary to control the bleeding.

Conclusions

The analysis of our data clearly shows that rFVIIa was an effective hemostatic drug, which significantly decreased bleeding and led to the rapid stabilization of our patients' conditions. Clearly, the early use of this agent decreases the amount of transfused preparations. An important secondary observation was the contraction of the uterus after the drug application in patients who had qualified for hysterectomy shortly before the drug was administered. We suggest that rFVIIa should be administered in every case in which embolization of uterine arteries is being considered. Coagulation parameters showed typical shortening of PT and APTT; however, the clinical effect – control of bleeding – was the most important overall effect of the drug. There were no complications of rFVIIa administration. The dose, timing of administration after the diagnosis of postpartum hemorrhage, and the apparent ability to enhance uterine contractility will need further study in the future.

WORLD-WIDE EXPERIENCE

Tables 6–8 present the world-wide experience with rFVIIa in obstetric hemorrhage. The results reported in the literature support the benefit of rFVIIa therapy in obstetric cases with major/life-threatening hemorrhage, even in the presence of disseminated intravascular coagulopathy (DIC)-like 'coagulopathy'. They demonstrate that rFVIIa is highly effective and safe in allowing quick arrest of life-threatening postpartum hemorrhage unresponsive to conventional treatments. Treatment with rFVIIa led to a reduction in the use of blood products in this relatively large group of patients, decreasing blood product exposure for patients and

Table 5 Selected laboratory tests before and after rFVIIa administration. Data are given as median (range)

Parameter	*Normal range*	*Before rFVIIa*	*2 hours after rFVIIa*	*4 hours after rFVIIa*	*12 hours after rFVIIa*
PT (s)	11.5–13.5	17.35 (11.9–26.7)	11.10 (9.1–18.3)	11.25 (9.1–17.6)	12.65 (11.2–17.1)
APTT (s)	25–37	55.00 (26–81)	35.00 (26–76)	36.80 (22–69)	39.10 (24–60)
PLT (Gpt/l)	140–440	76.50 (21–223)	70.00 (20–197)	69.50 (19–186)	70.50 (37–165)

PT, prothrombin time; APTT, activated partial thromboplastin time; PLT, platelets

sparing an expensive and limited resource. Administration of rFVIIa should be also considered before hysterectomy and as an adjunct to invasive/surgical procedures, before they are undertaken. This is particularly true in patients who wish to preserve fertility

Conclusions

Randomized controlled studies are required to determine the optimal dose and dose schedule of rFVIIa for intractable postpartum hemorrhage and to investigate whether the need for hysterectomy/surgical procedures and overall morbidity rates can be reduced by earlier treatment with higher doses of rFVIIa. In the meanwhile, clinicians caring for acutely bleeding obstetric patients should be aware of the potential of rFVIIa to arrest life-threatening postpartum hemorrhage. Although an expensive product, a trial of one to four doses of rFVIIa can be justified in cases of uncontrolled bleeding which persists despite maximal medical and surgical treatment to achieve hemostasis.

Although the limitations of anecdotal case data are recognized, in the absence of efficacy and safety data from randomized trials, voluntary registry submissions are being used to provide a preliminary insight into the scope of the low incidence of clinical problems, as well as the usefulness and adverse effects of this medication when it is used 'off-label'.

rFVIIa dose

When a rationale for using rFVIIa was stated, it was most commonly 'last-resort' therapy, after other clinical measures had failed. There was no clear correlation between the severity of bleeding and the dose of rFVII administered. Possibly the 'timing' determined the level of the dosing.

Efficacy

Bleeding either stopped, markedly decreased or decreased following rFVIIa administration in 54 of the cases. In one patient, there was no response to therapy with rFVIIa. Also only in one patient after an early significant reduction of bleeding, recurrence was observed. In general, however, the rapid onset of action means that rFVIIa can be used in the perioperative period. There was no clear correlation between the speed of response and either the type of procedure performed, the severity of the bleeding condition, or the dose of rFVIIa given.

Most patients continued to require some form of blood product replacement therapy during the 24 h following rFVIIa administration, but the need was greatly reduced compared with the 24 h prior to rFVIIa administration. No correlation existed between baseline and post-rFVIIa administration in laboratory measurements and the predictability of response to rFVIIa (data obtained from references but not presented in tables). Furthermore, of great importance, the results observed in these tables of cases of postpartum hemorrhage suggest that rFVIIa may be administered even in the presence of DIC-like 'coagulopathy'. In the patients shown in Tables 6–8, major conditions reported to be associated with postpartum hemorrhage included some

Table 6 Clinical characteristics of patients with risk of severe, recurring and uncontrollable blood loss during delivery and postpartum: literature review

Year	*Ref.*	*n*	*Provocation of bleed*	*Type of delivery*	*Surgical treatment*	*Blood products given pre-rFVIIa* (units) *(hemostatic agents)*	*Blood loss before rFVIIa* (ml)	*Timing (when rFVIIa given)*	*Dose of rFVIIa* (μg/kg) *(number of doses)*	*Overall bleeding response to rFVIIa* (min)	*Comments*
2001	47	1	DIC, liver dysfunction, renal failure; severe intra-abdominal bleeding after CS	CS	HYS	NA	3000	Post hysterectomy; last resort	90 (9) 3-h intervals	Response after 2 single doses; significantly reduced	
2002	48	1	Congenital FVII deficiency (1% before application of rFVIIa)	VD	No	No	No evidence of bleeding	Prophylactic first dose at complete dilatation of the cervix	50; 35 4-h intervals	No evidence of bleeding	The first case of a pregnant woman with FVII deficiency receiving rFVIIa intrapartum
2002	49	1	Acquired hemophilia (FVIII 0.5%)	VD	HYS	RBC (65); FFP (60); CRYO (60); vWF (3 × 500); FVIII (30 × 1068); FIX (26 × 600); 18 g sandoglobulin	NA (massive)	11 days post-delivery; last resort	160	Bleeding stopped (rapidly)	
2002	50	1	2-h post CS massive vaginal bleeding; shock; DIC, HELLP	CS	No	RBC (12); FFP (10); PPTs (8); CRYO (950)	NA	Last resort	90	Bleeding stopped	Normalization of coagulation tests
2003	51	1	Bleeding from the placenta bed in lower uterine segment and cervical canal	CS	Under-running sutures in the placenta bed; application of hot packs; direct manual tamponade with surgical gauze; insertion of intra-cervical Foley's catheter balloon	RBC (1.5); FFP (500 ml)	> 3000	Last resort	90	Bleeding stopped (15)	The balloon was removed on the first postoperative day

2003	52	2	*(case 1)* uterine rupture, shock *(case 2)* uterine atony	*(case 1)* VD *(case 2)* eCS	*(case 1)* subtotal HYS	*(case 1)* RBC (10); FFP (4) *(case 2)* RBC (5)	NA	*(case 1)* intraoperative *(case 2)* before planned hysterectomy	NA	Bleeding stopped (few minutes)	*(case 2)* Hysterectomy was avoided
2003	53	1	Uterine atony; shock	IVD	laparotomy: bilateral artery ligation; subtotal HYS; packing of pelvis	Before 1st administration RBC (42); FFP (31); PPTs (4); (desmopressin) before 2nd administration FFP (3); PPTs (2)	NA	Post laparotomy	60; 120 2-h interval, (2nd for consolidation)	Bleeding stopped	Cardiac arrest, resuscitation; high-pressure ventilation, pulmonary edema, pneumothorax, ARDS
2003	54	1	Uterine atony, pre-eclampsia	CS	HYS	RBC (3); FFP (2); CRYO (6)	NA	Intraoperative (CS) before hysterectomy	12	Bleeding significantly reduced	During general anesthesia induction, failed intubation was followed by cardiac arrest; postoperatively DIC; ARDS; transit encephalopathy, and brachial venouse thrombosis (Folckmann syndrome)
2003	55	2	*(case 1)* congenital deficiency of FVII (2% before application rFVIIa) *(case 2)* liver dysfunction	*(case 1)* VD *(case 2)* CS	No	No	No evidence of bleeding	*(case 1)* Prophylactic first dose at complete dilatation of the cervix *(case 2)* prophylactic before CS	*(case 1)* 60; 30 (5) every 2 h. *(case 2)* 90	No evidence of bleeding	*(case 2)* No evidence of FVII deficiency
2003	56	1	AFE, DIC	CS	HYS; pelvic packing	RBC (12); FFP (8); (aprotinin)	NA	Last resort	60	Bleeding significantly reduced	MOF, died

continued

Table 6 *Continued*

Year	*Ref.*	*n*	*Provocation of bleed*	*Type of delivery*	*Surgical treatment*	*Blood products given pre-rFVIIa* (units) *(hemostatic agents)*	*Blood loss before rFVIIa* (ml)	*Timing (when rFVIIa given)*	*Dose of rFVIIa* (μg/kg) *(number of doses)*	*Overall bleeding response to rFVIIa* (min)	*Comments*
2004	57	1	Uterine rupture; shock; DIC	IVD	3 laparotomy: 1st: HYS; 2nd: packing of pelvis; 3rd: small arteries ligated in the broad ligaments	*Before 1st* administration: RBC (26); FFP (11); PPTs (10); PCC (1200). *Total*: RBC (27); FFP (27); PPTs (10); 22 plateletpheresis; (tranexamic acid)	4000 to 2nd laparotomy; before 3rd laparotomy sudden increase of bleeding 1350 l in 1 h	Before, intra- and postoperative period; last resort	120 (19), start before 2nd laparotomy, repeated following next 2 days. First two doses (1st laparotomy) at 1-h intervals, next doses during the 2nd day 3 doses; next day two doses at 1-h intervals followed further doses every 3 h	Bleeding significantly reduced or stopped; recurrent bleeding was observed	Cardiac arrest, resuscitation before 2nd laparotomy (hyperkalemia 8.5 mmol/l, hypothermia 32°C); MOF Recurrent bleeding was observed because patient developed severe hypothermia, acidosis, hypoxia, dilution coagulopathy, all these reduced the efficacy of rFVIIa *in vivo*.
2004	58	2	Uterine atony, shock; severe coagulopathy	(*case 1*) CS (*case 2*) CS	(*case 1*) ligation of hypogastric arteries (*case 2*) laparotomy; ligation of hypogastric arteries	(*case 1*) RBC (19); FFP (3350 ml); PPTs (900 ml); fibrinogen (3 g); [aprotynin] (*case 2*) RBC (22); FFP (3400 ml); PPTs (3400 ml); PPTs (300 ml); fibrinogen (2 g); [aprotynin]	(*case 1*) 200 ml/h (*case 2*) 2000 ml, hemo-peritoneum	Last resort	(case 1) 60 (case 2) 60	Bleeding stopped (rapidly)	(*case 1*) 4 weeks later developed thrombosis of both ovarian veins
2004	59	1	Placenta previa; accreta; DIC	CS	No	RBC (11); FFP (4); CRYO (6)	1000 (in the drain) 5 h after CS		12 mg	Bleeding stopped (few hours)	
2004	60	1	Glanzmann's thrombasthenia	VD	No	PPTs (4)	No evidence of bleeding	Prophylactic	36 (2) 1st during vaginal delivery, 2nd 2 h after delivery	800 ml (intra- and postpartum blood loss)	rFVIIa may offer an alternative option in patients with Glanzmann's thrombasthenia during delivery

2004	61	1	AFE; DIC (developed 2 min after delivery)	CS	No	RBC (6); FFP (1); PPTs (2)	3000		90	Hemostasis was secured within 30 min	
2004	62	3	*(case 1)* Eclampsia; HELLP; consumptive coagulopathy; subcapsular liver hematoma with capsule rupture *(case 2)* placenta percreta, pre-eclampsia; HELLP *(case 3)* pre-eclampsia; HELLP; placenta accreta; consumptive coagulopathy; severe vaginal bleeding and uterine cramping	*(case 1)* CS *(case 2)* CS *(case 3)* CS	No	*(case 1)* RBC (16); FFP (14); PPTs (18); CRYO (10); *(case 2)* RBC (8); FFP (4); PPTs (6) *(case 3)* RBC (2); FFP (4); PPTs (6); CRYO (10)	*(case 1)* 2500 *(case 2)* 3000 *(case 3)* 1300	last resort	*(case 1)* 90 (2) *(case 2)* 120 (3); 90 (2) 2-h intervals *(case 3)* 90 (2) 2-h interval	Bleeding controlled	*(case 1)* patient developed anuric renal failure; cardiac arrest; patient died; no evidence of systemic thrombosis identified *(case 2)* no future transfusion requirement; coagulation profile stabilized
2004	63	1	Pre-eclampsia; HELLP; DIC; shock	eCS	Laparotomy 12 h after CS, because intra-abdominal hemorrhage	RBC (22); FFP (18); PPTs (30); CRYO (20); (aprotynin)	3500 in abdominal cavity and 600 postoperatively from drains	Post laparotomy	90	Bleeding reduced (30), Bleeding stopped (180)	
2005	64	3	*(case 1)* Uterine atony, shock *(case 2)* placenta previa, uterine atony *(case 3)* laceration of vagina, atony, consumptive coagulopathy	*(case 1)* CS *(case 2)* VD *(case 3)* IVD	*(case 1)* relaparotomy with intracavitary oxytocin injected into the uterus; ligature of both uterine arteries; placement of B-Lynch sutures	*(case 1)* RBC (7); FFP (9); *(case 2)* RBC (10); FFP (13); PPTs (2) *(case 3)* RBC (13); FFP (16); PPTs (2)	NA	*(case 1)* before relaparotomy *(cases 2, 3)* last-resort	*(case 1)* 120 (2) 1-h interval *(case 2)* 60 (2) within 3 h *(case 3)* *120 (2)*	*(case 1)* Bleeding stopped *(case 2)* Bleeding stopped *(case 3)* Bleeding stopped	Improve coagulation parameters

continued

Table 6 *Continued*

Year	*Ref.*	*n*	*Provocation of bleed*	*Type of delivery*	*Surgical treatment*	*Blood products given pre-rFVIIa* (units) *(hemostatic agents)*	*Blood loss before rFVIIa* (ml)	*Timing (when rFVIIa given)*	*Dose of rFVIIa* (μg/kg) *(number of doses)*	*Overall bleeding response to rFVIIa* (min)	*Comments*
2005	65	1	Uterine atony; shock; DIC	CS	HYS; packing of the pelvis	NA	NA	Before relaparotomy and ligation hypogastric artery	2.4 mg	Bleeding controlled (rapid response)	Resolution of the coagulopathy
2005	66	4	Uterine atony	VD	Uterus and vagina tamponade	NA	*(case 1)* 1600 *(case 2)* 2400 *(case 3)* 1100 *(case 4)* 2500	before developed severe coagulopathy, surgical procedures; avoided massive transfusion	*(case 1)* 82 *(case 2)* 73 *(case 3)* 61 *(case 4)* 72	*(case 1)* Bleeding stopped (15) *(case 2)* Bleeding stopped (25) *(case 3)* Bleeding stopped (35) *(case 4)* Bleeding stopped (40)	Lower than standard doses may be effective when respect good timing, before complication develops
2005	67	3	*(case 1)* dehiscence of uterine scar *(case 2i)* placenta percreta, adherent; dehiscence of uterine scar (previous CS) *(case 3)* NA	*(case 1)* eCS *(case 2)* VD *(case 3)*ieCS	*(case 1)* 3 laparotomy; bilateral internal iliac ligation *(case 2)* subtotal HYS	*(case 1)* WB (12); FFP (17); PPTs (2); *(case 2)* WB (11); FFP (7)	*(case 1)* 225 ml/h *(case 2)* 600 within 40 min *(case 3)* 500 hematoma		*(case 1)* 90 *(case 2)* 90 *(case 3)* 80	*(case 1)* Bleeding controlled (16) *(case 2)* Bleeding stopped (14) *(case 3)* Bleeding stopped	

RBC, red blood cell concentrates; FFP, fresh frozen plasma; PPTs, platelets; CRYO, cryoprecipitates; WB, whole blood; PCC, prothrombin complex concentrate; vWF, von Willebrand factor; CS, Cesarean section (e, emergency); VD, vaginal delivery; IVD, instrumental vaginal delivery; DIC, disseminated intravascular coagulation; MOF, multiple organ failure; NA, not available; HYS, hysterectomy; laceration – uterine or vaginal; AFE, amniotic fluid embolism; HELLP, hemolysis, elevated liver enzymes, low platelets; 'last resort', therapy, after other clinical measures had failed; *n*, number of cases

Table 7 Patients with severe postpartum hemorrhage, presented by Ahonen and colleagues (2005)[68]. The authors concluded that treatment with rFVIIa may be of benefit in life-threatening postpartum hemorrhage of up to 20 l of blood in 5–8 h. For comments on this article, see reference 69

Case	*Provocation of bleed*	*Type of delivery*	*Additional surgeries (number of surgery)*	*Blood products given pre-rFVIIa* (units)	*Blood loss before rFVIIa* (l)	*Timing (when rFVIIa administered)*	*Dose of rFVIIa* (μg/kg) *(number of doses)*	*Overall bleeding response to rFVIIa* (min)
1	Placenta accreta	VD	HYS	RBC (42); FFP (25); PPTs (40)	25.0	After HYS	44	Partial
2	Adherent placenta	CS	HYS	RBC (35); FFP (14); PPTs (24)	20.0	After HYS	95	Good
3	Uterine atony, LAC	VD	Surgery (3)	RBC (19); FFP (8); PPTs (8)	11.0	Before HYS	78	Good
4	Laceration	VD	Surgery (2), embolization	RBC (25); FFP (16); PPTs (24)	14.0	NA	103	Partial
5	Laceration	CS	HYS (3 laparotomy)	RBC (32); FFP (20); PPTs (40)	19.0	After HYS	90	Good
6	Uterine atony	CS	Surgery, embolization	RBC (10); FFP (8); PPTs (16)	5.5	NA	116	Partial
7	Placenta accreta	VD	HYS	RBC (14); FFP (6); PPTs (4)	7.5	After HYS	42	Partial
8	Laceration	CS	Surgery (2), right uterine artery ligation	RBC (11); FFP (4); PPTs (8)	5.3	NA	120	None
9	Placenta percreta	CS	HYS (2)	RBC (25); FFP (14); PPTs (16)	14.0	After HYS	77	Good
10	Laceration	IVD	Surgery, embolization	RBC (12); FFP (10); PPTs (32)	8.8	NA	74	Partial
11	Laceration	VD	Surgery	RBC (11); FFP (6); PPTs (6)	5.5	NA	86	Good
12	Laceration	VD	Surgery, embolization	RBC (10); FFP (8); PPTs (16)	5.8	NA	96	Partial

RBC, red blood cell concentrates; FFP, fresh frozen plasma; PPTs, platelets; CS, Cesarean section (e, emergency); VD, vaginal delivery; IVD, instrumental vaginal delivery; DIC, disseminated intravascular coagulation; MOF, multiple organ failure; NA, not available; HYS, hysterectomy; laceration – uterine or vaginal; AFE, amniotic fluid embolism; HELLP, hemolysis, elevated liver enzymes, low platelets; 'last resort', therapy, after other clinical measures had failed

Table 8 Patients with severe postpartum hemorrhage presented by Segal and colleagues[70,71]

Case	*Provocation of bleed*	*Type of delivery*	*Additional surgeries*	*Blood products given pre-rFVIIa* (units)	*Blood loss before rFVIIa* (l)	*Timing (when rFVIIa administered)*	*Dose of rFVIIa* (μg/kg) *(number of doses)*	*Overall bleeding response to rFVIIa* (min)
1	Placenta accreta	CS	HYS; ligation of internal iliac arteries; packing	RBC (44); FFP (24); PPTs (60); CRYO (54)	NA	NA	90 (2)	Bleeding stopped
2	Uterine rupture	VD	HYS; ligation of internal iliac arteries	RBC (20); FFP (16); PPTs (60); CRYO (60)	NA	NA	100	Bleeding stopped
3	Uterine atony	CS	CS, packing of uterus; laparotomy; packing of tears on liver	RBC (19); FFP (8); PPTs (8)	NA	NA	90	Bleeding reduced
4	Uterine atony	NA	Subtotal HYS; ligation of internal iliac arteries	RBC (14); FFP (12); PPTs (10); CRYO (10)	NA	NA	90	Bleeding stopped
5	Uterine rupture	NA	Ligation of internal iliac arteries; subtotal HYS	RBC (26); FFP (16); PPTs (30); CRYO (60)	NA	NA	90	Bleeding stopped
6	Placenta accreta	NA	Arterial embolization; HYS; iliac ligation; 4 laparotomies; packing	RBC (100); FFP (50); PPTs (50); CRYO (50)	NA	NA	90	Bleeding controlled
7	Uterine rupture	NA	HYS; ligation of internal iliac arteries; packing	RBC (10); FFP (6); CRYO (4)	NA	NA	90	Bleeding reduced
8	Uterus myomatosus, menorrhagia	NA	HYS	RBC (6); FFP (9)	NA	NA	60	No bleeding
9	Uterine rupture	NA	HYS	RBC (15); FFP (6); PPTs (15); CRYO (30)	NA	NA	90	Bleeding stopped
10	Placenta accreta	NA	HYS; ligation of internal iliac arteries; aortic clamp	RBC (27); FFP (30); PPTs (10); CRYO (30)	NA	NA	90	Bleeding stopped

RBC, red blood cell concentrates; FFP, fresh frozen plasma; PPTs, platelets; CRYO, cryoprecipitates; CS, Cesarean section; VD, vaginal delivery; NA, not available; HYS, hysterectomy

individuals with HELLP syndrome and others with both laboratory and clinical signs of DIC before rFVIIa was administered. However, none of these patients developed an objectively confirmed, clinically manifest thromboembolism (deep vein thrombosis, pulmonary embolism, myocardial infarction, cerebrovascular embolism) after rFVIIa therapy, even if some patients had pre-existing signs of DIC (often severe).

Patients with HELLP syndrome who develop DIC are recognized as being at particular risk for life-threatening complications. The HELLP syndrome is a form of severe pre-eclampsia, and may be confused with the development of DIC. Data presented in Tables 6–8 suggest a high efficacy and safety profile of rFVIIa in the treatment of HELLP syndrome and/or DIC with massive bleeding. These findings are supported by clinical experiences about the therapeutic effectivity of rFVIIa in three patients with massive obstetric hemorrhage due to placenta previa, accreta, rupture of the uterus and pre-eclampsia with HELLP recently published by an Israeli group[71]. As mentioned by Segal and colleagues, these results raise the possibility that rFVIIa may be administered in obstetric cases with life-threatening bleeding episodes, even in the presence of DIC-like coagulopathy. Injection of rFVIIa should be also considered before hysterectomy in a young patient with severe bleeding, or after internal iliac artery ligation, if bleeding continues.

The series of patients reported here provides data on the safety and efficacy of rFVIIa in intractable early postpartum hemorrhage. However, as with any case series, there are difficulties in data analysis because data were collected retrospectively after the bleeding episode had occurred.

Safety

Adverse thromboembolic events were reported in one case that was considered to be directly related to the use of rFVIIa[54]. In general, rFVIIa administration was associated with an excellent safety profile.

PROPOSAL OF RECOMMENDATION FOR THE USE OF rFVIIa IN SEVERE POSTPARTUM HEMORRHAGE

Based on our own experience and data from the literature[36,72–80], we have prepared guidelines for treatment of postpartum hemorrhage that include administration of rFVIIa.

Definitions of severe hemorrhage

(1) Loss of entire blood volume within 24 h;

(2) Loss of 50% of blood volume within 3 h;

(3) Blood loss at a rate of 150 ml/min (for 20 min > 50% blood volume);

(4) Blood loss at a rate of 1.5 ml/kg/min for ≥ 20 min;

(5) Sudden blood loss > 1500–2000 ml (uterine atony; 25–35% blood volume).

Definition of insufficient standard management

The hemorrhage continues despite:

(1) All standard pharmacological and surgical treatment methods have been used;

(2) Replacement therapy was performed;

(3) Coagulopathy was confirmed by laboratory testing

  (a) PT or APTT > 1.5 × times the control value

  (b) Thrombocytopenia < 50×10^9/l

  (c) Fibrinogen < 0.6–0.8 g/l.

Preconditions for rFVIIa administration

(1) Hematological parameters

  Hemoglobin levels > 70 g/l (4.3 mmol/l)
  International normalized ratio (INR) < 1.5
  Fibrinogen levels ≥ 1 g/l
  Platelets levels ≥ 50×10^9/l

(2) pH correction (≥ 7.2) (suggest using $NaHCO_3$)

(3) Body temperature should be restored if possible to physiological values: rFVIIa retains its activity in the presence of hypothermia

Correction of the pH to ≥ 7.2 is recommended before rFVIIa administration (efficacy of rFVIIa decreases at a pH ≤ 7.1). We also suggest using bicarbonate to elevate the serum pH. It should be noted that $NaHCO_3$ has not been shown to provide benefits to patients in hemorrhagic shock.

Recommended replacement therapy

(1) Fresh frozen plasma: 5–10 ml/kg (4–5 units);

(2) Cryoprecipitates: 1–1.5 units/10 kg (8–10 units);

(3) Platelets: 1 units/10 kg (5–8 units);

(4) Correction of acidosis (defined as pH ≥ 7.2);

(5) Warming of hypothermic patients (recommended, but not mandatory for administration of rFVIIa).

Dosing administration protocol proposal

(1) The recommended initial dose of rFVIIa for treatment of severe postpartum hemorrhage is ~40–60 μg/kg administered intravenously.

(2) If bleeding still continuous beyond 15–30 min, following the first dose of rFVIIa, an additional dose of ~40–60 μg/kg should be considered. Repeat 3–4 times at 15–30-min intervals if clinical signs of bleeding are still present (based on visual evidence).

(3) If the response remains inadequate following a total dose of > 200 μg/kg, the preconditions for rFVIIa administration should be re-checked, and corrected as necessary before another dose is considered.

(4) Only after these corrective measures have been applied should the next dose of rFVIIa ~100 μg/kg be administered.

Recommended timing of administration

Because our experience suggests that rFVIIa permits effective control of obstetric bleeding, especially in situations of coexisting coagulopathy, we therefore recommend administration of rFVIIa as soon as possible under the following circumstances:

(1) When no blood is available;

(2) Before metabolic complications develop;

(3) In women refusing transfusions (e.g. Jehovah Witnesses) (see Chapter 15);

(4) In acquired hemophilia (see Chapter 25);

(5) Before the symptoms of severe thrombocytopathies, hypoxia and organ injury appear;

(6) If correction of INR (PT) is urgently needed;

(7) Before packing of the uterus or pelvis;

(8) Before surgical procedures such as hysterectomy, laparotomy;

(9) Before medical procedures such as embolization, ligation of the uterine and internal iliac arteries (see Chapter 32).

Information obtained from the literature allows us to summarize the advantages and disadvantages of rFVIIa as follows.

Advantages

(1) Recombinant product;

(2) Not subject to blood shortage;

(3) No viral transmission;

(4) No human protein;

(5) Localized hemostasis;

(6) Low risk of anaphylaxis;

(7) No anamnestic responses;

(8) Low thrombogenicity;

(9) Effective during and after surgery.

Disadvantages

(1) Short $t_{1/2}$ requires frequent, repetitive dosing;

(2) Not 100% effective;

(3) No measurable lab parameter for efficacy;

(4) Limited vial sizes;

(5) Venous access;

(6) Cost.

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Section VII

Therapy for atony

27

STANDARD MEDICAL THERAPY

F. Breathnach and M. Geary

INTRODUCTION

Failure of the uterus to contract and retract following childbirth has for centuries been recognized as the most striking cause of postpartum hemorrhage. Uterine atony is a condition which, in spite of the presence of effective medical interventions, still claims thousands of maternal lives. In the developing world, lack of access to uterotonic therapies that have been available for almost a century represents one of the most glaring disparities in obstetric care today.

In the 19th century, uterine atony was treated by intrauterine placement of various agents with the aim of achieving a tamponade effect. 'A lemon imperfectly quartered' or 'a large bull's bladder distended with water' were employed for this purpose, with apparent success. Douching with vinegar or iron perchloride was also reported[1,2]. Historically, the first uterotonic drugs were ergot alkaloids, followed by oxytocin and, finally, prostaglandins.

Ergot, the alkaloid-containing product of the fungus *Claviceps purpurea* that grows on rye, was recognized for centuries as having uterotonic properties and is the substance referred to by John Stearns in 1808 as 'pulvis parturiens' (a powder [for] childbirth), at which time it was used as an agent to accelerate labor[3]. By the end of the 19th century, however, recognition of the potential hazards associated with ergot use in labor, namely its ability to cause uterine hyperstimulation and stillbirth, had tempered enthusiasm for its use. Focus was diverted toward its role in preventing and treating postpartum hemorrhage at a time when, according to an 1870 report, maternal mortality in England approached one in 20 births[4]. Attempts to isolate the active alkaloids from ergot were not successful until the early 20th century, when Barber and Dale isolated ergotoxine in 1906[2]. Initially thought to be a pure substance, this agent was subsequently found to comprise four alkaloids and in 1935 Moir and Dudley were credited for isolating ergometrine, the active aqueous extract 'to which ergot rightly owes its long-established reputation as the pulvis parturiens'[5,6]. Moir reported on its clinical use in 1936, stating[6]:

> '. . . the chief use of ergometrine is in the prevention and treatment of postpartum haemorrhage. Here the ergometrine effect is seen at its best. If after the delivery of the placenta the uterus is unduly relaxed, the administration of ergometrine, 1 mg by mouth or 0.5 mg by injection, will quickly cause a firm contraction of the organ. If severe haemorrhage has already set in, it is highly recommended that the drug should be given by the intravenous route. For this purpose one-third of the standard size ampoule may be injected or, for those who wish accurate dosage, a special ampoule containing 0.125 mg is manufactured. An effect may be looked for in less than one minute.'

Oxytocin, the hypothalamic polypeptide hormone released by the posterior pituitary, was discovered in 1909 by Sir Henry Dale[7] and synthesized in 1954 by du Vigneaud[8]. The development of oxytocin constituted the first synthesis of a polypeptide hormone and gained du Vigneaud a Nobel prize for his work.

The third group of uterotonics comprises the ever-expanding prostaglandin family. The prostaglandins were discovered in 1935 by a group led by Swedish physiologist Ulf von Euler[9] who found that extracts of seminal vesicles or of human semen were capable of causing contraction of uterine tissue and lowering blood pressure. The term 'prostaglandin' evolved

from von Euler's belief that the active material came exclusively from the prostate gland. This family of 'eicosanoids', 20-carbon fatty acids, was subsequently found to be produced in a variety of tissues and capable of mediating a myriad of physiologic and pathologic processes. Prostaglandins, by virtue of their ability to cause strong myometrial tetanic activity, are increasingly being employed as adjunctive therapy to standard oxytocin and ergometrine to treat postpartum hemorrhage resulting from uterine atony (see Chapter 12).

This chapter is devoted to critical evaluation of the standard pharmacological methods available to overcome uterine atony, with particular focus on agent selection based on effectiveness, safety profile, ease of administration, cost and applicability in low-resource settings.

UTERINE ATONY

Powerful efficient contractions of the myometrium are essential to arrest blood loss after delivery. The resultant compression of the uterine vasculature serves to halt the 800 ml/min blood flow in the placental bed. Recognition of a soft, boggy uterus in the setting of a postpartum bleed alerts the attendant to uterine atony. The contribution that uterine atony makes toward postpartum hemorrhage is so well-known that a universal reflex action when faced with excessive postpartum bleeding is to massage a uterine contraction. Prompt recognition of this condition and institution of uterotonic therapy will effectively terminate the majority of cases of hemorrhage. Once effective uterine contractility is assured, persistent bleeding should prompt the search for retained placental fragments, genital tract trauma or a bleeding diathesis (see Chapters 9 and 25).

Astute risk assessment is crucial in identifying women at increased risk of uterine atony, thereby allowing for preventive measures to be instituted and for delivery to take place where transfusion and anesthetic facilities are available. The established risk factors associated with uterine atony are outlined in Table 1. It is worth noting that multiparity, hitherto believed to be a significant risk factor, has not emerged as having an association with uterine atony in recent studies[10-12]. Previous postpartum hemorrhage confers a 2–4-fold increased risk of hemorrhage compared to women without such a history[12,13].

Table 1 Risk factors for uterine atony

Factors associated with uterine overdistension
Multiple pregnancy
Polyhydramnios
Fetal macrosomia
Labor-related factors
Induction of labor
Prolonged labor
Precipitate labor
Oxytocin augmentation
Manual removal of placenta
Use of uterine relaxants
Deep anesthesia (especially halogenated anesthetic agents)
Magnesium sulfate
Intrinsic factors
Previous postpartum hemorrhage
Antepartum hemorrhage (abruptio or previa)
Obesity
Age > 35 years

It is appropriate that women with these predisposing risk factors should deliver in a hospital with adequate facilities to manage postpartum hemorrhage. Prophylactic measures adopted include appropriate hospital booking for women at risk, active management of the third stage of labor, intravenous access during labor and ensuring the availability of cross-matched blood. However, it is noteworthy that uterine atony occurs unpredictably in women with no identifiable predisposing risk factors. This underpins the need for strict protocols for the management of postpartum hemorrhage to be in place in every unit that provides obstetric care.

OXYTOCIN

With timely and appropriate use of uterotonic therapy, the majority of women with uterine atony can avoid surgical intervention. Stimulation of uterine contraction is usually achieved in the first instance by bimanual uterine massage and the injection of oxytocin (either intramuscularly or intravenously), with or without

ergometrine. The mode of action of oxytocin involves stimulation of the upper uterine segment to contract in a rhythmical fashion. Owing to its short plasma half-life (mean 3 min), a continuous intravenous infusion is required in order to maintain the uterus in a contracted state[14]. The usual dose is 20 IU in 500 ml of crystalloid solution, with the dosage rate adjusted according to response (typical infusion rate 250 ml/h). When administered intravenously, the onset of action is almost instantaneous and plateau concentration is achieved after 30 min. By contrast, intramuscular administration results in a slower onset of action (3–7 min) but a longer lasting clinical effect (up to 60 min).

Metabolism of oxytocin is via the renal and hepatic routes. Its antidiuretic effect, which amounts to 5% of the antidiuretic effect of vasopressin, can result in water toxicity if given in large volumes of electrolyte-free solutions. This degree of water overload can manifest itself with headache, vomiting, drowsiness and convulsions. Furthermore, rapid intravenous bolus administration of undiluted oxytocin results in relaxation of vascular smooth muscle, which can lead to hypotension. It is therefore best given intramuscularly or by dilute intravenous infusion. Oxytocin is stable at temperatures up to 25°C but refrigeration may prolong its shelf-life.

A disadvantage of oxytocin is its short half-life. The long-acting oxytocin analog carbetocin has been studied in this context as its more sustained action, similar to that of ergometrine but without its associated side-effects, may offer advantages over standard oxytocic therapy[15]. Comparative studies of carbetocin for the prevention of postpartum hemorrhage have identified enhanced effectiveness of this analog when compared with an oxytocin infusion[16,17].

ERGOMETRINE

In contrast to oxytocin, the administration of ergometrine results in a sustained tonic uterine contraction via stimulation of myometrial α-adrenergic receptors. Both upper and lower uterine segments are thus stimulated to contract in a tetanic manner[14]. Intramuscular injection of the standard 0.25 mg dose results in an onset of action of 2–5 min. Metabolism is via the hepatic route and the mean plasma half-life is 30 min. Nonetheless, the clinical effect of ergometrine persists for approximately 3 h. The co-administration of ergometrine and oxytocin therefore results in a complementary effect, with oxytocin achieving an immediate response and ergometrine a more sustained action.

Common side-effects include nausea, vomiting and dizziness and these are more striking when given via the intravenous route. As a result of its vasoconstrictive effect via stimulation of α-adrenergic receptors, hypertension can occur. Contraindications to use of ergometrine therefore include hypertension (including pre-eclampsia), heart disease and peripheral vascular disease. If given intravenously, where its effect is seen as being almost immediate, it should be given over 60 s with careful monitoring of pulse and blood pressure. Relevant to the developing world in particular is its heat lability. It is both heat- and light-sensitive and should be stored at temperatures below 8°C and away from light.

The product Syntometrine® (5 units oxytocin and 0.5 mg ergometrine) combines the rapid onset of oxytocin with the prolonged effect of ergometrine. The mild vasodilatory property of oxytocin may counterbalance the vasopressor effect of ergometrine.

First-line treatment of uterine atony, therefore, involves administration of oxytocin or ergometrine as an intramuscular or diluted intravenous bolus, followed by repeat dosage if no effect is observed after 5 min and complemented by continuous intravenous oxytocin infusion. Atony that is refractory to these first-line oxytocics will warrant prostaglandin therapy.

CARBOPROST

Carboprost (15-methyl $PGF_{2\alpha}$) acts as a smooth muscle stimulant and is a recognized second-line agent for use in the management of postpartum uterine atony unresponsive to oxytocin/ergometrine. It is an analog of $PGF_{2\alpha}$ (dinoprost) with a longer duration of action than its parent compound, attributed to its resistance to inactivation by oxidation at the 15-position. Available in single-dose vials of

0.25 mg, it may be administered by deep intramuscular injection or, alternatively, by direct intramyometrial injection. The latter route of administration is achieved either under direct vision at Cesarean section or transabdominally or transvaginally following vaginal delivery and has the advantage of a significantly quicker onset of action[18,19]. Peripheral intramuscular injection yields peak plasma concentrations at 15 min in contrast to less than 5 min for the intramyometrial route. Using a 20-gauge spinal needle, intravascular injection can be avoided by pre-injection aspiration, and intramyometrial rather than intracavitary placement of the needle can be confirmed by observing resistance on injection, as described by Bigrigg and colleagues[20]. The dose may be repeated every 15 min up to a maximum cumulative dose of 2 mg (eight doses), although, in reported case series, the majority of patients require no more than one dose.

Reported efficacy is high. Successful arrest of atonic hemorrhage is reported in 13/14 patients by Bigrigg and colleagues[20]. The largest case series to date[19] involved a multicenter surveillance study of 237 cases of postpartum hemorrhage refractory to standard oxytocics and reported an efficacy of 88%. The majority of women in this study required a single dose only.

Owing to its vasoconstrictive and bronchoconstrictive effects, carboprost can result in nausea, vomiting, diarrhea, pyrexia and bronchospasm. Contraindications therefore include cardiac and pulmonary disease. The cost of carboprost makes it unsuitable for consideration in low-resource settings. Furthermore, it is both light- and heat-sensitive and must be kept refrigerated at 4°C.

MISOPROSTOL

Misoprostol is a synthetic analog of prostaglandin E_1 which selectively binds to myometrial EP-2/EP-3 prostanoid receptors, thereby promoting uterine contractility. It is metabolized via the hepatic route. It may be given orally, sublingually, vaginally, rectally or via direct intrauterine placement. The rectal route of administration is associated with a longer onset of action, lower peak levels and a more favorable side-effect profile when compared with the oral or sublingual route. The results of an international multicenter, randomized trial of oral misoprostol as a prophylactic agent for the third stage of labor showed it to be less effective at preventing postpartum hemorrhage than parenteral oxytocin[21]. Fifteen percent of women in the misoprostol arm required additional uterotonics compared with 11% in the oxytocin group. This may be due to its longer onset of action (20–30 min to achieve peak serum levels compared to 3 min for oxytocin). However, owing to the fact that its more prolonged time interval required to achieve peak serum levels may make it a more suitable agent for protracted uterine bleeding, there is mounting interest in its role as a therapeutic rather than a prophylactic agent.

The use of rectal misoprostol for the treatment of postpartum hemorrhage unresponsive to oxytocin and ergometrine was first reported by O'Brien and colleagues[22] in a descriptive study of 14 patients. Sustained uterine contraction was reported in almost all women within 3 min of its administration. However, there was no control group included for comparison. A single-blinded, randomized trial of misoprostol 800 μg rectally versus Syntometrine® intramuscularly plus oxytocin by intravenous infusion found that misoprostol resulted in cessation of bleeding within 20 min in 30/32 cases (93%) compared to 21/32 (66%) for the comparative agents[23]. A Cochrane review supports these findings, suggesting that rectal misoprostol in a dose of 800 μg could be a useful 'first-line' drug for the treatment of primary postpartum hemorrhage[24].

A strong need exists for high-dose misoprostol to be evaluated in randomized control trials. As an alternative to the aforementioned uterotonics, misoprostol has the significant advantage of low cost, thermostability, light stability and lack of requirement for sterile needles and syringes for administration, making it an attractive option for use in the developing world. It has a shelf-life of several years.

Side-effects of misoprostol are mainly gastrointestinal and are dose-dependent. A frequently reported side-effect of misoprostol is the occurrence of shivering and pyrexia. Side-effects are less marked when the rectal route of administration is used.

OTHER PROSTAGLANDINS

Dinoprost (prostaglandin $F_{2\alpha}$) has been used via intramyometrial injection at doses of 0.5–1.0 mg with good effect[25]. Low-dose intrauterine infusion via a Foley catheter has also been described, consisting of 20 mg dinoprost in 500 ml saline at 3–4 ml/min for 10 min, then 1 ml/min. The bleeding was arrested in all but one of 18 patients and no adverse outcome was reported. As mentioned earlier, however, this agent has a shorter duration of activity than carboprost and indeed has been unavailable in the US since the 1980s where its withdrawal was attributed to financial reasons.

Prostaglandin E_2 (dinoprostone), in spite of its vasodilatory properties, causes smooth muscle contraction in the pregnant uterus, thus making it a potentially suitable uterotonic agent. Its principal indication is in pre-induction cervical priming, but intrauterine placement of dinoprostone has been successfully employed as a treatment for uterine atony[26]. The vasodilatory effect of dinoprostone, however, renders it unsuitable for use in the hypotensive or hypovolemic patient. It may, however, be of use in women with cardiorespiratory disease in whom carboprost is contraindicated.

Experience with gemeprost, a prostaglandin E_1 analog, in pessary formulation delivered directly into the uterine cavity or placed in the posterior vaginal fornix, is again largely anecdotal[27-29]. Its mode of action resembles that of $PGF_{2\alpha}$. Rectal administration has also been reported. A retrospective series of 14 cases in which rectal gemeprost 1 mg was used for postpartum hemorrhage unresponsive to oxytocin and ergometrine reported prompt cessation of bleeding in all cases, with no apparent maternal adverse sequelae[30].

HEMOSTATICS: TRANEXAMIC ACID AND RECOMBINANT ACTIVATED FACTOR VII

The antifibrinolytic agent tranexamic acid, which prevents binding of plasminogen and plasmin to fibrin, may well have a role in the control of intractable postpartum hemorrhage, particularly where coagulation is compromised. However, to date there is only one case report in the literature of the use of this agent in the setting of postpartum hemorrhage; that particular case involved a placenta accreta where the source of the persistent bleeding was the lower uterine segment and the uterine body was described as being well contracted[31]. The dose employed was 1 g given intravenously 4-hourly to a cumulative dose of 3 g.

The use of recombinant activated factor VII (rFVIIa) as a hemostatic agent for refractory postpartum hemorrhage has recently been described in a number of case reports[32,33]. The mode of action of this agent involves enhancement of the rate of thrombin generation, leading to formation of a fully stabilized fibrin plug that is resistant to premature lysis. Reported cases involve hemorrhage unresponsive to a myriad of conventional treatments including hysterectomy and pelvic vessel ligation, where use of this agent was remarkably successful at arresting seemingly intractable bleeding within a matter of minutes. Doses of 60–120 μg/kg intravenously were used. A more complete discussion of this agent is found in Chapter 26.

CONCLUSIONS

The identification of 'substandard care' in 71% of maternal deaths attributed to hemorrhage in the 2000–2002 Confidential Report (UK)[34] underscores the need for a standard of care to be established in every unit where childbirth takes place and for all relevant health-care workers to be keenly familiar with that standard (see Chapter 22). Integral to any protocol on management of postpartum hemorrhage will be a stepwise approach to achieving effective uterine contractility. The successful management of uterine atony will depend on staff being familiar with the pharmacologic agents available to them with respect to dosage, route of administration and safety profile (Table 2). Application of such protocols has been shown to achieve successful reduction in the morbidity associated with postpartum hemorrhage[35].

It is tempting to credit the second- or third-line agent with successfully controlling a postpartum hemorrhage; however, it is certainly plausible that a synergistic effect is observed where a combination of uterotonics is used.

Table 2 Medical uterotonic therapy

Agent	*Dose*	*Cautions*
Oxytocin (Pitocin®, Syntocinon®)	10 IU i.m./i.v. followed by i.v. infusion of 20 IU in 500 ml crystalloid titrated versus response (e.g. 250 ml/h)	Hypotension if given by rapid i.v. bolus. Water intoxication with large volumes
Ergometrine (Ergonovine®)	0.25 mg i.m./i.v.	Contraindicated in hypertensive patients. Can cause nausea/vomiting/dizziness
Carboprost (15-methyl $PGF_{2\alpha}$) (Hemabate®)	0.25 mg i.m./myometrial. Can be repeated every 15 min. Max. 2 mg	Bronchospasm (caution in patients with asthma, hypertension, cardiorespiratory disease)
Dinoprost ($PGF_{2\alpha}$) (Prostin $F_{2\alpha}$®)	0.5–1 mg intramyometrial or 20 mg in 500 ml N/saline infused via Foley catheter into uterine cavity	Bronchospasm, nausea, vomiting and diarrhea can occur
Dinoprostone (Prostin®/ Prepidil®)	2 mg p.r. 2-hourly	Hypotension
Gemeprost (Cervagem®)	1–2 mg intrauterine placement/ 1 mg p.r.	Gastrointestinal disturbance
Misoprostol (Cytotec®)	600–1000 μg p.r./intracavitary	Gastrointestinal disturbance, shivering, pyrexia
Tranexamic acid (Cyclokapron®)	1 g 8-hourly i.v.	Can increase risk of thrombosis
rFVIIa (Novoseven®)	60–120 μg/kg i.v.	Fever, hypertension

i.m., intramuscularly; i.v., intravenously; p.r., per rectum

The global quest for an 'ideal' uterotonic agent must take into account the fact that what is applicable in one setting may have no relevance in another. This is particularly true of the need to study the potential of a low-cost agent such as misoprostol for use in the developing world. The cost and instability of standard oxytocic drugs are prohibitive in many low-resource settings. Safety and parallel efficacy should therefore suffice as parameters whereby an agent such as misoprostol is judged rather than demonstration of clinical superiority over established uterotonics.

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28

INTERNAL UTERINE TAMPONADE

D. Danso and P. W. Reginald

INTRODUCTION

The origin of the word tamponade appears to have come from an old French word for tampon, which carries the connotation of a plug, a bung or a stopper inserted into an open wound or a body cavity to stop the flow of blood[1]. Today, the common usage of this term includes the collection of menstrual effusion by insertion of a preformed sanitary pledget into the vagina.

In the context of postpartum hemorrhage, tamponade refers to plugging the uterus with some type of device to stop the flow of blood. Normally, this is in the form of a gauze pack or a balloon catheter. Internal tamponade procedures have been used successfully alone[2–5] or in combination with the Brace suture[6] to reduce or arrest massive postpartum hemorrhage.

PRINCIPLES OF UTERINE TAMPONADE

Uterine tamponade requires developing intrauterine pressure to stop bleeding. This can be accomplished in two ways:

(1) By insertion of a balloon that distends in the uterine cavity and occupies the entire space, thereby creating an intrauterine pressure that is greater than the systemic arterial pressure. In the absence of lacerations, the blood flow into the uterus should stop the moment the pressure in the tamponade balloon is greater than that of the systemic arterial pressure.

(2) By insertion of a uterine pack consisting of a gauze roll that is tightly packed into the uterus in such a manner that pressure is applied directly on capillary/venous bleeding vessels or surface oozing (of the deciduas) from within the uterus, thereby resulting in either a significant reduction or stoppage of uterine bleeding.

BASIC GENERAL PRINCIPLES

After failure of medical intervention to stop or reduce postpartum hemorrhage, one should consider performing internal uterine tamponade. This should be carried out in the operating theater with anesthetic and nursing staff present as well as blood transfusion service back-up. The woman should be placed in the Lloyd Davies or lithotomy position with an indwelling urethral catheter. Examination under anesthesia should be carried out to exclude lacerations, retained placenta, and to empty the uterus of clots. Only then should tamponade procedures be attempted. Uterotonics and hemostatics are advised as adjunct therapy and may be given simultaneously. Any of the internal uterine tamponade methods described below can be embarked upon before resorting to surgical interventions.

The following is a description of the 'tamponade test' and various other methods of tamponade with their potential advantages and disadvantages.

THE TAMPONADE TEST

This test, first described in 2003 by Condous and colleagues[7], was proposed as a prognostic index as to whether laparotomy would be needed in patients with major postpartum hemorrhage unresponsive to medical therapy. In the original description, a Sengstaken–Blakemore esophageal catheter was inserted into the uterine cavity via the cervix, using ultrasound guidance when possible, and filled with warm saline

until the distended balloon was palpable per abdomen surrounded by the well-contracted uterus, and visible at the lower portion of the cervical canal. The position of the Sengstaken–Blakemore esophageal catheter was checked to ensure it was firmly fixed *in situ* within the uterine cavity by the application of gentle traction. If no or only minimal bleeding was observed via the cervix or there was only minimal bleeding into the gastric lumen of the Sengstaken–Blakemore esophageal catheter, the tamponade test result was considered to be positive. If this were the case, surgical intervention, with possible hysterectomy, was avoided. On the other hand, if significant bleeding continued via the cervix or the gastric lumen of the tube, the tamponade test was deemed a failure and laparotomy was performed. In this study, 14 out of 16 women (87%) with intractable hemorrhage responded positively. Of the women who did not respond, one continued to bleed because of an overlooked cervical extension of the lower transverse uterine incision at Cesarean delivery. The balloon was inadequately inflated in the other. The Rüsch urological balloon has also been used successfully for the tamponade test[3]. Chapter 29 describes in more detail a longitudinal study still in progress to determine the effectiveness of the Rüsch urological balloon for the tamponade test.

SENGSTAKEN–BLAKEMORE TUBE

The Sengstaken–Blakemore esophageal catheter was originally designed for the treatment of esophageal variceal bleeds and the introduction of contrast media. It is a three-way catheter tube with stomach and esophageal balloon components (see Figure 1). It can be inflated to volumes greater than 500 ml. Several reports on its successful use to arrest major postpartum hemorrhage are available[2,7,8–11]. Before insertion of the tube, the distal end of the tube beyond the stomach balloon is severed to minimize the risk of perforation. The main advantage is its simplicity of use and, therefore, junior residents can easily learn and perform the test while waiting for help.

The main disadvantages are that it is not purpose-designed for postpartum hemorrhage and may not easily adapt to the shape of the uterine cavity. Moreover, it contains latex and may not be affordable in resource-poor settings.

RÜSCH HYDROSTATIC UROLOGICAL BALLOON

This is a two-way Foley catheter (simplastic 20 ch, 6.7 mm, 30 ml), which can also be used for postpartum hemorrhage. It has a capacity greater than 500 ml (see Figure 2)[3]. The technique of insertion is similar to the description already given for the Sengstaken–Blakemore esophageal catheter. A 60-ml bladder syringe can be used for inflating the balloon with warm saline via the drainage port. It is a simple technique and therefore junior residents can easily learn and become adept in its use, especially if practised after a manual removal of the placenta.

BAKRI BALLOON

The SOS Bakri tamponade balloon catheter (Cook Ob/Gyn) is marketed as 100% Silicon (no latex), purpose-designed two-way catheter, to provide temporary control or reduction of postpartum uterine bleeding when conservative management is warranted (see Figure 3)[4]. Again, the insertion technique is simple. Insert the balloon portion of the catheter in the uterus, making sure that the entire balloon is inserted past the cervical canal and internal os, under ultrasound guidance if possible. At Cesarean delivery, the tamponade balloon can be passed via the Cesarean incision into the uterine cavity with the inflation port passing into the vagina via the cervix. An assistant pulls the shaft of the balloon through the vaginal canal until the deflated balloon base comes into contact with the internal cervical os. The uterine incision is closed in the usual fashion, taking care to avoid puncturing the balloon while suturing. A gauze pack soaked with iodine or antibiotics can then be inserted into the vaginal canal to ensure maintenance of correct placement of the balloon and maximize the tamponade effect. The balloon is then inflated with sterile fluid to the desired volume for tamponade effect. Gentle traction on the balloon shaft ensures proper

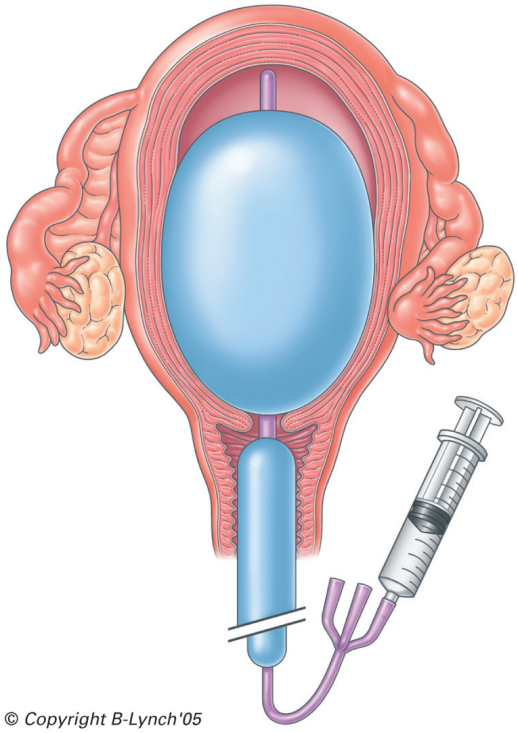

Figure 1 Sengstaken–Blakemore tube

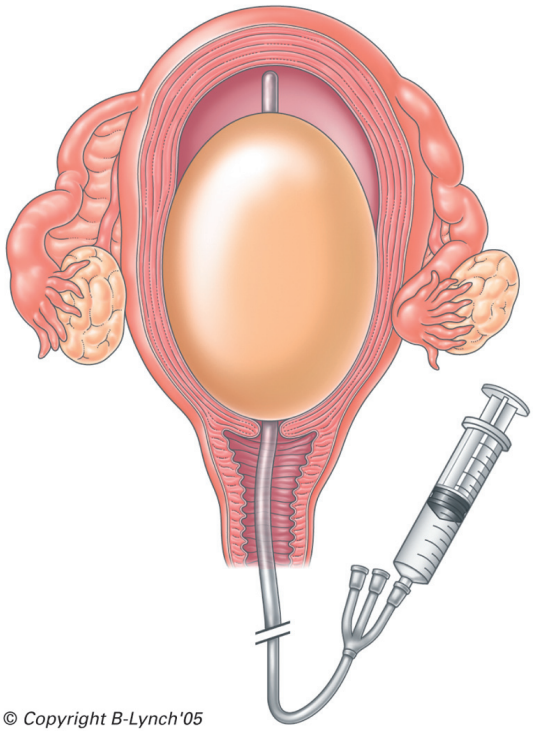

Figure 3 Bakri balloon

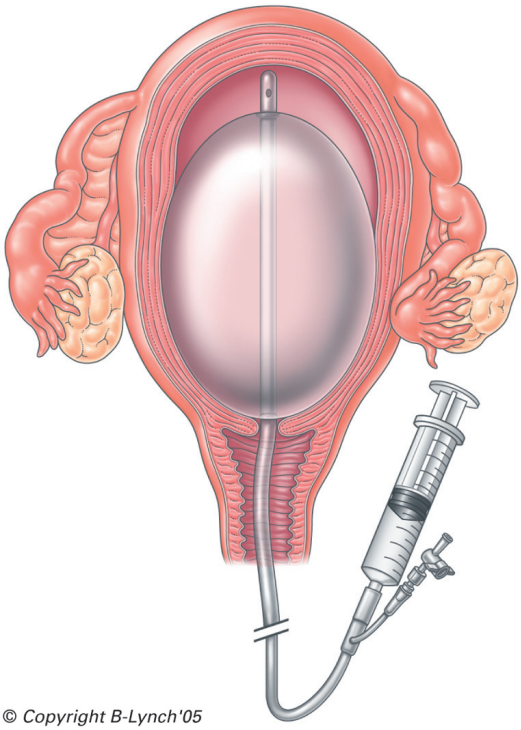

Figure 2 Rüsch hydrostatic balloon catheter

contact between the balloon and the tissue surface and may enhance the tamponade effect. Success can be judged by the declining loss of blood seen through the drainage port and the fluid connecting bag.

The main disadvantage of this method is that it may not be affordable in resource-poor countries because of the expense.

FOLEY CATHETER

The successful use of the Foley catheter balloon for internal uterine tamponade is also described[12,13]. A Foley catheter with a 30-ml balloon capacity is easy to acquire and may routinely be stocked on labor and delivery suites. Using a No. 24F Foley catheter, the tip is guided into the uterine cavity and inflated with 60–80 ml of saline (anecdotally, a volume of 150 ml can be reached before it bursts). Additional Foley catheters can be inserted, if necessary, until bleeding stops. As attractive, easy and cheap as this method is, some concerns

have been raised regarding the use of the Foley catheter for uterine tamponade. First, the capacity of the immediate postpartum uterine cavity, especially if term, is too large for effective tamponade to be achieved with one inflated balloon, and the risk of one balloon falling out of the uterus is increased[14]. Second, significant bleeding may occur above the Foley bulb, as it may not fill the entire uterine cavity. Even the use of multiple Foley catheters cannot ensure a complete compression effect on the entire uterine surface.

HYDROSTATIC CONDOM CATHETER

This innovative approach from Bangladesh uses a sterile rubber catheter fitted with a condom as a tamponade balloon device[14]. The sterile catheter is inserted within the condom and tied near the mouth of the condom with a silk thread, and the outer end of the catheter is connected to a saline set. In its original description, after placement in the uterus, the condom is inflated with 250–500 ml normal saline according to need, and the outer end of the catheter was folded and tied with thread after bleeding had stopped[14]. Vaginal bleeding is observed and further inflation is stopped when bleeding has ceased. To keep the balloon *in situ*, the vaginal cavity is packed with roller gauze and sanitary pads. Success is gauged by the amount of blood loss per vaginum. Hemorrhage was arrested within 15 min in all 23 cases in the original series[14]. Although the sample size was small, this method represents a cheap, simple and quick intervention which may prove invaluable in, especially, resource-poor countries.

UTERINE PACKING

Uterine packing entails placing, carefully and systematically, several yards of gauze inside the uterine cavity to occlude the whole intrauterine space and, thus, control major hemorrhage. The technique fell out of favor in the 1950s, as it was thought to conceal hemorrhage and cause infection. It re-emerged in the 1980s and 1990s after these concerns were not verified[15]. The main disadvantages of this technique are:

(1) Experience is required to pack properly and tightly and therefore junior residents may not be able to perform proficiently, especially if they have large hands. Speed is also necessary because the intrauterine/vaginal hand becomes numb rapidly;

(2) Delay in recognizing continual hemorrhage as blood needs to soak through yards of gauze before it becomes evident;

(3) Success of the procedure will not be known immediately, as the blood must soak through the pack to reveal itself;

(4) The tightness of the pack is difficult to determine, especially if blood soaks through, leading to a loss of the tamponade effect;

(5) Potential risk of trauma and infection;

(6) Removing the pack may often require a separate surgical procedure to dilate and extract the intrauterine material, thus falling short of an ideal option.

Notwithstanding, uterine packing remains an option, especially, if balloon catheters or balloons are not available. The risk of intrauterine infection can be minimized by prophylactic antibiotics.

CARE AFTER SUCCESSFUL UTERINE TAMPONADE

All patients should be managed in a high-dependency or intensive care unit with very close monitoring of their vital signs, fluid input/output, fundal height and vaginal blood loss. Continued oxytocin infusion may be necessary to keep the uterus contracted over 12–24 h. Prophylactic broad-spectrum antibiotic cover should be administered. The mean time for leaving tamponade balloons or uterine packs ranges from 8 to 48 h[2,7,9–12]. A graduated deflation of the balloon is advised to reduce the potential risk of further bleeding.

In summary, tamponade procedures are simple, cheap, easy to use, and effective measures that should be considered in women with intractable postpartum hemorrhage, especially when other options may be unavailable.

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29

THE BALLOON INTERNAL UTERINE TAMPONADE AS A DIAGNOSTIC TEST

S. Ferrazzani, L. Guariglia and C. Dell'Aquila

INTRODUCTION

During the last several years, a number of new and simpler techniques have been developed in the attempt to avoid major surgical procedures for treatment of postpartum hemorrhage[1–8]. Although a variety of surgical options have been proposed to avoid hysterectomy including uterine artery ligation, ovarian artery ligation, internal iliac artery ligation, and B-Lynch Brace suture[9], a suitable conservative technique is still lacking[1] and all proposed options have risks as well as advantages[10].

In most cases, procedures are effective in avoiding hysterectomy, but a delay carries a poorer prognosis. Moreover, each of these techniques entails a laparotomy and skilled personnel must perform the procedure. Rarely, major complications follow radical surgery for postpartum hemorrhage; these include loss of fertility, other morbidity and even maternal death[11].

B-Lynch and colleagues[12,13] used brace sutures to compress the uterus without compromising major vessels. The advantage of the B-Lynch procedure is that identification of specific blood vessels is not necessary, a process which is often difficult. Although helpful during Cesarean section, the B-Lynch procedure requires a laparotomy and therefore may not be ideal as the first approach in cases of postpartum hemorrhage following vaginal delivery[14].

This chapter will focus on one of the recently reported conservative measures to control hemorrhage – internal uterine tamponade. Although uterine atony is the main indication for internal uterine tamponade, this methodology is also useful for postpartum hemorrhage arising from placenta previa/accreta. The technique can be easily carried out by doctors in training while awaiting help from a senior colleague.

UTERINE PACKING

Control of postpartum hemorrhage by uterine packing is not new[15]. For many years, uterine packing with sterile gauze has been used in the clinical management of severe postpartum hemorrhage and as the last resort before hysterectomy[16]. Because of the availability of better uterotonic medications, this practice lost its appeal, but reports on its successful use continued to appear[17–19]. Recently, some authors raised concerns about concealed bleeding and infection[20]; a newer technique, however, has allayed some of these concerns[21].

Uterovaginal packing may sometimes obviate the need for surgery altogether. In cases of deliveries complicated by postpartum hemorrhage, after excluding uterine rupture, genital tract lacerations, and retained placental tissue, efforts are directed toward contracting the uterus by bimanual compression and uterotonic agents. If these are not successful, one must resort to surgical techniques. At this stage, an alternative option to remember is uterovaginal packing. Easy and quick to perform, it may be used to control bleeding by tamponade effect and stabilize the patient until a surgical procedure is arranged.

Chapter 28 describes the technique of uterine packing in more detail.

BALLOON TAMPONADE

Tamponade with different types of balloon catheters used prior to surgery is a conservative

procedure that is available before invasive surgical techniques are needed[1,3]. Chapter 28 describes the various types of balloon catheters that are available.

Balloon tamponade of the uterus is a recognized procedure in those with massive and intractable hemorrhage[17,22–29].

The use of the Sengstaken–Blakemore esophageal or gastric catheter is described in the literature for the control of massive postpartum hemorrhage due to an atonic uterus not responding to oxytocics including prostaglandins[3,17,23,30,31] or due to placenta accreta[32]. Multiple Foley catheters in the case of a vaginal delivery[22,25] have also been used and even rubber catheters fitted with a condom have been used successfully to control postpartum hemorrhage in undeveloped countries[33]. Urological fluid-filled catheters (300–500 ml)[26,28,29] or of silicone balloons designed for tamponade function[27] also seem to be very effective, with further possibilities in cases of hemorrhage after Cesarean section for placenta previa/accreta.

Theoretical principle of action

The theoretical principle of the balloon tamponade is that temporary and steady mechanical compression of the bleeding surface of the placental site can be performed while waiting for the natural hemostatic mechanisms of the blood to take effect. The balloon, inflated inside the uterine cavity in order to stretch the myometrial wall, can exert an intrauterine pressure that overcomes the systemic arterial pressure, resulting in cessation of the intrauterine blood flow. Probably, a quite different mechanism can be advocated for its efficacy in the case of uterine atony. With separation of the placenta, the many uterine arteries and veins that carry blood to and from the placenta are severed abruptly. Elsewhere in the body, hemostasis in the absence of surgical ligation depends upon intrinsic vasospasm and formation of blood clots locally. At the placental implantation site, the most important factors for achieving hemostasis are contraction and retraction of the myometrium in order to compress the vessels and obliterate their lumens. Uterine atony from any origin can prevent this physiological mechanism, leading to massive hemorrhage.

The first therapeutic approach to this situation is mechanical stimulation by massage of the uterus and then the use of uterotonic drugs. In this case, the efficacy of the tamponade balloon may derive from the mechanical stimulation of myometrial contraction caused by the balloon's elasticity pressing against the myometrial wall. The simultaneous and continuous stimulation of myometrial contraction and the tamponade effect on the open vessels, reached with the contraction, explain its efficacy. However, the uterus must be empty for the tamponade to be successful.

In the presence of placenta accreta, the balloon must be used with great caution, as a failure or delay to control hemorrhage in such patients could be catastrophic.

In the small series reported in the literature, in which the different types of balloon catheter were filled with various volumes, ranging from 30 to 500 ml, Seror and colleagues chose an inflation volume of 250 ml, since this value corresponds to the approximate volume of the uterine cavity after delivery[31].

BALLOON TAMPONADE AS A TEST

To date, there is no diagnostic test to identify those patients with intractable hemorrhage who will need surgery. Condous and colleagues[3] proposed the use of an inflated Sengstaken–Blakemore balloon catheter as a test to create tamponade and identify patients who will or will not need surgery ('tamponade test'). When its results are positive, the tamponade test not only halts the blood loss and preserves the uterus, but also gives an opportunity to reverse and correct any consumptive coagulopathy. More than 87% of their patients (14/16) with intractable postpartum hemorrhage responded to the tamponade test[3]. More recently, Seror and colleagues reported that, in a series of 17 cases, tamponade treatment prevented surgery in 88% of patients[31].

According to these clinical experiences, an early use of the balloon catheter may reduce the total blood loss, and it is probable that any type of inflatable balloon with high fluid-filling capacity could be used for the same purpose.

The experience at the Catholic University of Rome, Italy

A longitudinal study is currently running in the Obstetrics and Gynecology Department of the Catholic University of Rome, Italy; it started in January 2002 and the Institute review board approved the study.

Patients and methods

In the period January 2002–August 2005, 10 773 patients delivered in our maternity ward. During this period, there were 124 (1.15%) instances of postpartum hemorrhage. Of these, 13 were considered critical and the women underwent treatment by intrauterine tamponade.

An atonic uterus caused postpartum hemorrhage in one case and placenta previa/accreta was noted in 12 cases, of which two were associated with uterine atony.

The mean age of the patients was 35 years (26–39 years). The mean gestational age at delivery was 36 weeks from the first day of the last menstrual period (26 weeks and 5 days to 40 weeks and 1 day). Nine patients were multiparous (69.2%). The mean parity was 2.1.

Labor was spontaneous in three cases, and stimulated with dinoprostone intravaginal gel or oxytocin infusion in two cases. The mean duration of labor was 6 h and 42 min (5–9 h). Three patients had a vaginal delivery, and ten had a Cesarean section (of which seven were planned).

Routinely, the patients who delivered by the vaginal route had prophylactic intramuscular oxytocin/ergometrine in the third stage of labor and all the patients who underwent Cesarean section had intramyometrial and intravenous oxytocin during/after the placenta was delivered.

In the 13 cases of postpartum hemorrhage considered in this study, patients were treated with appropriate oxytocic agents and prostaglandin analogues (intravenous infusions of oxytocin (40–100 U), intramyometrial oxytocin (20 U), intramuscular ergometrine (0.25–0.5 mg), and/or intravenous infusion of sulprostone (500 mg)).

In the three patients delivering by the vaginal route, an examination was performed under regional or general anesthesia for retained tissue and lacerations and, when necessary, retained tissue or placenta was removed and lacerations were sutured.

Coagulation studies were carried out simultaneously to exclude coagulopathy as the first or the complimentary cause of the hemorrhage.

In those patients considered for the study who showed no response to these measures, a sterile hydrostatic (bladder distention) balloon catheter size Ch. 16, 5.3 mm (Rüsch UK High Wycombe, England) (Figure 1) was inserted into the uterine cavity via the cervix. This was achieved using minimal analgesia or regional anesthetic. The insertion was facilitated by grasping the anterior and lateral margins of the cervix with sponge forceps and placing the balloon into the uterine cavity with another sponge forceps. The balloon catheter was then filled with 120–300 ml of warm saline solution until a contracted uterus was palpable through the abdomen. Applying gentle traction at this stage confirmed that the filled balloon was firmly

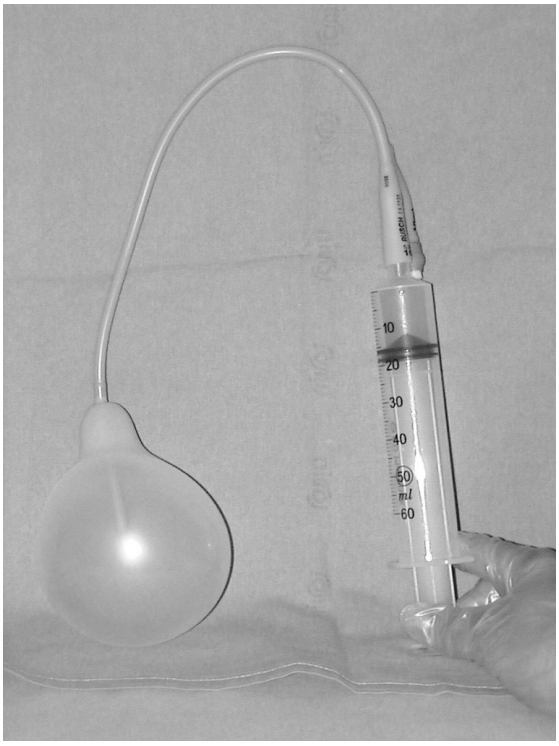

Figure 1 The Rüsch hydrostatic balloon catheter

fixed in the uterine cavity. If no or minimal bleeding was observed through the cervix, laparotomy was avoided and a gauze packing of the vagina was performed to avoid self-expulsion of the balloon from the completely dilated cervical os. If significant bleeding continued through the cervix, the 'tamponade test' had failed and laparotomy was performed.

In all the patients delivering by urgent or planned Cesarean section, the problem of abnormal insertion or suspicion of morbid adhesion of the placenta was detected by ultrasound scan before surgery. The placenta was delivered by firmly controlled cord traction, or by manual removal if it was abnormally adherent to the uterine wall. If severe bleeding persisted despite a contracted uterus after local intramyometrial and endovenous infusion of oxytocin and prostaglandin analogues, the hydrostatic balloon catheter previously described was inserted intrabdominally, through the uterine incision, into the cervical opening and through the cervical canal by a sponge forceps, leaving the balloon in the uterine cavity (Figure 2). The balloon was then filled with 180–300 ml of warm saline solution, using a 60 ml bladder syringe. Tamponade was achieved by pulling the distal extremity of the catheter shaft out of the vagina. The uterine contraction over the balloon was maintained, after the uterine closure, by a slow oxytocin infusion (20–40 U) that was given over the next 24 h. A single-layer closure of the uterine incision was performed, taking care not to include the balloon in the suture line. The Cesarean section was concluded following the classical technique. Only when the bleeding was adequately controlled was the abdominal wall closed.

Those who responded to the balloon catheter therapy were stabilized in the labor and delivery unit for ongoing management. In all cases, intravenous broad-spectrum antibiotics were administered for at least the first 24 h. The balloon catheter was left *in situ* until the next day. During this time interval, blood transfusion and coagulopathy correction were possible. Once the above parameters were within acceptable limits, the balloon catheter was slowly deflated and withdrawn and the patient observed for any active bleeding.

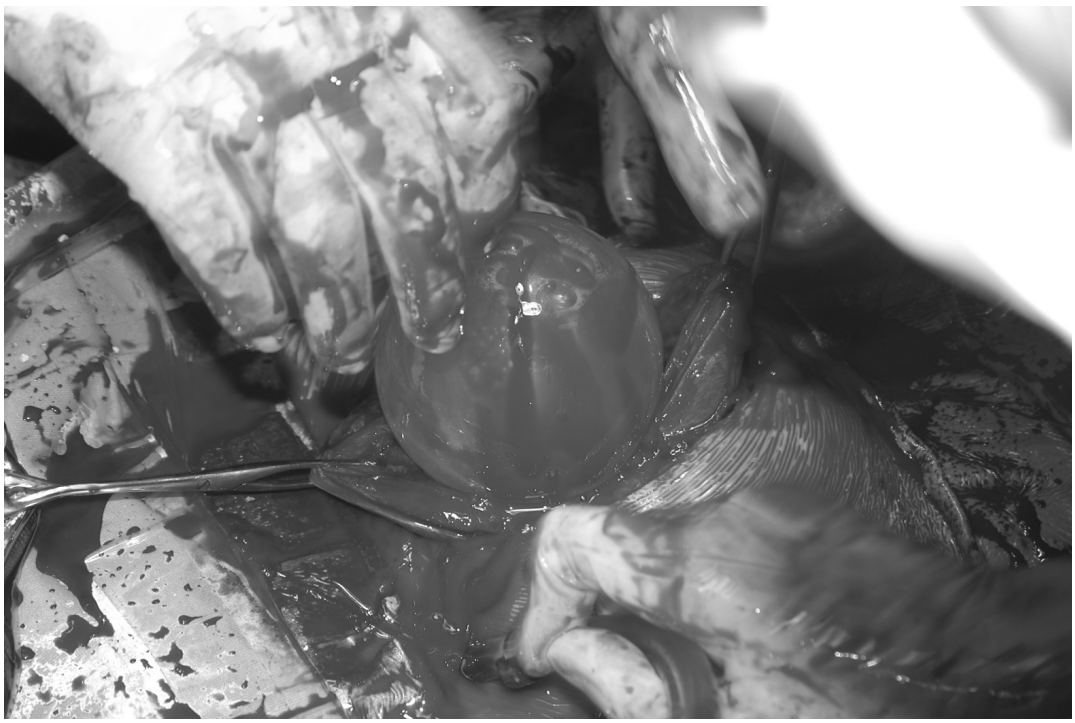

Figure 2 Intra-abdominal insertion of the hydrostatic balloon catheter into the uterine cavity

Table 1 Clinical details of patients with postpartum hemorrhage who underwent a balloon tamponade

Case	*Age* (years)	*Gravidity*	*Parity*	*Gestation* (weeks)	*Duration of labor* (h)	*Mode of delivery*
1	36	2	1	35	–	planned CS
2	29	5	1	35	–	planned CS
3	38	4	2	37	–	planned CS
4	30	1	0	37	–	planned CS
5	36	1	0	40	6	spontaneous labor
6	34	3	0	34	–	urgent CS
7	34	2	1	37	–	planned CS
8	36	2	1	36	–	planned CS
9	39	5	1	30	–	urgent CS
10*	35	2	0	26	–	urgent CS
11	39	3	2	40	9	induced/oxytocin
12	33	6	1	38	5	induced/oxytocin
13	26	4	1	35	–	planned CS

CS, Cesarean section; *failed 'tamponade test'

Results

The 'tamponade test' was positive in 12 out of 13 cases and the hydrostatic catheter immediately arrested hemorrhage. In one case, tamponade failed after 3 h and bleeding re-occurred. In our series of 13 cases, the primary cause for postpartum hemorrhage was bleeding at the placental site alone (ten cases), uterine atony associated with bleeding at the placental site (two cases), and uterine atony with cervical laceration and pre-eclampsia-associated disseminated intravascular coagulation (one case). Tables 1 and 2 provide details of the 13 cases.

Because, according to Benirschke and Kaufmann[34], the diagnosis of accreta cannot be made when the placenta is not removed with the uterus, in such a condition the diagnosis of placenta accreta was based on clinical criteria and consisted of the inability to remove it by controlled cord traction because of a severe adherence to the underlying myometrium and failure to develop a cleavage plane between the placenta and uterus.

Among the three patients delivering by the vaginal route, two deserve a more detailed description. One patient (case 5) had a pre-delivery ultrasound diagnosis of marginal placenta previa. The woman had a normal labor, but soon after delivery of the placenta a profuse hemorrhage began. The uterine cavity was explored and the placenta accurately removed. A 3-cm fragment of the placenta was lacking but even a very vigorous examination of the uterine cavity was unsuccessful in removing that fragment. A catheter balloon inserted through the vagina soon arrested the severe bleeding. The patient was administered 2 units of blood and the balloon was removed after 24 h. The patient was discharged from the hospital 7 days later and her progress was uneventful until 11 days, when she was re-admitted to hospital for further hemorrhage due to the expulsion of the placental fragment. An examination of the uterine cavity resolved the case with no other intervention or further blood transfusion.

Another patient (case 12) had a normal vaginal delivery with no pre-delivery suspicion of abnormal adherence of the placenta. After delivery of the placenta, the lack of a 3-cm placental fragment was observed. The examination of the uterine cavity was unsuccessful but, in the absence of further bleeding, the patient was kept under observation with no other intervention. During the subsequent 24 h, sub-acute vaginal bleeding was associated with a progressive fall of the hematocrit level. A further examination of the uterine cavity was planned, and the removal of the retained placental fragment caused a severe hemorrhage that was quickly stopped by introducing a balloon catheter through the vagina into the uterine cavity.

Table 2 Cause of bleeding and medical treatment before tamponade procedure

Case	*Cause of bleeding*	*Estimated blood loss* (ml)	*Intrapartum RBC and FFP*	*Postpartum RBC*	*Medical treatment*	*Postpartum hospital admission* (days)
1	total placenta previa	1000	0	0	intramyometrial oxytocin, oxytocin infusion	5
2	total placenta previa	3000	RBC 2 U	0	intramyometrial oxytocin, oxytocin infusion	11
3	total placenta previa	1000	0	0	intramyometrial oxytocin, oxytocin infusion	4
4	total placenta previa	1200	RBC 1 U	RBC 2 U	intramyometrial oxytocin, oxytocin infusion	6
5	marginal placenta previa, focally accreta	1200	0	RBC 2 U	oxytocin infusion, i.m. ergometrine	8
6	total placenta previa	1500	0	0	intramyometrial oxytocin, oxytocin infusion	5
7	total placenta previa	1500	0	0	intramyometrial oxytocin, oxytocin infusion	5
8	focal placenta accreta	1000	0	0	intramyometrial oxytocin, oxytocin infusion	4
9	focal placenta accreta, atony	3300	RBC 6 U, FFP 6 U	0	intramyometrial oxytocin, oxytocin infusion, sulprostone infusion	5
10*	marginal placenta previa, focally accreta, atony	5000	RBC 9 U	0	intramyometrial oxytocin, oxytocin, sulprostone infusion	6
11	atony, cervico-isthmic tear and DIC in pre-eclampsia	1100	0	RBC 2 U	i.m. oxytocin, oxytocin infusion	7
12	focal placenta accreta	1500	RBC 2 U	RBC 2 U	oxytocin and sulprostone infusion, i.m. ergometrine	5
13	total placenta previa/accreta	1100	0	0	intramyometrial oxytocin, oxytocin infusion	5

RBC, red blood cell; FFP, fresh frozen plasma; DIC, disseminated intravascular coagulation; i.m., intramuscular; *failed 'tamponade test'

Among the ten cases resulting in Cesarean section, one patient (case 13) showed at ultrasound scan high suspicion of morbid adhesion of the placenta (accreta/increta) before the planned Cesarean section for total placenta previa. During Cesarean section, in order to prevent severe bleeding at delivery of the placenta by reducing the blood flow to the uterus, a prophylactic O'Leary suture[35] was positioned around the uterine arteries immediately after delivery of the infant, with the placenta still *in situ*, using a 2-monofilament absorbable suture on a high-curve needle. Subsequently, a bilateral utero-ovarian vessel ligation was performed with a 1-monofilament absorbable suture, including the broad ligament close under the tubal insertion to

the uterus and the utero-ovarian ligament. The placenta was found to extend across the internal cervical os. The inability to remove it by firmly controlled cord traction because of a severe adherence to the underlying myometrium and to develop a cleavage plane between the placenta and uterus became the clinical confirmation of placenta accreta[34]. Therefore, the placental tissue was manually removed in fragments and the placental site inspected. No myometrial defects were found, as the adhesion was limited to the myometrial layer. In order to control a persistent, although moderate, bleeding from the placental site which did not respond to pharmacological uterotonic therapy, a hydrostatic balloon catheter was inserted through the uterine incision, leaving the balloon in the uterine cavity as previously described. The patient did not need blood transfusion and a 6-month follow-up by Doppler ultrasound demonstrated regular reperfusion of the uterus.

Conservative treatment with the balloon catheter was unsuccessful in two cases and hysterectomy was performed (cases 9 and 10). In case 9, the balloon catheter was inserted, after Cesarean section was concluded, by the vaginal route because of a persistent vaginal bleeding. The 'tamponade test' was successful and the patient was monitored for 3 h. However, the patient then had a hemorrhage due to secondary uterine atony not responding to oxytocics and sulprostone infusion. Even further filling of the balloon was unsuccessful and, soon after the removal of the balloon, a large amount of blood and clots were expelled from the cervical os, so that urgent hysterectomy was mandatory. In case 10, the 'tamponade test' failed and no other surgical approach was attempted before hysterectomy. The reason for the failure of the 'tamponade test' was uterine atony refractory to any pharmacological treatment.

The 13 patients had a total estimated blood loss of 23.4 liters. The lowest and highest estimated blood losses experienced were 1 and 5 liters. A total of 28 U of blood and 6 U of fresh frozen plasma were transfused.

Discussion

The effectiveness of the Rüsch urological hydrostatic balloon as a conservative procedure in the therapy of postpartum hemorrhage has been shown in two cases described by Johanson[36] and in four cases more recently reported[28,29]. However, its efficacy in severe postpartum hemorrhage needed to be evaluated in a larger series. In the present provisional study, the insertion of the Rüsch urological hydrostatic balloon in patients with massive postpartum hemorrhage was very successful and was associated with no significant complications. The procedure failed in only two cases. As opposed to the traditional gauze uterine packing, the technique with the balloon catheter provides immediate knowledge of its effectiveness in controlling the postpartum hemorrhage, so that subsequent surgery can be expedited in failed cases.

If bleeding continues despite the insertion of a balloon, the Rüsch urological hydrostatic balloon gives less information than a Sengstaken–Blakemore catheter, since bleeding is noted only through the cervix but not from the uterine fundal cavity. However, the Rüsch urological hydrostatic balloon is simpler and cheaper than the other. At the same time, its overturned pear-shape better fits in the uterine cavity, with probably less risk of self-expulsion. The uterus must be empty for successful tamponade. If the uterine cavity is completely empty and uterine contraction sustained by adequate pharmacological assistance, there is probably no need for monitoring bleeding from the uterine fundal cavity. A larger series of cases will be necessary to support this last opinion.

The Rüsch urological hydrostatic balloon takes a few minutes to insert, is unlikely to cause trauma and is easy to place with minimal or no anesthesia, whereas its removal is painless and simple. Whether the patient is going to bleed after removal of the balloon is a general concern, but this series demonstrates that there were no cases of rebleeding after the planned removal of the Rüsch urological hydrostatic balloon. In case of rebleeding, it is possible to replace the balloon while planning an opportune uterine arterial embolization in a patient who is now in a stable condition[36–39].

There were two cases of failure; atony was the cause of failure and subsequent hysterectomy in both. In these cases, an attempt to mechanically favor uterine contraction by applying a B-Lynch Brace suture of the uterus

combined with an additional insertion in the uterine cavity of a balloon catheter could possibly have resolved the problem, with the combined conservative approach already described by Danso and Reginald[40].

One of the difficulties in the management of patients with intractable postpartum hemorrhage, not responding to uterotonic agents, is the decision to perform a laparotomy and, in case of Cesarean section, the decision to perform a hysterectomy. The delay can be catastrophic. In the present series, average blood loss was considerably less than that of other series recently reported[3,31]. In all the cases but two, the risk of postpartum hemorrhage was known in advance. When there is confidence that the management of postpartum hemorrhage can be conservative, easy and effective, as in the case of application of a balloon catheter, there is no reason for a delay.

In conclusion, the safe, low-cost, and easy procedure of utilizing a balloon catheter can be applied in any situation of life-threatening postpartum hemorrhage and avoids radical surgery in patients so that reproductive capacity is preserved.

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30

EMBOLIZATION

K. Choji and T. Shimizu

INTRODUCTION

The standard treatments of postpartum hemorrhage are described throughout this book. When they are unsuccessful, however, percutaneous transcatheter arterial embolization (hereafter referred to as embolization) may be indicated. The main objective of embolization is to stop active bleeding from the uterus or the birth canal and to prevent

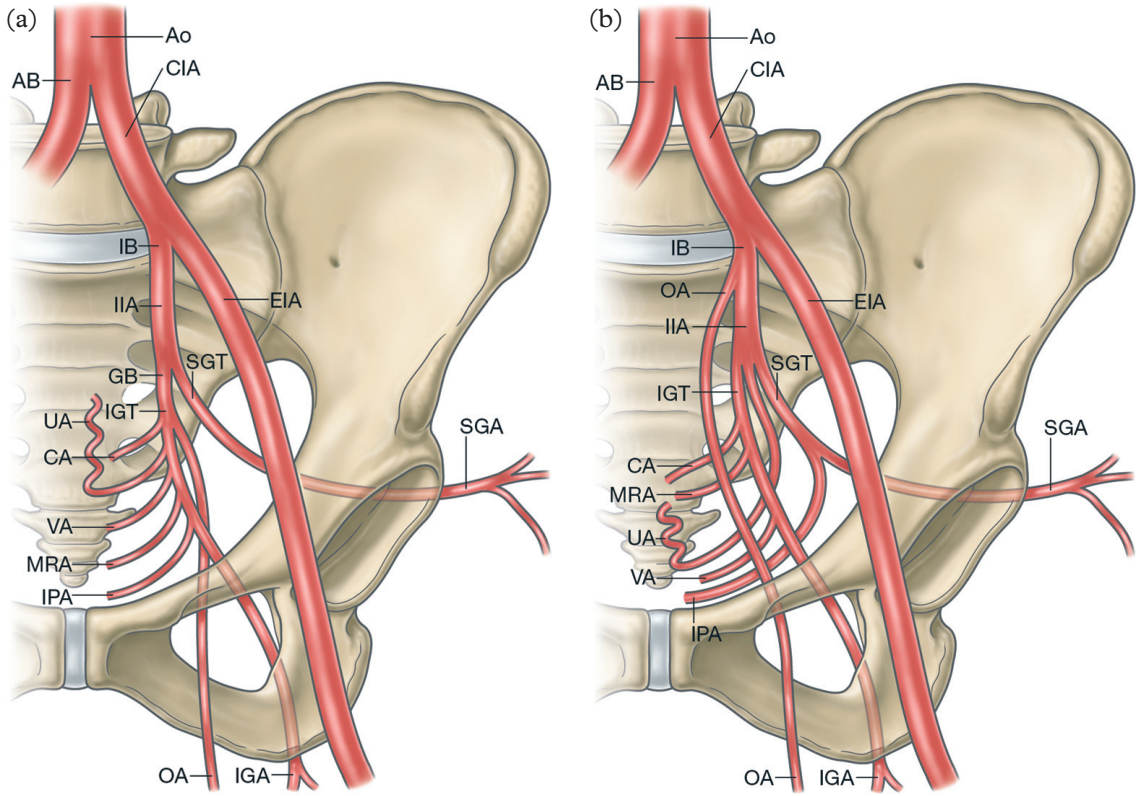

Figure 1 Branch patterns of the arteries to the uterus and the birth canal. (a) The most frequent pattern of branching. The internal iliac artery (IIA) is initially divided into the superior and inferior gluteal trunks (SGT and IGT, respectively), i.e. the gluteal bifurcation (GB). The uterine, vaginal and inferior pudendal arteries (UA, VA and IPA, respectively) are the branches of the IGT together with the obturator and cystic arteries (OA and CA, respectively). (b) Example of less common patterns include the uterine artery (UA) arising at the gluteal bifurcation, the obturator artery (OA) arising directly from the internal iliac artery (IIA) proximal to the iliac bifurcation, the internal pudendal artery (IPA) arising from the superior gluteal trunk (SGT). Ao, aorta; AB, aortic bifurcation; IB, iliac bifurcation; CIA, common iliac artery; EIA, external iliac artery; MRA, middle rectal artery; SGA, superior gluteal artery; IGA, inferior gluteal artery

recurrent hemorrhage. In case this is not possible, the last resort is to occlude the internal iliac arteries on a temporary basis to aid subsequent surgical intervention.

When embolization is successful, on the other hand, the patient can rapidly recover without undergoing additional surgery. Embolization not only saves the life of the patient, but also the uterus and adnexal organs, thus preserving fertility. Significant radiation effect is unlikely, as described below. The procedure is also useful in those patients who cannot accept transfusion due to religious or other reasons (see Chapter 15). In those hospitals where embolization is available, it should be the procedure of choice for postpartum hemorrhage prior to surgical intervention.

High success rates in achieving hemorrhage cessation are possible. In an extensive review of the literature by Vedantham and colleagues in 1997[1], cessation of hemorrhage was reported in 100% of 49 cases after vaginal delivery and 89% in 18 cases after Cesarean sections. Other recent reports include 75%[2], 83%[3] and 100%[4].

VASCULAR ANATOMY ON IMAGING

The internal iliac artery is the first major branch of the common iliac artery, which descends into the pelvis (see Chapter 32). There is only minimal variation in the distance between the aortic and the iliac bifurcations, making the identification of the internal iliac artery easy. In contrast, a number of variations in the distribution of the branches of the internal iliac artery are possible[5,6]. The proximal bifurcation of the internal iliac produces two trunks that are commonly termed the anterior and posterior branches. The posterior branch supplies the superior gluteal artery, whilst the anterior supplies the remainder of the pelvis. In the majority of instances, the branches of this anterior trunk include the uterine, vaginal, superior cystic, middle rectal, obturator, internal pudendal and inferior gluteal arteries (Figure 1a). In 30% of patients, these arteries have more proximal origins at the level of the bifurcation of the anterior and posterior branches (Figure 1b). This is especially true with the obturator and uterine arteries. In addition, the internal pudendal artery may arise from the posterior branch that supplies the superior gluteal artery. To avoid confusion due to anatomical variation, we would like to refer to the anterior and posterior branches as the inferior and superior gluteal trunks, respectively. This nomenclature becomes more appropriate when performing angiography.

On angiographic images, the inferior gluteal artery is seen as descending laterally and extending lower than bony pelvis. The importance of this artery gives off the sciatic branch which supplies the sciatic nerve. Therefore, the accidental embolization of the inferior gluteal artery could result in transient or long-term injury to the sciatic nerve.

The intramural portion of the uterine artery has a distinctive tortuous configuration. However, its origin lacks any characteristic appearance and is often superimposed on other branches in the frontal projection. Therefore, oblique views of the inferior gluteal trunk are frequently required to clarify the branching point of the uterine artery. The superior cystic artery can be identified by superselective catheterization and manual contrast injection which demonstrates either the distal network of the artery in the bladder wall or sometimes the cystic artery on the opposite side. The internal pudendal artery, which is usually a branch from the inferior gluteal trunk, is harder to confirm, often requiring some guess work. Further difficulties may arise from the presence of a hematoma which can alter the appearances and distribution of these arteries.

The middle rectal and the inferior rectal arteries originate from the inferior gluteal and the internal pudendal arteries, respectively. These supply the middle and lower portions of the rectum, anal canal and the perianal skin. Theoretically, superselective embolization of the middle rectal or the inferior rectal artery may result in necrosis of these areas. However, surprisingly such serious complications have not been reported so far.

The vaginal artery may originate from the uterine artery at the level of the cervix or from the inferior gluteal trunk. In addition, the vagina is also supplied by branches of the internal pudendal artery.

TECHNICAL ASPECTS

Preparation

Unless it is an absolute emergency, obtaining a coagulation panel including the platelet count, APTT and PT (INR) is worthwhile (see Chapter 25). Deranged coagulation does not necessarily contraindicate arteriography or embolotherapy[7]; however, its correction may help in preparation for post-procedural hemostasis and the prevention of complications relating to this. Occult coagulopathy may also be revealed[8]. As embolization is an invasive procedure, informed consent from the patient is essential, with explanation and discussion of the possible complications, future fertility and the effects of the radiation. In situations where the patient is sedated or unable to consent, the appropriate consenting process should be considered. Ideally, the patient is kept nil by mouth for an appropriate duration prior to procedure in order to avoid complications from vomiting. Bladder catheterization is not essential, although it is helpful in preventing the bladder from filling with contrast-containing urine during the procedure.

Cross-sectional imaging

Localization and measurement of the size of the hematoma prior to arteriography and embolization can be extremely useful, although not essential. Confirming whether the hematoma is within or outside the uterus and its relationship to pelvic structures will dictate the course of the embolization (Figures 2a and b). Magnetic resonance imaging (MRI) is the best test of the pelvis, requiring a small number of examinations with different radiofrequency signal maneuvers (sequences), demonstrating the sagittal, coronal and axial cross-sections. It is recommended to include both T1- and T2-weighted sequences in two to three examinations, such as T1-weighted coronal and T2-weighted sagittal scans. Should MRI be unavailable, either computed tomography (CT) or ultrasound examination may be an option.

Premedication

The interventional radiologist needs to decide the type and quantity of agents for premedication. If no interacting drugs have been administered, the authors recommend the combination of opiate and sedative antihistamines, such as pethidine 50–100 mg i.m. (in two divided doses if more than 50 mg is given) and promethazine hydrochloride 25–50 mg i.m.

Location for embolization and arterial puncture

The best location for embolization is the interventional suite where vascular procedures routinely take place. However, interventional radiologists may be requested to perform procedures in surgical theaters in some emergency situations.

The optimal method in embolization is to achieve superselective catheterization of the arterial branches that are the sources of hemorrhage, such as the uterine arteries on both sides. When this is not possible, temporary occlusion of the internal iliac arteries using balloon catheters is an option to stabilize the patient's condition and facilitating subsequent surgical procedures. Removal of a uterine compression pack may be attempted under such transient arterial occlusion. If the temporary occlusion has been performed outside the angiography suite (such as in the operating theater) in an emergency, the patient could be subsequently transferred to the angiography suite for proper embolization. In some cases, temporary bilateral occlusion of the iliac bifurcations may be performed using angioplasty balloon catheters placed and inflated at the iliac bifurcation bilaterally. Acute ischemia of the lower limbs will occur as a result. The risk of injury to the nervous and muscular systems of the lower limb is minimized by shorter occlusion time of external iliac arteries. Occlusion times of less than 1–2 h are safe; irreversible injury may occur if it is more than 6 h.

The order of arteriogram and catheter maneuvers

At the puncture site in the groin, an introducer sheath is used to stabilize the arterial entrance. The standard diameter of the sheath is 5 French gauge; a 6 French gauge sheath is necessary for balloon occlusion.

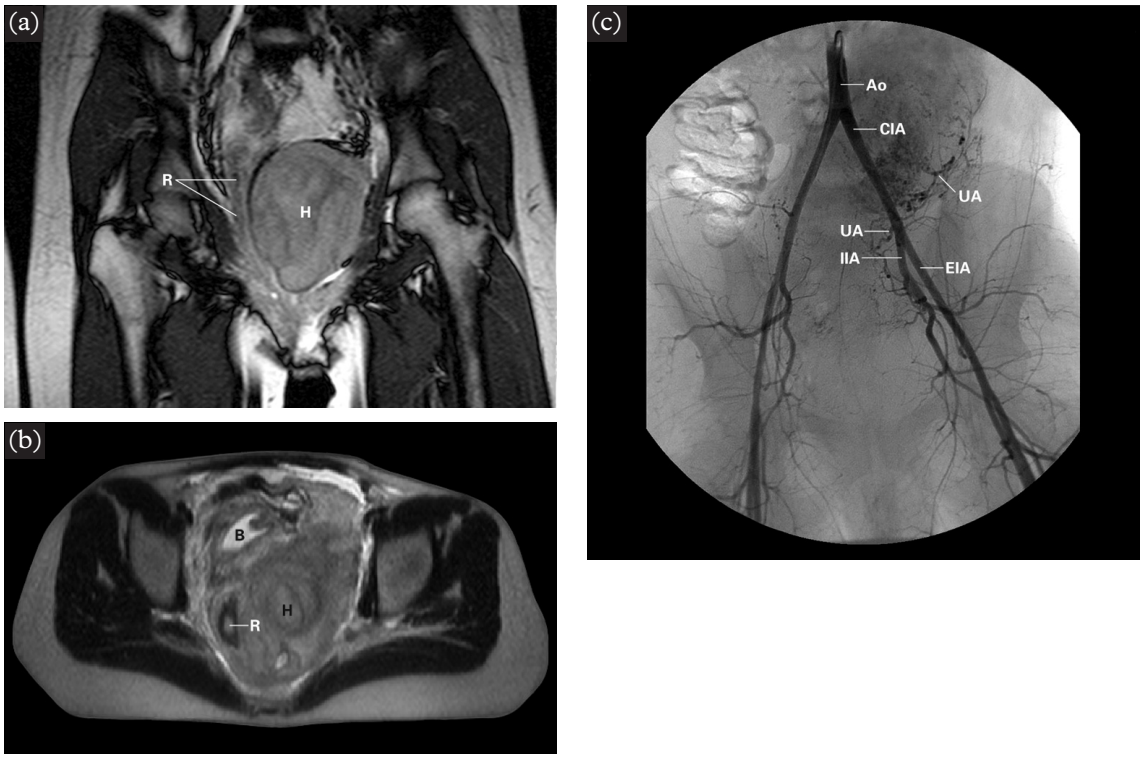

Figure 2a–g Case study: a 23-year-old woman, who had been diagnosed to have double uterus and double vagina, with the right uterus having been removed several years before. Following vaginal delivery at full term weeks, she became anemic, with the hemoglobin measuring approximately 6.0 g/dl. Intrapelvic pain was reported, mainly on the left. Hemorrhage per vagina was only of a moderate degree. (a and b) T2-weighted magnetic resonance images of the pelvis, in coronal (a) and axial (b) cross-sections. A hematoma (H) is detected in the left pelvic floor. The right side of the pelvis is preserved. R, rectum and adjacent tissue; B, bladder. It was anticipated that left-sided embolization would achieve hemostasis based on these images. (c) Whole pelvic arteriography. The right common femoral artery was punctured and a 5 French gauge hook-shaped catheter was inserted to the distal aorta (Ao) where radiological contrast was infused. The outline of the common, internal and external iliac arteries (CIA, IIA and EIA, respectively) and their major branches are demonstrated. The intramural branches of the uterine artery (UA) distribute both above and within the pelvis. The hematoma is shown as a relatively hypovascular zone (H). (d) Left internal iliac arteriography in the left anterior oblique position (LAO). Identification of the uterine and vaginal arteries (UA and VA, respectively) is achieved: the origin of the uterine artery (UAO) is shown. The superior and inferior gluteal trunks are superimposed (*). This falls into the category of vascular anatomy shown in Figure 1b. A 5 French cobra-shaped catheter is used. (e) Left uterine arteriography. Superselective catheterization was achieved using a 3 French gauge catheter inserted through the 5 French cobra-shaped catheter. The intramural branches with their characteristic tortuosity are shown. Although no extravasation is demonstrated, unilateral and partial embolization using grated particles of gelatine sponge was performed in view of increased hemorrhage per vagina and the anatomical communication between the uterine artery and the arteries to the upper vagina. (f) Left vaginal arteriography. Extravasation is clearly revealed (arrowheads) on hand injection of radiological contrast through the 3 French catheter (arrow). Embolization was performed using grated particles of gelatine sponge until the extravasation was barely detectable. (g) Left inferior gluteal arterial trunk post-embolization. The uterine artery (UA) and a smaller number of its intramural branches are opacified, the vaginal artery and the branches to the hematoma are no longer opacified. Following embolization, the hemorrhage per vagina reduced to within normal losses; hemoglobin increased to 11 g/dl on the next day and 12 g/dl on the following day. The patient was discharged 2 days post-embolization without undergoing any other intervention; outpatient follow-up confirmed satisfactory recovery

continued

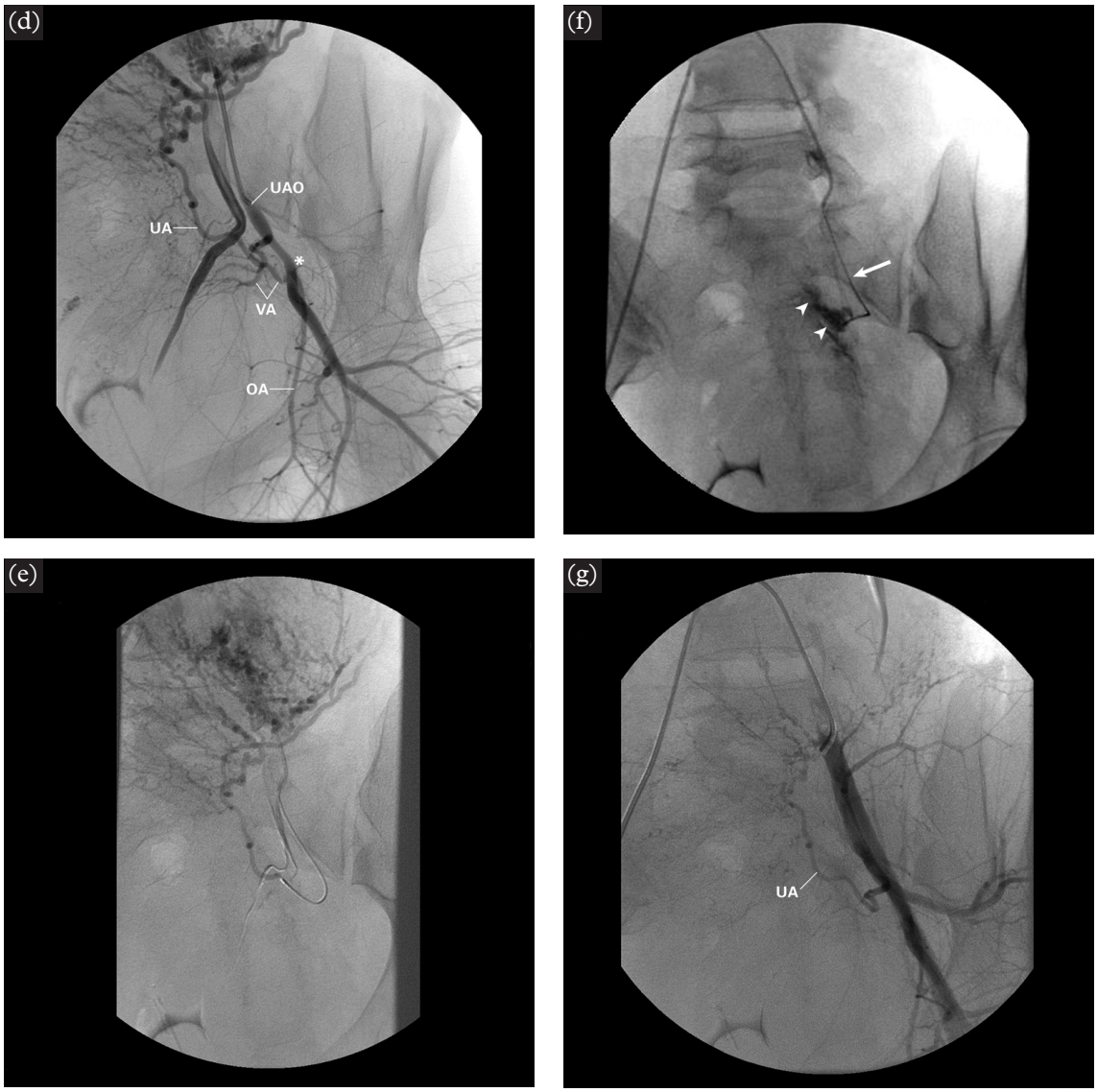

Figure 2a–g *Continued*

The first arteriogram is an image of the pelvis from the aortic bifurcation to the groins, in order to obtain a global view of the pelvic arteries (Figure 2c). A range of hook-shaped catheters are useful, as they are helpful in accessing the common and internal iliac arteries on either side (Figure 3). Subsequently, the internal iliac artery is selectively catheterized and its arteriogram should be obtained (Figure 2d). Oblique views may aid demonstration of the uterine artery origin and facilitate its catheterization.

A 4 or 5 French gauge Cobra tip is a suitable standard catheter for superselective access to the uterine artery and other smaller branches, if the hook catheter is inadequate for superselective catheterization (Figure 3). It is preferably made of soft polyurethane. 5 French gauge catheters have a risk of causing spasm when inserted into the uterine artery and other branches of the inferior gluteal trunk. This can be prevented and treated by nitrate vasodilators, such as isosorbide dinitrate 0.05–0.20 mg per branch. Where suitable 4 French gauge

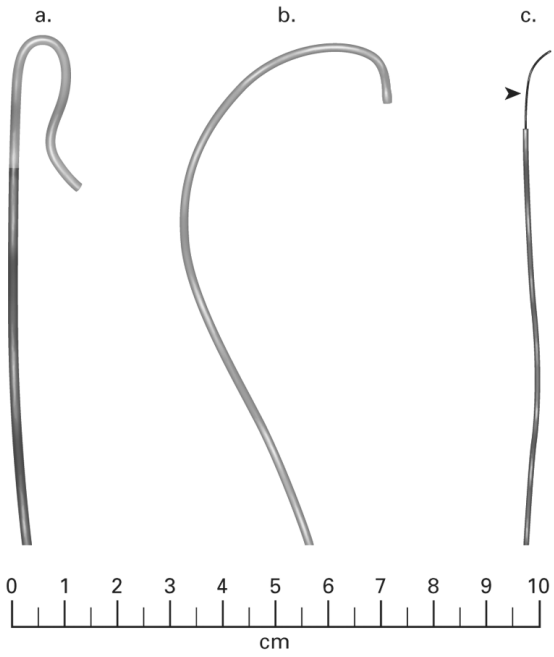

Figure 3 Standard catheters of use in embolization. (a) A 5 French gauge hook-shaped (Modified hook 2 catheter, Merit Medical, USA); (b) a 5 French gauge cobra-shaped (Terumo, Japan) and (c) a 3 French gauge microcatheter which goes through 5 French gauge catheters (Terumo, Japan): this catheter is coupled with a hydrophilic polymer-coated floppy guidewire with an angled head (arrowhead)

catheters are available, they would reduce the risk of vasospasm. Guidewires with angled tips and hydrophilic coatings are also extremely useful tools. For difficult branches with steep angulation and tortuosity, finer catheters (less than 3 French in diameter) with their own specific fine and floppy wires are indicated (Figure 3), although they are costly in general. These are fed through the standard catheters and preferably have an angled tip.

Targets of embolization

The prime target of embolization is the source artery of hemorrhage. Commonly, this is the uterine artery when the source of hemorrhage is in the myometrium, cervix or endometrium (Figure 2e). If the hemorrhage is due to laceration of the birth canal below the level of the uterus, the source is likely to be a branch such as the vaginal or internal pudendal artery. If branches other than the uterine artery are the source of hemorrhage, superselective catheterization and arteriogram of each branch are required to assess the extent of extravasation (Figure 2f). The advent of smaller diameter catheters and hydrophilic coated guidewires has made such superselective catheterization less challenging. Extravasation is unlikely to be demonstrated on non-superselective angiograms such as the global pelvic arteriogram and the internal iliac arteriogram.

In case extravasation is confirmed, embolic material is infused to occlude the artery (Figures 2f and g). If extravasation is not proven, embolization of each of the branches supplying the region of hemorrhage is performed. Hemostasis can be achieved with embolization of the regional arteries, including the source of hemorrhage, even without actual demonstration of the bleeding artery[9,10]. The most accurate demonstration of the flow distribution of transcatheterally infused material is obtained with combined angiography C-arm and CT equipment. Unfortunately, such machines are not universally available. Therefore, the interventional radiologist needs to judge the vascular anatomy and the distribution of the embolic material mainly on the basis of the simple two-dimensional angiography radiographs in frontal or oblique projections.

Embolic material

Practical embolic materials are summarized in Table 1. Gelatine particles are the most commonly used embolic material in embolization for postpartum hemorrhage as they are expected to dissolve in several weeks' time, leading to recanalization of the embolized artery. However, these are not free from embolic complications[2,11]. Other advantages of gelatine particles include that they are economical and easily available. Where the particle form of gelatine is unavailable, gelatine plate or sponge could be cut into particles or grated. Despite the popular usage of gelatine particles, there is no evidence to contraindicate the use of permanent embolic material, such as polyvinyl alcohol (PVA) particles (Figure 4).

Table 1 Embolic materials

Materials	*Duration of effect*	*Approximate size*	*Mechanism of effect*	*Advantages*	*Disadvantages*
Particles					
Gelatin sponge (cut)	temporary	1–5 mm	blockage of blood vessel, inflammatory occlusion (partly)	economic, safe	cutting is time-consuming, proximal embolization due to particle size
Gelatin sponge (grated)	temporary	0.3–5 mm	blockage of blood vessel, inflammatory occlusion (partly)	economic, safe, easy to make	effect could be short-lived, proximal embolization could occur
Polyvinyl alcohol (PVA)	permanent	100–700 μm	blockage of blood vessel, inflammatory occlusion (partly)	readily available	could be expensive, proximal embolization could occur
Autologous blood clot	temporary	1–5 mm	blockage of blood vessel, inflammatory occlusion (partly)	available by adding thrombin *in vitro*	duration of effect is unreliable
Autologous blood clot (degenerate)	permanent	< 1 mm to 5 mm	blockage of blood vessel, inflammatory occlusion (partly)	available by heating or exposing to alcohol or its derivatives	
Liquid					
Alcohol	permanent		destruction of blood vessel by ablating the intima, producing degenerate thrombi	economic and ultra-potent	painful, unwanted vessels could be affected
Ethanolamine oleate	permanent		similar to alcohol but milder effect	similar to alcohol but milder effect; the effect could be stabilized when combined with gelatin sponge	similar to alcohol but milder effect
Glues such as cyanoacrylate	permanent		blockage of blood vessel	readily available, stable	requires expertise in the use of material; adherence of the delivery catheter could occur

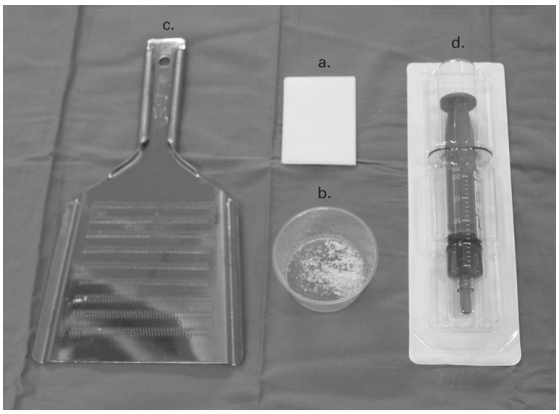

Figure 4 Embolization materials. (a) Gelatin sponge; (b) grater for gelatine sponge; (c) grated gelatine sponge; and (d) polyvinyl alcohol (PVA) particles in a bottle syringe

Embolic material should not be infused into the inferior gluteal artery for the reason described above. In spite of this, there are reports where infusion of gelatine particles into the inferior gluteal trunk either did not result in sciatic nerve symptoms[3] or only in a minority of instances[2]. It is assumed that the amount of embolic material infused is the key factor as to whether sciatica presents or not. Even if superselective catheterization is achieved, care needs to be taken to minimize overflow of embolic material. As embolization of a branch approaches completion, some overflow is usually unavoidable. Particular caution is necessary when liquid embolic material is used, such as cyanoacrylate, alcohol and its derivatives.

COMPLICATIONS

The reported frequency of complications is small. The causes of complications include:

(1) *Technical errors* These include hematoma at the puncture site (groin)[12] and vascular injury[13]. Allergic reactions to iodine contrast and nephrotoxicity are also possible.

(2) *Post-embolic ischemia* Infarct and necrosis of the uterus requiring hysterectomy[11], as well as the cervix and upper vagina[2] and bladder[11] have been reported. A decision between surgical and conservative management needs to be made in each case.

(3) *Sciatica* This is described above.

(4) *Infection* Intra-pelvic abscess formation[14,15], post-embolic pyrexia and pain/tenderness in the pelvis are frequently observed, all of which can be managed with anti-inflammatories and antibiotics.

(5) *Coagulopathy* Difficult hemostasis at the groin may be a result of coagulopathy.

(6) *Acute intra-arterial thrombosis of the lower limb* This may be due to limited arterial flow in the lower limb following arterial puncture and catheter maneuver; thrombosis and occlusion of the lower limb artery may occur[2]. The risk is increased when balloon occlusion is performed for a long period.

(7) *Ischemia of the lower limb* This is described above.

(8) *Radiation* The biological effect of radiation has been studied from the data of measured absorption doses of the skin and estimated doses to the ovaries in a series of 20 cases of uterine artery embolization[16]. In this study, fluoroscopy was performed up to a maximum of 52.5 min with a mean of 21.9 min, resulting in a maximum skin dose of 304 cGy (mean 162 cGy). The estimated maximum ovarian dose was 65 cGy (mean 22.3 cGy). These figures were greater than the doses of other image examinations of the pelvis such as hysterosalpingography (0.04–0.55 cGy), recanalization of the Fallopian tube (0.2–2.75 cGy), computed tomography of the body trunk (0.1–1.9 cGy); on the other hand, they were smaller than the dose in radiotherapy for intrapelvic Hodgkin's lymphoma (263–3500 cGy). On the basis of the known risks of pelvic irradiation for Hodgkin disease, the dose associated with uterine artery embolization is unlikely to result in acute or long-term radiation injury to the patient or to a measurable increase in the genetic risk to the patient's future children. In embolization for postpartum hemorrhage, there may be cases where longer fluoroscopy time is required than uterine artery only embolization; however, it would be still in the similar region to that of uterine artery

embolization, and, therefore, the injury from irradiation in embolization is unlikely.

(9) *Fertility* A 35-month follow-up survey on six patients, who underwent uterine artery embolization with polyvinyl alcohol (PVA) particles for therapy of fibromyomata and wished subsequent conception, confirmed eight pregnancies in five patients (83%), seven births including five transvaginal and two Cesarean deliveries, and an abortion due to the patient's request for termination[17]. The authors of this study concluded that uterine embolization with PVA particles did not affect fertility. In embolization for postpartum hemorrhage, although the non-uterine artery branches could be embolized and the embolic material could be others than PVA, the effect on fertility is unlikely.

LOGISTICS

Postpartum hemorrhage is essentially an emergency situation, which may arise at any time. The incidence of truly intractable hemorrhage is small, and, in the majority of cases, there is time during which the obstetricians perform the first line of treatment, including transfusion, and wait for preparation by the interventional radiology team. However, urgent intervention is requested in the minority of cases. This could cause a strain in the management of staff in the interventional radiology department. It could also be a reason why embolization has not been widely recognized or discussed among the obstetricians and radiologists as the choice of treatment, despite a number of successful reports both in postpartum and post-Cesarean cases[8–10,12–15,18–27]. Nevertheless, the safety, feasibility and low complication rate of embolization cannot be emphasized enough. The idea of offering embolization is simply kinder to the patient compared to hysterectomy or other surgical intervention. The ability to offer embolization would require an obstetric department which is well aware of the implications of embolization in postpartum uterine hemorrhage. Such a change in thinking will invariably necessitate a proactive protocol providing easy access for the obstetricians to an emergency appointment with the interventional radiology team. Such a protocol should be established with input from both the obstetricians and interventional radiologists. It would include a list of the resources required, including the personnel involved, the equipment, the consumables and the setting. It should also make consideration for out-of-hours emergency work and the case load. Therefore, the protocol will depend on the requirements and resources of each specific department.

CONCLUSION

Though embolization has had a relatively short life of practice, it is a highly feasible, safe and beneficial procedure, as it may preclude an indication for further laparotomy and hysterectomy. Therefore, embolization should be the choice of treatment prior to surgical intervention, anywhere in the world, when the first line of conservative treatment fails.

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31

CONSERVATIVE SURGICAL MANAGEMENT

C. B-Lynch

INTRODUCTION

A key factor in the surgical management of postpartum hemorrhage is the awareness of predisposing factors[1–3] and the readiness of therapeutic teams consisting of obstetric, anesthetic and hematology staff[3,4].

In the past, the surgical management of postpartum hemorrhage included use of an intrauterine pack, with or without thromboxane[5], thrombogenic uterine pack[6], ligation of uterine arteries[7], ligation of internal iliac artery[8], stepwise devascularization[9] and, finally, subtotal or total abdominal hysterectomy[10]. Most of these are discussed in detail in other chapters of this text.

A more conservative procedure, now colloquially known as the Brace suture technique, was first described by B-Lynch and colleagues in 1997[3]. Along with later modifications by Hayman and colleagues[11] and Cho and colleagues[12], this[13] may prove more effective than radical surgery for the control of life-threatening postpartum hemorrhage[3,11,12]. Although subtotal and total abdominal hysterectomy are still available and indeed useful in their own right, they should be considered as a last resort.

Common causes of postpartum hemorrhage are listed in Table 1, which is not to mean that additional causes cannot or do not exist. Most, if not all, are considered in references to postpartum hemorrhage in modern standard textbooks of obstetrics and further described in the other chapters of this volume. Three important points merit attention.

First, there is significant increase in cardiac output in pregnancy in accordance with red cell

Table 1 Common causes of postpartum hemorrhage

Pre-existing conditions	*Uterine overdistention, atony and disseminated intravascular coagulation (DIC)*	*Disorders of placenta, uterine and genital tract trauma*
Thrombocytopenic purpura	Polyhydramnios	Acute uterine inversion
Hypertensive disease	Multiple gestation	Lower segment Cesarean section
Uterine myoma	Macrosomia	Operative vaginal delivery
Anticoagulation therapy	Prolonged labor	Precipitate delivery
Coagulation factor deficiency	Chorionamnionitis	Previous uterine surgery
Systemic disease of hemorrhagic nature	Tocolytic agents	Internal podalic version
	Halogenated anesthetic agents	Breech extraction
Consumptive coagulopathy	High parity	Mid-cavity forceps
Müllerian malfunction	Abruptio placentae	Obstructed labor
Anemia	Courvelliar's uterus	Abnormal fetal presentation
	Placenta previa	Vacuum site extraction
	Placenta accreta, increta, percreta	Placental subinvolution
		Retained products of conception
		Ruptured uterus

mass and plasma volume, which provides a compensative reserve for acute blood loss and hemostatic response following massive hemorrhage[14]. Second, the arrangement of the uterine muscle fibers, vis-à-vis the course of the uterine arteries, facilitates the use of compression techniques for effective control of postpartum hemorrhage and, finally, conservative treatment such as bimanual compression of the uterus may control blood loss (Figure 1), whilst intensive resuscitative measures are undertaken according to established labor ward protocols, which involve the anesthetists, hematologists, the obstetric team and intensive care support (see Chapters 13 and 22).

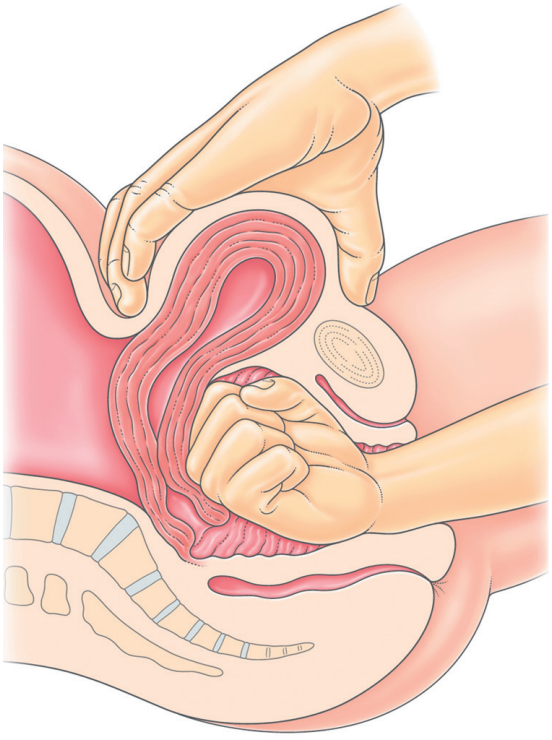

Figure 1 Bimanual compression of the uterus, illustrating the first-line approach to mechanical hemostasis. This in itself might control bleeding significantly by assisting the uterus to use its anatomical and physiological properties such as the cross-over interlinked network of myometrial fibers for vascular compression and bleeding control. The patient should be placed in stirrups or frog-legged position in the labor ward or in theater whilst intravenous fluid and/or appropriate blood product runs freely. In some cases and commonly so, there may be failure to achieve satisfactory and lasting hemostasis by this method

NEW DEVELOPMENTS IN THERAPEUTIC OPTIONS

The type of surgical intervention depends upon several factors, paramount of which is the experience of the surgeon. Other factors include parity and desire for future children, the extent of the hemorrhage, the general condition of the patient and place of confinement. Women at high risk of postpartum hemorrhage should not be delivered in isolated units or units ill-equipped to manage sudden, life-threatening emergencies. Immediate access to specialist consultant care, blood products and intensive care are essential.

The B-Lynch suture compression technique

The procedure was first performed and described by Mr Christopher B-Lynch, a consultant obstetrician, gynecological surgeon, Fellow of the Royal College of Obstetricians and Gynaecologists of the UK and Fellow of the Royal College of Surgeons of Edinburgh, based at Milton Keynes General Hospital National Health Service (NHS) Trust (Oxford Deanery, UK), during the management of a patient with a massive postpartum hemorrhage in November 1989. This patient refused consent to an emergency hysterectomy[3]! Table 2 provides an audit summary of five case histories of other patients with severe life-threatening postpartum hemorrhage managed with this technique.

The principle

The suture aims to exert continuous vertical compression on the vascular system. In the case of postpartum hemorrhage from placenta previa, a transverse lower segment compression suture is effective.

The technique[2–4]

See Figures 2a (i and ii), 2b and 2c.

Surgeon's position In outlining the steps involved, we assume that the surgeon is right-handed and standing on the right-hand side of the patient. A laparotomy is always necessary to exteriorize the uterus. A lower segment transverse incision is made or the recent lower segment Cesarean section suture (LSCS) removed to check the cavity for retained placental fragments and to swab it out.

Test for the potential efficacy of the B-Lynch suture before performing the procedure The patient is placed in the Lloyd Davies or semi-lithotomy position (frog leg). An assistant stands between the patient's legs and intermittently swabs the vagina to determine the presence and extent of the bleeding. The uterus is then exteriorized and bimanual compression performed. To do this, the bladder peritoneum is reflected inferiorly to a level below the cervix (if it has been taken down for a prior LSCS, it is pushed down again). The whole uterus is then compressed by placing one hand posteriorly with the ends of the fingers at the level of the cervix and the other hand anteriorly just below the bladder reflection. If the bleeding stops on applying such compression, there is a good chance that application of the B-Lynch suture will work and stop the bleeding.

Even in the presence of coagulopathy, bimanual compression will control diffuse bleeding points. If this test is successful, the application of the suture will also succeed.

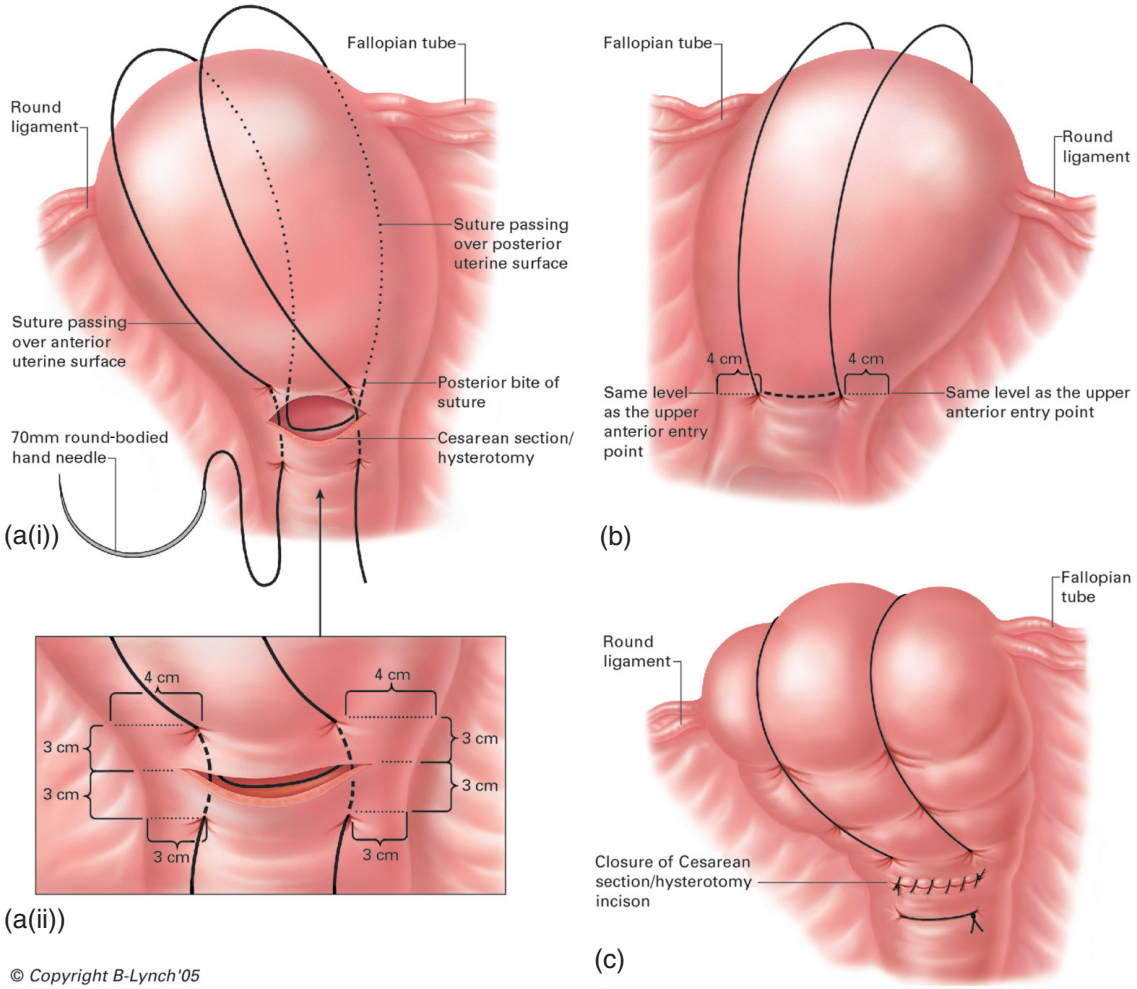

Figure 2a–c Summary of the application of the B-Lynch procedure

Table 2 Audit summary of five selected case histories of patients with severe life-threatening postpartum hemorrhage treated by ecbolics and the B-Lynch brace suture application in the period 1989–1995 at Milton Keynes General Hospital, UK[2]

Age (years)	*Parity*	*GA*	*Presenting diagnosis*	*Mode of delivery*	*Infant sex and weight* (g)	*Apgar score at 5 and 10 min*	*Type of PPH*	*Treatment and volume transfused*	*Intensive care admission*	*Outcome*
28	PP	39/40	placental abruption, PPH, DIC	spontaneous vertex	male (2800)	4, 7	primary	ecbolics, 20 units fresh blood, 8 units FFP	48 h; full antibiotic cover	good; 3 years later spontaneous vertex delivery; female (3890 g); no problems
22	PP	43/40	prolonged labor, persisting occipito position?, cephalopelvic disproportion	emergency CS	male (4190)	7, 10	primary	ecbolics, 13 units blood, 5 units packed cells, BSA	48 h; full antibiotic cover	good; normal CT pelvimetry 2 years later; elective CS at 39 weeks; female (3820 g); no problems
23	PP (twin)	37/40	eclampsia in labor, PPH, DIC	emergency CS	(1) female (2735), (2) female (2430)	(1) 3, 8 (2) 5, 8	primary	ecbolics, 19 units blood, 5 units FFP, BSA	72 h; full antibiotic cover	good; no complications
35	PP (IVF)	38/40	major placenta previa	elective CS	female (3370)	9, 10	secondary, 9th day readmission	ecbolics, 15 units blood, 5 units FFP, BSA	72 h; full antibiotic cover	good; no complications
30	PP	40/40	uterine atony	spontaneous vertex	female (3890)	9, 10	primary	ecbolics, 15 units blood, 7 units packed cells, BSA	48 h; full antibiotic cover	good; no complications

PP, primiparous; GA, gestational age in weeks; PPH, postpartum hemorrhage; CS, Cesarean section; CT, computerized tomography; DIC, disseminated intravascular coagulations; BSA, brace suture application; IVF, *in vitro* fertilization; FFP, fresh frozen plasma

However, application of the B-Lynch suture is not a substitute for the medical treatment of coagulopathy, which should take place along with the operative intervention (see Chapter 25).

Suture application Given that the test criteria for the B-Lynch suture placement are met, the uterus remains exteriorized until application of the suture is complete. The senior assistant takes over in performing compression and maintains it with two hands during the placement of the suture by the principal surgeon.

(1) *First stitch relative to the low transverse Cesarean section/hysterotomy wound*. With the bladder displaced inferiorly, the first stitch is placed 3 cm below the Cesarean section/hysterotomy incision on the patient's left side and threaded through the uterine cavity to emerge 3 cm above the upper incision margin approximately 4 cm from the lateral border of the uterus (Figure 2a(i)).

(2) *The fundus* The suture is now carried over the top of the uterus and to the posterior side. Once situated over the fundus, the suture should be more or less vertical and lie about 4 cm from the cornu. It does not tend to slip laterally toward the broad ligament because the uterus has been compressed and the suture milked through, ensuring that proper placement is achieved and maintained (Figure 2a).

(3) *The posterior wall* The location on the posterior uterus where the suture is placed through the uterine wall is actually easy to surface mark posteriorly. It is on the horizontal plane at the level of the uterine incision at the insertion of the uterosacral ligament (Figure 2b).

(4) *Role of the assistant* As the operation proceeds, the assistant continues to compress the uterus as the suture is fed through the posterior wall into the cavity. This will enable progressive tension to be maintained as the suture begins to surround the uterus. Assistant compression will also help to pull the suture material through to achieve maximum compression, without breaking it, at the end of the procedure. Furthermore, it will prevent suture slipping and uterine trauma. The suture now lies horizontally on the cavity side of the posterior uterine wall.

(5) *The fundus* As the needle pierces the uterine cavity side of the posterior wall, it is placed over the posterior wall, bringing the suture over the top of the fundus and onto the anterior right side of the uterus. The needle re-enters the cavity exactly in the same way as it did on the left side, that is 3 cm above the upper incision and 4 cm from the lateral side of the uterus through the upper incision margin, into the uterine cavity and then out again through 3 cm below the lower incision margin (Figure 2a(ii)).

(6) *Later role of the assistant* The assistant maintains the compression as the suture material is milked through from its different portals to ensure uniform tension and no slipping. The two ends of the suture are put under tension and a double throw knot is placed for security to maintain tension after the lower segment incision has been closed by either the one- or two-layer method.

(7) *Relation to the hysterotomy incision* The tension on the two ends of the suture material can be maintained while the lower segment incision is closed, or the knot can be tied first, followed by closure of the lower segment (Figure 2c). If the latter option is chosen, it is essential that the corners of the hysterotomy incision be identified and stay sutures placed before the knot is tied. This ensures that, when the lower segment is closed, the angles of the incision do not escape it. Either procedure works equally well. It is important to identify the corners of the uterine incision to make sure no bleeding points remain unsecured, particularly when most of these patients are hypotensive with low pulse pressure at the time of the B-Lynch suture application.

(8) *Post-application and hysterotomy closure* It is probable that the maximum effect of suture tension lasts for only about 24–48 h. Because the uterus undergoes its primary involutionary process in the first week after vaginal or Cesarean section delivery, the suture may have lost some tensile strength,

but hemostasis would have been achieved by that time. There is no need for delay in closing the abdomen after the application of the suture. The assistant standing between the patient's legs swabs the vagina again and can confirm that the bleeding has been controlled.

Application after normal vaginal delivery If laparotomy is required for the management of atonic postpartum hemorrhage, hysterotomy is necessary to apply the B-Lynch suture. Hysterotomy will also allow exploration of the uterine cavity, exclude retained products of conception, evacuate large blood clots and diagnose abnormal placentation and decidual tears, damage and bleeding. B-Lynch suture application or any modification of it (see below) without hysterotomy or re-opening of the Cesarean section wound runs the potential risk of secondary postpartum hemorrhage. Therefore, confirmation that the uterine cavity is completely empty is essential. Furthermore, hysterotomy ensures that the correct application of the suture provides maximum and even distribution of the compressive effect during and after application of the B-Lynch suture (Figures 2 and 3). Also, it avoids blind application of the suture and the possibility of obliteration of the cervical and/or uterine cavities that may lead to clot retention, infected debris, pyometria, sepsis and morbidity[3,11,12,15].

Application for abnormal placentation The B-Lynch suture may be beneficial in cases of placenta accreta, percreta and increta. In a patient with placenta previa, a figure-of-eight or transverse compression suture to the lower anterior or posterior compartment or both is applied to control bleeding. If this is not completely successful, then, in addition, the longitudinal Brace suture component may be applied for further/complete hemostasis[3].

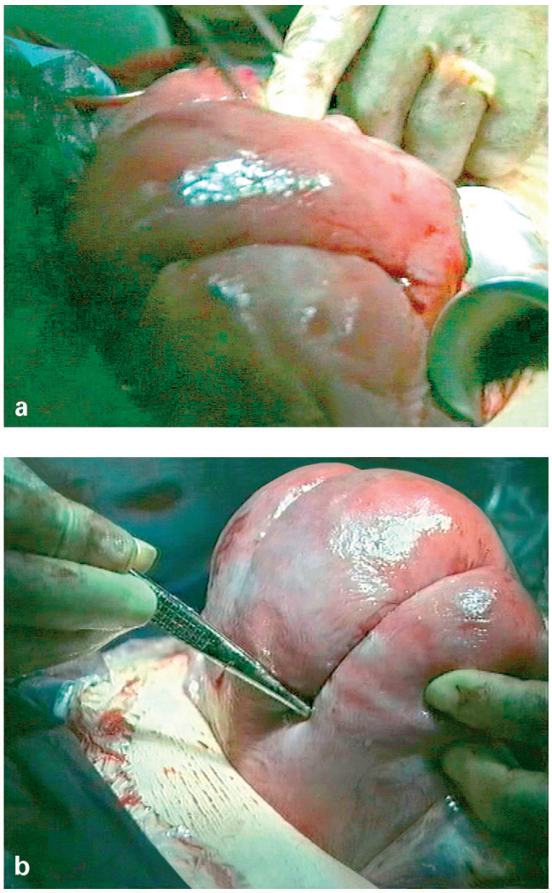

Figure 3 The *in vivo* effect of correct application of the B-Lynch surgical technique seen immediately after successful suture application. No congestion, no ischemia and no 'shouldering' of the sutures at the fundus

POSTOPERATIVE FOLLOW-UP

Three patients from the original series had laparoscopy postoperatively for sterilization, suspected pelvic inflammatory disease or appendicitis. One patient who had a history of ileostomy for surgical reasons had laparotomy 10 days after her B-Lynch suture for suspected intestinal obstruction (unpublished data, B-Lynch). Magnetic resonance imaging and hysterosalpingography were performed on one patient, showing no intraperitoneal or uterine sequelae[16] (Figure 4a–c). No complications have been observed in the five patients of the first published series[2] (see Table 1). Moreover, all have succeeded in further pregnancy and delivery[17,18].

Tables 3–5 lists the clinical points of the B-Lynch surgical technique, the Hayman uterine compression suture (see Figure 5) and the Cho multiple square sutures (see Figure 6).

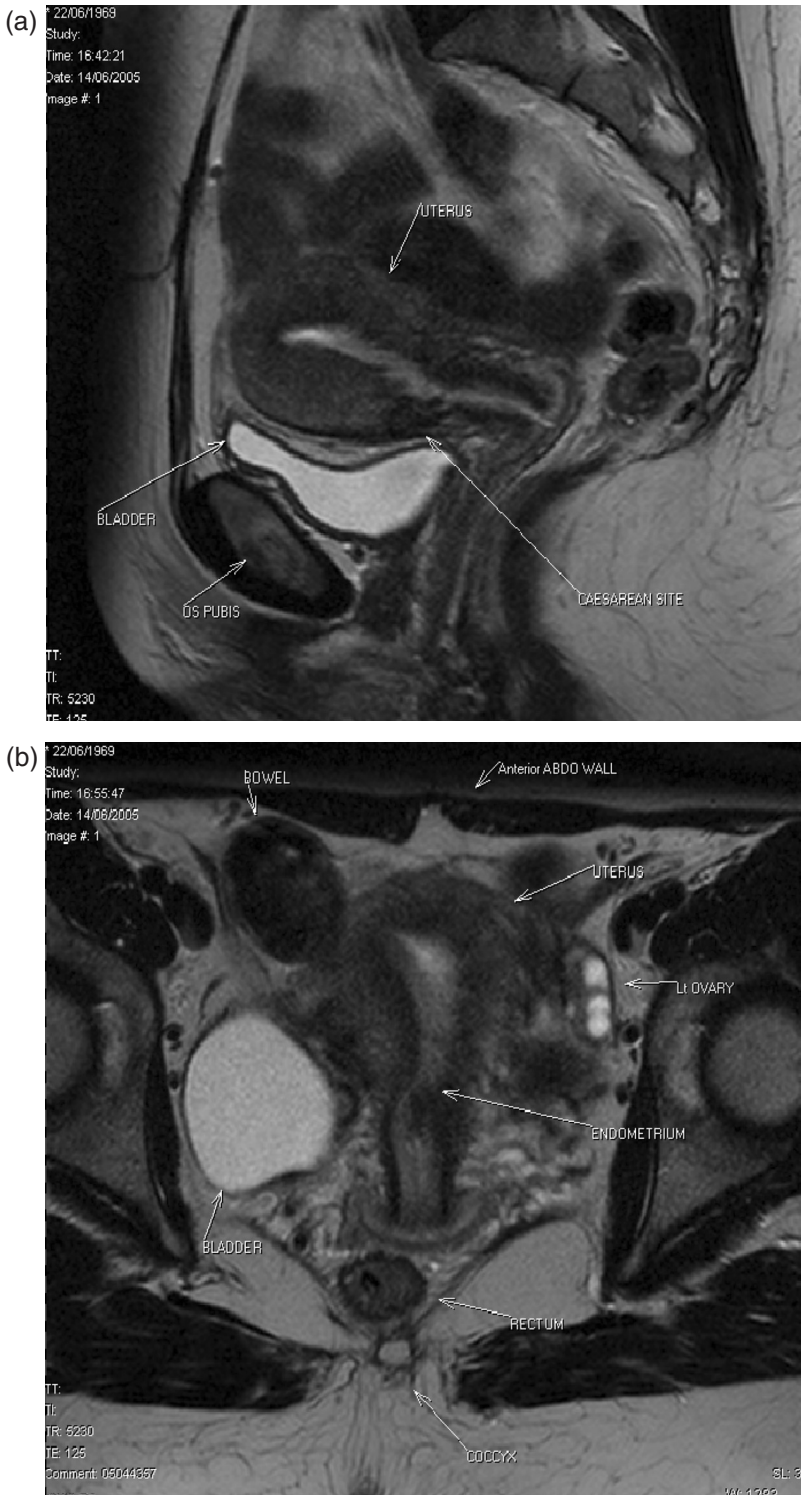

Figure 4a–c Normal MRI 6 months after massive postpartum hemorrhage treated by B-Lynch surgical technique followed by uneventful spontaneous vertex vaginal delivery 22 months later. (a) Sagittal view showing normal endometrial cavity and treated Cesarean incision site; (b) coronal view, with no uterine cavity synechiae[19]; (c) view at level of incision for Cesarean section, showing well-healed features

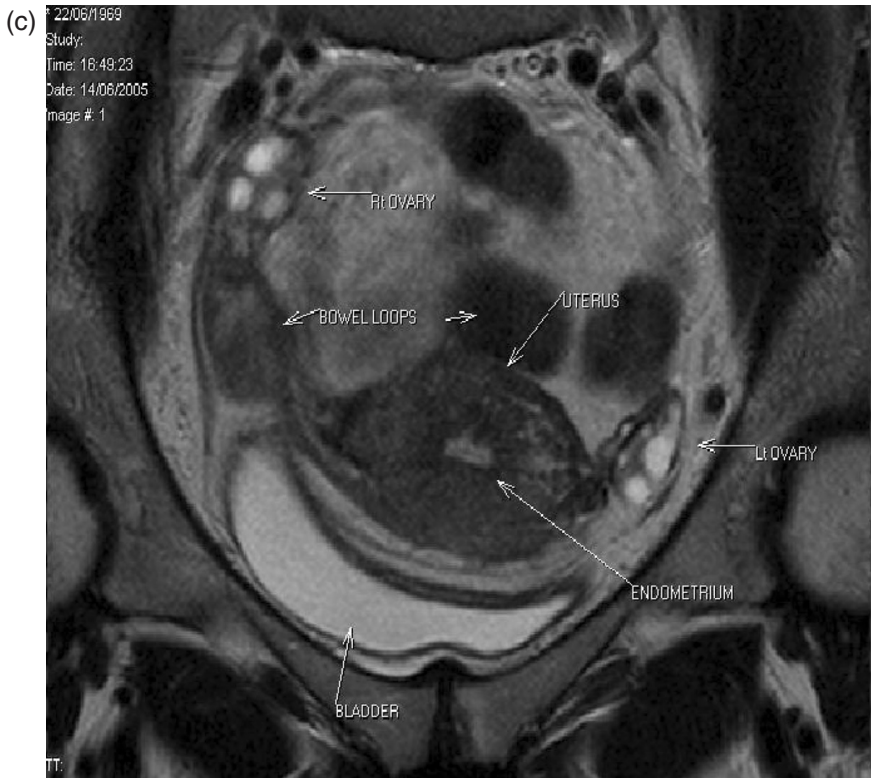

Figure 4a–c *continued*

Table 3 The B-Lynch surgical technique: clinical points

1. User-friendly suture material monocryl No.1 mounted on 90-cm curved ethigard blunt needle (codeW3709) (Ethicon, Somerville, NJ). Other rapidly absorbable sutures can be used according to the surgeon's preference. A good length and needle are essential[19]
2. Basic surgical competence required
3. Uterine cavity checked, explored and evacuated
4. Suture bends maintain even and adequate tension without uterine trauma or 'shouldering'
5. Allows free drainage of blood, debris and inflammatory material
6. Transverse compression suture applied to the lower segment for abnormal placentation effectively controls bleeding
7. Simple, effective and cost-saving
8. Fertility preserved and proven[3]
9. Mortality avoided[3]
10. World-wide application and successful reports (> 1300) (B-Lynch, personal data base, christopherbl@aol.com)
11. Potential for prophylactic application at Cesarean section when signs of imminent postpartum hemorrhage develop, e.g. placenta accreta, or where blood transfusion is declined, e.g. placenta previa surgery on a Jehovah's Witness

WORLD-WIDE REPORTS

The current level of application of the B-Lynch suture world-wide includes over 1300 successful cases; of these, there are only 19 failures. The Indian subcontinent has the largest number of reported successful applications, over 250, followed by Africa, South America, North America, Europe and other countries. The

Table 4 The Hayman uterine compression suture: clinical points

1.	Lower uterine segment or uterine cavity not opened
2.	Uterine cavity not explored under direct vision
3.	Probably quicker to apply
4.	No feed-back data on fertility outcome
5.	Morbidity feed-back data limited
6.	Unequal tension leads to segmented ischemia secondary to slippage of suture – 'shouldering' with venous obstruction

Table 5 The Cho multiple square sutures: clinical points

1.	Multiple full-thickness square sutures applied, probably time-consuming if many square sutures required
2.	Uterine cavity drainage restriction – pyometra risk[15]
3.	No feed-back data on fertility outcome
4.	Morbidity feed-back data limited
5.	Rhythmic contraction not facilitated and involution impeded
6.	The production of multiple uterine senechiae (see Chapter 24)

17 reported failures were because of delay in application, poor technique, defibrination and inappropriate material. Various suture materials have been used. However, the monocryl suture (code WC3709) is recommended because it is user- and tissue-friendly with uniform tension distribution and is easy to handle[20]. Holtsema and colleagues recently opined, in a review, that the B-Lynch technique for postpartum hemorrhage should be an option for every gynecologist[21]. Wohlmuth and colleagues published outcome of a large series with a 91% success rate (world-wide cumulative success rate 98%)[22].

CONCLUSION

Of the compression suturing techniques described above, the B-Lynch procedure has been recommended by the 2000–2002 Triennial Confidential Enquiry into Maternal Deaths in the United Kingdom[23], The Royal College of Obstetricians and Gynaecologists in the UK, and the Cochrane Database of systematic reviews. To date, no serious adverse outcomes have been associated with the B-Lynch surgical technique[3,17,20,22,24]. Furthermore, the latest 2000–2002 Triennial Confidential Enquiry states that no deaths were reported in women who had had interventional radiology or B-Lynch suture in the management of postpartum hemorrhage[23].

It is important to remember that, if a patient is a known or appreciated risk for postpartum hemorrhage, then the elective delivery should be performed in the day time, with prearranged co-operation between the imaging department and the obstetric team. Theater staff should be alerted in time so that conservative surgery can be carried out quickly if needed. Patients at particular risk are those with obesity, cardiomyopathy, coagulopathy, abnormal placentation, polyhydramnios and specific religious convictions contraindicating blood transfusion.

PLACEMENT OF LIGATURES IN STEPWISE DEVASCULARIZATION

The essential requirements are not simple and may not be available in every unit. First, there is a need for a competent obstetrician who is conversant and competent at pelvic gynecological procedures, and who has a working knowledge of the pelvic anatomy, including the vascular and neurological supply of the pelvic organs. Second, there is a need for an obstetric anesthetist, as well as a vascular and/or gynecological cancer surgeon on standby. Finally, provisions must be available for admission postoperatively to the intensive care unit.

This set of requirements takes full account of the extraordinarily generous blood supply to the uterus and the pelvic organs (see Figure 7). The surgical approach starts with ligature of the uterine artery and its distribution to the uterus, preferably as it emerges from crossing over the ureter or as it approaches the uterine wall to penetrate and establish its division[25]. This could be carried out unilaterally or bilaterally about 2 cm from the uterine angle at Cesarean section or where the lower segment is opened after conservative surgery for postpartum hemorrhage has failed (Figure 8).

It is absolutely essential to remember that the internal iliac (hypogastric artery) gives off independent branches that descend to the cervix and vagina (vaginal branch), respectively (see Chapter 32). Devascularization can be achieved by independent ligation sutures applied bilaterally to the cervix and/or vagina. The ovarian vascular supply to the uterus is also ligated, either unilaterally or bilaterally. Unilateral or bilateral ligature of the internal

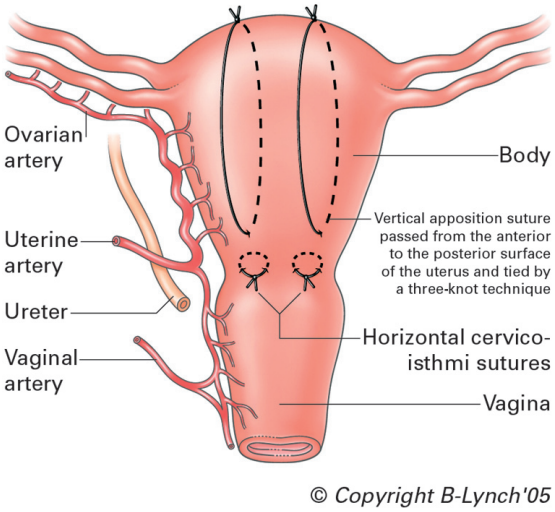

Figure 5 The Hayman uterine compression suture without opening the uterine cavity[11]

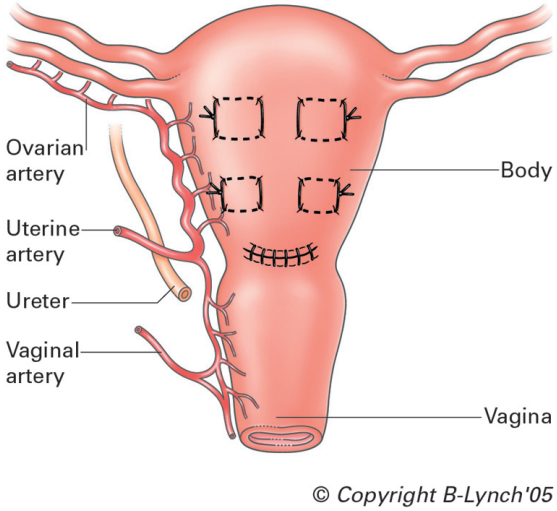

Figure 6 The Cho multiple square sutures compressing anterior to posterior uterine walls[12]

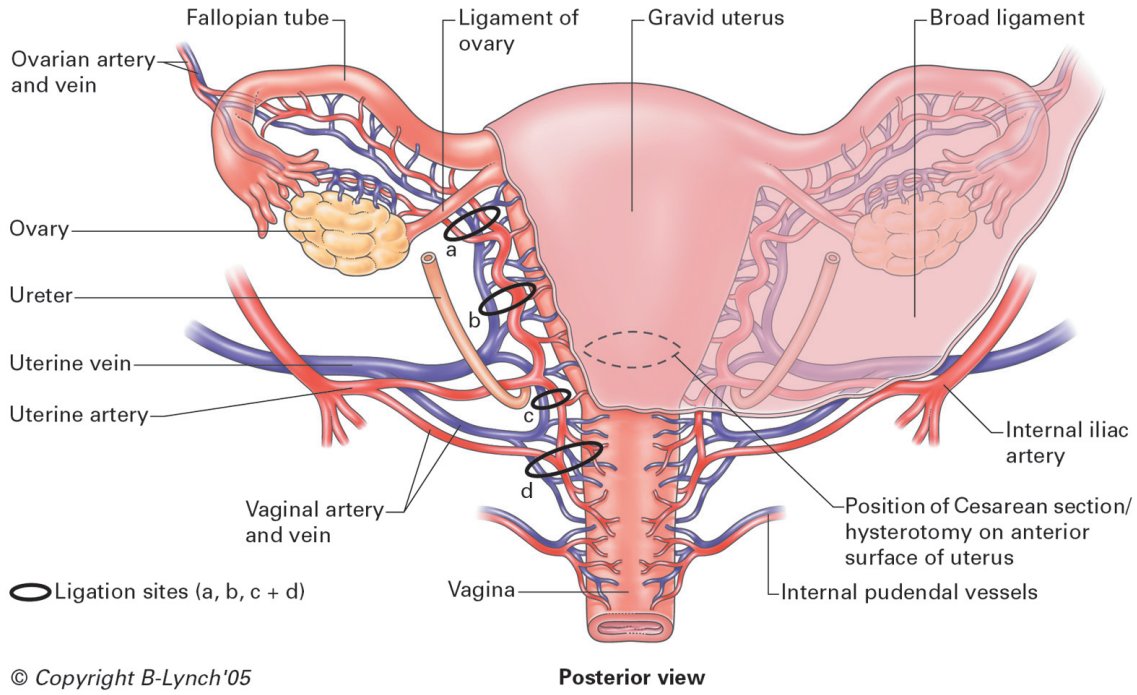

Figure 7 Placement of ligatures in the process of stepwise devascularization, including ligature of the descending uterine and vaginal arteries

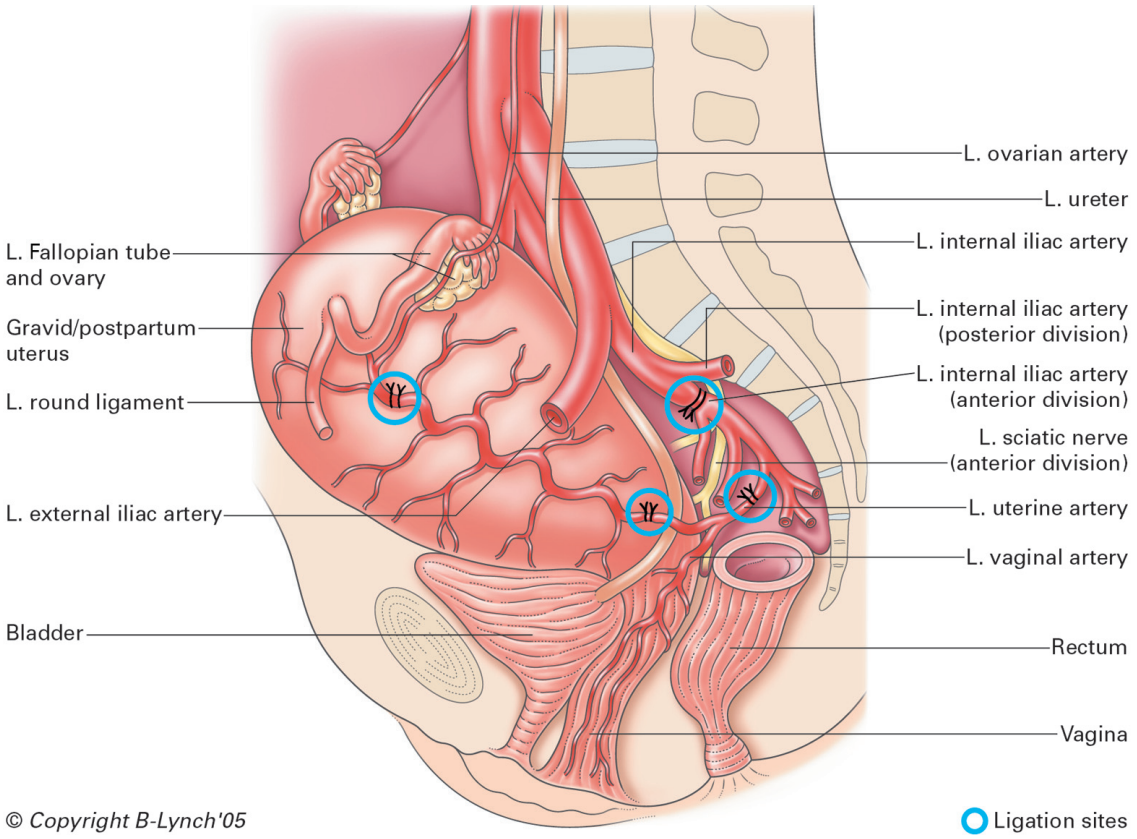

Figure 8 The complex vascular distribution to the pelvic organs. In this procedure of stepwise devascularization, the patient must be in the Lloyd Davis or modified lithotomy position, with one of the assistants able to access and swab the vagina to assess bleeding control

iliac artery may become necessary as a further step to control massive postpartum hemorrhage. A skilful surgeon should aim to ligate the anterior division of the internal iliac artery in order to achieve further devascularization of the uterus without compromising blood supply to the posterior division. However, ligation of the internal iliac directly could be done unilaterally or bilaterally without devascularizing the pelvic organs[8,26]. This may save time, life and organ.

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32

INTERNAL ILIAC (HYPOGASTRIC) ARTERY LIGATION

C. B-Lynch, L. G. Keith and W. B. Campbell

BACKGROUND HISTORY

The historical background of ligature of the internal iliac artery for the control of hemorrhage is not clear[1]. Numerous publications have attributed the procedure to different surgeons in diverse specialties world-wide[2–4]. In the United Kingdom and the United States, the operation was reported before 1900 and, since then, many surgeons have practiced it and found it useful.

Howard Kelly first pioneered ligation of the internal iliac (hypogastric) artery in the treatment of intraoperative bleeding from cervical cancer prior to this technique being applicable to postpartum hemorrhage[5]. Studies have shown that, in postpartum hemorrhage, the reduction of pulse pressure may only be achieved in 48% of cases. It is for this reason that other workers have advocated bilateral ligation of the internal iliac arteries to significantly improve the chances of reducing pelvic pulse pressure and facilitate hemostasis[5]. Reported complications include nerve injury, inadvertent ligature of the common iliac artery, prolonged blood loss and prolonged operative time. It has also been reported that there is a high rate of complication and low rate of success for hemostasis if the procedure is not done correctly[6]. Therefore, this procedure should be reserved for hemodynamically stable patients of low parity in whom future child-bearing itself is of paramount concern.

Unilateral or bilateral hypogastric artery ligation can be life-saving in patients with massive postpartum hemorrhage[6,7]. Although surgeons may be reluctant to perform bilateral hypogastric artery ligation for fear of injury to the pelvic viscera, there is no evidence that this is the case or that there is any significant impairment of function of the pelvic viscera. If the procedure is performed correctly, there is no morbidity, either short- or long-term[7].

Historically, the practice of internal iliac ligation was within the competency of most obstetricians and gynecologists. Today, however, subspecialization means that their training and experience may be insufficient, so pelvic floor specialists or vascular surgeons are often called upon when internal iliac artery ligation is required.

INTRODUCTION

In 1963, Lane and Aldemann reported that hemorrhage was one of the major causes of maternal mortality in the United States[8]. Eastman correlated this in an extensive review of the literature[9]. Any obstetrician who attends and experiences a case of severe postpartum hemorrhage clearly understands the risk of losing a patient from hemorrhage. The memory will last for ever. Modern methods offer the likelihood of resuscitation and survival through competent management by medical means or conservative surgery before such patients reach the point of exsanguination[10]. However, when it becomes obvious that conservative methods have failed, unilateral or bilateral internal iliac artery ligation should be considered urgently[5,11,12].

ANATOMICAL CONSIDERATIONS

The pelvic vasculature is arranged in such a manner that there is ample collateral circulation[13] (Tables 1–3). The common iliac artery bifurcates into two main branches – the external iliac artery (which becomes the femoral artery at the inguinal ligament) and the internal iliac

(hypogastric) artery which descends into the true pelvis. The latter divides into anterior and posterior branches. It is essential to identify this division because the uterine artery branches off from the anterior division.

Clinical anatomy

The level of bifurcation of the common iliac artery is quite constant, and there are two easily identifiable guides. These are the sacral promontory and a line drawn between both anterior superior iliac spines. The bifurcation of the common iliac artery is found at the level of both of these landmarks in the majority of patients. Reich and co-workers in 1964[14] used dissection of fresh cadavers to show that numerous variations occur in the anatomy of these vessels. It is not always true, for example, that one or both of the internal iliac (hypogastric) branches of the common iliac artery are of similar diameter along the entire length. Therefore, visual observation alone can be misleading. Likewise, there may be some difference in the length and diameter of the right and left internal iliac arteries. Surgeons should therefore be aware of the fact that subdivision of the main internal iliac trunk may be into branches that are not significantly narrower than the main trunk.

The important anatomical relations of the internal iliac (hypogastric) artery can be summarized as follows:

(1) Anterior medial – covered by peritoneum (the internal iliac artery is entirely retroperitoneal);

Table 1 Branches of the internal iliac artery

Posterior division	*Anterior division*
Parietal	*Visceral*
Iliolumbar	Umbilical
Lateral sacral	Superior vesical
Superior gluteal	Middle hemorrhoidal
Obturator	Uterine
Internal pudendal	Vaginal
Inferior gluteal	

Table 2 Anastomoses of internal iliac arteries

Branch of internal iliac	*Anastomotic vessels*
1. The uterine arteries	1. Right and left ovarian arteries (direct branches of the aorta)
2. Inferior and middle hemorrhoidal	2. Superior hemorrhoidal artery (branch of inferior mesenteric)
3. Pubic branches of obturator	3. Inferior epigastrics (branch of external iliac)
4. Inferior gluteal	4. Circumflex and perforating branches of the deep femoral artery
5. Superior gluteal	5. Lateral sacral (posterior branches)
6. Iliolumbar	6. Lumbar artery (from aorta)
7. Lateral sacral	7. Middle sacral
8. Vesical arteries	8. Branches of the uterine and vaginal arteries

Table 3 Major pelvic anastomoses

Vertical
1. Ovarian artery (branch of aorta) with the uterine artery
2. Superior hemorrhoidal artery (branch of inferior mesenteric) with middle hemorrhoidal artery
3. Middle hemorrhoidal artery with inferior hemorrhoidal (branch of internal pudendal from hypogastric)
4. Obturator artery with inferior epigastric artery (branch of external iliac)
5. Inferior gluteal artery with circumflex and perforating branches of deep femoral artery
6. Superior gluteal artery with lateral sacral artery (posterior branches)
7. Lumbar arteries with iliolumbar artery

Horizontal
1. Branches of vesical arteries from each side
2. Pubic branches of obturator from each side

(2) Anterior – the ureter (retroperitoneal and attached to the peritoneum);

(3) Posterolateral – the external iliac vein and the obturator nerve;

(4) Posteromedial – the internal iliac vein;

(5) Lateral – the psoas major and minor muscles.

Physiology of internal iliac artery ligation

Because of the excellent collateral circulation in the pelvis, vascular compromise does not occur when one or both internal iliac arteries are ligated. At one time, ligation of the hypogastric system was regarded as equivalent to shutting off all the blood to the area. Fortunately, this is not true. If it were, it is likely that the procedure would not be harmless. In reality, the hypogastric artery distal to the point of ligation is never emptied of blood because the rich anastomotic network starts to function immediately after ligation[15]. What does occur is the virtual abolition of the arterial pulse pressure. This is associated with reduced mean blood pressure and rate of blood flow in the collateral system. As a result, the trip-hammer effect of arterial pulsations is abolished. The surgeon must be aware that bilateral ligature of the internal iliac artery is more effective than the unilateral procedure in that the patient has less chance of returning to theater for secondary surgery to control hemorrhage. The reduced pressure and lack of pulsation do, however, mean that thrombosis in the vessels may remain *in situ*.

INDICATIONS FOR LIGATION OF THE INTERNAL ILIAC ARTERY

Prophylactic

Differentiation between prophylactic and therapeutic use of internal iliac artery ligation is by no means absolute. Conditions that may indicate ligation as a prophylactic measure include postabortion bleeding, postpartum hemorrhage, atonic uterus prior to hysterectomy, abruptio placenta with uterine atony, abdominal pregnancy with pelvic implantation of the placenta, placenta accreta with intractable bleeding, and prior to total or subtotal hysterectomy when all conservative measures have failed.

Patients also considered to be at high risk for recurrent postpartum hemorrhage, those with recurrent major placenta previa, or Jehovah's Witnesses with important risk factors may be candidates for prophylactic internal iliac ligation. Good clinical judgement is essential and, if prophylactic ligation is thought to be the best course, then it should not be delayed.

Therapeutic

Therapeutic ligation may become necessary:

(1) Before or after hysterectomy for postpartum hemorrhage;

(2) Where bleeding continues from the base of the broad ligament;

(3) Where there is profuse bleeding from the pelvic side-wall;

(4) Where there is profuse bleeding from the angle of the vagina;

(5) Where areas of diffuse bleeding are present without a clearly identifiable vascular bed;

(6) In the case of ruptured uterus in which the uterine artery may be torn at the site of its origin from the internal iliac artery;

(7) When there are additional indications including atony of the uterus where conventional methods have failed;

(8) Where extensive lacerations of the cervix have occurred following difficult instrumental delivery;

(9) Where there is significant bleeding from the lower part of the broad ligament;

(10) When there are gunshot wounds to the lower abdomen;

(11) In the case of fracture of the pelvis and intraperitoneal hemorrhage.

In such circumstances, hysterectomy alone may not be sufficient to control hemorrhage. Internal iliac artery ligation, unilateral or bilateral, may become necessary and should not be delayed in such life-threatening situations.

SURGICAL TECHNIQUES

General considerations

All obstetric surgeons should be fully aware of the indications, timing and technical aspects of unilateral or bilateral hypogastric artery ligation.

Experimental evidence by Burchell has shown that it is the abolition of the 'trip-hammer effect' of arterial pulsations that allows effective clotting to take place, so that small vessels stop bleeding[2,3]. This may explain why bilateral ligation works better than unilateral ligation.

Either a mid-line or a transverse abdominal incision may be used. The surgeon should not use an unfamiliar incision. A transverse incision may take more time, especially in obese patients. Visualization is considerably better from the opposite side of the pelvis. To work on the contralateral side, the surgeon may elect to change sides during the operation.

In most situations, bilateral ligation is preferable to unilateral ligation. Not only is hemostasis more secure, but, in addition, it allows greater confidence in making a decision not to re-explore the patient. Although it is possible to perform the operation by the extraperitoneal approach, the intra-abdominal approach is preferable except in cases of extreme obesity.

Some surgeons advocate complete transection of the internal iliac artery between two ligatures. This has no practical or physiologic advantage. On the contrary, its practice may lead to injury of the underlying veins.

The choice of material for ligating the artery depends on the preference of the surgeon. For example, 1–0 Vicryl and umbilical artery tape have been used. Two ties should be placed firmly but gently in continuity approximately 0.5 cm apart and 0.5–1 cm below the bifurcation (Figure 1).

Transabdominal approach

The abdomen is opened and the viscera packed away in the usual manner. Identification of the bifurcation of the common iliac artery is made by the two bony landmarks: the sacral promontory and an imaginary line drawn through both anterosuperior iliac spines. A longitudinal incision is made into the posterior parietal peritoneum. If the uterus is present, this incision can be started in the peritoneum on the posterior surface of the round ligament, at the junction of the middle and medial thirds. The incision is extended proximally for about 10 cm. If the uterus is absent, the incision can be started over the external iliac artery and carried proximally to the level of the bifurcation. Another method is to incise into the peritoneum directly over the bifurcation. The incision is then extended distally a few centimeters. All these incisions have one feature in common: they result in the formation of a medial and lateral peritoneal flap. The ureter is always beneath the medial flap and may be visualized, reflected, and protected with ease. The ureter normally crosses the common iliac artery from lateral to medial at a point just proximal to the bifurcation.

Once the peritoneum is opened, loose areolar tissue is separated from it by blunt dissection in the direction of the vessels, not across them to avoid unnecessary trauma. Small pieces of dental cotton ('pledgets' on long, curved forceps) are effective. The fingers also may be used. When the areolar tissue has been separated, the bifurcation comes into view. If the arteries are difficult to find, feel for a pulse (but remember that pulses may be difficult to palpate if a patient is hypotensive). The bifurcation feels like an inverted Y. The branch coming off at right angles is the hypogastric (internal iliac) artery. It courses medially and inferiorly to the palpating finger. The continuing branch is the external iliac artery. It courses laterally and superiorly out over the psoas muscles to the leg, where it becomes the femoral artery.

The surgeon must accurately identify these two branches because inadvertent ligation of the external iliac artery will produce an acutely ischemic leg, and limb loss is then a risk. If the external iliac artery is ligated, the ligature can be cut but it must then be checked for adequate flow, because the inner layer of the wall may have been disrupted. If the artery has been transected, then it needs to be formally repaired and a graft may be required. The attendance of a vascular surgeon becomes essential.

The common and internal iliac arteries are often adherent to the underlying veins which can be difficult to see, particularly beneath the

origin of the internal iliac artery. This is the most hazardous part of the operation. Good retraction of the pelvic contents and displacement of the arteries are needed to visualize the veins. Meticulous dissection with scissors is required to separate the internal iliac vein from the artery if they are adherent. Once a plane has been developed between them, a Mixter or other fine right-angled forceps, or the forceps designed by Reich and colleagues[13] are gently introduced between them. This is best done onto the tip of a finger of the opposite hand, which allows gentle manipulation of the tips of the closed forceps, while feeling if there is still tissue present which requires division by sharp dissection. Simply pushing the forceps between the artery and the vein in an uncontrolled fashion is dangerous. It is also inadvisable to try separating the artery and the vein by opening the tips of the forceps forcibly until a path has been found between them.

The peritoneum should be closed with interrupted 2–0 Vicryl because a continuous suture can kink the ureter. The procedure on the left pelvic wall may be slightly more difficult because it is frequently necessary to mobilize the sigmoid flexure at the 'white line' to obtain adequate exposure.

Extraperitoneal approach

The skin incision in the inguinal area parallels the course of the external oblique muscle. It runs 10–15 cm in length in a line 3–5 cm medial to the anterosuperior iliac spine. After the fat and subcutaneous tissues are dissected away, a muscle-splitting incision exposes the peritoneum. This is gently reflected medially, together with the ureter. Ligation is performed as previously described. Closure is the same as for a herniorrhaphy and can be time-consuming if a bilateral approach is to be carried out.

Mid-line extraperitoneal approach (uncommon)

A mid-line extraperitoneal approach to the aorta has been advocated[16]. One hospital authority extended its use to bilateral ligation of the hypogastric arteries. A mid-line abdominal incision is made. After the anterior sheath of the rectus muscle is exposed and opened below the level of the umbilicus, dissection caudal to the semilunar line of Douglas is performed, and the peritoneal and preperitoneal fat are separated. The peritoneum and its contents are reflected to the right (or left), thus exposing the retroperitoneal structures[16].

ESSENTIAL SURGICAL CONSIDERATIONS

(1) The ureter crosses the common iliac artery at the level of its bifurcation;

(2) An incision is made inferolaterally and parallel to the ureter, which can be identified visually for safe identification and dissection;

(3) Following such incision, the peritoneal flap under which the ureter runs is displaced medially and retracted away (the ureter may be controlled with a sling for safety);

(4) The internal iliac at the point of its bifurcation into the anterior and posterior divisions can be seen and palpated with its vein and the obturator nerve. It is extremely important not to damage the internal iliac vein. The main arterial branch of the internal iliac is ideal for identification and ligature by passing a right angle, blunt-ended eye needle upon which is threaded a non-absorbable suture such as silk of 0 caliber or vicryl suture of the same caliber and passed between the artery and the vein.

Postoperative care

Intensive care is necessary because these women may be moribund and have required huge blood transfusion. Large hematomas or collections of serosanguineous fluid can be drained through separate stab wounds. Usually, this is unnecessary. Antibiotics are not indicated after ligation of the arteries. Their use is dictated only by the presence of infection. Early ambulation is advisable in all cases. An indwelling catheter may be necessary to facilitate adequate assessment of urinary output in women who are at risk of serious morbidity.

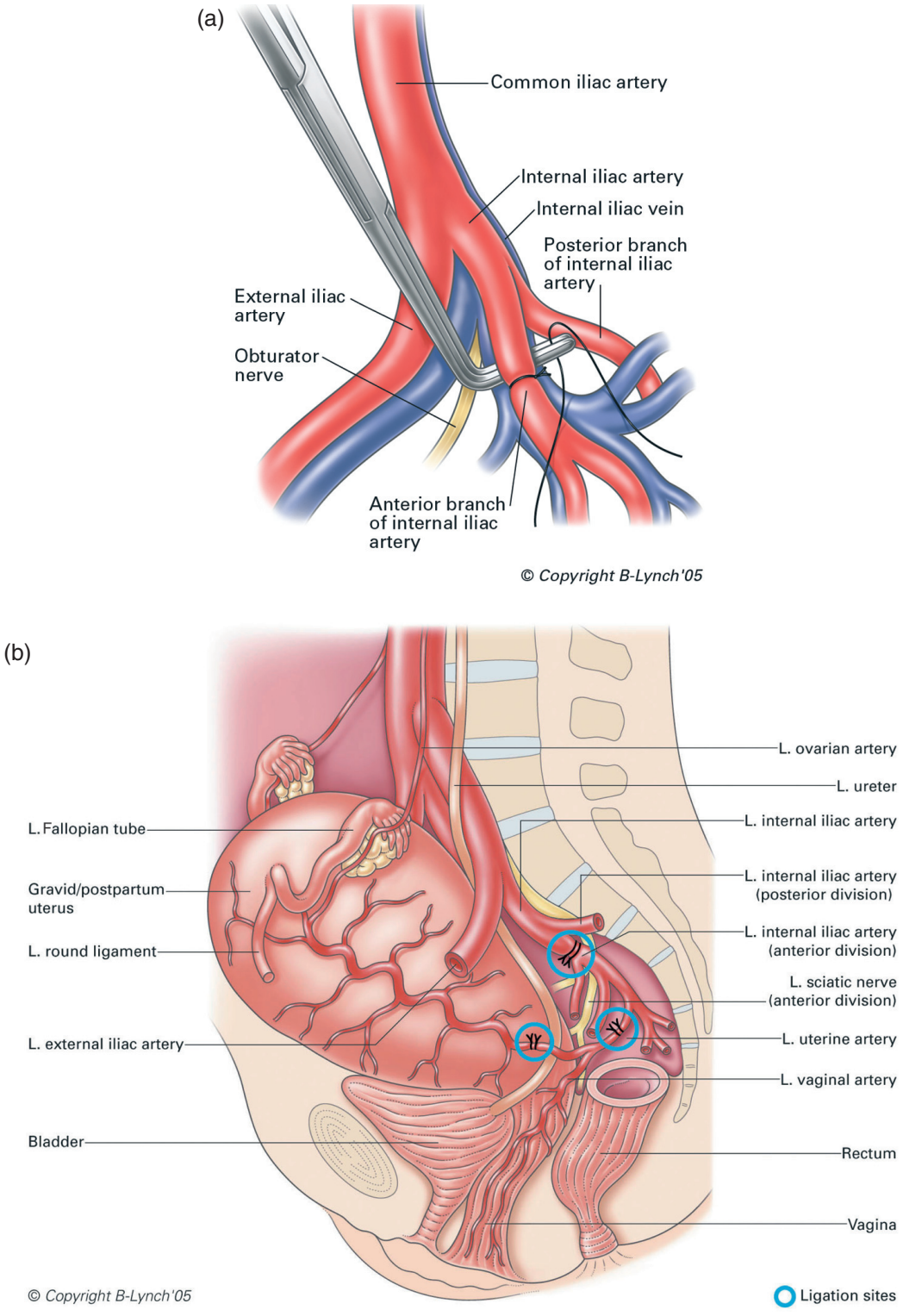

Figure 1 Ligation of the anterior branch of the internal iliac artery with its associated vein. (a) Demonstrable vulnerability of internal iliac vein and obturator nerve in close proximity; (b) A 'skeletal' anatomy, showing proximity of external iliac artery, ureter and anterior branches of sciatic nerve

Special clinical considerations

The major pitfall associated with ligation of the hypogastric artery is delay. When hemorrhagic shock is irreversible, this operation will not overcome it. Inadequate transfusion is another pitfall in the therapy of patients with severe hemorrhage. Blood loss is often seriously underestimated.

Failure to remember that the vaginal artery is a separate branch of the hypogastric artery, rather than a branch of the uterine artery, may lead the surgeon into the pitfall of an unnecessary and ineffective hysterectomy for control of bleeding. Injury to the external iliac artery from retractors or mistaken ligation of this vessel can lead to lower limb amputation. Also, accidental ligature of one or both ureters would lead to renal function impairment. Accidental incorporation of the anterior division of the sciatic nerve may lead to foot drop (Figure 1b).

Most authors consider internal iliac artery ligation to be a very safe procedure. The available data suggest that this operation does not result in necrosis of vital pelvic structures. The only report to the contrary is by Tajes[4] who cited a case of his own in which this operation resulted in necrosis of the buttocks. Tajes also reviewed two previously reported cases: in one case, the bladder mucosa sloughed, in the other, scrotal necrosis ensued. However, his report was 50 years ago.

Maintenance of reproductive function

It has not always been possible to follow young patients for whom this operation has been performed. More important, many patients do not understand the exact nature or extent of their operation. A patient may remember only that she was sick and bleeding, that she was operated on and that she recovered.

The incidence of postoperative amenorrhea is not known. It is common for menses to resume after the operation. There have been reports of normal pregnancy and delivery occurring after bilateral hypogastric artery ligation, although it is impossible to say how frequently this occurs. It is entirely reasonable to believe that reproductive capacity is not lost after this operation, provided that the patient has a normal uterus. It is important to remember that pituitary necrosis (Sheehan's syndrome is discussed in Chapter 38) can affect the ability to reproduce after postpartum hemorrhage, especially if blood replacement has been delayed or inadequate, hemorrhage has been severe, and shock profound. Fortunately, this is not a common occurrence in many modern and well-equipped obstetric units.

Potential failures and consequences[18]

Occasionally, ligation of the hypogastric arteries fails to stem pelvic hemorrhage. The reason for this is not clear, but some suggestions are:

(1) Massive necrosis after infection with destruction of the vessels;

(2) The presence of large, aberrant branches feeding blood to the area;

(3) Dislodgement of clots when blood pressure rises;

(4) Concomitant severe venous bleeding; however, this is rare;

(5) Coagulopathy with deranged hematological indices.

Avoiding accidental ligation of the common or external iliac artery

It is essential to identify the internal iliac artery clearly. Ligation of the common or external iliac produces an acutely ischemic leg. The classical signs are whiteness or pallor of the foot and absence of distal pulses – but these may be difficult to assess in a hypotensive, vasoconstricted patient. If there is concern that the main artery to the lower limb may have been ligated, check for a pulse in the external iliac artery above the inguinal ligament, beyond the area of ligation; the femoral pulse in the groin; or the Doppler signals at the ankle, using a hand-held Doppler. If the wrong artery has been tied, the ligature should be removed. If this fails to restore a good pulse (or if the artery has been transected), a vascular surgeon should be called to repair the vessel (either by end-to-end anastamosis or with the use of a short bypass graft of vein or synthetic material).

Damage to the ureter

Damage to either or both ureters should be avoided by careful visualization and dissection. In life-threatening surgery or delayed intervention to control massive hemorrhage, accidental damage to a ureter may occur. Ligature is more probable than transection. Prompt diagnosis and remedial surgery by a urological colleague are essential. Accidental ligature of one ureter may not lead to renal failure but increase morbidity.

Damage to other vessels

Damage to the common or iliac vein or one of its major tributaries results in brisk hemorrhage. Its source can be difficult to see and to control. It can threaten the patient's life, particularly in the context of pre-existing major blood loss from postpartum hemorrhage.

Steps to avoid damage to the iliac veins have been described in detail above: great care should be taken when dissecting in the area behind the origin of the internal iliac artery and when separating the arteries from the veins. If sudden venous bleeding does occur, the first step should be to apply firm pressure to the area. Adequate suction should be prepared – two suction tips may be helpful. Swabs mounted on sponge-holding forceps can then be applied distal and proximal to the site of damage to compress the veins and allow the defect to be visualized. If the venous defect cannot be seen, deep in the pelvis behind the iliac artery, then transaction of the iliac artery to expose the vein may solve the problem. The artery can then be re-anastamosed. When the defect in the vein has been seen, its edges can be held together using atraumatic forceps such as Stiles, before being sutured.

Repair of the vein is best performed with a non-absorbable vascular suture, such as polypropylene on a round-bodied needle. For large iliac veins, a 3/0 is a reasonable choice: needles smaller than those supplied with 4/0 sutures can be difficult to retrieve during repair of large veins and present a small danger of becoming 'lost' inside the vein. Finally, it is most important to avoid incorporating branches of the anterior division of the sciatic nerve into any ligatures[17] (Figure 1b).

USEFUL HINTS

The position of the surgeon relative to the patient

The surgeon should stand where he/she is most comfortable and this may be influenced by right- or left-handedness. The choice of the surgeon's position also depends on the ability and dexterity of the assistant. If the assistant is relatively inexperienced, then it may be particularly helpful for the surgeon to changes sides during the procedure in order to deal with each internal iliac artery from the opposite side of the operating table.

Checking for thorough control of bleeding before closure of abdomen

(1) Whilst the patient is in the frog-leg or Lloyd Davis position throughout the operation, an assistant stands between the legs and swabs the vagina to confirm bleeding has stopped.

(2) The abdomen is examined to ascertain that the ligatures have been correctly placed.

(3) The posterior abdominal wall peritoneum, which had been incised to access the posterior abdominal wall, may or may not need closure.

(4) The abdomen is checked once again thoroughly to ensure all instruments, swabs and foreign materials have been removed.

(5) The abdomen is closed according to type of the initial incision, i.e. large, pfannenstiel or mid-line. The mid-line incision is commonly closed by the mass closure technique.

(6) The sick patient should be quickly transferred directly to a high-care setting such as ITU for an appropriate length of time, to ascertain hemostasis, to ensure that pulse and blood pressure have returned to normal, and to permit surveillance of the urinary systems with a bladder catheter *in situ*.

(7) Counselling for post-traumatic stress, depression, panic attacks and flashbacks should be provided.

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33

THE PELVIC PRESSURE PACK

G. A. Dildy III

When pharmacologic and surgical interventions fail to correct postpartum hemorrhage, hysterectomy becomes the option of last resort[1]. The incidence of hysterectomy on the Louisiana State University obstetric service at Charity Hospital of New Orleans during 1975–1981 was 1.21 per 1000 deliveries[2]. Contemporary reports of the incidence of obstetric hysterectomy range between 0.33 and 0.70 per 1000 deliveries[3–6]. Under these circumstances, a moderately busy obstetric unit with 4000 deliveries per year may expect to perform as many as three emergency hysterectomies annually.

The maternal mortality associated with obstetric hysterectomy is significant (4.0–4.5%) for a number of reasons, not the least of which have been outlined elsewhere and much of which relates to the often moribund condition of the patient when the operation commences, the difficulty of the procedure itself, especially in the presence of factors which make the anatomy unclear, and the extent of the bleeding which may accompany the operation[4,5]. Indeed, Clark and colleagues reported an average blood loss of 3.5 liters during emergency obstetric hysterectomy[7]. As recounted in several other chapters in this textbook, severe hemorrhage and emergency hysterectomy are often accompanied by secondary coagulopathy. In the setting of acquired coagulopathy, post-hysterectomy bleeding may continue despite secure surgical pedicles, much to the consternation of the surgeon and the members of the operating team.

Abdominal and pelvic post-surgical packing is an old concept and one that has been used to control hemorrhage from a variety of sources, including liver trauma[8], pre-eclampsia-induced hepatic rupture[9], rectal cancer[10], and gynecologic cancer surgery[11]. Various packing methods have been described, such as the 'bowel bag'[11] or packing with dry laparotomy packs[12]. These methods, however, require re-laparotomy after initial stabilization and volume control to remove the packing materials. Other recently reported methods for packing, not requiring re-laparotomy but with limited cumulative obstetric experience, include transcutaneous placement of an inflated condom over a 22-Fr catheter[13] or ribbon gauze within a Penrose drain[14].

In 1926, Logothetopoulos described a pack for the management of uncontrolled post-hysterectomy pelvic bleeding[15]. This technique has subsequently been called the *mushroom*, *parachute*, *umbrella*, *pelvic pressure*, or *Logothetopoulos* pack. It is important to note that this pelvic pressure pack described is applied *post-hysterectomy*, and it should not be confused, as it often is, with uterine packing[16], or with various intrauterine balloons[17–19] for treatment of postpartum hemorrhage due to uterine atony or placental site bleeding.

The pelvic pressure pack controls hemorrhage from large raw surfaces, venous plexuses and inaccessible areas by exerting well-distributed pressure, compressing bleeding areas against the bony and fascial resistance of the pelvis[20,21]. According to Parente and colleagues[21], several references to the pelvic pressure pack appeared in European medical journals during the decades following the original report. The first reported cases appearing in the English literature were not until the 1960s, and these pertained specifically to gynecologic post-hysterectomy hemorrhage[20,21]. Several case reports and a case series for obstetric post-hysterectomy bleeding have since been published[22–26]. Table 1 summarizes these, 23 cases for control of gynecologic and 13 cases for obstetric post-hysterectomy hemorrhage, with

Table 1 Summary of contemporary reported cases of the pelvic pressure pack for obstetric and gynecologic post-hysterectomy hemorrhage. The success rate is defined as the pelvic pressure pack being the last intervention to control bleeding. Modified from Dildy *et al.*[26]

Series	*Gynecology success rate*	*Obstetric success rate*
Parente, 1962[21]	14/14	–
Burchell, 1968[20]	8/8	–
Cassels, 1985[22]	–	1/1
Robie, 1990[23]	–	1/1
Hallak, 1991[24]	–	1/1
Howard, 2002[25]	–	1/1
Dildy, in press[26]	1/1	7/9
Total	23/23 (100%)	11/13 (85%)

success rates of 100% and 85%, respectively. Admittedly, accurate success rates are difficult to determine based on rare cases collected retrospectively, with possible under-reporting of unfavorable outcomes. Nonetheless, successful control of hemorrhage seems to have been achieved in the majority of cases.

As seen in Figure 1, the pack is constructed by filling a bag (we prefer a sterile X-ray cassette drape, but other materials also have been described) with gauze rolls tied end-to-end (in this case, five 11.4 cm × 2.8 m Kerlix rolls), starting at the 'dome' of the pack (A), with the 'tail' of the gauze protruding from the 'neck' of the pack (B–D). Gauze should be removed, as visually indicated, from the pack before placement, in order to fit the true pelvis. The pack is introduced transabdominally into the pelvis (Figure 2), and the 'neck' is delivered transvaginally through the introitus by passing a surgical clamp from below through the vagina. The surgeon should avoid trapping small bowel behind the pack. Traction and thereby pressure are applied to the pack by tying intravenous (i.v.) tubing to the neck of the pack and suspending a 1-liter i.v. fluid bag off the foot of the bed. A 1-liter glass i.v. bottle and mild

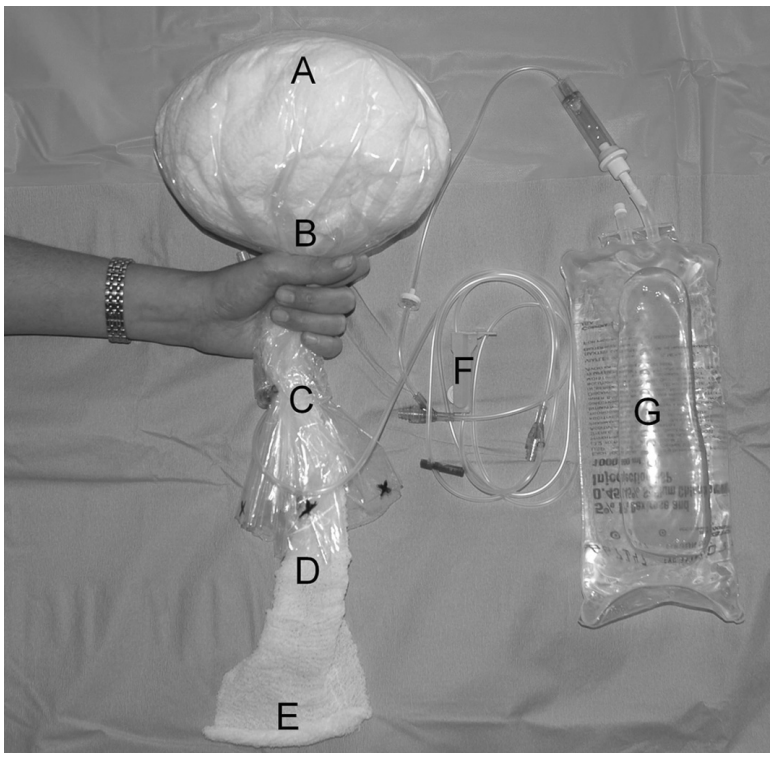

Figure 1 Photograph of a pelvic pressure pack, as constructed from an X-ray cassette drape, sterile gauze rolls, and an intravenous infusion set-up. Please see text for further explanation

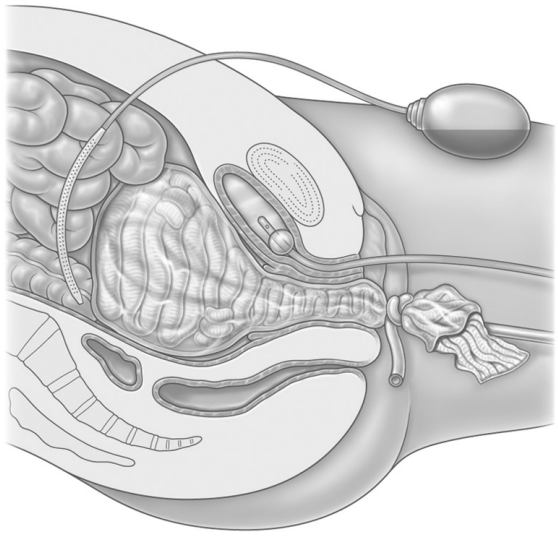

Figure 2 Diagram of the pelvic pressure pack *in situ*. Please see text for further explanation

Trendelenburg position provide additional weight and traction if needed. The i.v. tubing or a cord can simply be hung over the foot of the bed, or over an orthopedic pulley attached to the foot of the bed. Compression of the pack can also be maintained by placing the 'neck' of the pack through a #80 doughnut pessary (not shown), applied flush against the perineum with a surgical clamp. However, caution must be taken to avoid perineal pressure necrosis.

We advise placement of an intraperitoneal large-gauge closed-system (e.g. Jackson-Pratt) drain to monitor for postoperative bleeding. An indwelling urinary catheter allows monitoring of urine output and avoidance of urinary outflow obstruction. After stabilization of the patient, an attempt to remove the pack transvaginally is made by slowly removing the gauze rolls under intravenous sedation, to allow gradual decompression without inciting bleeding. The optimal time to leave the pack *in situ* will vary, but extended placement has certain risks (see below). Usually transvaginal pack removal is successful, but in some cases the pack will have to be removed by re-laparotomy or with laparoscopic assistance.

In one study of trauma patients suffering intra-abdominal hemorrhage, Garrison and colleagues found that patients who experienced hypothermia, refractory hypotension, coagulopathy, and acidosis required *early packing* if they were to survive[27]. Thus, packing should be considered early on when homeostasis is significantly altered. Febrile morbidity is very common in these critically ill postoperative patients who have already received massive blood component therapy and have a foreign body placed into a contaminated operative field[26]. Prophylactic broad-spectrum antibiotics should be administered whenever a pelvic pressure pack is placed, and this regimen should be continued after pack removal until the patient is afebrile at least 24–48 h. Another study of abdominal trauma patients showed those packed for ≤ 72 h had lower abscess, sepsis, and mortality rates than those packed for > 72 h[28]. Thus pack removal should be accomplished as soon possible following stabilization.

In summary, the pelvic pressure pack is simple to construct from commonly available medical materials, and control of hemorrhage is successfully achieved in the majority of cases. If the pelvic pressure pack fails to control bleeding, other medical[29], surgical[30], or interventional radiology[31] approaches will be necessary to ultimately control bleeding. The pelvic pressure pack should be particularly useful in developing countries where more advanced surgical skills for pelvic vascular ligation and technologies, such as selective arterial embolization, are not readily available. In developed countries, however, the pelvic pressure pack may serve as a temporizing measure pending transport to a tertiary-care facility. In the majority of instances, the pelvic pressure pack will afford transfer of the critically ill patient to a post-surgical recovery setting, where restoration of hemodynamic, temperature, hematologic, and acid-base homeostasis can be accomplished.

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34

PERIPARTUM HYSTERECTOMY

T. F. Baskett

HYSTERECTOMY

Emergency peripartum hysterectomy is an unequivocal marker of severe maternal morbidity and 'near-miss' mortality[1,2]. Reviews of published data in the past 25 years show a variable incidence, from one in 331[3] to one in 6978 deliveries[4]. In developed countries, the incidence is approximately one in 2000 deliveries, with one population-based study in a Canadian province showing an incidence of 0.53 per 1000 deliveries[2].

Because of the increasing Cesarean section rate world-wide and the concomitant rise in placenta previa and placenta previa accreta, the incidence of emergency peripartum hysterectomy is rising in many countries. For example, in Canada from 1991 to 2000 the rate rose from 0.26/1000 deliveries to 0.46/1000 deliveries (relative risk 1.76; 95% confidence interval 1.48–2.08)[5]. Compared to vaginal delivery, emergency hysterectomy and delivery by Cesarean section are strongly associated[6,7]. In addition, a recent study has shown that multiple pregnancy had a six-fold increased risk of emergency peripartum hysterectomy compared to singleton pregnancies[8]. Within this group, higher-order multiple pregnancies (triplets and beyond) had an almost 24-fold increased risk of hysterectomy[8]. It seems logical to conclude that the increase in multiple pregnancy rates associated with assisted reproductive technology provides a further contribution to the rising peripartum hysterectomy rates.

Maternal mortality rates associated with emergency hysterectomy range from 0 to 30%, with the higher rates in regions with limited medical and hospital resources[9]. How valid these rates are today is unclear, as they were calculated more than a decade ago. Nonetheless, even in countries with low maternal mortality rates, associated maternal morbidity can be high due to hemorrhage, blood transfusion, disseminated intravascular coagulation, infection and potential injury to the adjacent lower urinary tract[7,10,11]. This chapter describes emergency hysterectomy in the immediate postpartum period following vaginal or Cesarean delivery.

INDICATIONS

By far the most common indication for hysterectomy is hemorrhage associated with the following conditions[7,9–20].

Abnormal placentation

In developed countries, placenta previa, with or without associated accreta, is the most common indication for hysterectomy. This is due to the rising incidence of these conditions associated with the increasing number of women previously delivered by Cesarean section. Despite the fact that numerous other techniques aimed at preserving the uterus have been proposed and are discussed in other chapters in this book, hysterectomy is used to stem the sometimes frightening hemorrhage associated with placenta previa or accreta in the majority of hospitals.

In addition, on rare occasions, abruptio placentae, particularly of the concealed variety, may be associated with such a degree of extravasation of blood into and through the full thickness of the myometrium (Couvelaire uterus) as to make it unresponsive to oxytocic drugs, so necessitating hysterectomy. It must be emphasized, however, that in the majority of cases of abruptio placentae with Couvelaire uterus the response to oxytocic drugs is

appropriate and the hemorrhage is due to disseminated intravascular coagulation rather than failure of the uterus to contract.

Uterine atony

As outlined elsewhere in this book (Chapter 27), the range of modern oxytocic drugs has greatly improved the management of uterine atony. Nonetheless, there are cases in which the uterus is refractory to all applications of such agents. This is most commonly found in the prolonged, augmented and/or obstructed labor: simply stated, the exhausted and infected uterus may respond poorly to oxytocic agents. The majority of these cases occur at the time of Cesarean section for dystocia or cephalopelvic disproportion.

Uterine rupture

The most common cause of complete uterine rupture is within a previous Cesarean section scar. If the rupture is extensive and hemorrhage cannot be contained by suture of the ruptured area, then hysterectomy may be necessary. In addition, rupture of the intact uterus can occur in multiparous women in response to inappropriate use of oxytocic agents in the first and second stages of labor.

Uterine trauma

Traumatic rupture, that is, perforation or laceration of the uterus, can occur with a variety of obstetric manipulations, including internal version and breech extraction in obstructed labor; instrumental manipulation, such as the classical application of the anterior blade of Kielland's forceps; manual exploration of the uterus and manual removal of the placenta or its fragments after obstructed labor with a ballooned and thin lower uterine segment; and during curettage for secondary postpartum hemorrhage.

Cesarean section in the second stage of labor with the fetal head deeply impacted in the vagina may be associated with lateral traumatic extension of the lower uterine segment incision into the major vessels[21]. On rare occasions, the extent of this tear may necessitate hysterectomy, especially if one or both uterine arteries is lacerated and a hematoma obscures the surgical repair. External traumas, such as assault, a fall or motor vehicle accident, are relatively rare causes of uterine perforation and rupture.

Sepsis

In the era of modern antibiotics, sepsis is not a common reason for emergency hysterectomy. However, it still may be necessary in cases with extensive uterine sepsis, particularly with clostridial infections and myometrial abscess formation, in which antibiotic treatment fails to control the sepsis. Other septic causes of secondary postpartum hemorrhage include Cesarean scar infection and necrosis, arteriovenous fistula formation secondary to uterine trauma and infection, and endomyometritis associated with hemorrhage. All may rarely require hysterectomy.

SURGICAL PRINCIPLES

Although the technique of obstetric hysterectomy is similar in principle to that of abdominal hysterectomy in gynecology, numerous anatomical and physiological changes in pregnancy create potential surgical difficulties.

(1) The uterine and ovarian vessels are enlarged and distended, often markedly so, and the adjacent pelvic tissues are edematous and friable.

(2) Abdominal entry may have been via Pfannestiel or lower midline incision, depending on the urgency and speed required.

(3) Maneuvers to obtain immediate hemostasis will depend on the cause of the hemorrhage. In cases of uterine rupture, Green–Armytage clamps or sponge forceps can be used to compress the bleeding edges of torn uterine muscle. The uterus should be eventrated from the abdominal wound. The structures of the adnexa on each side are pulled laterally by an assistant and the surgeon applies straight clamps adjacent to the top sides of the uterus to include the round ligament, the Fallopian tube and the utero-ovarian ligament. This serves to control the collateral

blood flow to the uterus from the ovarian arteries. Using transillumination, the avascular spaces in the broad ligament, roughly opposite the level of a transverse lower Cesarean incision, should be identified and a catheter passed through on each side to encircle the lower uterine segment just above the cervix. This should be twisted tightly closed with a clamp and should serve to compress the uterine arteries. These two maneuvers should occlude the main collateral ovarian and uterine artery supply to the uterus.

(4) The vascular pedicles are thick and edematous and should be double clamped. Remove the proximal clamp first and apply a free tie and then replace the distal clamp with a transfixing suture. The proximal free tie should ensure that there is no hematoma formation in the base of the pedicle.

(5) If the cervix and paracolpos are not involved as the source of hemorrhage, subtotal hysterectomy should be adequate to achieve hemostasis and is safer, faster and easier to perform than total hysterectomy. However, if the lower segment and paracolpos are involved in the hemorrhage, such as in cases of placenta previa and/or accreta, total hysterectomy will be necessary for hemostasis.

(6) Avoid the ureters by placing all clamps medial to those used to secure the uterine arteries.

(7) It can be difficult to identify the cervix, particularly when the hysterectomy is being done at full cervical dilatation. If there is a Cesarean incision, a finger can be placed through this and the cervical rim palpated. It is safest to enter the vagina posteriorly, identify the rim of the cervix and then proceed anteriorly.

(8) The bladder is particularly vulnerable in cases previously delivered by Cesarean section, as it may be adherent to the lower uterine segment and cervix. It is therefore essential to check the integrity of the bladder intraoperatively. This can be done by manipulating the bulb of the Foley catheter to see if it is visible through the bladder wall. The bladder also can be filled with a colored fluid such as methylene blue or sterile milk taken from the neonatal nursery. The latter is preferable as it does not cause permanent staining of the tissues. Thus, after repair of any bladder injury, it is easier to see that this has been successful with subsequent installation of milk in the bladder. Any tear in the bladder should be repaired with two layers of 3/0 polyglactin (vicryl) or equivalent suture. Otherwise, No. 1 polyglactin (vicryl) or equivalent is used throughout the procedure.

(9) If there is any doubt about the integrity of the bladder wall or ureters, and after repair of any bladder injury, it is wise to perform a postoperative cystoscopy to confirm that they are intact. This can be done by observing urine come from each ureteric orifice; this may be facilitated by giving intravenous indigo carmine and waiting 10–15 min.

(10) Perioperative antibiotic prophylaxis should be continued for 24–48 h. Thromboprophylaxis with heparin should be instituted as soon as one is satisfied that hemostasis is secure.

(11) Detailed notes should be made to include the preoperative events, indications for hysterectomy and the surgical details. After the initial postoperative recovery, the woman should receive a comprehensive outline of events from an experienced obstetrician.

In a number of series, as many as 25% of women who received an emergency obstetric hysterectomy were primigravid, for whom the fertility-ending nature of the procedure can be devastating[7]. Therefore, particularly in this group of women, obstetricians should be familiar with and be prepared to perform alternative procedures to control the hemorrhage. The application of other techniques to arrest hemorrhage that can be both life-saving and uterus-preserving are outlined in several chapters in this book. When conditions are recognized in the antenatal period that lead to increased risk

of severe obstetric hemorrhage, such as placenta previa and/or accreta, referral of these cases to hospitals with the equipment and personnel to provide the alternative techniques to hysterectomy should be undertaken where feasible.

Ultimately, however, one has to strike a balance between spending excessive time on alternative techniques that are proving ineffective, leading to delay, further hemorrhage and probable disseminated intravascular coagulation, and moving to the definitive and life-saving hysterectomy. Such is the art of obstetric judgement in trying circumstances.

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35

THE MANAGEMENT OF SECONDARY POSTPARTUM HEMORRHAGE

K. M. Groom and T. Z. Jacobson

INTRODUCTION

Secondary postpartum hemorrhage is defined as excessive vaginal bleeding from 24 h after delivery up to 6 weeks postpartum[1]. Unlike primary postpartum hemorrhage, there is no clear definition for quantity of blood loss and this can vary from 'increased lochia' to massive hemorrhage. The diagnosis is therefore subjective, which may account for the variation in reported incidence. The reported overall incidence of secondary postpartum hemorrhage in the developed world varies from 0.47% to 1.44%[2,3].

The etiology of secondary postpartum hemorrhage is diverse and management is dependent on identifying the cause and tailoring treatment appropriately. The published work on the management of secondary is limited compared with primary postpartum hemorrhage[4]. However, with falling maternal mortality rates, there is increasing interest and attention to maternal morbidity and the important topic of management of secondary postpartum hemorrhage. The majority of cases of secondary postpartum hemorrhage are associated with minor morbidities but may still require re-admission to hospital, use of antibiotics and surgical intervention. In more extreme cases, major morbidity requiring hysterectomy, arterial ligation or radiological intervention is possible[5] and maternal death may still result from massive secondary postpartum hemorrhage despite the use of all available interventions.

ETIOLOGY OF SECONDARY POSTPARTUM HEMORRHAGE

Subinvolution/uterine atony

The major cause of secondary postpartum hemorrhage is subinvolution of the uterus. This results in failure of obliteration of blood vessels underlying the placental site, leading to prolonged bleeding. The two main causes of this are infection (see Chapter 44) and inflammation (endometritis) and retained placental tissue.

Endometritis is more common following prolonged rupture of membranes, prolonged labor, emergency Cesarean section or with a retained placenta requiring manual removal. A history of offensive lochia, maternal pyrexia and uterine tenderness is often present and retained placental tissue is more common in women with a previous history of retained placenta or if there were concerns at the time of delivery of incomplete placenta and/or membranes. It is less likely following delivery by Cesarean section. Differentiation between the two causes is often difficult and both conditions may co-exist.

Lower genital tract trauma

Missed vaginal lacerations and hematomas may present as secondary postpartum hemorrhage. These are often associated with traumatic deliveries or those requiring ventouse or forceps. They usually present within the first few days after delivery. Infected suture lines and episiotomy sites may lead to wound breakdown and result in excessive vaginal bleeding.

Placental abnormalities

Placenta accreta, increta and percreta are all known causes of massive primary postpartum hemorrhage. When managed conservatively with placental tissue left *in situ* (with or without methotrexate therapy), they can also be associated with delayed bleeding and the need for hysterectomy[6,7] (see Chapter 24).

Uterine abnormalities

Fibroids are associated with primary postpartum hemorrhage. They cause uterine enlargement and prevent involution of the uterus, therefore leading to prolonged bleeding from the placental bed. More rarely, they can be associated with secondary postpartum hemorrhage. Fibroids have usually been identified by ultrasound in the antenatal period.

Abnormalities of uterine vasculature such as arteriovenous malformations and false aneurysms may also lead to secondary postpartum hemorrhage. Arteriovenous malformations are due to an abnormal communication between an artery and vein with proliferation of each vessel with interconnecting fistula. It is believed these malformations may result from venous sinuses becoming incorporated in scars within the myometrium after necrosis of the chorionic villi. The majority are acquired after pregnancy and may result from trophoblastic disease, previous uterine curettage, uterine or cervical malignancy[8,9] or Cesarean section[10,11]. Diagnosis is made using ultrasound with color Doppler analysis.

Cesarean section wound dehiscence or surgical injury

Surgical injury to pelvic blood vessels at the time of Cesarean section[10] usually presents within 24 h. However, later presentations, in particular those causing broad ligament hematomas, have been described[5] and should be considered in women presenting acutely with signs of intra-abdominal hemorrhage. Delayed presentation of bleeding from non-union/dehiscence of the Cesarean section uterine scar has also been described. This is believed to be due to local infection at the site of uterine closure causing erosion of blood vessels. In the cases reported, this has lead to massive postpartum hemorrhage 2–3 weeks after Cesarean section and the need for subtotal hysterectomy[12]. Diagnosis of uterine dehiscence post-Cesarean section associated with infection has also been made at hysteroscopy[13], although causing less significant postpartum hemorrhage and only requiring treatment with antibiotics.

Choriocarcinoma

The majority of cases of choriocarcinoma after a non-molar pregnancy present with secondary postpartum hemorrhage or irregular vaginal bleeding[14]. In addition, secondary symptoms of metastatic disease may be present. The diagnosis is made by serum β-human chorionic gonadotropin (β-hCG), histological diagnosis and radiological imaging including ultrasound, plain film X-ray and computed tomography (CT) scan.

Bleeding disorders, coagulopathies and use of anticoagulants

Women with congenital hemorrhagic disorders such as von Willebrand's disease (quantitative or qualitative deficiency of von Willebrand factor), carriers of hemophilia A (factor VIII deficiency), hemophilia B (factor IX deficiency) and factor XI deficiency are at an increased risk of postpartum hemorrhage. Often, these abnormalities of the coagulation system are undetected until challenged by trauma, surgery or childbirth and so may be undiagnosed prior to pregnancy. These women are not at increased risk of antepartum hemorrhage[15] but at significant risk of both primary and secondary postpartum hemorrhage. The risk of secondary postpartum hemorrhage may be even greater than primary postpartum hemorrhage as the pregnancy-induced rise in maternal clotting factors falls after delivery. The reported incidence for secondary postpartum hemorrhage in these conditions is 20–28% for von Willebrand's disease, 11% for hemophilia carriers and 24% in factor XI deficiency[16–19]. Postpartum acquired hemophilia has also been described. This is a rare condition but can cause severe hemorrhage. It is caused by antibodies to factor VIII which partially or completely suppress factor

VIII procoagulant activity in women with previously normal levels and activity of factor VIII. Bleeding usually commences within 3 months of delivery but may be delayed for up to 12 months[15].

The use of anticoagulants in the postpartum period may also cause delayed bleeding. In particular, women using warfarin should be carefully monitored and informed of the risks of hemorrhage.

MANAGEMENT OF SECONDARY POSTPARTUM HEMORRHAGE

Evidence regarding the management of secondary postpartum hemorrhage is limited. A Cochrane review searched and assessed all randomized or quasi-randomized comparisons of drug therapies, surgical therapies and placebo or no treatment for secondary postpartum hemorrhage. Forty-five papers were identified, but none met the inclusion criteria, and the review concluded there was no evidence from randomized trials to show the effects of treatments for secondary postpartum hemorrhage[4].

The main aims of treatment are to provide basic resuscitation, establish a cause for the bleeding, and tailor the treatment (medical and/or surgical) according to the cause.

Resuscitation

Approximately 10% of cases of secondary postpartum hemorrhage will present with massive hemorrhage[20] and require immediate attention. In these cases, resuscitation should be commenced prior to establishing a cause and should include the involvement of senior staff at the earliest opportunity (see Chapter 20).

Restoration of circulating blood volume should be achieved by gaining intravenous access with two large-bore cannulae and administering intravenous fluids initially with physiological saline (up to 2 liters) and then with plasma expanders until blood is available. Blood should be obtained for full blood count, coagulation screen and cross-match. High-concentration oxygen (10–15 liters per minute) should be administered by a tight-fitting mask[21]. Close observation of vital signs including pulse, blood pressure, oxygen saturation and urine output should be maintained throughout resuscitation. Blood and blood products should be given according to blood loss, response to initial fluid administration and hemoglobin and coagulation results. If hemorrhage is life-threatening, transfusion with uncross-matched O rhesus-negative or type-specific blood may need to be considered. Identification of the cause of bleeding should then be made and further management planned accordingly.

In cases of less significant hemorrhage, basic resuscitation should be instigated as appropriate but blood transfusion may be delayed whilst establishing a cause for the bleeding.

Clinical presentation

Ninety-five percent of women present within the first month after delivery, 19% within 7 days, 41% in 8–14 days, 23% in 15–21 days and 12% in 22–28 days[2]. The amount of blood loss at presentation varies but most are hemodynamically stable. A thorough history will provide information relating to cause and should include details regarding parity, labor, mode of delivery, third-stage or puerperal complications and any relevant medical and family history. Clinical signs and symptoms at the time of presentation may include offensive lochia, abdominal cramping, uterine tenderness, pyrexia, enlarged uterus and an open cervical os.

Normal postpartum loss may continue beyond 6 weeks in up to 25% of women, especially if breast-feeding[20] and the first period may be heavy, prolonged and painful as a result of an anovulatory cycle. Women should be given this information during normal postpartum care to avoid unnecessary concern and presentation for medical investigation.

Investigations

Baseline blood tests should include full blood count, coagulation studies, C-reactive protein, a group and hold specimen and serum β-hCG. Vaginal swabs should be taken at the time of examination for aerobic as well as anaerobic bacterial growth, including swabs from episiotomy or vaginal tear sites. In women with signs of infection, a mid-stream urine specimen

should be collected and, if maternal temperature is > 38°C, blood cultures should be taken.

Ultrasound imaging of the pelvis should be considered if there are concerns of retained placental tissue. If this is within 7–14 days of delivery, interpretation may be difficult as remaining blood clots may appear as mixed echogenic material in a similar manner to retained tissue. The use of duplex color Doppler helps to improve diagnostic accuracy in differentiating clot and tissue[22], as retained placental tissue will often maintain a blood supply unlike necrotic decidua and clot[23].

The over-diagnosis of retained placental tissue on ultrasound may lead to unnecessary surgical intervention and its potential complications. However, ultrasound does have significant benefits, as it has a good negative predictive value and therefore is helpful in excluding a diagnosis of retained placental tissue. Neill and colleagues assessed 53 women undergoing ultrasound for secondary postpartum hemorrhage. Definitive diagnosis of retained placental tissue was either made histologically or, in those women managed conservatively, absence of retained tissue was assumed if bleeding diminished within 1 week. They demonstrated the diagnostic value of ultrasound assessment to have a positive predictive value of 46% (95% confidence interval (CI) 31–70%), a negative predictive value of 96% (95% CI 88–100%), with a sensitivity of 93% (95% CI 80–100%) and a specificity of 62% (95% CI 48–79%)[24]. This study also suggested that a standardized approach to reporting an ultrasound investigation of secondary postpartum hemorrhage would be helpful. This is shown in Table 2.

Additional imaging should also be considered for specific causes of secondary postpartum hemorrhage such as plain chest film and CT scanning for metastases in cases of choriocarcinoma, magnetic resonance imaging (MRI) for placenta accreta[25,26] and angiography for intractable bleeding of unknown origin[10].

Table 1 Causes of secondary postpartum hemorrhage

Subinvolution of the uterus – retained placental tissue and/or endometritis, fibroid uterus
Lower genital tract lacerations/hematoma
Surgical injury
Dehiscence of Cesarean section scar
Vascular abnormality – arteriovenous malformation
Placental abnormality – placenta accreta, percreta and increta
Choriocarcinoma
Coagulapathies, bleeding disorders, use of anticoagulants

Table 2 A proposed standardized system for reporting postpartum ultrasound scan. Adapted from Neill *et al.*, 2002[24]

1. Normal endometrial cavity
2. Endometrial cavity containing fluid only
3. Endometrial cavity enlarged (anteroposterior (AP) depth > 1 cm). Maximum AP dimensions noted
4. Endometrial cavity containing echogenic foci. Dimensions of largest foci noted. Doppler evaluation of blood flow in foci

Table 3 The management of secondary postpartum hemorrhage

Medical	*Surgical*
Oxytocics	Uterine evacuation
Prostaglandins	Uterine tamponade balloon
Antibiotics	Uterine compression sutures
Tranexamic acid	Hysterectomy
Vasopressin	Pelvic arterial ligation
Clotting factor concentrates	
Chemotherapy	*Radiological*
Oral contraceptive pill	Selective arterial embolization

Treatment

The majority of cases of secondary postpartum hemorrhage are due to subinvolution of the uterus caused by uterine infection and/or retained placental tissue. Initial management should include resuscitation as discussed above, the use of uterotonic agents, administration of antibiotics and consideration of surgical evacuation of the uterus.

Uterotonic agents

Syntocinon can be administered as an intravenous or intramuscular bolus (10 units) or in combination with ergometrine (Syntometrine®)

1 ampoule as an intramuscular injection. This can be followed by a syntocinon infusion (40 units in 500 ml normal saline at an infusion rate of 125 ml/h). Prostaglandin $F_{2\alpha}$ (Haemabate®/ Carboprost) can be given by intramuscular injection at a dose of 250 μg every 15 min, up to a total of 2 mg (i.e. 8 doses). Misoprostol can also be given as an alternative prostaglandin (400–800 μg orally or rectally).

Antibiotics

Endometritis is likely to play a significant role in many cases of secondary postpartum hemorrhage and the majority of women are prescribed antibiotics. In a 3-year study of almost 20 000 women, 132 women (0.69%) had a secondary postpartum hemorrhage and 97% of these were treated with antibiotics[2]. However, only three-quarters of these women had microbiological specimens collected and a positive culture was obtained in only 13.5%. In a similar observational study of 83 women with secondary postpartum hemorrhage, 45% presented with pyrexia, and 64 had bacteriological swabs taken, of which only 12.5% were positive. Organisms identified included group B streptococcus, bacteroides, *E. coli*, *Clostridium perfringens* and Lancefield group D streptococcus. Despite the lack of evidence to support the presence of a specific bacterial pathogen, 92% of the women received antibiotics[3]. Recommended choices of antibiotic treatment include amoxycillin with clavulanic acid (Augmentin®)[27] and a combination of amoxycillin, metronidazole and gentamicin[3]. Endometritis is a major contributor to subinvolution of the uterus. Although infection may not be confirmed in a large population of cases, we recommend that antibiotics are always given for secondary postpartum hemorrhage (see Chapter 44).

Uterine evacuation

Examination under anesthetic and surgical evacuation of the uterus should be considered if retained placental tissue is suspected clinically or after ultrasound examination. This has good reported success rates, with bleeding stopping promptly in all 72 women undergoing evacuation of the uterus for secondary postpartum hemorrhage in one study, despite only 36% having proven histological evidence of retained tissue[3]. This study was unable to find any clear association with presence or absence of retained tissue at the time of evacuation and day of onset of bleeding or morbidity at the time of secondary postpartum hemorrhage. However, retained tissue was more likely if membranes were incomplete at delivery, primary postpartum hemorrhage had occurred or if secondary postpartum hemorrhage was judged to be heavy or moderate (compared with light) in volume[3]. The use of ultrasound prior to surgical evacuation of the uterus does not appear to significantly alter the chances of histological diagnosis confirming retained tissue. In one study, 33% of those with no preoperative scan had retained placental tissue compared to 37% following a scan[2].

Retained placental tissue is likely to be associated with infection and, therefore, broad-spectrum intravenous antibiotics should be given in conjunction with surgical evacuation. As serum concentrations of most antibiotics peak 1 h after intravenous administration, these should be administered just prior to surgery[20]; however, in women who are hemodynamically stable, it may be appropriate to give 12–24 h of antibiotic cover prior to consideration of surgery[1]. At the time of surgery, uterotonic agents such as syntocinon, ergometrine and prostaglandins may be given to aid uterine contractility and control hemorrhage.

There is no clear evidence to support which method of evacuation should be used. Manual removal of tissue, use of a suction catheter and sharp curettage with a metal curette have all been described[2]. The risk of uterine perforation is much higher in uterine evacuation postpartum and may be even further increased if associated with endometritis. Hoveyda and colleagues describe uterine perforation in three of 85 women undergoing the procedure for secondary postpartum hemorrhage. These were performed from 4 days to 28 days after delivery with both a suction and metal curette. In all cases, the procedures were performed by senior medical staff. One woman went on to require a hysterectomy, but the other two were managed conservatively[2]. Perforation after Cesarean section is more likely and, as these women have a lower risk of retained placental tissue, surgical

evacuation in these cases should be very carefully considered.

Additional complications include the risk of Asherman's syndrome. There is limited evidence to ascertain if this risk is increased for postpartum uterine evacuation; however, in a large study of intrauterine adhesions, 21.5% of cases had a postpartum curettage as a preceding event[28]. The need for a second procedure due to incomplete evacuation of retained tissue may also occur[2]. Hysterectomy may be required to control bleeding in up to 5% of cases[20].

In view of these significant complications, women should always be fully counselled of the risks and informed consent obtained prior to the procedure. Surgery should be performed by experienced senior medical staff.

Other surgical procedures

In the event of a large secondary postpartum hemorrhage, other surgical procedures may need to be considered. This includes cases of bleeding from an infected placental bed or placental abnormality such as placenta accreta, bleeding from retained placental tissue not controlled with uterine evacuation, non-union/dehiscence of Cesarean section scar, bleeding from a surgical injury or uncontrolled bleeding from a lower genital tract laceration.

Insertion of an intrauterine tamponade balloon, such as the Bakri[29] or Rüsch balloon[30], has been successfully described for treatment of primary postpartum hemorrhage and may be considered in cases of secondary postpartum hemorrhage due to uterine subinvolution/atony once retained placental tissue has been excluded (see Chapters 28 and 29). Laparotomy may also be required which allows further investigation into the cause of bleeding and treatment by the use of surgical compression sutures, hysterectomy and pelvic arterial ligation as appropriate.

The B-Lynch brace suture is well described for the treatment of primary postpartum hemorrhage[31] and has now been reported in 72 cases of secondary postpartum hemorrhage (B-Lynch C, personal communication, August 2005). The use of a surgical compression suture may avoid the need for hysterectomy in women wishing to conserve fertility.

Within an Australian population with an overall incidence of secondary postpartum hemorrhage of 1.44% over 15 years, only nine cases required hysterectomy (0.9%)[3]. However, in a subgroup of women with massive intractable obstetric hemorrhage, two out of seven with secondary postpartum hemorrhage required hysterectomy. In one of these cases, hysterectomy was performed 7 days after delivery due to intractable bleeding from lower genital tract laceration but maternal death still resulted. The second case had further morbidity following her hysterectomy for secondary postpartum hemorrhage with bleeding from wound disunion and sepsis and required bilateral hypogastric artery ligation 14 days after delivery[5]. Hysterectomy in such situations carries significant risks but can be life-saving and should be considered early in cases of massive hemorrhage, whether primary or secondary.

Pelvic artery ligation may also be considered for cases of massive secondary postpartum hemorrhage uncontrolled by medical and simple surgical measures. Lédée and colleagues report the use of bilateral hypogastric artery ligation in 49 of 61 cases of intractable hemorrhage; this includes four out of seven cases of secondary postpartum hemorrhage, all of which were successful at arresting bleeding[5] (see Chapter 32). As with primary postpartum hemorrhage, arterial ligation should be performed by an experienced surgeon and his/her involvement should be considered whilst planning a laparotomy in such cases.

Selective arterial embolization

Pelvic angiography to assess the internal iliac artery, uterine artery and its vaginal branches is a helpful tool in the assessment of ongoing hemorrhage (Figure 1). It also allows the introduction of embolization agents to arrest bleeding (see Chapter 30).

Pelage and colleagues studied 14 women presenting with uncontrollable secondary postpartum hemorrhage at a mean of 16 days after delivery. Six women (43%) had delivered by Cesarean section and the remainder by spontaneous vaginal delivery. Eight women had evidence of endometritis (57%), with four of those associated with histologically proven retained

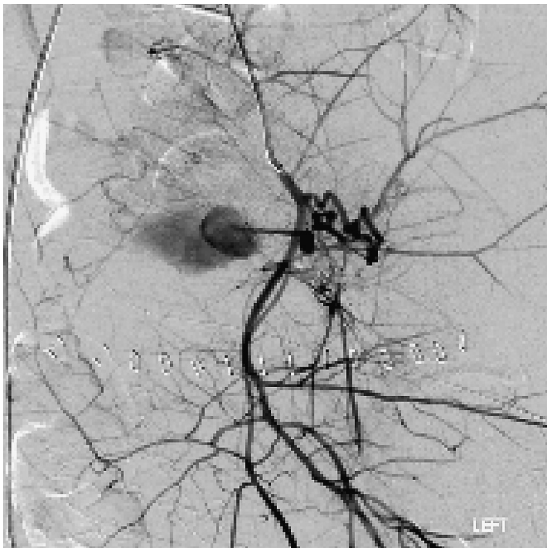

Figure 1 Angiogram demonstrating brisk hemorrhage from false aneurysm prior to embolization

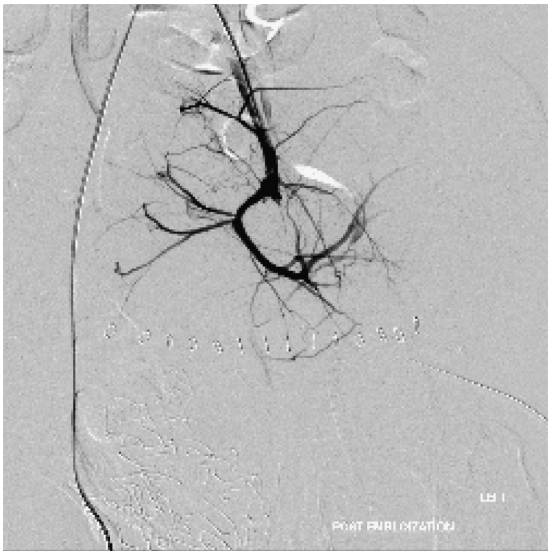

Figure 2 Angiogram after embolization

placental tissue; a further four women had genital tract lacerations, and the remaining two had no obvious cause for bleeding. Basic resuscitation with use of medical treatments and/or uterine curettage were performed. Angiography found no extravasation in eight women, active bleeding in three women from uterine and vaginal vessels, a false uterine artery aneurysm in two women, and evidence of an arteriovenous fistula in one woman. Pledgets of absorbable gelatin sponge were introduced to embolize both uterine arteries in 12 women. Unilateral embolization of a false aneurysm and an arteriovenous fistula were performed for the other two women. External bleeding disappeared immediately, and hemodynamic stability and correction of coagulopathy were obtained for all cases. There were no general or local complications[10].

One of the authors (T.J.) recently managed a case of massive secondary postpartum hemorrhage presenting 4 days after a Cesarean section. An emergency subtotal hysterectomy was performed with good initial results. Two hours later, vaginal bleeding restarted. There was no evidence of significant coagulopathy. Pelvic angiography was performed and a bleed from a false aneurysm related to a middle branch of the anterior division of the left internal iliac artery was identified (Figure 1). The vessels were embolized with four coils. There was immediate cessation of bleeding and the patient's vital signs normalized (Figure 2). The patient made a good recovery despite needing 24 units of blood during the postpartum hemorrhage. Subsequent histology of the uterus showed acute inflammation and subinvolution of the placental bed.

Other measures

In cases of massive hemorrhage unsuccessfully treated with surgical measures, the use of intravenous tranexamic acid[32], recombinant factor VIIa[33] and local vasopressin[34] have been reported for primary postpartum hemorrhage. There are no reports of their use in secondary postpartum hemorrhage but, if available, it may be appropriate to consider their use in combination with other therapies and resuscitative support.

Chemotherapy

The mainstay of treatment for choriocarcinoma is chemotherapy. A low-risk chemotherapy regimen includes the use of methotrexate with folinic acid rescue on a 2-weekly cycle[35].

Medium- and high-risk regimens include the use of etopside, methotrexate, actinomycin, vincristine, cyclophosphomide and 6-mercaptopurine[36,37]. Women with choriocarcinoma are most appropriately treated through specialist trophoblastic disease referral centers[14].

Coagulopathies

Women with inherited coagulation disorders such as von Willebrand's disease and carriers of hemophilia A and B are likely to bleed postpartum if maternal clotting factors are low (< 50 IU/dl). Prophylactic administration of desmopressin (DDAVP) and clotting factor concentrates may prevent postpartum hemorrhage[15]. The aim is to raise factor levels above 50 IU/dl during labor and delivery and maintain these for up to 5 days after delivery. In the event of postpartum hemorrhage[15], replacement of deficient clotting factors should be made and identification and treatment of the cause be instigated. Management should be in close liaison with hematologists and specialist hemophilia centers as available. In cases of prolonged or intermittent secondary postpartum hemorrhage[15], the use of tranexamic acid (a fibrinolytic inhibitor)[38] or combined oral contraceptive pill has been reported[15].

Hemorrhage from postpartum acquired hemophilia is treated acutely with factor VIII (either human, porcine) or recombinant factor VIIa[15]. Immunosuppressive drugs such as corticosteroids, cyclophosphamide and azathioprine may be used to accelerate the disappearance of factor VIII inhibitors, although complete remission is likely to occur spontaneously with time.

Reversal of bleeding due to anticoagulants should follow normal protocols. Vitamin K should be considered in women with uncontrolled bleeding secondary to warfarin use and protamine sulfate may be considered if hemorrhage results from the use of heparin, although this has a much shorter half-life.

Secondary postpartum hemorrhage is an important cause of maternal morbidity and mortality. Basic resuscitation followed by investigation and treatment of the specific cause of hemorrhage are essential. The diverse nature of its etiology and often acute presentation make research in the form of a randomized controlled trial difficult. However, particularly for the treatment of hemorrhage due to uterine infection and/or retained placental tissue, this should be achievable and would provide valuable information to further our understanding of the management of secondary postpartum hemorrhage.

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Section VIII

Consequences of postpartum hemorrhage

36

PATHOLOGY OF THE UTERUS

P. Kelehan and E. E. Mooney

BACKGROUND AND AIMS

Significant postpartum hemorrhage may occur immediately after delivery, or may be delayed weeks or months. In either case, a Cesarean or later postpartum hysterectomy may be life-saving. The uterus will normally be sent for laboratory examination. To facilitate a useful surgical pathology report, the pathologist must be given details of the antepartum course and delivery. Considering how uncommon these specimens are, direct communication between pathologist and clinician is recommended. The aim of this chapter is to provide a structured approach to the analysis of the specimen, in order to permit a clinically relevant and pathologically sound diagnosis.

CLINICAL CORRELATION

The parity and gestation should be provided. Any abnormality of the clinical course, in particular pre-eclampsia or polyhydramnios, may be of relevance. Magnetic resonance imaging (MRI) may have been performed for fibroid, placenta creta or congenital abnormality and these images should be reviewed. A history of the use of instruments such as forceps is important. The clinical appearance of the uterus at operation may provide valuable information on atony. Any therapeutic measures undertaken such as uterine massage or compression suture should be noted, along with transfusion and fluid replacement. A description of the surgery will help the pathologist to interpret the tears and sutures that characterize these specimens. The patient's postoperative condition will help to guide sampling in the event that amniotic fluid embolism is a consideration. Finally, the placenta must also be available for examination.

GROSS EXAMINATION

Photography is essential at each step of the dissection, with notes as to what each picture is intended to show. Without a clinical input, however, much effort may be wasted on documenting features of little relevance at the expense of missing more important ones. A detailed macroscopic description of sutures, tears, etc. is important and may be medico-legally relevant. Our approach is to examine the specimen in its fresh state, with photography, and then to open the specimen, avoiding tears and sutures, to permit fixation and further examination. It may be opened laterally, but more information can be gained by complete longitudinal anteroposterior section of the uterus. The approach should be modified to suit the circumstances as predicted from the clinical information. A useful technique that allows good exposure and photographic demonstration is the placing of two parallel complete longitudinal anteroposterior sections about 2–3 cm apart on either side of the mid-line. How well the uterine cavity has compressed is immediately apparent, contraction band formation can be demonstrated, and blood clot and placental tissue fragments can be assessed in the lumen.

In the immediate postpartum period, the uterus is characteristically large. It will weigh 700–900 g and will have substantially reduced in size and volume from its antepartum state. Clamp marks on the broad and round ligaments should be inspected for residual hematoma, remembering that the pathology may be outside the clamp. In the fresh specimen with intact vessels, it may be possible to perfuse the vasculature for contrast angiography or vascular casting[1].

Figure 1 Fixed uterus showing a large anterior and right-sided diverticulum originating in a Cesarean section scar. The specimen was sutured at operation, but placental villous tissue can be seen adjacent to the suture

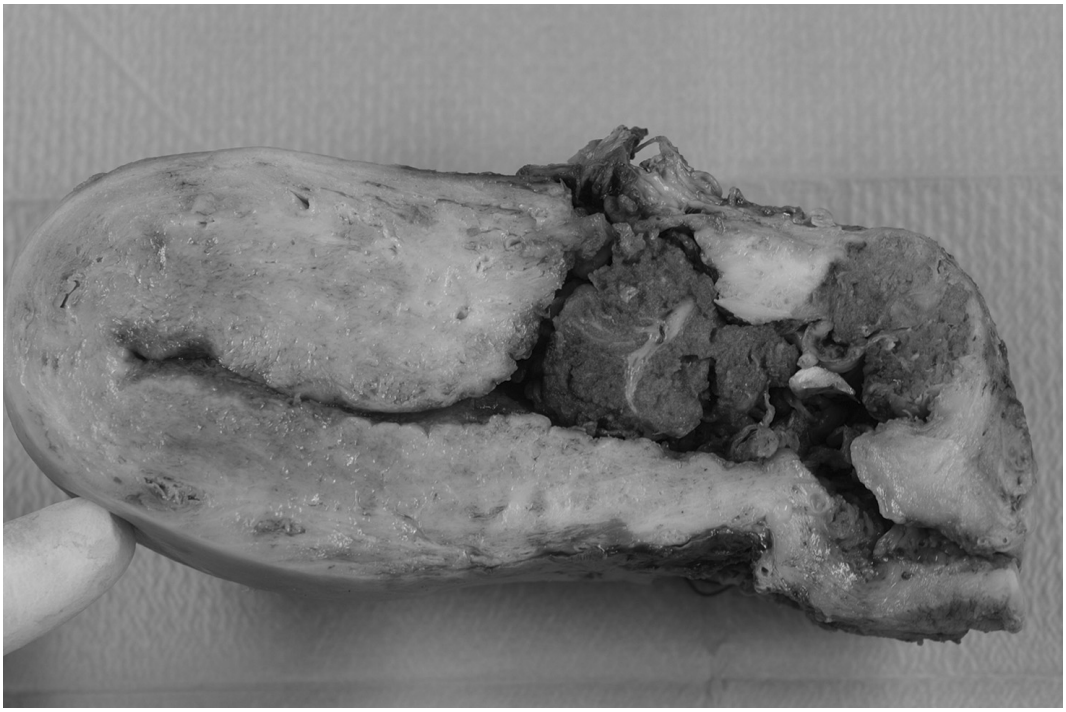

Figure 2 Anteroposterior section of uterus from Figure 1 showing anterior placenta creta

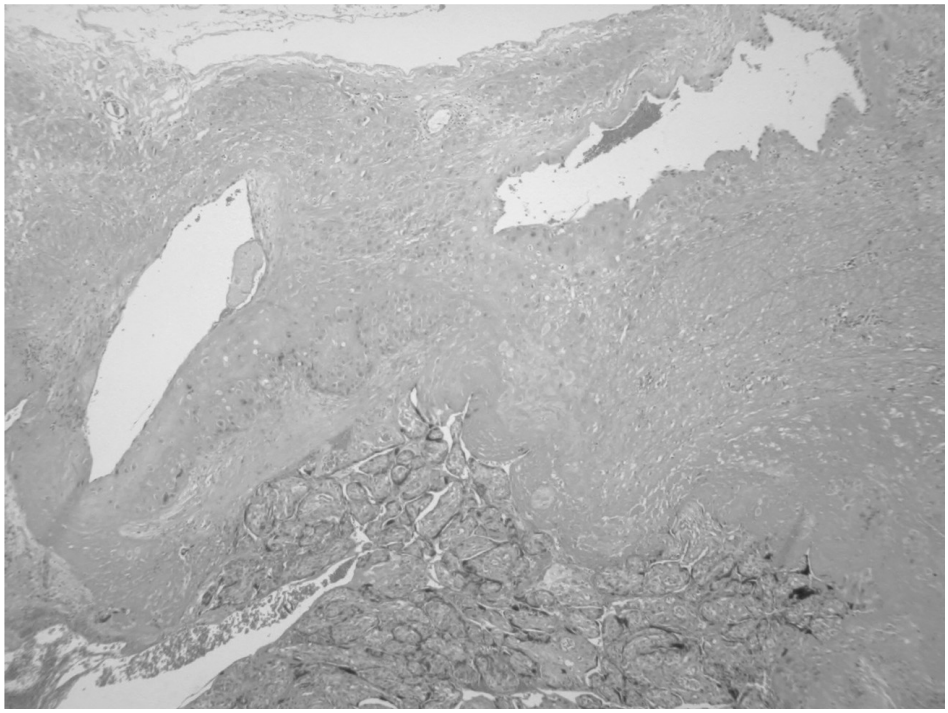

Figure 3 H/E section of lower uterine segment showing placenta creta and large vessels in thin myometrium

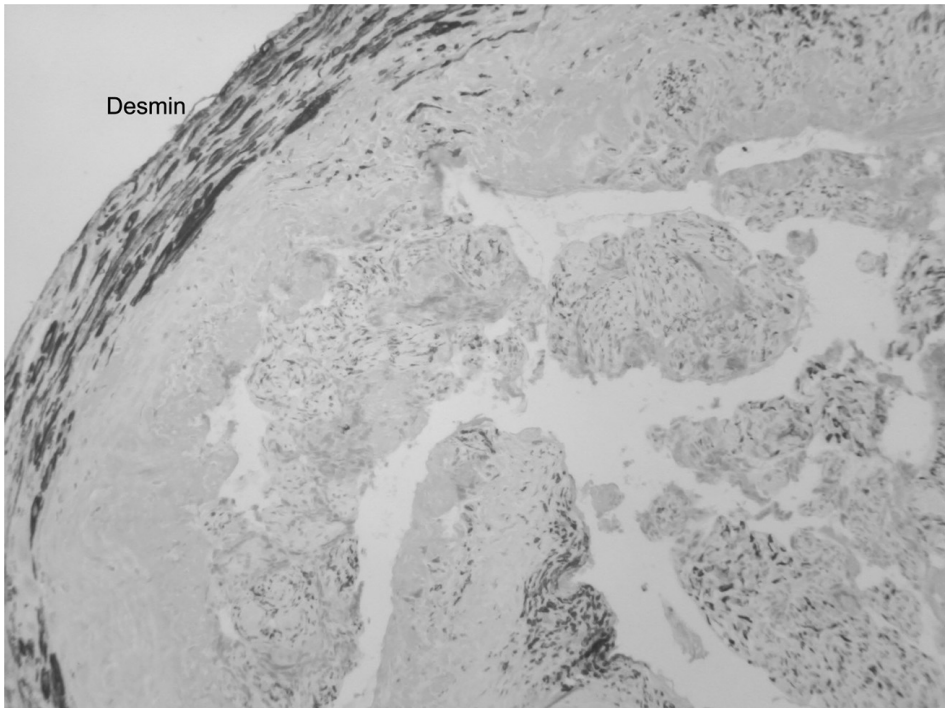

Figure 4 Immunohistochemical stain for desmin accentuates the thin myometrial fibers in scar

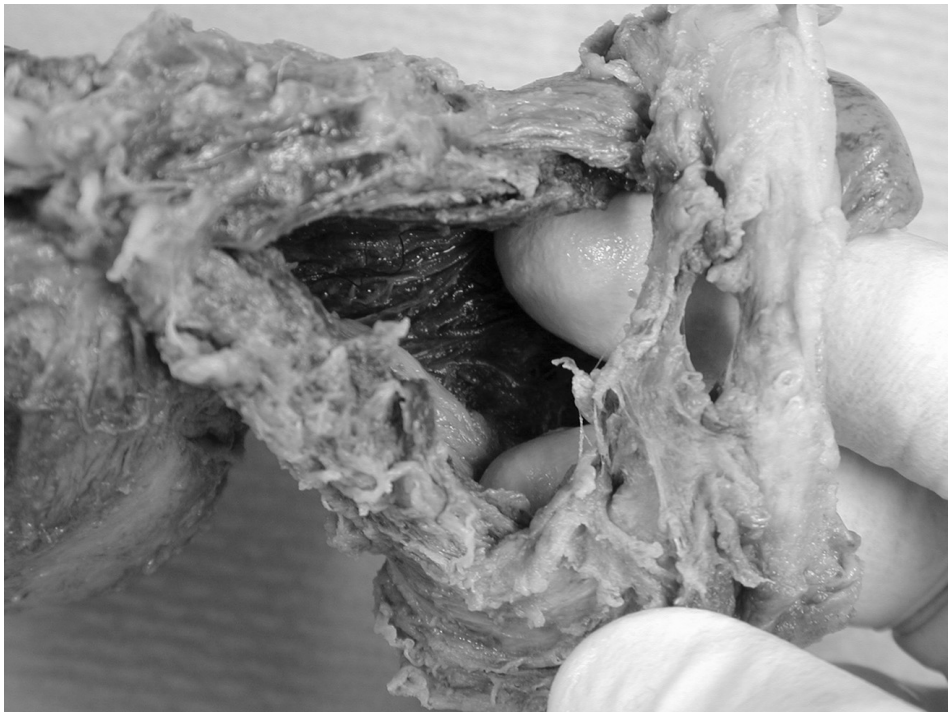

Figure 5 Right lateral endocervical tear at hysterectomy for postpartum hemorrhage

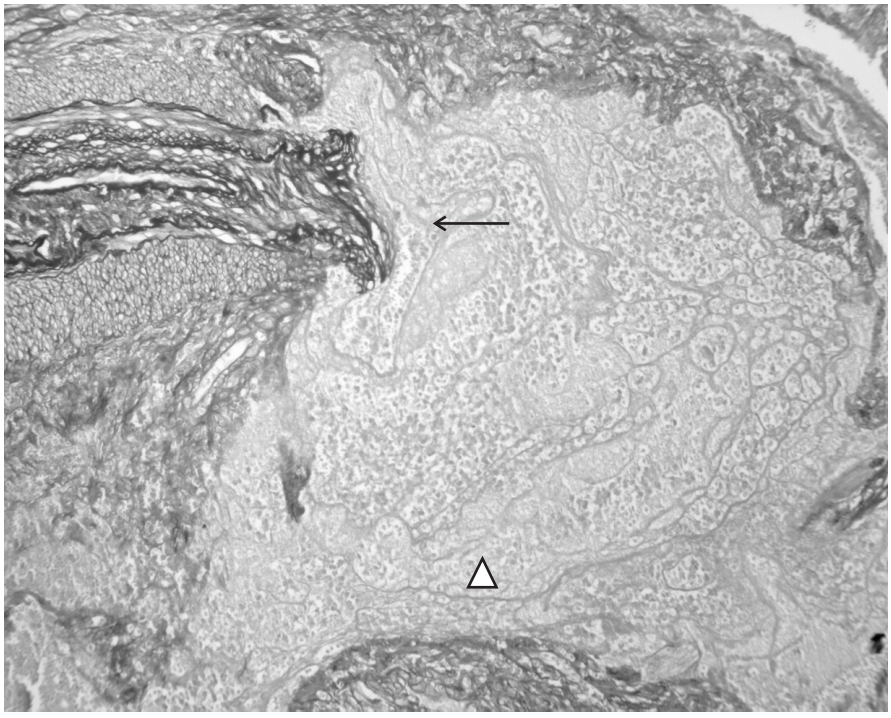

Figure 6 Elastin Van Geisson stain showing torn artery at apex of tear (×10). Arrow, torn elastic artery; arrowhead, thin fibrin blood clot

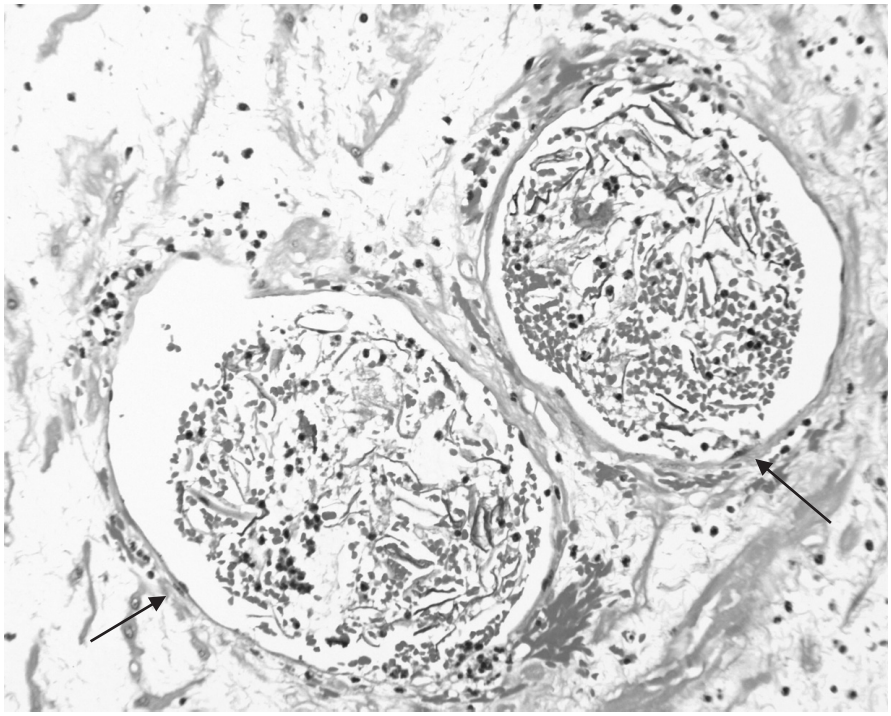

Figure 7 Amniotic debris in venules (arrows) of cervical stroma following a small endocervical tear in labor. Postpartum hemorrhage and disseminated intravascular coagulopathy necessitated hysterectomy (×20)

CERVIX

Important pathologies in the cervix include tears. Small shallow endocervical tears are almost invariably found in the postpartum uterus, and may be present even in those cases where there has been a Cesarean section. Significant and deep tears tend to be lateral in location. These tears may penetrate through to the serosa, with or without hematoma formation, and may extend up into the lower segment or down the cervix into the vagina. Involvement of large uterine arteries should be sought. It is common to find meconium staining of the mucus of the endocervix with fetal distress, and meconium may contaminate the tear. A tear may have severe consequences: an endocervical tear may cause severe blood loss despite a fully contracted uterus. Tears are associated with amniotic fluid embolus or with amniotic infusion and local defibrination. Bleeding can extend into the broad ligament with formation of a large hematoma. Suturing of the tear may not prevent a deep hematoma from forming and secondary rupture can result in shock, despite cessation of external vaginal hemorrhage.

In the dilated postpartum cervix, edema, hemorrhage and fiber disarray may make it difficult to identify tears on histologic examination. Torn and contracted muscle fibers and torn arteries with fibrin plugs and tense hematomas provide corroboratory evidence of a tear. Histologic sampling should include blocks from above the apex and from below the tear for deep extension and for identification of large torn vessels.

Examination of the uterus histologically following amniotic fluid embolism will show no evidence of intravascular disease in most cases. Very occasionally, there may be fibrin clots adherent to vascular endothelium and, rarely, squames admixed with fibrin have been found in vessels in the body of the uterus. In some cases of postpartum hemorrhage, when there have been no clinical features of amniotic infusion but bleeding and unexpected severe onset of consumptive coagulopathy, histological

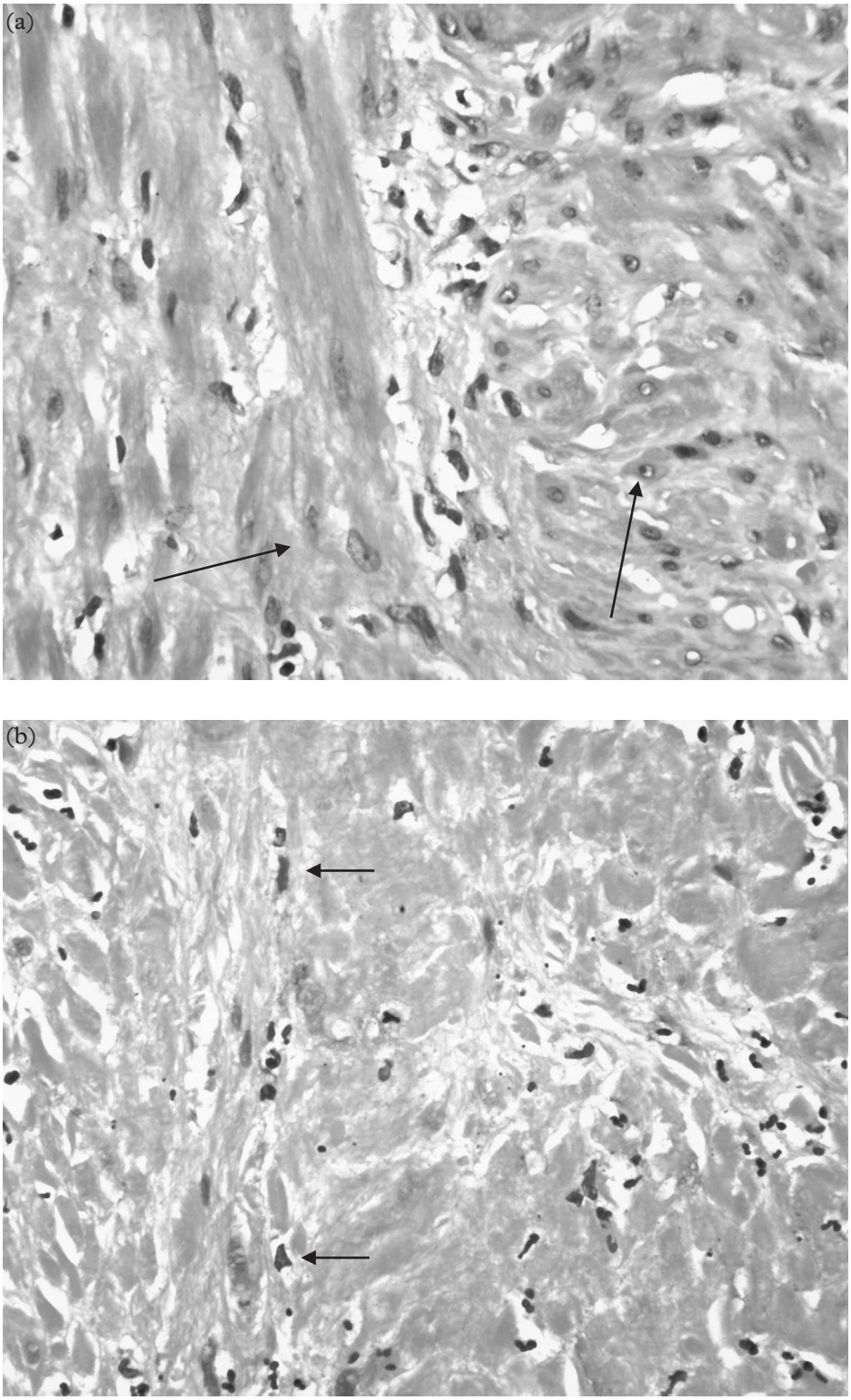

Figure 8 H/E comparison of (a) normal myometrial fibers and (b) myonecrosis in lower uterine segment in hysterectomy specimen for postpartum hemorrhage following Cesarean section (×40). Long arrows, normal viable cell nuclei; short arrows, non-viable necrotic cells

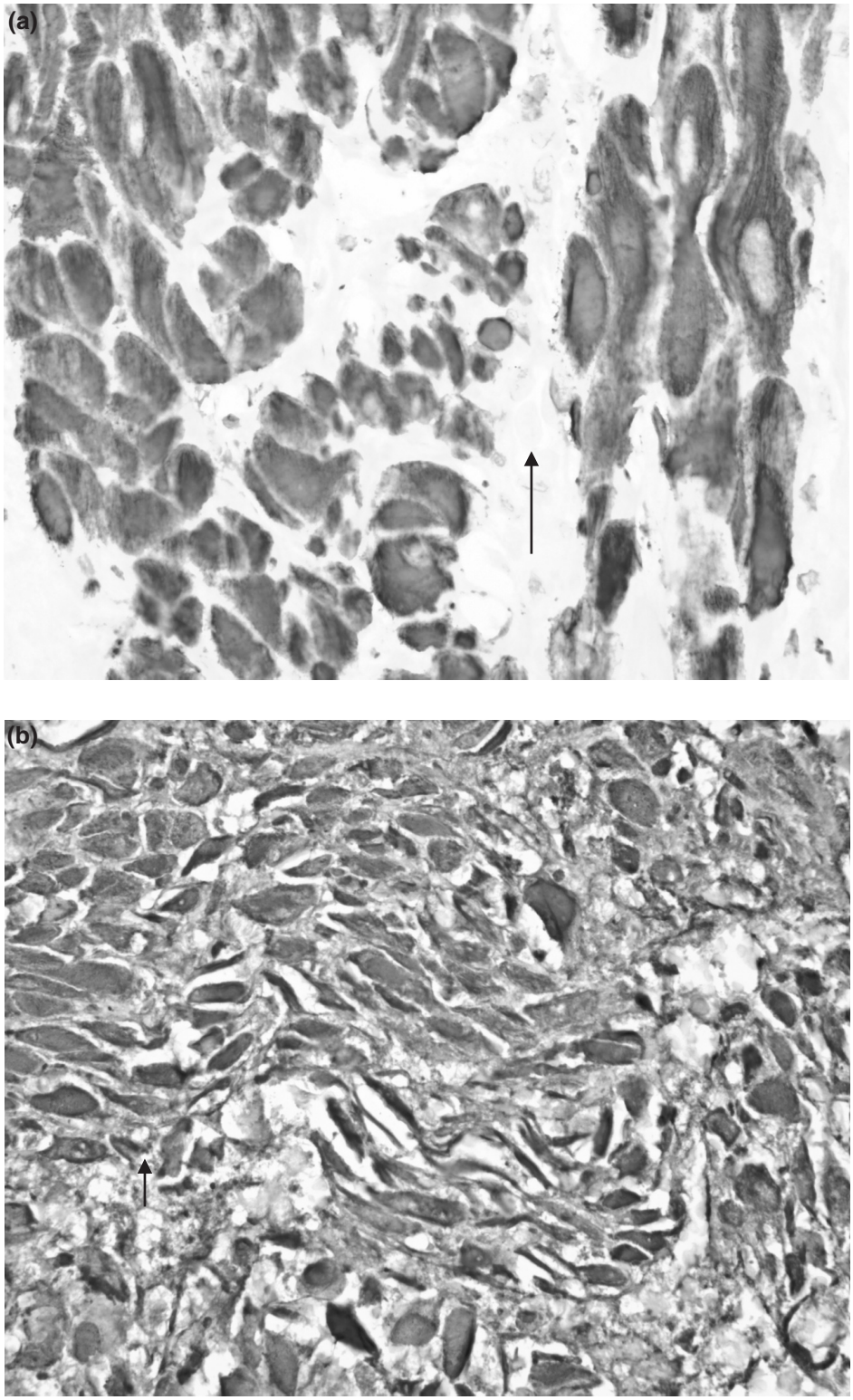

Figure 9 Desmin comparison of same myometrial fibers accentuates the necrosis. (a) Normal; (b) myonecrosis (×40). Long arrow, normal myometrial cells with intercellular edema; short arrow, dense, compacted necrotic myometrial cells at same magnification

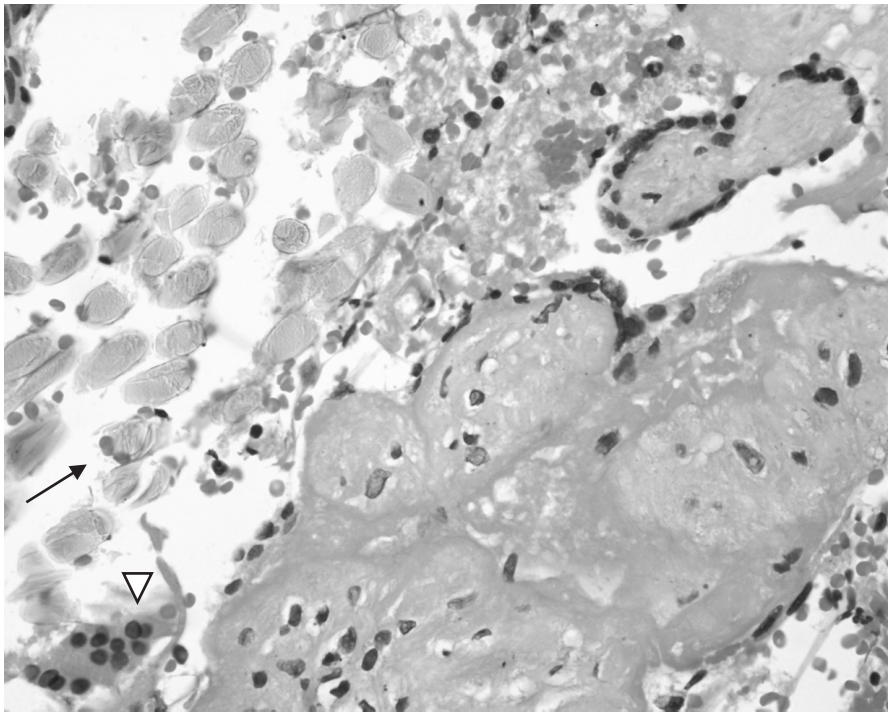

Figure 10 H/E section showing stitch material in uterine curettings following Cesarean section. Arrow, absorbable suture; arrowhead, giant cell reaction to suture material (×40)

sections of the endocervix will reveal localized areas where amniotic debris fills and expands venules and capillaries. This dramatic appearance is present not just adjacent to the endocervical surface and tears: its presence deeper in the stroma distinguishs it from contamination of the surface mucosa by meconium and amniotic fluid at delivery.

A subgroup of patients have a lesion of local amniotic infusion associated with disseminated intravascular coagulopathy and postpartum hemorrhage without systemic collapse. Squamous cells may be present in only one or two sections taken from around the circumference of the cervix. It is usually on one side. Extensive sampling of the cervix may be required to demonstrate amniotic debris in cases of suspected amniotic fluid embolism[2]. It is possible that ongoing blood loss from a tear in this site may occur before the onset of systemic disseminated intravascular coagulopathy, because local thromboplastin effect alone of the amniotic debris in the wound may inhibit hemostasis.

LOWER UTERINE SEGMENT

Important pathologies here involve implantation on a previous Cesarean section scar, with abnormal adherence or formation of a diverticulum.

A Cesarean section results in chronic changes in the lower uterine segment, including distortion and widening, inflammation, giant cell reaction and adenomyosis[3]. In some cases, a distinctive V-shaped defect of the anterior wall ('tenting') may be present.

An important cause of weakening of a Cesarean section scar is infection. Postoperative wound infection is not uncommon following Cesarean section, particularly emergency section. Prophylactic antibiotics can modify the extent and rate of infection, as can the quality of closure, the amount of local tissue trauma, the technique used (one- or two-layer), swelling, hematoma and the nature of the organisms infecting the wound. There may be extensive disruption and inflammation in the uterine wall despite a normal healing appearance of the skin wound. Conservative treatment of the wound

is normal, and surgical debridement the exception. Accordingly, the consequences may be only appreciated in a subsequent pregnancy. If the patient does present before this, hemorrhage and/or vaginal discharge may prompt internal examination. A defect may be identified on palpation. Curettage may be undertaken and may retrieve inflammatory exudate, degenerating decidua, polypoid endometrium or fragments of necrotic myometrium that have prolapsed into the endocervical lumen from the internal edge of the Cesarean section scar. Sometimes, quite large pieces of myometrial tissue with edema and coagulative necrosis are obtained. This myonecrosis, or incisional necrosis, is caused by local ischemia[4]. Remodelling of blood vessels may influence implantation. Implantation on either a normally healed or on a diseased scar will not have the protective effect of the decidua vera (see below), and so postpartum separation is less likely to occur. A Cesarean section at first birth is associated with increased risks of placenta previa and abruption in second pregnancies[5].

Implantation in the lower segment (adjacent to the defect) can cause expansion of the defect, dehiscence of the wall and the formation of a pulsion diverticulum which will further enlarge and progress with growth of the placenta. If the implantation is fundal, a fortuitous elective section may reveal a thin, almost transparent anterior lower segment wall. This should be more easily resected at closure since the scar will not be excessively vascular. If implantation is in the lower segment or in the scar, then there is a potential for catastrophic hemorrhage on attempt at delivery of the placenta.

In examining a postpartum hysterectomy specimen where there is a history of previous Cesarean section, the points noted above should be borne in mind. The recently sutured section incision should be carefully reopened. Following photography, the edges and margins should be inspected for thinning and scar tissue formation. An enlarged, ragged and open defect of the anterior lower uterine segment, now tightly contracted and rigid with formalin fixation, may be all that is left of a huge, thin-walled, placenta-filled diverticulum, the result of scar dehiscence and rupture. It is easy to destroy this thin structure with precipitate dissection. Examination of the lateral margins of the defect may indicate left- or more often right-sided extension of the bulging diverticulum into parametrial soft tissue of the pelvis. A complete section through the anterior lower uterine segment can identify previous Cesarean section scars with tenting defects and the shape and edges of a recent section. Most importantly, en-face examination of the lateral sides of the lower segment will show the cavity and lateral extension of a dehiscence diverticulum, fresh tears and/or adherent placenta. The issue of abnormal adherence is addressed below.

FUNDUS

Important pathologies include retained products, placenta creta, and subinvolution. Placenta creta is the name given to abnormally adherent or ingrowing placenta that does not detach with full contraction of the uterus after expulsion of the fetus. This term covers placenta accreta (abnormal attachment to the wall), increta (extension of villi into the myometrium) and percreta (extension of villi through to the serosa). The intimate relationship of villous tissue to myometrium, without intervening decidua, is the key to the diagnosis. Descriptions of placenta percreta based on illustrations or descriptions of chorionic villi displaced between torn myometrial fibers should be evaluated critically.

MRI may show the loss of zonation associated with penetration rather than invasion of chorionic villi.

Full-thickness anteroposterior sections of the fundus make it easier to recognize the position of the contracted placental site. It is surprisingly difficult to identify the exact site on inspection of the raw decidual surface that is seen if the uterus is opened laterally.

Detachment of the placenta is dependent on the presence of a normal spongy decidua vera, where shearing of the placenta from the myometrium occurs. This soft compressible area is not seen when the postpartum uterine lining is examined histologically, because its many mucous glands are disrupted to facilitate the normal plane of cleavage. It is seen to its full extent in the tragic case of maternal death prior to labor. Either Alcian blue stain or diastase-PAS to

demonstrate mucopolysaccharides in the swollen gland crypts can help to identify this layer. Deficiency of this layer may be focal or, rarely, complete. When it is absent, the thinned Nitabuch's layer with anchoring villi lies in close proximity to muscle fiber bundles or interstitial fibrous Cesarean section scar. An occasional finding is the presence of abundant intermediate trophoblast infiltrating between muscle fibers beneath a firmly adherent Nitabuch's layer. Histological examination of multiple sections can show anchoring villi penetrating Nitabuch's fibrinoid and ghost villi in dense fibrin adherent to muscle. The often described appearance of chorionic villi infiltrating between muscle fibers is characteristic only of invasive mole; the key to placenta percreta is absence of decidua. An increased number of implantation site intermediate trophoblasts has been shown in cases of placenta creta compared with controls[6]. Retained placental fragments reflect some degree of placenta creta and are more common in women with a spectrum of changes in previous pregnancies, such as pre-eclamptic toxemia, growth restriction, spontaneous abortion and retained placental fragments. It has been hypothesized that these reflect abnormal maternal–trophoblast interaction[7].

Placenta creta is therefore due to a deficiency of the decidua. The end result of penetration of the placenta though a weakened part of the uterine wall includes rupture and secondary changes, including serosal peritoneal reaction. Curette penetration may cause secondary infection or hematoma formation and provide the nidus for dehiscence into the adherent bladder wall, if this had been injured at previous surgery.

Placenta creta is only part of the problem of uncontrolled postpartum hemorrhage. The thin myometrium, with little muscle, interstitial fibrosis and increased intermediate trophoblast will contain large dilated arteries of pregnancy and often widespread extrauterine extension of these changes into the parametrium, as described on Doppler ultrasound. The degree of constriction–contraction of the myometrium is insufficient to close off these vessels. Where there is severe thinning of the muscle of the lower segment with diverticulum formation, abnormal adhesion is not necessary to sustain bleeding. Conversely, on histological examination of the lining of the postpartum uterus, the finding of chorionic villi in clefts in the placental bed may be an artefact rubbed in following clearance of uterine contents and is of no diagnostic consequence. Smearing of DNA due to crush artefact may be helpful in distinguishing this from true extension.

RETAINED PRODUCTS OF CONCEPTION

The failure of total expulsion of the placenta may lead to postpartum hemorrhage. A fragment of placenta remains, assumes a polypoid shape ('placental polyp'), and undergoes compression and devitalization. Some viable cells may remain in stem villi. Vessels below the retained fragments may show persistent dilatation. There may be a plasma cell infiltrate in the adjacent myometrium – this is not diagnostic of (infective) endometritis in this context. The frequency of detection of retained products varies from 27 to 88%[7], but much of this literature is decades old. Retained placental fragments are more common in women who have had complications such as pre-eclampsia or growth restriction in previous pregnancies. This has been interpreted as indicative of an abnormal maternal–trophoblast relationship[7].

SUBINVOLUTION

Subinvolution of the blood vessels of the placental bed, in the absence of retained placental fragments, is an important and distinctive cause of secondary postpartum hemorrhage.

Normal arterial involution involves a decrease in the lumen size, disappearance of trophoblast, thickening of the intima, re-growth of endothelium and regeneration of internal elastic lamina. These changes occur within 3 weeks of delivery. With subinvolution, arteries remain distended and contain red cells or fresh thrombus, and trophoblast persists in a perivascular location[8]. In some cases, endovascular trophoblast may be present. Hemorrhage from subinvolution is maximal in the second week postpartum, although it may occur up to several months later. It is commoner in older, multiparous women and may recur in subsequent deliveries.

Subinvolution is not related to the method of delivery and may be regarded as a specific entity, possibly due to an abnormal immunologic relationship between trophoblast and the uterus[8]. Despite this, it did not show the association with markers of such an abnormal relationship seen with retained placental fragments in another study[7].

The changes may be recognized on curettage specimens. The hysterectomy specimen will show a uterus that is soft and larger than expected[8]. As normally involuted vessels may be present adjacent to subinvoluted ones, multiple blocks of placental bed should be taken to exclude this process.

ATONY

This is well-recognized obstetric phenomenon, but there may be relatively little to report in the way of pathology. The diagnosis is one of exclusion. The uterus is enlarged, edematous and soft, with edema and hemorrhage apparent microscopically. The diagnosis will depend on clinical information, combined with adequate histologic sampling to exclude other causes.

ARTERIOVENOUS MALFORMATIONS

Uterine arteriovenous malformations (AVMs) are rare and may present with profuse hemorrhage, including hemorrhage in the postpartum period. Congenital AVMs consist of multiple small connections and may enlarge with pregnancy. The more common acquired AVMs are rare in nulliparous women, and are thought to arise following uterine trauma: curettage, myomectomy or even previous uterine rupture[9,10]. AVMs may co-exist with retained products of conception or trophoblastic proliferation. Pathologically, vessels of arterial and venous caliber are present, along with large vessels of indeterminate nature.

OTHER CAUSES

Lacerations of the inner myometrium have been reported to cause postpartum hemorrhage[11]. Women with leiomyomas are at an increased risk of postpartum hemorrhage[12]. Less commonly, endometrial carcinomas and congenital anomalies may also result in reduced decidua formation and subsequent postpartum hemorrhage. Trophoblastic disease has also been reported in this context.

ENDOMETRITIS

An acute endometritis is reported as a cause of sepsis and postpartum hemorrhage. It is relatively uncommon in modern obstetric practice in the West and may be due to a variety of organisms. It accounted for < 5% of cases of delayed postpartum hemorrhage in one series[7].

PLACENTAL PATHOLOGY

The placenta should be examined in cases of postpartum hemorrhage. Pre-eclampsia may cause retroplacental hemorrhage: recent and old hemorrhages and infarcts may be seen. The characteristic changes of acute atherosis are only present in 50% of cases of pre-eclamptic toxemia. However, examination of the parenchyma will usually show so-called accelerated villous maturation (distal villous hypoplasia) in response to uteroplacental ischemia. Sampling from the center of the disc is important to avoid overinterpretation of physiologic changes[13].

THE AUTOPSY IN POSTPARTUM HEMORRHAGE

In data drawn from the Confidential Enquiries into Maternal Deaths in the UK for the period 1970–90, approximately 10% of direct maternal deaths are due to hemorrhage[14]. Roughly half were antepartum and half postpartum. Excess blood loss is more common in older women (> 35 or 40 years, depending on the study)[15].

Before beginning an autopsy in a case of maternal death following postpartum or intrapartum hemorrhage, it is critical to plan the procedure and the sequence of the autopsy in the light of the information received and the suspected cause or causes and mode of death. The autopsy must be unhurried and methodical; it is a fundamental mistake to seek to demonstrate immediately the proposed cause of death. Members of the clinical team should be asked to attend the autopsy, but it is unwise to have everybody there during what will be a long

phase of inspection, measurement and initial systematic dissection. When all is ready, the procedure is stopped and members of the team attend. In this way, the history can be reviewed, pre-existing conditions or disease discussed and demonstrated, e.g. chronic pyelonephritis, and the dissection and demonstration of the focus of main clinical interest can begin.

A fundamental aspect of good autopsy practice is the confident exclusion of specific diseases and conditions in a systematic approach. The understandable desire and pressure to skip to the seat of disease must be resisted. The parametrium, pelvic side-wall and vagina are as important objects of attention as the uterus.

At the time of external inspection of the body, the pathologist must consider in turn each of the major causes of maternal death. Many require modification of routine techniques, e.g. air embolism, amniotic fluid embolism, ruptured aneurysm, and these modifications are detailed elsewhere[16]. Preparation and sampling of blood and fluids for hematology, hemophilia, toxicology and microbiology should be planned, e.g. sample containers should be pre-labelled and set out in sequence. Cardiopulmonary resuscitation attempt most likely preceded death and therefore the features and sequence of sustained unsuccessful resuscitation must be identified and complications and agonal changes interpreted in this context. It is important from a medicolegal aspect not to allow such artefact to be construed as a major factor in the cause of death, e.g. liver or mesenteric tear, blood in the abdomen, bone marrow embolus.

The traditional Y-shaped autopsy incision should be extended to an abdominal inverted Y with the incision continued to the inguinal femoral triangle on each side. This allows better examination of the ileofemoral vessels and better exposure of the pelvis. Blood and blood clots are removed from the abdomen and the amounts measured. The relative size and position of the abdominopelvic organs are assessed. The peritoneal lining of the pelvis is inspected, noting color, texture and degree of congestion. Patches of peritoneal decidual reaction of pregnancy can be identified by their gelatinous appearance.

In traditional autopsy practice, the state of pregnancy can be suspected, even when the uterus is still small, by the characteristic dilated and congested appearance of retroperitoneal veins. The degree of dilation and turgidity of the pelvic veins should be noted at autopsy as they will be dissected and examined in detail later. Retroperitoneal hematoma and broad ligament hematoma should be identified or excluded at this stage as these may be less easily assessed and measured following organ removal. The uterus may be examined and opened *in situ*, but it is better to remove adrenal, renal and pelvic organs as one complete block.

The traditional method of blunt dissection along the pelvic side-wall and pubis with transection at the mid to upper vagina is extended in the investigation of postpartum hemorrhage. Following knife separation of the symphysis pubis, the legs are externally rotated and a knife cut is made along the lower edge of the pubic bone. The pubic bones are forcefully separated by 8–10 cm. This, together with the inguinal femoral incisions, gives good exposure of the paracervical and paravaginal soft tissues. Lateral vaginal wall tears and hemorrhage can be inspected and well demonstrated by this modified technique. The ileofemoral vessels are transected and inspected. The complete urogenital block is placed on a dissection board where it can be opened in layers, beginning with the urethra and bladder, then the vagina and cervix. Alternatively, the block can be placed in formalin and later dissected after short fixation.

The aorta is opened posteriorly and incision is extended into the branches of the iliac arteries for a short distance. The inferior vena cava is opened from the anterior side, probed and dissected into the right and left renal veins; the ovarian veins are identified and opened and dissection is continued into the branches of the pelvic veins out to the limits of the excised specimen. The intima is examined for evidence of tear or abrasion and for adherent thrombus. Pieces of tissue containing venous plexus from the broad ligament and parametrium are selected for formalin fixation and histological examination.

When the patient has died of hemorrhage and where there has been attempt to stem the bleeding by hysterectomy and under-sewing of bleeding sites and pedicles, it may be very

difficult to identify the exact sites of bleeding, and ancillary techniques may be helpful. Prior to pelvic dissection, an infusion of saline through an intravenous infusion set and cannula into the clamped abdominal aorta can identify a bleeding point. With special preparation and ligation of all peripheral vessels, post-mortem specimen angiography may be very valuable in selected cases.

The most useful of all techniques is the histological examination of carefully selected blocks of tissue demonstrating vital reaction to injury and the presence or absence of conditions predisposing to disease.

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37

SEVERE ACUTE MATERNAL MORBIDITY

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INTRODUCTION

For every woman who dies of postpartum hemorrhage, a host more suffer short- and long-term consequences from postpartum hemorrhages or their sequelae, even when well-managed. During the 1990s, the concept of severe adverse maternal morbidity (SAMM) emerged in response to the need for a more sensitive marker of quality of obstetric care[1,2]. This term has the advantage over maternal death of drawing attention to surviving women's reproductive health and lives and is equally applicable in developing as well as developed countries.

In developed countries, maternal death from postpartum hemorrhage has become too rare for adequate surveillance of services. For example, the United Kingdom (UK) triennial Confidential Enquiry into Maternal Deaths has revealed that, over the past 50 years, the number of maternal deaths from hemorrhage has fallen from 40 to 3 per annum[3]. Currently, the overall maternal mortality rate in the UK is around 7 per 100 000 maternities[4]. However, the same causes of death persist as in the 1950s, with hypertensive disorders and hemorrhage as the most common causes of direct obstetric deaths[5]. Seventeen out of a total of 106 direct obstetric deaths were attributed to hemorrhage during 2000–2002 (i.e. 16%). Of these, ten were due to postpartum hemorrhage[3]. Compared to the previous report (seven deaths in 1997–1999)[6], there was a slight rise in incidence. Although this is not statistically significant, it needs to be watched as a possible trend alongside a rising Cesarean section rate. A potentially far more worrying factor is that substandard care was implicated in 80% of the cases attributed to hemorrhage[3].

The UK remains one of the few developed countries in which every maternal death is investigated. This was also the case in the United States (US) after 1930, but the rapid decline in maternal mortality in the latter part of the 20th century diminished the vigor used to investigate each individual case. It is not clear how many developed countries have policies similar to that of the UK. As a result of perceived racial discrepancies in maternal mortality in the US, as well as evidence that not all maternal deaths were reported to the National Vital Statistics System (NVSS)[7], a parallel, voluntary system of reporting was introduced in 1983, termed the Pregnancy-related Mortality Surveillance System (PMSS)[8]. While the NVSS collects information from death certificates alone, the PMSS combines data from maternal death certificates with fetal death certificates, autopsy reports and reports produced by maternal mortality review committees[8]. This has led to better ascertainment of cause of death, and a more accurate maternal mortality rate of 11.8[8,9] rather than 7.7[7,8] per 100 000 live births for the period 1991–1999.

WHAT IS THE DIFFERENCE BETWEEN A 'NEAR-MISS' AND A SAMM?

A 'near-miss' used to be thought of as a case where a woman had a near brush with death; she would have died were good fortune and medical care not on her side. This characterization was also used for women with severe organ dysfunction or organ failure who survived[10,11], that is, with intensive medical intervention, a maternal death was avoided and turned into a survival[12]. However, the term

'near-miss' is no longer used, as the 'near-miss' concept was originally derived from the aviation industry and referred more to risk management than the effect on the woman. In contrast, SAMM refers to the morbidity a woman actually suffers. Essentially, we can think of a pyramid of disease in pregnancy (see Figure 1), the base being the numerically larger general pregnant population, the 'tip of the iceberg' being maternal death and much hidden morbidity beneath the surface[9–11]. A clinical insult may be followed by a systemic response and subsequent organ dysfunction, which leads to organ failure and eventual death[1,10]. Figure 1 illustrates both the severity continuum of morbidity as well as factors that move a woman up or down the pyramid. For example, a faulty ambulance or wrongly cross-matched blood might lead to an anemic woman dying of hemorrhage unnecessarily (arrow A). If she is well managed and treated promptly, there may be no residual morbidity at all (arrow B). A wrongly labelled blood bag that is spotted in time still constitutes a 'near-miss' requiring follow-up of the error, although the woman did not experience a transfusion reaction. 'Near-miss' now refers to avoidable risks whereas SAMM retains the concept of the harmed or damaged mother.

An agreed and accurate definition of SAMM is not available, as studies in different parts of the world use different criteria. The two main definitions of SAMM to date are as follows:

(1) An organ system approach[10,11,13], e.g. shock from hemorrhage, severe pre-eclampsia or specific organ failure; these are best identified as they occur;

(2) Management, or process, based[12,14], e.g. admission to a high-dependency unit (HDU) or intensive care unit (ICU) or transfer to another health-care facility (usually higher level); these are usually retrospective studies.

A diligent unit is more likely to pick up cases via the organ system approach and carefully record them; this will translate into a disproportionately higher rate of SAMM[11]. On the other hand, a poor-quality unit that does not recognize and treat hemorrhage promptly may have more severe sequelae as the natural history progresses. Use of the management-based approach relies on more easily agreed parameters, but also on the availability of HDU/ICU beds. Units have different policies and thresholds for transfer. There may be an underestimation of the true incidence of SAMM, especially

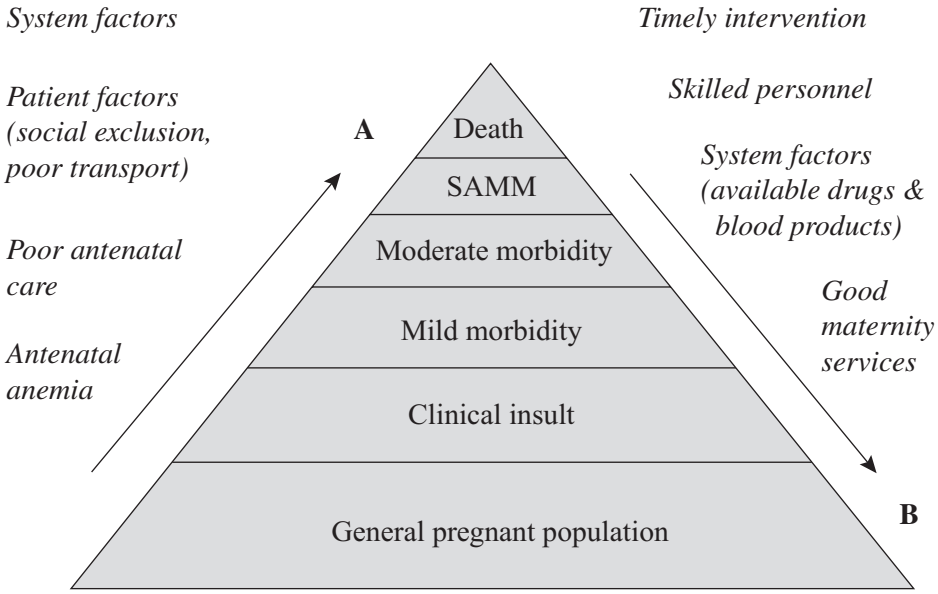

Figure 1 A representation of the morbidity–mortality continuum

in smaller, more isolated units and in developing countries.

INCIDENCE OF SAMM

Quantifying SAMM is problematic as there is no international definition and recording is haphazard at best. Thus, there is a wide variation in the estimate of incidence. Tables 1 and 2 summarize studies to date. Wide variations are present in study settings, definitions and main causes. Some studies use admission to ICU[14,15], others define the actual conditions responsible for the morbidity[10,11], and some list both[12]. Two methods have been described to address the relationship between severe morbidity and mortality. These are the *mortality-to-morbidity ratio*[1,13] and the *mortality index*[11,16]. The mortality-to-morbidity ratio simply describes the number of severe morbidity cases for each maternal death[1,13]. The mortality index, on the other hand, is defined as the number of maternal deaths divided by the sum of women with SAMM and maternal deaths, and is expressed as a percentage[11,16]. Both can be expressed as totals (all-cause) or by condition. They both reflect the impact of a condition on severe morbidity and mortality and identify those conditions that are more or less amenable to intervention. In general, the risk of mortality depends on the prior health of the mother, the severity of the particular condition, the access to skilled help and the availability and quality of medical intervention. Postpartum hemorrhage is common, and has a very favorable morbidity-to-mortality ratio (or low mortality index)[1,11,13,16]. Stated another way, the condition, at least in developed countries, is very amenable to treatment. More women's lives can be saved with medical interventions than for a comparable number of cases of infection or cardiac disease. Many lives can be, and indeed are being, saved daily by the provision of adequate maternity services world-wide. As hemorrhage is so obviously both avoidable and treatable, and because all parturients are at risk, it is tragic that so many women die unnecessarily. Unfortunately, complacency in developed countries about the daily marvels achieved in childbirth[4] has made any sudden unexpected threat to life almost unbelievable and unbearable.

CAUSES OF SAMM

Most cases of SAMM fall into three major categories:

(1) Hemorrhage;

(2) Hypertensive disorders of pregnancy (including eclampsia and HELLP syndrome);

(3) Sepsis.

Table 1 summarizes both the all-cause incidence of SAMM as well as the three major causes. Rates in European countries are similar for the three major causes of severe morbidity despite the use of different definitions. Regardless of geographical factors, hemorrhage is the largest contributor, accounting for one-fifth[17] to one-half[10,18,19] of cases. Hypertensive disease and its consequences account for 10%[18] to 45%[20] of cases of SAMM, whereas morbidity secondary to sepsis is much lower (1.5%[18] to 20%[10]). Other rarer causes of severe morbidity include uterine rupture, thromboembolic disease and psychiatric illness[5,21]. The Mothers' Mortality and Severe Morbidity Survey was conducted during the 1990s by an international team which spanned 11 European countries. There are two parts to the survey: MOMS-A and MOMS-B[20]. MOMS-A collected and compared data on maternal deaths, while MOMS-B identified cases of severe morbidity[20]. The survey established that, in European countries with the highest SAMM rates, i.e. Belgium, Finland and the UK, most of the difference was due to higher incidence of hemorrhage. However, maternal mortality was no higher than in other European countries. This suggests either that ascertainment of cases in these three countries is more complete or that hemorrhage is not a major cause of death; therefore the higher incidence of SAMM does not affect overall mortality data. Alternatively, it may be that mortality rates are associated more closely to the quality of care than the prevalence of morbidity[20]. The geographical areas chosen in different countries had very different demographics, and this also may have affected the rates of morbidity; Belgium and the UK were represented by Brussels and the South-East Thames region, areas with significant inner-city and migrant

Table 1 The incidence of each major cause of morbidity per 1000 deliveries

Study, country and year of publication	*Incidence of SAMM (all causes)*	*Incidence of hemorrhage (% of total)*	*Incidence of hypertension (% of total)*	*Incidence of severe sepsis (% of total)*	*Additional comments*
Stones[2], UK, 1991	8.8	3.23 (36.8%)	2.77 (31.5%)	not available	SAMM defined as 'potentially life-threatening episodes'. Incidence for total morbidity 267/1000. Incidence of all sepsis 30.5/1000 (severe sepsis not separated out). Hemorrhage includes antepartum and postpartum if over 2000 ml and also 1 case of secondary PPH due to sepsis which required hysterectomy
Bouvier-Colle[17], France, 1996	3.1	0.62 (20%)	0.81 (26.2%)	0.14 (4.36%)	3rd highest cause of morbidity is embolic events at 0.38/1000. Hemorrhage includes uterine rupture. Hypertensive disease includes cerebral hemorrhage
Bewley & Creighton[12], UK, 1997	4.97	2.3 (46.7%)	1.98 (40%)	0.49 (10%)	SAMM = ITU admission. Total 30 cases of SAMM. 14 cases classed as hemorrhage (blood loss > 2000 ml but a further 2 cases DIC/HELLP so proportion due to hemorrhage could be > 50%)
Baskett & Sternadel[22], USA, 1998	0.72	0.16 (22%)	0.18 (25%)	0.1 (14.5%)	SAMM = ITU admission
Mantel[10], South Africa, 1998	10.9	6.1 (55.8%)	2.82 (25.8%)	2.16 (19.7%)	Sepsis incorporates septic abortion, chorioamnionitis and puerperal sepsis. Hemorrhage incorporates antepartum and postpartum hemorrhage and emergency hysterectomy; PPH alone is 1.8/1000
Prual[18], West Africa, 2000	59.8	29.6 (49.5%)	6.15 (10.3%)	0.9 (1.5%)	Obstructed labor is significant cause for severe morbidity (20.5/1000 of which 1.2/1000 uterine rupture)
Waterstone[13] (COSMO), UK, 2001	12.0	6.7 (55.7%)	4.6 (38%)	0.35 (2.89%)	Clinically based definitions, not including management processes. Estimated blood loss > 1500 ml picked up 55% of cases of SAMM due to hemorrhage
Brace[19], Scotland, 2004	3.8	1.9 (50%)	1.15 (30%)	0.09 (3%)	Septic shock is the only category for sepsis. Number of SAMM due to hypertensive disease derived by adding the number of cases with eclampsia, renal dysfunction and pulmonary edema. Only one-third of patients with SAMM were admitted to ITU
Zhang[20] (MOMS-B), Europe, 2005	9.48	4.6 (48.8%)	4.33 (45.7%)	0.8 (8.2%)	Multinational study, rates differing widely between countries. Range of SAMM 6–14.7%, highest in Finland, Belgium and UK; lowest rates in Italy, Ireland, France

DIC, disseminated intravascular coagulation; SAMM, severe adverse maternal morbidity; ITU = intensive therapy unit; HELLP, hemolysis, elevated liver enzymes, low platelets; PPH, postpartum hemorrhage

Table 2 The incidence of SAMM and hemorrhage and definitions used to ascertain cases

Author, country, year of publication	*Type of study, type of unit*	*Number of deliveries, cases of SAMM, cases of hemorrhage*	*Incidence of SAMM or ITU (/1000 deliveries)*	*Incidence of hemorrhage (/1000 deliveries)*	*% of SAMM due to hemorrhage*	*Definition of severe hemorrhage (additional comments)*	*Perinatal outcome*	*Number of maternal deaths, MMR for SAMM overall, mortality per 100 000*
Graham & Luxton[41], UK, 1989	retrospective, general ITU	21 983 23 (ITU) 1 (5)*	1.04	0.05 (0.23)*	4.35% (21.7%)*	1 case of hemorrhage counted but 5 cases in total (3 abruptions: 1 was the hemorrhage and 2 cases of DIC). 9 patients showed some coagulopathy, 5 received > 4 units transfusion	1 intrauterine death	2 11.5 : 1 9.1
Mabie & Sibai[23], US, 1990	retrospective, 3-bed dedicated obstetric ITU	22 651 200 (ITU) 21	8.82	0.93	10.5%	massive hemorrhage not defined	not collected	not collected
Stones[2], UK, 1991	retrospective, single unit	2164 19 7	8.8	3.23	36.8%	hemorrhage > 2000 ml or DIC or hysterectomy	not collected	0 0
Killpatrick & Matthay[14], US, 1992	retrospective, general ITU	8000 32 (ITU) 4	4	0.5	12.5%	hemorrhage/hemodynamic instability. 52% of postpartum admissions were for hemodynamic instability	2 stillbirths delivered on ITU. No neonatal/ fetal deaths after admission to ITU	4 8 : 1 50
Monaco[15], US, 1993	retrospective, ITU admissions	15 323 38 (ITU) 4	2.47	0.26	10.5%	2 cases following PPH and 2 cases of hematologic dysfunction (local policy is to admit only for ventilatory support or pulmonary artery catheterization)	perinatal mortality rate 12% (4 of 33 pregnancies followed up)	7 5.4 : 1 45.7
Bouvier-Colle[17], France, 1996	retrospective, 2 French regions	140 323 435 (ITU) 87	3.1	0.62	20%	hemorrhage not defined but includes uterine rupture	stillbirth rate collected only 24.6% in hypertension, 17.3% in hemorrhage, 33.3% in sepsis	22 19.8 : 1 15.7
Bewley & Creighton[12], UK, 1997	retrospective, general ITU	6039 30 (ITU) 14	4.97	2.3	46.7%	transfer to ITU for blood loss > 2000 ml	not collected	not collected

Continued

Table 2 *Continued*

Author, country, year of publication	*Type of study, type of unit*	*Number of deliveries, cases of SAMM, cases of hemorrhage*	*Incidence of SAMM or ITU (/1000 deliveries)*	*Incidence of hemorrhage (/1000 deliveries)*	*% of SAMM due to hemorrhage*	*Definition of severe hemorrhage (additional comments)*	*Perinatal outcome*	*Number of maternal deaths, MMR for SAMM overall, mortality per 100 000*
Lapinsky[27], Canada, 1997	retrospective, ITU admissions in tertiary hospital	25 000 65 (ITU) 11	2.6	0.44	17%	hemorrhage requiring ITU admission, not defined. 52% of admissions involved hemodynamic instability; 4 hysterectomies	perinatal mortality rate 11%	0 0
Tang[25], Hong Kong, 1997	retrospective, single center	39 354 49 (ITU) 26	1.24	0.66	53%	blood loss 1000–8500, mean 3500 ml. Received blood transfusion (mean 12 units), platelet transfusion or FFP. DIC in 34% and mild coagulopathy in 27% of hemorrhage cases. Hysterectomy in 22 cases (84.6% of all hemorrhage)	perinatal mortality rate 10.2%	2 24.5 : 1 5.1
Mantel[10], South Africa, 1998	prospective, multicenter	13 429 147 82	10.9	6.1	55.8%	severe hemorrhage = hypovolemia requiring 5 or more units of blood for resuscitation or emergency hysterectomy	not collected	30 4.9 : 1 223.4
Mahutte[28], Canada, 1999	retrospective, 2 tertiary care units with general ITU	44 340 131 (ITU) 34	2.95	0.77	26%	hemorrhage causing admission due to abnormal placentation, atony, lacerations, RPOC, severe coagulopathy. 27 (79%) received blood products and 12 (35%) admitted after Cesarean hysterectomy	not collected	3 43.7 : 1 6.8
Waterstone[13,21], UK, 2001	prospective, case–control, multicenter	48 865 588 327	12.0	6.7	55.7%	blood loss > 1500 ml/peripartum hemoglobin drop ≥ 4 g/dl or acute transfusion ≥ 4 units	perinatal mortality rate 7.5%	5 118 : 1 10.2
Prual[18], West Africa, 2000	prospective, 6 countries	20 326 1215 601	59.8	29.6	49.5%	hemorrhage requiring transfusion, hospitalization > 4 days or hysterectomy (only 2.8% of deaths were due to severe hemorrhage)	not collected	38 32 : 1 187
Hazelgrove[24], UK, 2001	retrospective, multi-unit	122 850 210 (ITU) 70	1.7	0.6	33.3%	major hemorrhage not specified; 35% were short admissions (< 2/7) and no specific interventions. 7 patients required transfer to specialist ITUs	fetal mortality rate 20% (includes fetal losses < 24 weeks gestation)	7 30 : 1 5.7

Murphy & Charlett[29], US, 2002	retrospective cohort, general ITU in teaching hospital	51 576 50 (ITU) 12	0.97	0.23	24%	no definition/information on transfusion given but cause of hemorrhage given; 7 hysterectomies	perinatal mortality rate 14%.	3 16.7 : 1 5.8
Vandecruys[16], South Africa, 1997–1999	prospective, tertiary center, phase 1	26 152 305 44	11.7	1.68	14.4%	definitions not given. Data on hemorrhage refer to PPH	not collected	59 5.2 : 1 225.6
Vandecruys[16], South Africa, 2002	prospective tertiary center, phase 2 (re-audit)	13 854 121 23	8.7	1.66	19%	as above. SAMM and mortality declined compared to the first audit due mainly to reduction in abortion complications	not collected	26 4.7 : 1 188
Pattinson[11], South Africa, 2003	prospective, 3 geographic areas (urban and rural)	NA 423 130	NA	NA	30.7%	condition-based definitions same as Mantel10. Calculates mortality index but cannot define incidence as number of deliveries not given. Hemorrhage includes antepartum and postpartum; PPH alone is 18%. PPH is second most common cause of SAMM but 7th cause of death	not collected	128 3.3 : 1 NA
Brace[19], Scotland, 2004	prospective observational, (22 consultant-led units in Scotland)	51 165 196 98	3.8	1.9	50%	major hemorrhage = cases transfused at least 5 units during the acute episode of hypovolemia (13 categories of morbidity leading to ITU admission)	not collected	4 49 : 1 7.8
Gandhi[26], South Africa, 2004	prospective, 4 rural primary hospitals	5728 31 10	5.41	1.75	32%	Mantel's definitions adapted for use in primary hospital with limited resources. Includes antepartum and postpartum hemorrhage, DIC and hysterectomy	not collected	not disclosed
Zhang[20] (MOMS-B), Europe, 2005	Population based questionnaire, multi-unit, multi-national	182 734 1734 847	9.48	4.6	48.8%	blood loss > 1500 ml/blood loss requiring plasma expanders and/or blood loss > 2500 ml in 24 h/blood loss resulting in maternal death. Incidence range 0.7–8.8 according to country	fetal death rate 4.8%	4 433.5 : 1 2.2

SAMM, severe adverse maternal morbidity; ITU, admissions to intensive therapy unit; (ITU), SAMM cases defined as ITU admissions; MMR, morbidity to mortality ratio (calculated from rate of SAMM to mortality); PPH, postpartum hemorrhage; DIC, disseminated intravascular coagulation; HD, high-dependency unit; RPOC, retained products of conception; NA, not available

*Data in parentheses are calculations as applied for five cases

populations, whilst the three regions in France did not include major cities[20].

In general, severe hemorrhage and hypertension have much higher incidence (range 0.6[17]–29.6[18] and 0.18[22]–6.15[18] per 1000 deliveries, respectively) than severe sepsis (0.09[19]–2.16[10] per 1000). The same low rate for sepsis is observed in West Africa, where the second greatest cause of SAMM after hemorrhage is obstructed labor[18]. Uterine rupture has been combined with data for obstructed labor in one study[18] and with hemorrhage in another[17]. Waterstone and colleagues (2001)[13] considered uterine rupture as a separate entity; this is a more accurate way of using the data unless we have clear evidence of the blood loss associated with each case[13]. Few studies have looked at immediate moderate morbidity, although a number of studies of the puerperium examine moderate to minor morbidity[2,13]. For example, Stones and colleagues (1991) included less severe cases of morbidity in their analysis: anesthetic complications (usually post-spinal headache) 0.46%; urinary retention/incontinence 1.2%; late perineal complications 0.65%[2].

HEMORRHAGE AS A CAUSE FOR SAMM: THE EVIDENCE

Most studies of SAMM to date report severe hemorrhage as the largest single contributing factor. Severe hemorrhage was defined by one or a combination of factors:

(1) Estimated blood loss ≥ 1500 ml (or ≥ 2000 ml);

(2) Hemoglobin drop ≥ 40 g/dl;

(3) Transfusion of ≥ 4 units of blood.

Table 2 outlines the incidence of severe hemorrhage in a variety of studies to date. The problem of varied definitions is highlighted, making comparisons between studies difficult. The proportion of SAMM due to hemorrhage is also shown. This varies widely but tends to be lower in studies that are management-based, as not all cases require admissions to ICU. Local policies and availability of obstetric HDU beds on labor wards has a great influence on the management of massive postpartum hemorrhage as it avoids delays in treatment secondary to transfers and also ensures continuity of obstetric care[23]. Obstetric HDU beds are becoming more commonplace in tertiary centers in the UK[12,13,24] and US[14,15,23]. Comparisons are more valid between studies that have used agreed or similar definitions for hemorrhage[10,12,18,19,25]. Many of them are prospective[10,11,13,19,26] rather than retrospective[14,17,27–29], and they tend to find higher proportions of hemorrhage: 30–50% rather than 10–30%, although there is some overlap[12,18].The higher rate from prospective studies is likely to be due to better case ascertainment. Rates appear to be very similar in developed[13,19,20] and developing[10,18] countries when comparable definitions are used.

Emergency obstetric hysterectomy provides another means of examining SAMM caused by postpartum hemorrhage. It has the advantage of being relatively clearly defined, and is rare enough to be easy to collect data. The traditional advice is to perform hysterectomy early to avoid mortality[6]. The threshold for performing hysterectomy clearly varies with operator and unit, but evidence exists that early hysterectomy decreases morbidity[30]. The new United Kingdom Obstetric Surveillance System (UKOSS) requires units to report cases of specified rare conditions on a monthly basis. Hysterectomy has been chosen as the exemplar obstetric morbidity, and this large national surveillance should provide further information about best practice in the future.

RISK FACTORS FOR SAMM AS APPLIED TO HEMORRHAGE

Although it is challenging to define the size of the problem (i.e. the incidence of SAMM as a result of hemorrhage), it is necessary to understand the factors that increase the risk of severe hemorrhage. Table 3 has been adapted from the findings of a multicenter case–control study in the South East Thames region of the UK (COSMO)[13] and outlines the odds ratios of having a severe hemorrhage (as defined by blood loss ≥ 1500 ml, hemoglobin drop ≥ 40 g/dl, or blood transfusion ≥ 4 units), depending on a wide range of risk factors. The main predictors are:

Table 3 Risk factors for having a severe adverse maternal morbidity, or severe hemorrhage (from Waterstone *et al.*, 2001)[8]. Figures are odds ratios (95% confidence interval)

Risk factors	*Odds ratios for SAMM (all causes)*	*Odds ratios for SAMM due to hemorrhage*
Age > 35 years	1.46 (1.11–1.92)	1.41 (1.03–1.95)
Blood pressure at booking	1.23 (1.12–1.34)	1.18 (1.06–1.31)
Black	1.16 (0.85–1.58)	0.97 (0.66–1.42)
Other race	1.93 (1.24–2.99)	1.82 (1.09–3.03)
Social exclusion	2.64 (1.69–4.11)	2.91 (1.76–4.82)
Smoker	0.68 (0.49–0.93)	0.65 (0.44–0.96)
Previous postpartum hemorrhage	2.41 (1.53–3.77)	2.74 (1.69–4.44)
Hypertension	1.10 (0.63–1.95)	0.82 (0.37–1.80)
Diabetes	1.76 (0.43–7.20)	1.85 (0.38–9.14)
Multiple pregnancy	2.21 (1.24–3.96)	2.29 (1.2–4.37)
Antenatal admission	1.75 (1.37–2.23)	1.85 (1.39–2.47)
Taking iron at booking	5.53 (2.28–13.41)	5.98 (2.28–15.65)
Taking antidepressants at booking	4.3 (0.91–1.88)	10.55 (2.19–50.71)
Taking antiepileptics at booking	5.31 (1.4–20.13)	5.75 (1.28–25.72)
IOL because overdue	1.36 (0.99–1.88)	1.38 (0.95–1.99)
IOL on medical grounds	2.45 (1.68–3.57)	1.33 (0.87–1.07)
Oxytocin augmentation	0.99 (0.76–1.28)	1.61 (1.2–2.15)
Manual removal of placenta	9.60 (5.67–16.28)	13.12 (7.72–22.30)
Emergency Cesarean	4.31 (3.39–5.49)	3.09 (2.29–4.17)

SAMM, severe adverse maternal mortality; IOL, induction of labor

(1) *Demographic*: age ≥ 35 years, non-white race, social exclusion (this was a composite measure of a woman's social deprivation beyond the use of her marital or partner's employment status. It included concealed pregnancy, age < 16 years, poor housing, 'on income support' in the notes, previous minor or child in local authority or state care (currently or in the past), in trouble with the law (currently or previously), living alone, unbooked, unwanted pregnancy, currently or previously in foster care, care order being considered on potential child, social worker involved, or drug or alcohol dependency[21]);

(2) *General medical factors*: anemia, depression, diabetes, hypertension, epilepsy;

(3) *Obstetric factors*: previous postpartum hemorrhage, multiple pregnancy, antenatal admissions, obstetric interventions (augmentation with oxytocin, manual removal of placenta, emergency Cesarean section).

Other studies[31,32] find the same trend, with death and severe morbidity being more common in black women, multiparae and women of 'low status'[32] as defined by poor education, poverty, low antenatal care attendance, low contraceptive ever-use and little power to make decisions regarding access to health care. In Geller's study (2004)[31], the peak of mortality and SAMM occurred in the 20–34-year age group, with three times fewer women aged > 35 years in all categories of the morbidity-to-mortality continuum[31]. This is more likely to reflect the age distribution of the study population rather than a true difference between the USA and the UK, and emphasizes the need for the use of multiple logistic regression to tease out risk factors. Manual removal of placenta had the biggest impact[13], in keeping with abnormally adherent placentas being a major cause of postpartum hemorrhage. Antenatal anemia, Cesarean section, and the use of antidepressants or antiepileptics at booking also appear to have significant impacts, though their relative importance is difficult

to ascertain as the confidence intervals were wide. Induction of labor increases the risk of postpartum hemorrhage regardless of the indication[13].

OUTCOMES OF WOMEN WHO SUFFER SAMM

Few studies look at outcomes beyond survival or immediate morbidity. Studies of postnatal morbidity in general (low- and high-risk women analyzed together) found that the prevalence of problems is high (87%) and lasts up to 18 months[33]. A case–control study of outcome 6–12 months postpartum compared women who had suffered SAMM and women who had not[21]. Women who had suffered SAMM were twice as likely as controls to attend general practitioner services and three times as likely to attend Accident and Emergency departments. This may have been due in part to some underlying morbidity and its follow-up but clearly points to a continuing burden on health services with its personal, family and economic cost. Cases also suffered slightly more postnatal depression than controls (who were not entirely 'normal' women and included women with operative deliveries and smaller hemorrhages). Although this difference was not statistically significant, cases also scored higher on the Edinburgh Postnatal Depression Scale. Significantly more cases (50%) than controls (29%) were reluctant to re-establish sexual relations with their partners for fear of becoming pregnant, suggesting that a negative experience in one pregnancy may prevent a woman from achieving the family she initially intended[21]. Women with stillbirths are almost always excluded from postnatal studies[33], although a higher proportion of them also suffer SAMM by the nature of underlying conditions (e.g. abruptions, diabetes). Only half of the studies of SAMM quoted give data about perinatal loss. The figures quoted above are very likely underestimates of the true spectrum of postnatal morbidity.

DECREASING SAMM: MOVING FORWARD

Before designing studies into effective interventions for reducing SAMM, it will be necessary to develop standardized definitions for severe morbidity and its main causes. Intuitively, a condition-based approach will be better, as it would allow clinical comparisons to be made. Recommendations could be more easily applied to settings where ICU facilities are scarce. Two groups[10,31] have refined this clinical approach by classifying SAMM according to the initial obstetric cause (e.g. hypertensive disorders, hemorrhage or sepsis) as well as the organ dysfunction which led to the severe illness. Hemorrhage could be further classified by cause (atony, surgical, adherent placenta, disseminated intravascular coagulopathy (DIC), inverted uterus, etc.).

In the context of severe hemorrhage, possible components of an international definition might include:

- Measured blood loss ≥ 1500 ml at the time of pregnancy outcome (including abortion, ectopic, vaginal delivery or Cesarean)
- Peripartum hemoglobin drop ≥ 4 g/dl
- Acute transfusion ≥ 4 units of blood
- Presence of DIC or shock
- Use of additional, non-obstetric procedures, e.g. hysterectomy/ laparotomy/interventional radiology
- Blood loss resulting in vital organ dysfunction/ICU admission
- Blood loss resulting in maternal death

The first three components are imprecise and early indicators of morbidity. Moreover, the amount of blood loss is notoriously inaccurate, blood transfusion is practitioner- and protocol-dependent and hemoglobin decreases are not measured world-wide. The severity of the impact on the woman's health will depend on her prior hemoglobin level and further management of her condition. Blood loss in excess of 1500 ml is a sensitive predictor of SAMM. Some of the studies discussed so far[12,13] identified 50% of their cases of hemorrhage by using this measure. The latter categories are clear but late markers of severity. Potentially, a scoring system could be devised to increase the accuracy of assessment of severity. A woman who loses a large quantity of blood, is adequately

transfused with blood and blood products, and managed in an obstetric HDU is likely to suffer less long-term morbidity than a woman with the same blood loss, but also with a hysterectomy and ICU admission for ventilation and renal failure.

Based on the risk factors already identified and presently available treatments, interventions can be tested at different levels to reduce the rate of SAMM or to convert high-scoring cases to lower-scoring ones. One American group has devised a scoring system[31] which contains five categories, including organ system failure, ICU admission, extended intubation, transfusion > 3 units and surgical intervention. The maximum score is 15; women who scored more than 8 were classified as near-misses whereas those who scored less than 8 were classified as severe morbidity. The aim was to refine classification at the most extreme end of the morbidity-to-mortality continuum, thus enabling identification of the key factors responsible for moving women along the continuum and targeting interventions that shift women more towards morbidity rather than mortality[9,31].

To effectively improve outcome, change has to be implemented at various levels, from primary-care providers, through secondary and tertiary centers to health-care systems.

Basic antenatal care

This cannot be overemphasized, as ample evidence shows that antenatal follow-up decreases a woman's risk when it comes to labor and delivery[26,34]. Screening for complications antenatally, treatment and prevention of anemia, cleanliness during delivery, the presence of a skilled birth attendant and active management of the third stage of labor are all basic requirements advocated by the World Health Organization[35]. Staff attending deliveries in the primary-care sector need to be trained to recognize postpartum hemorrhage early and have access to simple drugs to treat it (e.g. misoprostol, ergometrine)[36], as well as recognize when to refer to a more specialized center[26]. In rural South Africa, health-worker problems were identified as causing substandard care in 35–49% of cases[26] out of a total of 65% where substandard care was an issue. Factors identified were delay in diagnosis, treatment, referral and monitoring. In the UK, substandard care was apparent in between 50%[12] and 80%[3] of cases of hemorrhage. Regular skills drills to train staff in estimating blood loss more accurately and recognize signs of compromise are beneficial[3,37]. Blood transfusion, although possible in rural South Africa, often fails because of depleted stocks[26], even if the need for transfusion is recognized[26]. When misoprostol is used at home births in Africa, it significantly reduces rates of postpartum hemorrhage and does not require a medically trained attendant[36,38]. New data[39,40] suggest that sublingual administration may be most effective, and the women can self-administer easily[38], further reducing the cost of an already cheap intervention.

Secondary and tertiary care

Some of the best data come comes from studies where cases were identified from daily audit meetings[10,11,16]. Results of audits and research should be fed back promptly to staff so that improvements can be implemented. In a two-phase study, a reduction in incidence of SAMM and maternal mortality was demonstrated over 4 years, when recommendations from the first audit were implemented[16]. However, in the same study, the incidence of hemorrhage was virtually unchanged: the main factor responsible for decreasing SAMM and mortality was improved care relating to abortion[16]. Clear management protocols and regular skills drills may both contribute to the maintenance of high standards in units[3,22]. Non-adherence to guidelines has been identified as a risk factor for increased maternal morbidity[3,37], whereas dissemination of guidelines and skills drills are associated with improved adherence to the agreed protocols and significant reduction in postpartum hemorrhage[37].

Access, transport, institutional or organizational change

Twenty percent of avoidable SAMM in rural South Africa is due to organizational or administrative causes such as the shortage of essential drugs, ambulances and lack of recruitment and

retaining of experienced staff[26]. These factors are less prominent in the developed world. However, implementation of guidelines and issues such as staff training and effective audit usually occur at organizational levels. Geller and colleagues (2004) analyzed the 'preventability' of events along the continuum of severe morbidity to near-miss to death and concluded that the same factors contributed to the outcome in all categories[31]. These were patient-factors (13–20%), system factors (33–47%) and provider-related factors (90%), mainly incomplete or inappropriate management[31]. Patient factors are potentially the hardest to rectify, especially in developing countries where access to education is limited. System factors figure higher in the US (33–47%)[31] than in South Africa (20%)[26], possibly because failures of well-established systems (as in the US) are likely to have a greater impact than in settings where transport or administrative systems are not established in the first place as, for example, in rural Africa[26]. Provider-related factors were more prominent as a cause of substandard care in the US (90%)[31] than in primary-care settings in South Africa (35–49%)[26]. This is more likely due to non-availability of specialist staff in the latter, with staff performing to the best of their ability in light of the skills they possess. US and European doctors working in obstetrics are specialists, who work to agreed protocols and participate in audit and research to maintain high standards[31].

Health systems

Wider factors relating to health systems can move a woman both up and down the risk pyramid for severity of morbidity. Social exclusion and inequity can be tackled at governmental level in both developing and developed countries[1,34]. Access to contraception, safe legal abortion and antenatal care can also be addressed. Special antenatal services for travellers, teenagers or the mentally ill may be set up by health-service planners[1]. The health insurance system in the US may play a role, as women most at risk are often not insured[31]. In the current era of increased migration, especially from deprived areas or as a result of war and conflict, the population in major cities is changing. Access to 24-h interpreters should become standard and might lead to significant reductions in severe morbidity[1].

CONCLUSION

The triennial UK Confidential Enquiry into Maternal Deaths started in the first half of the 20th century and witnessed a gradual decline in maternal mortality. The numbers of maternal deaths in the developed world are now relatively few, although still prevalent in developing countries. Severe maternal morbidity (SAMM) is prevalent throughout the world, mostly due to treatable conditions. It is often poor, socially excluded women that suffer most. For meaningful comparisons to be made, standardized, simple definitions need to be designed and agreed on as the benchmark for future research. Condition-based definitions are better than management-based ones[9,10,13,31], as the former can be used in poorly resourced areas[26]. Hemorrhage accounts for the largest proportion of SAMM, but it is not one of the major causes of maternal mortality, at least in developed countries[11]. This suggests that registering SAMM would be a valuable way to monitor and improve the quality of maternity services. The Scottish population survey[19] shows such a register is feasible at national level. As the causes of maternal deaths can be very different from the causes of SAMM[11], it would be most useful to have the two enquiries running in parallel. The last triennial report in the UK[5], published in 2004, has already incorporated a chapter on morbidity, thus acknowledging the need for SAMM to be taken into consideration. World-wide, avoidable maternal deaths remain a paramount issue of basic women's rights. Nevertheless, severe hemorrhages that women survive are much commoner. Understanding the relationship between morbidity and mortality should lead to reductions in substandard care and the global burden of both death and long-term morbidity from hemorrhage.

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38

SHEEHAN'S SYNDROME

L. Haddock

INTRODUCTION

In his excellent publications dating from 1938 to 1968, Sheehan described the natural history, clinical signs and pathological findings of the syndrome which bears his name and results from postpartum necrosis of the anterior lobe of the pituitary gland[1–10]. The exact pathogenesis of the disease is not well understood, for many women who suffer severe hemorrhage at delivery apparently escape damage to the anterior pituitary.

Although infrequently reported in the US literature, this clinical entity was the most common cause of hypopituitarism among indigent women of Puerto Rico in the decade of the 1950s to the late 1960s. During that period, 100 cases were diagnosed in the hospital attached to the University of Puerto Rico School of Medicine. Of these, 72 were diagnosed from 1960 to 1970 and came under our medical supervision. The clinical and endocrinological evaluations of 50 of the 72 cases which were available to close follow-up have been published[11]. This review summarizes these findings and comments on the condition.

RESULTS

Clinical data

Of 28 patients diagnosed between 1951 and 1959, 16 died of cortisol insufficiency precipitated by concurrent illnesses. In contrast, only two patients died in the group diagnosed between 1960 and 1970. This marked decrease in mortality was secondary to a better and regular follow-up and an improvement in their education regarding the nature and life-endangering risks of the disease.

Fifty of the 72 patients diagnosed between 1960 and 1970 were thoroughly studied (Table 1). Forty-three (86%) had panhypopituitarism, whereas seven (14%) displayed selective pituitary deficiencies. Of the latter group, one had isolated thyroid stimulating hormone (TSH) deficiency, one had selective human growth hormone (HGH) and gonadotropin deficiency, two lacked HGH and ACTH and three had combined HGH, ACTH, and gonadotropin deficiency.

The age at onset of disease ranged from 20 to 52 years, with an average age of 33.7 years. The age at diagnosis varied from 27 to 65 years, with an average of 43.8 years. The duration of preceding illness at the time of diagnosis ranged from 5 months to 28 years, with an average of 10.5 years.

Table 1 A study in 50 subjects with Sheehan's syndrome

	Number	*Percentage*
Panhypopituitarism	43	86
Selective hypopituitarism		
TSH deficiency	7	14
HGH and gonadotropin deficiency	1	2
HGH and ACTH deficiency	2	4
HGH, ACTH and gonadotropin deficiency	3	6

Age at onset of diagnosis, 20–52 years (mean 33.7 years); age at diagnosis, 27–65 years (mean 43.8 years)
Duration of preceding illness (at time of diagnosis), 5 months–28 years (mean 10.5 years)

The obstetric history of the 50 subjects is summarized in Table 2. Twenty-nine patients (58%) delivered at home and 21 (42%) in the local government hospitals.

Mean parity was 7 ± 3 deliveries. Forty-three (86%) had experienced postpartum bleeding, most commonly caused by retained placental fragments. Of the five patients who had antepartum bleeding, one had an abortion at 7 months' gestation (whether spontaneous or induced not clear from the records), two had abruptio placenta at 9 months' gestation, one had a subarachnoid hemorrhage and Gram-negative bacteremic shock at 7 months' gestation, and the remaining patient had placenta previa and silent rupture of the uterus at 8 months' gestation. Almost half (48%) of the patients had postpartum bleeding that led to the clinical picture of Sheehan's syndrome. Eight patients (16%) had bleeding in earlier pregnancies but were able to conceive. Of these eight patients, two had selective ACTH deficiency, five had a picture of panhypopituitarism at the time of study, and one had selective gonadal insufficiency. A clinical history of shock at delivery was present in 34 cases (68%); seven did not develop shock and information was not available in nine cases.

The salient clinical features are summarized in Table 3. Gonadal insufficiency was present in 94% of the patients, cortisol insufficiency in 96% and thyroid insufficiency in 88%. The earliest sign of pituitary failure was the inability to lactate. Three patients had scanty menses for

Table 2 Obstetric history of 50 patients with Sheehan's syndrome. Mean parity 7 ± 3

	Number	*Percentage*
Delivery		
Home	29	58
Local hospital	21	42
Bleeding in pregnancy		
Postpartum	43	86
Antepartum	5	10
No history of bleeding	2	4
Pregnancies complicated by bleeding		
One (last)	24	48
More than one and no bleeding in last	8	16
More than one and bleeding in last	18	36
Source of bleeding		
Retained placenta	21	42
Placenta abruption	3	6
Placenta previa	2	4
Abortion	1	2
Vaginal laceration	1	2
Uterine atony	4	8
Subarachnoid hemorrhage and septic shock	1	2
Information not available	16	32
Shock		
Present	34	68
Absent	7	14
Unknown	9	10
Subsequent pregnancies after episode causing disease	8	16

Table 3 Clinical features in 50 patients with Sheehan's syndrome

Symptoms and signs	*Percentage*
Gonadal insufficiency	94
Failure to lactate	86
Loss of libido	84
Amenorrhea	88
Breast atrophy	74
Vaginal atrophy	88
Uterine atrophy	86
Cortisol insufficiency	96
Anorexia	72
Weight loss	80
Asthenia, weakness	98
Cachexia	6
Thyroid deficiency	
Cold intolerance	88
Dry skin	94
Hypoactive DTRs	94
Myxedematous facies	44
Secondary sexual characteristics	
Loss of body hair	100
Loss of pubic hair	98
Loss of axillary hair	98
Other	
Pallor	92
Polyuria and polydipsia	4
Pigmentation in the face	4

several months after the episode of postpartum bleeding, after which they became amenorrheic. Cachexia was an infrequent finding; however, when present it was usually due to an associated illness. Of three cachectic patients, two had pulmonary tuberculosis and one was severely malnourished. Signs and symptoms of severe hypothyroidism were present in 22 patients. Severe pallor secondary to ACTH deficiency was the rule in hypopituitarism, although chloasma, for example pigmentation of the face, was seen in two patients. This has been previously described by Sheehan in 1939[3]. Two patients complained of marked polydipsia and polyuria immediately following the episode of bleeding. However, symptomatology was interpreted as secondary to transient diabetes insipidus from which the patients recovered. The study of one of these patients was the subject of a previous report[12].

Endocrinological work-up

Human growth hormone reserve was studied in all the patients. In the basal state, HGH was undetectable. With estrogen-priming and challenging with either insulin-induced hypoglycemia or arginine infusion, only the patient with selective TSH deficiency had HGH reserve, as shown by an increase to 20 ng/ml upon arginine infusion.

Pituitary ACTH reserve was also studied in all patients using the metyrapone test. Only two patients, one with selective TSH and the other with selective HGH and gonadal insufficiency, had a normal response.

Cortisol reserve was studied in all patients before replacement therapy. The basal urinary hydroxycorticosteroids ranged from undetectable values to 1.0 mg/day in the patients who did not show pituitary reserve. The response to ACTH, 40 units twice a day for 4 days (ACTHAR gel) was arbitrarily classified as excellent, good, limited or none, according to the increase inurinary hydroxycorticosteroids after ACTH administration and the ability of these patients to tolerate stress. Seventeen patients had an excellent response (increase over 20 mg/day), nine showed a good response (rise < 20 but > than 12 mg/day), 13 had a limited reserve (increase < 12 but > 6 mg/day) and 11 had poor to no reserve (increase < 6 mg/day) and their responses were similar to those of Addisonians. Two patients who had limited cortisol reserve (increase in urinary hydroxycorticosteroids respectively to 8.8 mg/ day and 6.6 mg/day post-ACTH) died, one of cortisol insufficiency in another hospital in the community and the other in an accident. Both patients were receiving a daily maintenance dose of 25 mg of cortisone acetate. The combined weight of both adrenals in one patient was 5.4 g; histologically, the glands showed atrophy. The adrenals of the other patient were not weighed but were described as atrophied, measuring each $1.8 \times 1.0 \times 0.2$ cm. A correlation was made between the duration of illness and the adrenal reserve found in these patients. Of 14 patients whose disease had existed for 5 years or less, 12 showed an excellent or good adrenal reserve. Of 36 patients whose disease dated from 5 to 29 years, 24 showed a limited, poor or no reserve, and the remaining patients had a good or excellent response.

The aldosterone reserve and ability to conserve sodium upon sodium deprivation was studied in 13 patients, seven of whom were chosen because they had initially shown hyponatremia when first admitted in cortisol insufficiency. All had dilutional hyponatremia which was corrected by fluid restriction and treatment with intravenous hydrocortisone and intramuscular cortisone acetate. None of the patients received desoxycorticosterone (DOCA). Of the seven who had hyponatremia, one had excellent cortisol reserve, two had good reserve, three had limited reserve and one had no reserve. The remaining six patients were selected because they had either a limited or very little cortisol reserve. Additional important clinical data included the presence of old pulmonary tuberculous lesions in three of the patients, two of whom showed no cortisol reserve and the other very limited cortisol reserve. These patients were kept on a 110 mEq sodium diet for 10 days and on the subsequent 7–10 days they were placed on a 8–14 mEq sodium diet. All the patients were kept on their maintenance dose of sodium levothyroxine and, in place of their maintenance dose of cortisone acetate, they were administered an equivalent dose of dexamethasone. Upon sodium restriction, 12

patients attained sodium balance in 2–7 days. One patient was unable to tolerate the low sodium diet and the study had to be stopped on the 4th day, at which time she had not attained sodium balance. No appreciable change in the serum sodium level was observed in all patients during sodium restriction. In nine patients, the aldosterone secretory rate (ASR) was measured on the 7th day of dietary sodium restriction. The ASR ranged from 169 to 535 μg/day. Values for ASR in healthy subjects on a sodium intake of 10–50 mEq of sodium diet are from 100 to 300 μg/day. In one patient, the ASR was measured on the 4th day of sodium restriction and was 283 μg/day. In the remaining patient, it was measured while on the 110 mEq sodium diet and was 160 μg/day. In two patients on a low sodium diet in whom ASR testing was not performed, urinary aldosterone was measured and was considered normal. The urinary aldosterone was low in one but did not correlate with the ASR, which was normal. An adequate response of aldosterone excretion or secretory rate therefore was seen in all patients, including the three in whom the possibility of tuberculosis of the adrenals was considered. The normal response to sodium restriction and the adequate aldosterone excretion or ASR ruled out the possibility of coexistent primary adrenal insufficiency secondary to tuberculous involvement of the adrenals.

Thyroid reserve

The thyroid reserve was determined by measuring the 24-h radioactive iodine (RAI) uptake before and after TSH stimulation in 32 subjects (29 hypothyroid and three euthyroid) and measuring the protein-bound iodine (PBI) before and after stimulation with 10 units of TSH daily for 2 days in 24 patients. The hypothyroid group were classified as responders or non-responders to TSH. In 21 patients with hypothyroidism, the difference in the 24-h RAI from the basal value ranged from 14 to 60%, with a mean difference of 26%. The remaining eight patients had a response similar to that seen in primary hypothyroidism, the difference in the post-TSH 24-h RAI ranging from 2 to 9%. Forty-eight percent of the responders had severe hypothyroidism, whereas 75% of the non-responders had a severe form of the disease. The inadequate response to TSH tended to correlate better with the severity of the disease than with the duration of the illness. The euthyroid group had a normal response to TSH. The PBI pre- and post-TSH was measured in 24 patients (15 already treated with sodium levothyroxine in whom it was discontinued 3 weeks before testing and six, all hypothyroid, but not treated; three were euthyroid). In the three euthyroid patients, the increase in PBI ranged from 1.4 to 2.6 μg/dl. The six hypothyroid patients had never been treated and the severity of their disease ranged from mild to severe. The change in PBI from the basal value was either decreased or had an insignificant rise in the three patients with myxedema. In the three patients with mild to moderate hypothyroidism, as well as in four of the patients receiving treatment, the increase in PBI corresponded to that seen in euthyroid patients; the remaining 11 had an insignificant or negligible change in PBI post-TSH.

Osteoporosis

When these patients were first studied, the technology for bone densitometry was not available. When it became available, Aguiló[13] proceeded to study a group of these patients still under our care using single photon absorptiometry. Bone mineral density, measured at the distal third of the non-dominant arm using a Norland SPA densitometer, showed in 40 of these patients that their bone mineral content and bone mineral density were significantly lower than that of age- and sex-matched controls in Puerto Rico. These patients received thyroid and adrenal physiologic replacement therapy but no estrogen replacement therapy. Twenty-three of these patients were enrolled in a longitudinal bone study with the aim of studying changes in bone mineral content (BMC) with passing time. At a mean of 5.5 years, ten (43.5%) had increased their BMC (Group 1), nine had decreased BMC (Group 2), and four remained unchanged. Group 1 had initial BMC measurements that were significantly lower (0.578 ± 0.04 g/cm) than those in Group 2 (0.764 ± 0.03 g/cm). The age of Group 1 was 65.5 ± 2.6 years and that of Group 2 was

65.2 ± 3.3 years. Group 1 was younger at the onset of the disease (29.2 ± 2.1 years vs. 35.9 ± 2.5 years), and the duration of the disease was 7 years longer (36.3 ± 2.6 years vs. 30.4 ± 3.1 years). There was no difference regarding race, body mass index, physical activity and sun exposure. Pertinent biochemical and hormonal parameters showed no differences except for serum alkaline phosphatase, which was higher than normal upper limit (115 IU/l) in both: 131 ± 17 in Group 1 vs. 121 ± 16 in Group 2; $p < 0.05$.

Upon loss of estrogen support, a rapid phase of bone loss ensues (Riggs type 1) followed by a more gradual age-related loss (Riggs type 2). Aguiló concluded that Group 1 resembled that reported by Kruse and Kuhlencordt[14] who found a positive bone balance in 25% of 108 postmenopausal females, based on histomorphometric data, and proposed a triphasic course of osteoporosis.

COMMENT

Panhypopituitarism is usually characterized by the sequential loss of somatotropic, gonadotropic, adrenocorticotropic and thyrotropic functions[15,16]. The same order holds true in most of the cases of Sheehan's syndrome. Whereas hypopituitarism associated with pituitary tumors often presents in an incomplete form, in Sheehan's syndrome the opposite is true. Indeed, 43 (86%) of our 50 studied cases exhibited a total deficiency of the hormones produced by the anterior pituitary gland.

Studies characterizing human growth reserve in adult hypopituitarism have dealt mainly with pituitary neoplasms. Only eight among a total of 79 cases included in the largest series[17–20] have been cases of Sheehan's syndrome. Of these 79, only four had significant levels of HGH, none of whom had Sheehan's syndrome. In this series of 50 patients, only one had HGH reserve and this patient also had isolated TSH deficiency. Of all pituitary functions evaluated, that of growth hormone secretion was the most consistently abnormal. Thus, a deficient output of growth hormone represents a sensitive and early index of pituitary failure.

With the use of metyrapone, the pituitary ACTH reserve in man can be studied in a quantitative manner. Our clinical experience in the use of this test is similar to that of other investigators. Liddle and associates[21], using the urinary 17-ketosteroids and 17-hydroxycorticosteroids as parameters to measure the response to metyrapone, encountered absent pituitary ACTH reserve in the two patients with Sheehan's syndrome that they studied. Kaplan[22] studied four patients with Sheehan's syndrome, none of whom showed pituitary ACTH reserve as measured by an increase in the urinary Porter Silber chromogens and 11-desoxycorticosteroid after metyrapone administration. Only two of our 50 patients showed pituitary ACTH reserve, both of whom had selective tropic deficiencies.

The response to intravenous and intramuscular ACTH has been described as an accurate means of quantitating adrenocortical reserve in several disease states[23,24]. The administration of ACTH, either intravenously or intramuscularly, to hypopituitary subjects must be repeated on several consecutive days in order to reactivate a dormant adrenal cortex resulting from prolonged absence of endogenous ACTH secretion. In Addison's disease, no steroid response to ACTH is seen, whereas in hypopituitarism a gradual increase in urinary steroid excretion has been described. Adrenal unresponsiveness to ACTH stimulation in hypopituitarism has also been documented[20,25,26]. Chakmakjian[20] reported no increase of urinary steroid excretion after the daily intravenous administration of ACTH for 5 days in five patients with Sheehan's syndrome.

Our data support the findings of others in demonstrating that a lack of adrenal steroid response to ACTH can be seen in hypopituitarism and that it does not necessarily means the presence of Addison's disease.

In our attempt to correlate the adrenal reserve with the duration of illness, we observed that 90% of the patients who had the disease for less than 5 years had a good or excellent adrenal reserve, in contrast to 38% of the patients who had the disease for longer than 5 years. Thus, a positive correlation exists between adrenal unresponsiveness and the duration of illness in approximately two-thirds of the patients, clearly showing that with time the adrenal cortex

becomes progressively atrophied due to severe lack of ACTH.

Aldosterone secretion is largely independent of ACTH regulation, and patients with hypopituitarism should be able to maintain sodium balance upon sodium restriction.

The hyponatremia seen in hypopituitarism is associated with water retention and mimics the syndrome of inappropriate secretion of antidiuretic hormone (ADH)[27]. Ahmed and colleagues demonstrated increased levels of arginine vasopressin in the plasma of patients with either hypopituitarism or Addison's disease[28]. A decrease in the plasma ADH activity and simultaneous improvement of water excretion were observed in these patients during therapy with glucocorticoids. Turin and colleagues[29] demonstrated a reduction in aldosterone secretion in patients with inappropriate secretion of ADH. In a study with an untreated patient with hypopituitarism who showed water retention, hyponatremia, urinary sodium loss and a low aldosterone secretory rate upon dietary sodium restriction, the same authors[30] suggested that the decreased secretion of aldosterone and wasting of sodium in chronic hypopituitarism are related to the persistence of excess ADH. This concept gains strength from the studies of Bartter and associates[31] who showed that volume expansion produced by the administration of vasopressin and water may increase the urinary excretion of sodium and decrease the excretion of aldosterone.

Our studies favor the latter concept and, in order to avoid the effect of antidiuresis in sodium excretion and aldosterone secretion, the studies of our patients were conducted during glucocorticoid and thyroid replacement. This past observation is of clinical and therapeutic importance in the management of hyponatremia in hypopituitarism. In these patients with Sheehan's syndrome, hyponatremia has always been associated with water retention, and prompt diuresis and correction of hyponatremia upon cortisol administration are well known. In contradistinction to Addisonians, never in our experience have hypopituitary patients needed mineralocorticoids for the maintenance of sodium balance. In this group of patients, the ASR upon ACTH stimulation has not been studied as Williams and co-workers[32] did in a group of patients with hypopituitarism and steroid suppression. These authors showed a higher urinary sodium excretion and a significant delay in increasing the ASR, although eventually a normal secretion was achieved. The mean ASR in the hypopituitary group was significantly less than in the normal or the steroid-suppressed subjects. Whether the abnormalities in aldosterone secretion on sodium restriction and ACTH stimulation play a role in the hyponatremia of hypopituitarism is questionable. If this were so, hyponatremia would not be corrected with fluid restriction and cortisol administration alone. The concept of inappropriate secretion of ADH is favored to explain the hyponatremia of hypopituitarism. At the time of our study, the response of the serum PBI and the RAI to TSH stimulation was the conventional test to differentiate primary from secondary hypopituitarism[33,38]. Taunton and colleagues[37] showed that the response in hypopituitary subjects was less the longer they had the disease. Sheehan[3] was the first to postulate that a dormant thyroid gland unstimulated by TSH might in time become fibrotic and therefore unresponsive to TSH. Fletcher and Berford[39] showed that the unresponsiveness to TSH correlated better with the severity of the disease than with the duration of the disease, as was the case in these patients with Sheehan's syndrome.

The findings in this series of Sheehan's syndrome suggest that, due to ACTH and TSH deprivation, the adrenals and the thyroid can become atrophied and unresponsive to stimulation to the tropic hormones; however, in the majority of the instances, the target glands are dormant rather than atrophied and are responsive to the tropic hormones.

Recently, Haddock and associates have shown an overall morphometric vertebral fracture weighted prevalence of 11.2% in a population-based study in a female population 50 years and older in the city of San Juan[40,41]. Of the 48 females out of 398 who had fractures, 19 had an early menopause at mean age 39 ± 4.7 years. Although the asssociation did not reach statistical significance, an early menopause at age less than 45 years is an important risk factor for fractures and osteoporosis, more so if patients do not receive estrogen replacement. Cooper and

associates[42] found that women with vertebral fractures had an earlier menopause, fewer births and higher prevalence of clinically diagnosed hyperthyroidism. Thus, women with Sheehan's syndrome who develop the disease in their reproductive years are more prone to develop osteoporosis and fractures, for they are diagnosed late in the course of the disease and have not received hormonal replacement therapy.

These patients received replacement therapy with cortisone acetate 25 mg daily divided in two doses, sodium levothyroxine in the amount that normalized the PBI, supportive treatment for underlying diseases and education about the disease and its life-threatening risks. A letter was given to every patient and her immediate family, stating the nature of the disease and what to do in case of illness or if taken unconscious to emergency rooms of government hospitals.

CONCLUDING REMARKS

In the last four decades, we have seldom seen new cases of Sheehan's syndrome in the University Hospital. The main reasons are improvements in the prenatal and delivery care of the indigent population. Whereas, in the past, 58% of the patients with Sheehan's syndrome were delivered at home, from the 1970s onwards all indigent patients delivered in hospitals. Since 1993, a Health Reform was implemented in Puerto Rico based on managed care. All but one of the secondary hospitals was sold to private enterprise and the main care of patients is now in the hands of primary physicians who seldom refer patients to the specialists as it affects their income, which is capitated. Fewer and fewer physicians are practicing Obstetrics because of the high insurance and fewer physicians are selecting Obstetrics and Gynecology for training. Responding to the urgent need of preparing a skilled health professional for the delivery of maternal and infant care services in Puerto Rico, the Graduate School of Public Health of the University of Puerto Rico Medical Sciences Campus has initiated a Nurse Midwifery Education Program, which offers a Graduate Certificate option and a Master of Public Health/Nurse Midwifery[43]. This program is supported by the US Department of Health and Human Service, Health Resources and Service Administration, the Government of Puerto Rico, and the Department of Health of Puerto Rico, and is accredited by the American College of Nurse-Midwives. The nurse-midwife is a registered nurse educated in two disciplines, nursing and midwifery. The nurse-midwife cares for essentially healthy women before, during and after childbirth.

The nurse-midwife works as an interdependent health-team member in a setting that provides physician consultation and referrals for complications[44]. Thus, the time will eventually come when deliveries in the indigent population may again be performed by midwives, as was the case in the first half of the 20th century, but this time by a skilled health professional who is part of the health team. The Department of Health of the Commonwealth of Puerto Rico must follow closely all the statistics regarding prenatal and delivery care so as to identify all cases with postpartum hemorrhage or the deliveries complicated with bleeding in order to identify the potential cases that may develop Sheehan's syndrome. Good prenatal and delivery care is a must to be able to prevent Sheehan's syndrome.

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39

AN INSTITUTIONAL EXPERIENCE

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The White Memorial Medical Center (WMMC) is a private community hospital located in East Los Angeles, California. Established in 1913 by the Seventh-day Adventist Church, the WMMC promotes its mission to provide quality health services, medical and health education, and outreach services to the Los Angeles community, with care and compassion. With a capacity of 369 beds, WMMC serves a densely populated community, with more than two million people living within a 5-mile radius of the Medical Center. The demographics of this service area reflect an ethnic homogeneity, whereby 70.7% of residents are Hispanic and 7.5% Asian. The population can be characterized as low income, with about 62% of households having an annual income of $25 000 or less[1]. As a direct result of this circumstance, government-sponsored health care is relied upon to a great extent and fully insured coverage is relatively uncommon.

The WMMC conducts graduate and continuing medical education activities as an affiliate institution for Loma Linda University School of Medicine. Four residency-training programs are in place: Obstetrics and Gynecology, Family Medicine, Internal Medicine, and Pediatrics. The Department of Obstetrics and Gynecology is comprised of 25 medical staff members, seven of whom serve as full-time faculty for the residency-training program. The remaining medical staff members serve as consulting and part-time faculty. The resident house staff participates in the care of all patients and its members are an integral part of the health-care team. The obstetric service performs approximately 3500 deliveries per year. As is the case in obstetric practice of this magnitude, hemorrhage is encountered and often is unanticipated.

In the spring of 1997, the chief obstetric resident encountered an instance of postpartum hemorrhage, which required life-saving emergency hysterectomy in a young woman. Moved by her concern for her patient, by her observation of the morbidity associated with postpartum hemorrhage, and her intellectual curiosity, she conducted a literature search and encountered the publication 'The B-Lynch surgical technique for the control of massive postpartum hemorrhage: an alternative to hysterectomy? Five cases reported', published in the *British Journal of Obstetrics and Gynaecology* in March 1997, by B-Lynch and associates[2]. This article was then presented to other residents and staff at Journal Club, thus introducing the then new concept of uterine compression by brace suture. In the years since 1997, the operation has been used regularly.

CASE SERIES

The study design was as follows: cases with B-Lynch suture utilization for severe postpartum hemorrhage were identified, from March 1, 1997 to March 31, 2005, at WMMC. Case records were reviewed, and postoperative follow-up was conducted by telephone interview and outpatient clinic chart review. The historical characteristics and outcome of these patients are described in Table 1.

The B-Lynch suture operation was performed on 22 patients to control intractable postpartum hemorrhage at Cesarean section not responding to uterotonic agents. In 12 instances, the B-Lynch suture was the only surgical intervention, whereas in ten it was combined with discrete vessel ligation. The procedure, either alone or combined with vessel ligation, resulted

Table 1a Biodata and clinical details of women who had B-Lynch suture for postpartum hemorrhage

Case number	*Age* (years)	*Gravidity/ parity*	*GA* (weeks)	*Reason for Cesarean section*	*Length of labor* (h)	*Estimated blood loss* (ml)	*Transfusion*
1	19	2/0	39 4/7	Arrest of dilation	17	2000	
2	26	1/0	42 3/7	Arrest of dilation	18	1600	
3	25	2/1	41 6/7	Arrest of dilation, unsuccessful VBAC	22	1500	1 unit PRBC
4	27	4/0	40 6/7	Failed induction for pre-eclampsia	15	3500	5 units PRBC, 2 units FFP
5	19	2/1	43	Elective repeat Cesarean section	0	3000	2 units PRBC
6	27	2/1	42	Elective repeat Cesarean section	0	2600	4 units PRBC, 2 units FFP
7	40	9/6	37	Elective repeat Cesarean section	0	1700	2 units PRBC
8	20	1/0	41 3/7	Arrest of dilation	20	2200	3 units PRBC
9	19	1/0	38 6/7	Arrest of dilation	12	1800	2 units PRBC
10	16	2/0	38 2/7	Arrest of dilation	7	1500	
11	27	2/1	41 5/7	Arrest of dilation, unsuccessful VBAC	18	1500	
12	20	2/0	39 2/7	Arrest of dilation	14	1100	
13	23	3/1	38 3/7	Non-reassuring fetal heart tracing, previous Cesarean section	0	1600	
14	27	2/1	40 1/7	Arrest of dilation, unsuccessful VBAC	7	2000	
15	38	3/1	40 5/7	Failed induction, unsuccessful VBAC	20	2200	
16	33	1/0	41	Failed induction	12	2300	3 units PRBC
17	32	2/1	38 3/7	Elective repeat Cesarean section	0	2000	2 units PRBC
18	28	1/0	40 2/7	Arrest of dilation	15	1500	
19	26	2/1	38 6/7	Elective repeat Cesarean section	0	2400	6 units PRBC, 1 unit FFP
20	27	1/0	40 1/7	Arrest of dilation	18	2500	
21	33	4/3	40 1/7	Arrest of descent	17	1250	
22	27	3/2	39	Prior Cesarean section × 2	0	2000	1 unit PRBC

VBAC, vaginal birth after Cesarean section; GA, gestational age; PRBC, packed red blood cells; FFP, fresh frozen plasma

Table 1b Biodata and clinical details of women who had B-Lynch suture for postpartum hemorrhage

Case number	*Uterotonic drugs given** (IV, IM, IMY)	*Postpartum hemorrhage management procedures†*
1	Oxytocin IV 70 U + IMY 10 U, methylergonovine ×2, carboprost ×5	Uterine artery ligation, ovarian vessel ligation, B-Lynch
2	Oxytocin IV + IMY 40 U, methylergonovine ×2, carboprost ×5, IV + IM	Uterine artery ligation, B-Lynch
3	Oxytocin IV 30 U + IMY 40 U, carboprost ×5, IV + IM	Uterine artery ligation, ovarian vessel ligation, B-Lynch
4	Oxytocin and carboprost	Over-sewing placental bed, uterine artery ligation, ovarian vessel ligation, B-Lynch, hysterectomy
5	Oxytocin IV 60 U, carboprost IM ×3	Uterine artery ligation, B-Lynch
6	Oxytocin IV + IMY 20 U, methylergonovine IM ×1, carboprost IM ×2	B-Lynch, hysterectomy
7	Oxytocin IV + IMY 20 U, carboprost IM ×1 + IMY ×3	Uterine artery ligation, ovarian vessel ligation, B-Lynch, hysterectomy
8	Oxytocin IV + IMY 70 U, methylergonovine IM ×4, carboprost IM ×3 + IMY ×3	Uterine artery ligation, ovarian vessel ligation, B-Lynch
9	Oxytocin IV 40 U, carboprost IM ×2	B-Lynch
10	Oxytocin IV 20 U + IMY 20 U, carboprost IM ×1 + IMY ×1	B-Lynch
11	Oxytocin IV 50 U, carboprost IM ×4	Uterine artery ligation, B-Lynch
12	Oxytocin IV 30 U + IMY 30 U, carboprost IM ×2 + IMY ×2	B-Lynch
13	Oxytocin IV 30 U + IMY 20 U, methylergonovine IM ×1, carboprost IM ×2	B-Lynch
14	Oxytocin IV + IMY 40 U, carboprost ×4, IM + IMY	B-Lynch, uterine artery ligation, hysterectomy
15	Oxytocin IV + IMY, methylergonovine IM ×1, carboprost IM ×1 + IMY ×4	B-Lynch
16	Oxytocin IV + IMY 50 U, methylergonovine IM ×2, carboprost IM ×2 + IMY ×4	B-Lynch
17	Oxytocin IV + IMY 30 U, carboprost IM ×4 + IMY ×2	B-Lynch
18	Oxytocin IV 30 U + IMY 20 U, carboprost IM ×2 + IMY ×2	B-Lynch
19	Oxytocin IV 70 U + IMY 40 U, methylergonovine IM, carboprost IM ×2 + IMY ×2,	Uterine artery ligation, B-Lynch, supracervical hysterectomy
20	Oxytocin IV, methylergonovine IM ×2, carboprost IM ×2 + IMY ×3	B-Lynch
21	Oxytocin IV + IMY 40 U, methylergonovine IM ×1, carboprost IM ×3 + IMY ×3	B-Lynch
22	Oxytocin IV, carboprost IM ×2 + IMY ×1	B-Lynch

*Methylergonovine 200 μg per dose, carboprost 250 μg per dose; IV, intravenous; IM, intramuscular; IMY, intramyometrial; †each procedure is listed in order of execution

in control of bleeding, with uterine preservation in 77% of the cases. In those instances in which the etiology of postpartum hemorrhage was uterine atony, the B-Lynch suture was successful in 85% of the cases. Hysterectomy was thus avoided in 17 of the 22 cases.

Table 1 describes the biodata and clinical details of the 22 patients. The patients' ages ranged from 16 to 40 years, with a mean age of 26.2 years. Ten patients were para 0, nine para 1, and one was para 6. ('Para' refers to parity at the start of the pregnancy, a reference point that is consistent with other case reports in the literature. These patients had delivered when hemorrhage was diagnosed.) The estimated gestational ages (EGA) ranged from 37 to 43 weeks, with an average EGA of 40.1 weeks.

All cases were delivered by Cesarean section. Uterine atony was the intraoperative clinical working diagnosis for postpartum hemorrhage in all 22 instances. All cases received intraoperative uterine compression and medical uterotonic agents. Of the 22, 11 achieved hemorrhage control with the B-Lynch suture alone. Six cases achieved control with combined B-Lynch suture and vessel ligation. The other five proceeded to hysterectomy for intractable bleeding in spite of placement of the B-Lynch suture. Two of these five were found to have focal placenta accreta on histological study. The other three had no specific pathologic finding.

Antenatal obstetric problems described in these patients included: prior Cesarean section (11 cases), arrest disorder of labor (12 cases), oxytocin labor induction/augmentation (11 cases), chorioamnionitis (eight cases), preeclampsia (five cases), pre-operative magnesium sulfate (four cases), macrosomia (seven cases), and gestational diabetes (two cases). Obviously, many patients had more than one problem that preceded hemorrhage.

All cases received intraoperative uterine compression and medical uterotonic agents (oxytocin, methylergonovine, 15-methyl prostaglandin $F_{2\alpha}$[3] (carboprost)). Twelve patients did not receive methylergonovine, seven of whom had hypertensive disease.

Three surgical approaches were noted when the B-Lynch suture was used:

(1) B-Lynch technique was the only uterine-preserving hemostatic surgical procedure performed (12 cases);

(2) Uterine artery ligation (nine cases, five with additional ovarian vessel ligation) was performed first, followed by B-Lynch technique; and

(3) B-Lynch suture was performed first, followed by uterine artery ligation.

In the 12 patients where the B-Lynch was the only surgical procedure performed to achieve hemostasis, 11 resulted in hemorrhage control with uterine preservation. The estimated blood loss ranged from 1100 to 2600 ml. Five patients received transfusion of packed red blood cells. Two patients developed dilutional coagulopathy. Only one B-Lynch suture case required hysterectomy for intractable uterine hemorrhage. That patient, who had undergone an elective repeat Cesarean section at term, developed severe uterine atony, unresponsive to uterine manual massage and uterotonics. Despite placement of a B-Lynch suture, brisk bleeding continued, and the patient developed dilutional coagulopathy intraoperatively. In face of continued life-threatening hemorrhage and the patient's preoperative desire and consent for permanent sterilization, the surgeon proceeded to hysterectomy for intractable hemorrhage. The patient received 4 units packed red blood cells and 2 units fresh frozen plasma (FFP), and had an uncomplicated postoperative course. Histological study did not reveal placenta accreta.

Nine patients first underwent uterine artery ligation (five with ovarian vessel ligation) followed by B-Lynch technique. Six of these nine cases resulted in hemorrhage control with uterine preservation. The estimated blood loss in these cases ranged from 1500 to 3500 ml. Six patients received transfusion of packed red blood cells. Two cases of coagulopathy required FFP transfusion.

In 13 instances, the B-Lynch technique was the surgical procedure applied first. Among these, one case was followed by uterine artery ligation to achieve hemorrhage control, and one proceeded to hysterectomy, as previously noted. The cases in which the surgeons chose to apply

first the B-Lynch technique occurred in the latter years of the study (after 1999). This may reflect the surgeons' preceding experiences of successful B-Lynch cases, thus fostering greater willingness and less suspicion for the brace suture application. A total of seven surgeons and approximately 20 residents managed these cases.

Of the 22 cases, 17 resulted in hemorrhage control with uterine preservation. Among the five B-Lynch cases that proceeded to hysterectomy, two were noted to have focal placenta accreta. Seven patients with uterine preservation developed postoperative endometritis. Five of these cases had preceding chorioamnionitis during labor. There were no cases of postoperative pyometrium[4]. None of the B-Lynch cases required readmission for recurrent bleeding.

Twelve of 17 B-Lynch patients with uterine preservation were contacted for follow-up 1 month to 7 years after the operation. Five patients could not be reached due to changes in address and phone number and, therefore, were lost to follow-up. Nine patients were on reversible contraception. One patient underwent laparoscopic tubal sterilization 3 months after B-Lynch procedure. The uterus was described as normal in the laparoscopy operative note.

One patient is presently pregnant at 28 weeks' gestation, with an uncomplicated course. Conception occurred 1 year after the B-Lynch procedure.

Two patients delivered live births after receiving the B-Lynch procedure. One patient had a term vaginal delivery (vaginal birth after Cesarean section), 3.5 years after the B-Lynch procedure, resulting in a liveborn female infant, Apgar scores 9 and 9. A second patient underwent a repeat Cesarean section, 2 years after B-Lynch procedure, at 24 5/7 weeks' gestation for preterm premature spontaneous rupture of membranes and non-reassuring fetal heart rate tracing. No uterine anomalies or marks from the prior B-Lynch procedure were noted intraoperatively.

When the B-Lynch procedure was used alone, it was effective in 92% of cases of postpartum hemorrhage in our institution. When used in combination with vessel ligation, it was effective in 60% of cases.

COMMENT

In 1997, Christopher B-Lynch introduced a uterine compression suture for the control of postpartum hemorrhage after Cesarean section[2]. The B-Lynch technique or 'brace suture' is performed at laparotomy, with a hysterotomy incision in the lower uterine segment. Of the five cases presented by B-Lynch, three were delivered by Cesarean section, and two by the vaginal route. The patients who delivered vaginally underwent laparotomy and hysterotomy for B-Lynch suture placement. The etiology of postpartum hemorrhage in the original B-Lynch series was variable, including uterine atony, placenta previa and coagulopathy.

In our case series, all 22 cases involved placement of B-Lynch suture at Cesarean section, and, therefore, the laparotomy and hysterotomy prerequisites of suture placement were already in place. All 22 of our cases had the intraoperative diagnosis of uterine atony (two cases also had diagnosis of placenta accreta).

Since the B-Lynch technique was introduced, several case reports and small case series, ranging from one to seven cases, have been published[5–19]. These publications are summarized in Table 2. Of the 43 cases reported since B-Lynch's report, 35 were delivered by Cesarean section, six were delivered vaginally, and two were without specification of delivery route. Uterine atony was the etiology in 36 of these 43 cases. Placenta accreta and placenta previa were the causes of postpartum hemorrhage in four instances[6,8,12,15]. Lower uterine segment bleeding was reported in two cases[16]. B-Lynch brace suture prophylactic application was reported in one case of triplet pregnancy in a Jehovah's Witness[10]. One case of B-Lynch suture placement for uterine atony in the second trimester of pregnancy was also reported, with suture placement after uterine vacuum curettage for intrauterine fetal demise[18].

The cumulative 'success rate' (number of cases achieving control of postpartum hemorrhage with uterine preservation/total number of cases) is 98%. By combining the literature cases with our series, 70 cases are identified with a 'success rate' of 91%.

Table 2 B-Lynch suture: literature review

Author	*Date*	*Number of cases*	*'Success' rate**	*PPH etiology*		*Delivery route*	
B-Lynch *et al.*	1997	5	5/5	uterine atony	1	Cesarean	3
				placenta previa	1	vaginal	2
				DIC	2		
				unspecified	1		
Ferguson *et al.*	2000	2	2/2	uterine atony	2	Cesarean	2
Dacus *et al.*	2000	4	4/4	uterine atony	3	Cesarean	3
				placenta accreta	1	vaginal	1
Vangsgaard	2000	1	1/1	uterine atony	1	Cesarean	1
Hayman *et al.*	2002	3**	3/3	uterine atony	2	Cesarean	2
				placenta accreta	1	vaginal	1
Wergeland *et al.*	2002	5	5/5	uterine atony	5	Cesarean	2
						vaginal	1
						not stated	2
Kalu *et al.*	2002	1	1/1	prophylactic	1	Cesarean	1
Danso *et al.*	2002	1†	1/1	uterine atony	1	Cesarean	1
Mazhar *et al.*	2003	2	2/2	uterine atony	1	Cesarean	2
				placenta previa	1		
Smith *et al.*	2003	7	6/7	uterine atony	7	Cesarean	7
Pal *et al.*	2003	6	6/6	uterine atony	6	Cesarean	6
Chaudhary *et al.*	2003	1	1/1	placenta increta	1	Cesarean	1
Holtsema *et al.*	2004	7	7/7	uterine atony	5	Cesarean	6
				lower uterine segment bleeding	2	vaginal	1
Grotegut *et al.*	2004	1	1/1	uterine atony	1	Cesarean	1
Hillaby *et al.*	2004	1	1/1	uterine atony	1	vaginal (curettage for fetal demise 2nd trimester)	1
Malibary	2004	1**	1/1	uterine atony	1	vaginal	1

*Number of cases achieving hemorrhage control with uterine preservation/total number of cases; **modified B-Lynch; †B-Lynch suture combined with intrauterine balloon catheter; DIC, dilatation & curettage

Eight live births are reported after B-Lynch. Four cases were reported by El-Hamamy and B-Lynch[20]. Holtsema and associates presented two cases of live births delivered by Cesarean section after B-Lynch[16]. The seventh and eighth cases of live births after B-Lynch brace suture are within the current series. Additionally, an uncomplicated 28-week gestation after B-Lynch is being followed in our case series.

Consistent with the original B-Lynch study, subsequently reported cases involved reopening the Cesarean section hysterotomy wound for brace suture placement. Pal and associates reported cases where the hysterotomy was left open until hemorrhage control was secured after placing the B-Lynch suture[14]. The Cesarean hysterotomy management in our series varied, including initial closure and reopening for brace suture placement, partial closure until brace suture placement, or closure after brace suture placement.

In 2002, Hayman introduced a 'modified' B-Lynch suture, whereby brace sutures are placed without hysterotomy incision[8]. Hayman described placing brace sutures in a patient who delivered vaginally and subsequently underwent laparotomy for postpartum hemorrhage. He describes an intact uterus with the lower segment relatively well contracted. Using four 1-vicryl sutures and passing the needle from

front to back in line where a lower segment incision would have been, uterine compression was achieved with resultant control of postpartum hemorrhage.

The B-Lynch technique appears to be a safe and efficacious procedure. The cases of postoperative endometritis responded to antibiotic treatment, and there were no injuries to bladder, ureters, broad ligament, or pelvic side-wall vessels. Patients with long-term follow-up demonstrated resumption of menses and normal reproductive health practices.

In 2004, Grotegut and associates reported one case of erosion of a B-Lynch suture through the uterine wall[17]. A 19-year-old primigravida underwent successful B-Lynch suture placement at Cesarean section, using No. 0 Maxon (US Surgical, Norwalk, Connecticut, USA). At 6 weeks postpartum, the suture was noted to be protruding through the cervical os and was removed without difficulty. Sonohysterography performed 6 months after the operation showed a small defect in the anterior wall of the lower uterine segment. The authors commented that the effect of the erosion on future fertility and labor is unknown.

Danso and Reginald[11] presented one case report of B-Lynch suture technique used in combination with intrauterine balloon catheter for control of postpartum hemorrhage. A 38-year-old primigravida underwent Cesarean section at 41 weeks and 3 days gestation for failure to progress. Uterine atony was encountered. Uterine massage, oxytocin and carboprost uterotonics, and B-Lynch brace suture all were applied. Although significant reduction in bleeding was noted after these measures, moderate blood loss continued from the vagina. Through the vagina, a three-way prostatic balloon catheter was inserted into the uterus and filled with 70 ml of water, resulting in tamponade. Bleeding was reported to have stopped immediately.

The B-Lynch suture cases at White Memorial Medical Center present the largest series to date using this procedure for uterine preservation. Reproductive outcome is also reported. Theoretical limitations of this case series study include the small sample size and absence of a controlled, randomized design. However, because postpartum hemorrhage cannot be anticipated and often occurs under urgent or emergent life-threatening situations, controlling for variables and randomization may be exceedingly difficult to implement and of highly questionable ethical value.

Within the limitation of only having case reports and case series in the literature and the unlikelihood of ever having data from a randomized trial, the authors propose an algorithm (Figure 1) for the use of the B-Lynch technique at Cesarean section, where the prerequisites of laparotomy and hysterotomy are part of the delivery process.

USING THE WMMC ALGORITHM

Given that 59 of 70 cases (84%) in the literature were for postpartum hemorrhage due to uterine atony, this diagnosis serves as a template for the B-Lynch procedure. After proceeding with uterine massage, close the hysterotomy to minimize blood loss from dilated myometrial vessels. Administer medical uterotonics: oxytocin, methyl ergonovine in the non-hypertensive, carboprost, and misoprostol[21]. Although oxytocin is often given as first-line prophylaxis at placental delivery, there is no evidence to support any specific sequence of use. If hemorrhage persists, continue bimanual compression. As described in the original article, decreased bleeding with compression serves as an assessment tool for the potential success of the B-Lynch technique[2]. If there is decreased bleeding with compression, proceed with the B-Lynch suture.

There is no evidence that either uterine artery ligation or B-Lynch is more effective or safer than the other. However, in the presence of uterine atony, the authors suggest that it makes clinical sense to proceed with surgical uterine compression. If the standard B-Lynch technique is used, the hysterotomy is reopened. If the hysterotomy is left intact, the modified B-Lynch by Hayman may be utilized[8].

If hemorrhage persists, after manual massage, multiple uterotonic agents and B-Lynch suture, proceed with step-wise uterine devascularization with uterine artery ligation and ovarian vessel ligation[22]. If hemorrhage remains brisk after these interventions,

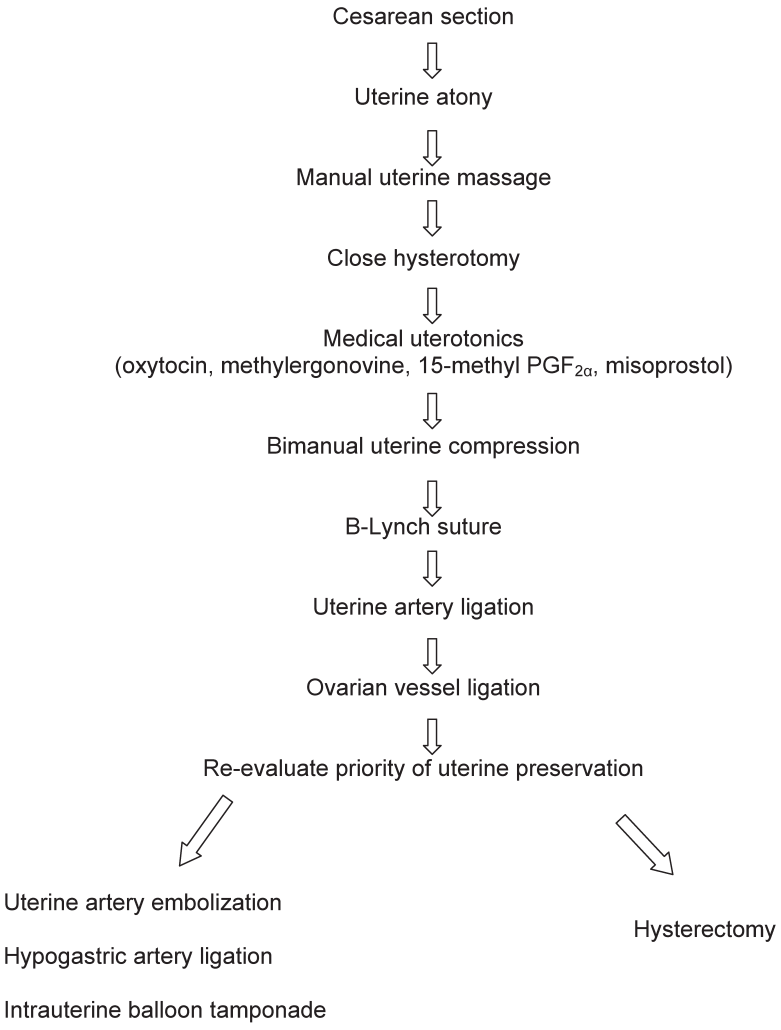

Figure 1 Postpartum hemorrhage due to uterine atony: management at Cesarean section

hysterectomy must be considered. Generally, the above measures are performed over time, with varying intervals between uterotonic agents and surgical procedures. As blood loss accumulates, continued consideration must be given to the patient's hemodynamic stability, presence of coagulopathy, and the potential for further compromise of the patient's already critical condition with continued delay rather than proceeding to hysterectomy. This is especially true if blood replacement supplies are diminishing or non-existent. If uterine preservation remains a high priority, assess the patient's stability for selective artery embolization if such facilities are available, hypogastric artery ligation, or intrauterine balloon tamponade.

Hypogastric artery ligation has a reported success rate of 50–60%, but carries with it the associated risks of retroperitoneal surgery[23]. Moreover, the technique is not familiar to all obstetric surgeons, and the use of hypogastric artery ligation precludes angiographic embolization as an option. Selective artery embolization has a reported success rate of 85–95%, but requires immediate proximity of an equipped invasive radiology set-up and experienced personnel[24]. Intrauterine balloon tamponade is dependent upon availability of the appropriate device[11]. At this point, the choice of procedure for control of postpartum hemorrhage in the algorithm is a judgment best decided by the treating physician.

CONCLUSION

In the presence of postpartum uterine hemorrhage, rapid diagnosis and intervention are paramount to effective treatment. When preservation of the uterus is desired, the surgeon must be knowledgeable in those techniques that will maximize this eventuality. The B-Lynch suture is one of a number of new options available to the obstetrician. It is an alternative uterus-preserving surgical procedure that is effective in controlling postpartum hemorrhage from uterine atony. In our experience, the B-Lynch technique is technically simple, easy to learn, can be performed quickly, and may be used in combination with traditional uterine preserving procedures.

Recent graduates of the White Memorial Medical Center's Obstetrics and Gynecology Residency Training Program, trained in the B-Lynch suture technique, continue to utilize the brace suture for management of postpartum hemorrhage in their practices. Their skills and knowledge are testimony to the impact of physicians' commitment to scholarly activity. Through discovery, dissemination and application of new approaches and new techniques, the care of the patient is continually improved and optimized.

ACKNOWLEDGEMENTS

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40

FAMILIAL CONSEQUENCES

V. Walvekar and A. Virkud

INTRODUCTION

Indian studies on maternal mortality reveal hemorrhage as the leading cause of maternal death[1]. What is particularly disturbing is that the women who survive postpartum hemorrhage are often not well and that this problem receives very little attention. Indeed, out of nearly 120 million women who give birth each year, it is estimated that more than 60 million will develop some kind of complication. Of these, 15–20 million will develop moderate- to long-term disabilities, however small or large[2]. Under these circumstances, the global problem is staggering. As the woman is both a wife and a mother, she is the center of the family's existence; her mortality or even morbidity affects the functioning of the entire family, as well as the nurturing of her children. Of equal importance, the woman is an important part of a country's workforce, so her disability has an impact on society as a whole.

THE HIDDEN PROBLEM IN DEVELOPING NATIONS

The sociocultural climate in developing nations is such that a woman's health is given least priority. Hence, maternal morbidities receive little or no attention, either from the society as a whole or from the government and it agencies. In stark contrast, a death causes major disturbance in the family environment, and its potential resolution, e.g. a single father or remarriage, often complicates a previously bad situation. Unfortunately, no real evidence-based studies are available to highlight this hidden problem. It is worthwhile, however, to look at the issue from a qualitative point of view.

CONSEQUENCES OF POSTPARTUM HEMORRHAGE

Consequences to the mother

The problem is more than one of mortality. Little doubt exists that for every woman who dies, there are at least 20–30 who suffer long-term disabilities.

The immediate consequences include:

(1) Failure of or impaired lactation leading to an undernourished child prone to infections, especially if born preterm;

(2) Anemia leading to susceptibility to postpartum infections, ranging from simple endometritis to severe puerperal sepsis, which in itself can be a cause of maternal death later in the puerperium;

(3) Deterioration of existent diseases, especially in mothers who are anemic, or have tuberculosis, HIV, and cardiac lesions, all of which often create disabling complications, more so if there has been a prior surgical intervention for the management of postpartum hemorrhage;

(4) Postpartum mental alterations, especially in the sick mother who cannot fend for her child. Here, the stage is set for a classic postpartum depression or even psychosis, which may end in dire consequences such as suicide or infanticide in some cases.

Delayed consequences may include:

(1) Prolonged collapse with pituitary failure and Sheehan's syndrome, with resultant secondary amenorrhea and infertility (see Chapter 38);

(2) Premature aging, apathy and mental confusion[3];

(3) Chronic and debilitating anemia. Between 50 and 90% of pregnant women worldwide, with or without prior postpartum hemorrhage, suffer from this problem. The causes of anemia include inadequate dietary intake of iron, folic acid, and vitamin A, and anemic losses due to parasitic infestations and malaria. Women with severe anemia are more vulnerable to infection during pregnancy and childbirth, are at increased risk of death due to obstetric hemorrhage, and are poor operative risks in the event that Cesarean delivery is required. World-wide, anemia is considered the most important indirect cause of maternal mortality and morbidity. WHO data estimate that anemia associated with maternal causes in less developed countries in 2000 alone resulted in a loss of women's productivity valued at more than US$5 billion[4].

Consequences to the children

The same postpartum hemorrhage that threatens women's survival can also cause death and disability in newborns. The vast majority of the estimated 8 million perinatal deaths that occur annually in less developed countries are associated with maternal health problems or poor management of labor and delivery[5]. As an illustration, obstructed and prolonged labor, both important causes of postpartum hemorrhage, asphyxiate an estimated 3% of newborns, resulting in death for nearly 25% of these infants and brain damage for another 25%. In addition, women suffering from severe anemia resulting from postpartum hemorrhage are more likely to have low birth-weight infants (< 2500 g) in subsequent pregnancies. These low birth-weight infants are 20–30 times more likely to die in the first week of life than infants of normal weight, and those who survive are more likely to suffer neurological disabilities including cerebral palsy, seizures, and severe learning disorders[2].

Consequences to the family and society

A mother's disability profoundly affects the family and the community at large due to changes in the household responsibilities and finances:

(1) The cost of her treatment can cripple the family finances;

(2) Her reduced productivity can affect family income and may force the children to leave school, enter the labor force and/or assume domestic responsibilities;

(3) Children often are neglected, undernourished and have health problems;

(4) Some surviving children may be forced into child prostitution. Of the estimated 2.3 million women who make their livelihoods in prostitution, a quarter are minors;

(5) The emotional cost to the family may be manifest by psychopathic behavior either in surviving children or in the father.

If such are the potential consequences when the mother survives, it is logical to ask what happens when she does not?

Death of the mother

The consequences of maternal death are dramatic, not only for the family but also for the medical community and the society at large.

Emotional cost

(1) The family is shattered as the central and sustaining core is suddenly withdrawn;

(2) The children are suddenly orphans, at the mercy of their relatives and institutions; some may become delinquent or street children;

(3) The father is lost, emotionally and financially, and may blame the newborn, an event which often proves disastrous for the surviving child(ren);

(4) Medicolegal suits against the doctor and/or the hospital may come forward out of desperation, anger or even the desire for vengeance.

Children

Orphan children are more likely to become juvenile delinquents or wayward members of the society, often leading a life of petty and serious crime or begging. They are also at risk of physical and/or sexual abuse by family or community members.

The father/husband

(1) He may remarry for the sake of children, which may or may not be beneficial and may lead to destruction of the original family unit;

(2) He is at risk for depression, reduced income and dwindling resources. This picture is not pleasant but the story goes even further;

(3) He may initiate medicolegal proceedings out of anger or financial need.

Consequences to the society at large

Today, women form an important world-wide workforce, contributing immensely to the growth and development of nations. This prospect is seriously weakened by the long-term impact of problems following childbirth such as postpartum hemorrhage. It is very aptly said that 'A woman's health, a nation's wealth'. What is more important is that not only an is an effective workforce in place with healthy women, but also that the national cost of health care can diminish. In India for example, health and family welfare ministries in various states run and subsidize many public hospitals and medical colleges. These hospitals provide medical services at a nominal cost, as the actual cost is subsidized by the government. By reducing preventable maladies, the national health-care cost can diminish by a ripple effect.

MEASURES TO REDUCE THE RISK OF POSTPARTUM HEMORRHAGE AND ITS IMPACT

Role of the obstetrician

WHO recommends four prenatal visits during pregnancy as a minimum. The initial visit should be within the first 3 months of pregnancy. Adequate supervision helps to anticipate, diagnose and treat many problems such as pregnancy-induced hypertension and anemia before their severity takes a grave turn.

Role of the skilled attendant

The term 'skilled attendant' refers exclusively to people with midwifery skills (for example, doctors, midwives, nurses) who have been trained to proficiency in the skills necessary to manage normal deliveries and diagnose or refer obstetric complications.

Ideally, skilled attendants live in, and are part of, the community they serve. They must be able to manage normal labor and delivery, recognize the onset of complications, perform essential interventions, start treatment, and supervise the referral of mother and baby for interventions that are beyond their competence or not possible in the particular setting[6]. Depending on the location, other health-care providers, such as auxiliary nurse/midwives, community midwives, village midwives, and health visitors, may also have acquired appropriate skills if they have been specially trained. These individuals frequently form the backbone of maternity services at the periphery, and pregnancy and labor outcomes can be improved by making use of their services, especially if they are supervised by well-trained midwives.

Home visits also give health workers the chance to educate women about diet and healthy behaviors and to offer women nutritional supplements. This health awareness goes a long way. Antenatal care providers should inform women about the importance of safe delivery with a skilled birth attendant, the warning signs of complications, and how to plan for emergency care. In developing nations such as India, the importance of a hospital delivery, which can provide an environment which is safer for delivery and childbirth, can never be overemphasized (see Chapter 49).

Role of the obstetric community

The national body of obstetricians, The Federation of Obstetricians and Gynecologists of India (FOGSI) recognizes this need and has

implemented the following programs (see also Chapter 49):

(1) Reproductive and Child Healthcare: under this banner, in collaboration with UNICEF, various awareness and training programs for trained birth attendants (TBA), and doctors at primary health centers are conducted to handle emergency obstetrics cases;

(2) Emergency Obstetrics Care (EMOC) program of FOGSI: in collaboration with Macarthur Foundation; FOGSI has initiated the training of doctors in three states of India to deal with complications of pregnancy and labor in rural areas of India.

In summary, this problem is huge; the efforts needed are Herculean, the resources inadequate, and the consequences far-reaching. It is only the persistent will that can minimize the problem, if not eradicate it!

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41

LITIGATION: AN INTERNATIONAL PERSPECTIVE

K. J. Dalton

INTRODUCTION

The history of litigation after postpartum hemorrhage spans more than 100 years, but only 34 decided cases have been reported in common law jurisdictions.

The LEXIS database includes reported legal cases from the common law jurisdictions, but it does not include civil law jurisdictions such as those that use Napoleonic law. This history was compiled using the following search terms: [(post-partum OR postpartum) AND (haemorrhage OR hemorrhage)]. First, databases of English, Commonwealth and Irish, US Federal and US States case law were searched. Then full-text or abbreviated-text reports of all potential cases were searched visually for key words to determine the relevance of each for inclusion. Most were discarded as irrelevant, for example: 'retinal hemorrhage in the postpartum period'; after this only 34 relevant cases remained. It is possible that some cases from lower courts may have been missed, as no straightforward method exists to retrieve all such cases across all the jurisdictions studied.

FIRST MATERNAL DEATH LITIGATED (1905)

Half (17) of 34 (i.e. 50%) of the litigated cases involved a maternal death. The first of these occurred in the US. On 27 February 1905, Florence Westrup delivered her first child at home outside Newport, Kentucky. She had *'a great aversion to physicians'*, and planned a natural home birth. The birth of the child (at term) went well, but she began to hemorrhage. Despite her protests, her husband called the family physician. He arrived, examined her, and found a retained placenta. He went home to fetch his bag of instruments and returned, but by this time Florence Westrup was dead. The local police charged the husband with involuntary manslaughter, and this was said to have been committed:

> 'by wilfully neglecting to furnish his wife . . . with such care and attention as were necessary during her confinement in childbirth, thereby causing her death'.

He was tried in Campbell Circuit Court, found guilty and sentenced to 8 months imprisonment. He appealed this decision to the Kentucky Court of Appeals, which expressed its own view of the matter[1]:

> 'Those of us who reverence the medical profession and implicitly trust the learning and skill of the family physician . . . [take the view that] . . . postpartum hemorrhage is nearly always fatal [and that] . . . the trial judge should have peremptorily instructed the jury to find appellant not guilty'.

Nowadays courts are rarely so deferential to the medical profession or to physicians and, as is shown in numerous other chapters of this book, fatality is less likely if physicians are present and well prepared to treat hemorrhage.

UNLAWFUL PRACTICE OF MEDICINE (1907)

In 1907, Hannah Porn, a diplomate of the Chicago Midwife Institute and a practising midwife of many years experience, was charged with practising medicine unlawfully. Among the reasons cited was the fact that she had used *'formulae'* for treating uterine inertia and postpartum hemorrhage, and also used obstetrical forceps for delivery. These were *'acts confessedly performed by the defendant'* but she did so only rarely, and *'never, if a physician could be called*

in time'. Nevertheless, she was convicted, and on appeal the Supreme Court of Massachusetts upheld her conviction on the grounds that:[2]

> 'The maintenance of a high standard of professional qualifications for physicians is of vital concern to the public health.'

Here, the Kentucky deference to physicians was not afforded to a midwife.

DANGEROUS SIDEWALK (1908)

The second maternal death case was heard in 1908. Mollie Short, the wife of an East St Louis physician, was 36 weeks pregnant. Out shopping on the evening of 17 November 1906, she walked along a wooden sidewalk situated 6 feet above the ground (i.e. a boardwalk). This had been damaged in the cyclone of 1896, but had not been properly repaired. Her left leg slipped down a hole, she dislocated her hip, and subsequently went into preterm labor. Although the baby survived, she suffered a postpartum hemorrhage from which she died. Her husband sued the city authority for having a dangerous sidewalk, and was awarded damages of $5700. He successfully argued that postpartum hemorrhage was a direct consequence of the preterm labor, which would not have happened had not the sidewalk been dangerous. On appeal, the trial court's verdict was affirmed[3].

TELEPHONE PROBLEM (1909)

At 3 am on an October morning in 1909 in Georgia, Mrs Glawson started bleeding in a pregnancy of unknown gestational age. Her husband telephoned the local physician who was situated 7 miles away. He advised that certain remedies be applied, but these did not ameliorate the situation. The husband repeatedly tried to make telephonic contact again with the physician, but the telephone operator did not answer for over 2 hours. Eventually, connection was re-established with the physician who set off to visit the home immediately. By the time he arrived, Mrs Glawson had miscarried, had a *'postpartum hemorrhage'*, and died. The husband sued the telephone company for gross negligence in not answering his telephone call for 2 hours. His lawyer argued that *'but for this negligence the physician could and would have reached the plaintiff's house in time to save the life of his wife'*. He won his case, and he was awarded $5000 in compensation. The telephone company appealed the decision to the Court of Appeals of Georgia, but their appeal failed[4]. The court held that generally failure of equipment in the telephone exchange would not be negligent, but in this case there was a failure of diligence on the part of the telephone operator in that he did not notice the incoming call.

ROAD TRAFFIC ACCIDENT (1930)

More than 20 years were to pass after the case of Mrs Glawson in 1909 before another postpartum hemorrhage case reached the courts and was reported. This was to be the first road traffic accident in pregnancy that was litigated.

In 1930, only 2 days after Mrs Peterson conceived her second pregnancy, she was involved in a road traffic accident near St Paul, Minnesota. The automobile in which she was travelling overturned. It was said to have been going too fast, but the driver claimed that a tire blew out. By the end of pregnancy, it was recognized that she had a central placenta previa, in which the maternal mortality was known to be *'very high'*. Her doctor consulted with another expert. Rather than carrying out the then relatively rare operation of Cesarean section, it was advised that she should be delivered vaginally. Her doctor used what was termed the *'Vorhees bag method'*, and he broke through her placenta by the vaginal route. The child died, the mother had a postpartum hemorrhage and she died too. The driver of the car in which she had been sitting 9 months previously was sued for negligence. In court, expert medical evidence said the road accident had caused the placenta to be situated in a previa position, and this directly led to the mother's postpartum hemorrhage and death. This evidence did not convince the jury, however, who found in favor of the driver. An appeal to the Supreme Court of Minnesota failed[5].

IATROGENIC OBSTETRIC INJURY (1955)

Occasionally, maternal death has occurred as a result of unusual management of labor. In

1955, Bette Goff had her labor induced by means of pituitrin. During the labor, her doctor diagnosed a constrictive band of cervical muscle, and he incised it just left of the 12 o'clock position. She delivered vaginally, but the cervical incision was not repaired. She had a postpartum hemorrhage over the course of the next few hours, but the two attendant nurses did not recall the doctor until it was too late, and the patient died of blood loss. The family took legal action against the doctor and the hospital as it was vicariously liable for the nurses' omissions. For legal reasons, the case went to retrial[6]. Negligence on the part of the doctor was admitted. As for the nurses, this was evidenced from the records. There was no later report on this case, so presumably it settled.

HEALTH INSURANCE (1956)

Postpartum hemorrhage has occasionally been at issue in insurance matters. The earliest reported case was that of Juanita Whitten in 1956. Her health insurance policy covered hospitalization for any complication of pregnancy. She had had seven pregnancies: two miscarried with severe bleeding, and she had a severe postpartum hemorrhage following the delivery of her last child, after which she was sterilized. Her gynecologist said the sterilization operation was undertaken to prevent further postpartum hemorrhage, a complication of pregnancy that was covered by her insurance policy. However, her insurance company and the Court of Appeals of Alabama disallowed her reimbursement claim, on the grounds that her policy covered only actual complications, and not potential complications that might or might not occur in the future[7].

TRANSFUSION OF THE WRONG BLOOD (1951, 1955, 1972)

Three cases involved allegations that the wrong blood was transfused.

In 1951, Mrs Madison bled heavily postpartum whilst in San Francisco Hospital, a county hospital and a state governmental institution. Unfortunately, she was given a blood transfusion that had been incorrectly cross-matched, and she died as a result. Her husband sued the City and County of San Francisco, but he lost his case as the court held that the state was immune from suit, in a manner akin to sovereign immunity. The appeal court judges said they were unhappy in delivering this decision, but they were bound to follow the precedent of other cases in which state immunity had been the issue, explaining themselves as follows[8]:

> 'This doctrine of non-liability of the state and its agencies for injuries caused by the negligence of an employee engaged in the discharge of a governmental function originated in the fiction that the king can do no wrong.'

[In English law, the Queen is still regarded as above the law, but her ministers of state (i.e. the government) are not above the law, and often a court will find against them.]

In 1955, Josephine Gillen delivered at the Brooke Army Hospital in Texas. She then had a postpartum hemorrhage and she was given a blood transfusion. Her condition deteriorated, and 2 days later she died of renal failure. The family sued the United States of America, alleging negligent military medical care which included the claim that there had been an incompatible transfusion of rhesus O-positive blood into a rhesus O-negative patient, and that this led to her renal problem. In defence, it was claimed that the patient was in fact rhesus O-positive, and she had been given rhesus O-negative blood, which would have been a group-compatible transfusion. The court found that there had been no incorrect blood transfusion, no renal problem arising from this, and no negligence in the medical care. This finding was affirmed on appeal[9].

More than 15 years passed until the case of Theda Parker in 1972. Her third labor was induced at 38 weeks gestation at her request. The birth went well, but she had a postpartum hemorrhage, and her obstetrician had to perform a hysterectomy. During the course of the operation, she needed a blood transfusion, but unfortunately she was given blood that had been cross-matched for another patient. She survived the ordeal, but in the long term she developed hematuria due to cystitis, and her marriage eventually broke down. In 1976, she and her husband sued her obstetrician for inducing her labor too soon (for convenience rather than for

medical reasons) which they said led to the postpartum hemorrhage; and for the transfusion error which they claimed had triggered the events that led to their marital breakdown. On appeal, most of their claims were dismissed, except that she was awarded $20 000 compensation to be paid by the hospital for the negligence of its employee in mixing up the bloods[10].

INFECTION FOLLOWING BLOOD TRANSFUSION (1981, 1982, 1985)

Four cases have been litigated where blood-borne infection occurred following transfusion for postpartum hemorrhage. Three cases involved HIV, and one hepatitis C.

HIV

AIDS was recognized in 1982, and the HIV virus was identified in 1983. Shortly thereafter, HIV infection was first reported as a consequence of postpartum hemorrhage. In 1984, the HIV-ELISA test was first marketed as a kit, and the FDA approved it for sale on 2 March 1985. Only 11 days later, on 13 March, the Belle Bonfils Memorial Blood Center in Denver, Colorado took delivery of its first testing kit, but its staff were not yet trained in its use. On that very same day, Mrs KW was admitted to hospital with a secondary postpartum hemorrhage following an apparently uneventful delivery of her baby son 2 weeks earlier. Her bleeding could not be stopped and so a hysterectomy was carried out. Six units of blood were transfused, none of which were tested for HIV. However, by 1986, donor blood was being routinely tested for HIV, and at this time one of her 1985 donors tested positive. All previous recipients of his blood were tracked and tested, and Mrs KW was found to be HIV-positive. She (and her husband and son) sued Belle Bonfils Memorial Blood Center on the grounds that the Center had not appropriately identified and excluded this donor as 'not a suitable person' to donate non-infected blood. (Specific testing for HIV, *per se*, was not an issue in this case.) Most of the legal arguments in the case revolved around confidentiality issues regarding access to the donor's medical records, and so they are not relevant here. The Supreme Court of Colorado ordered limited disclosure of his medical records[11].

In 1981 Matsuko Gaffney, the wife of a US naval man, was booked to deliver at the Long Beach Naval Hospital in California. Her pregnancy went overdue by 4 weeks *(sic)*, but her cervix was judged unfavorable for induction of labor. She was delivered vaginally, but had a postpartum hemorrhage for which she was transfused two units of blood. Various experts later agreed that, if she had had appropriate fetal monitoring, fetal distress would have been recognized, and she would have been delivered by Cesarean section, without intrauterine death, infection, postpartum hemorrhage, and blood transfusion, all of which she did have. In 1983, she delivered her next child, a healthy girl, and then in 1985 she delivered a boy. He proved to be a sickly child and was diagnosed with AIDS, from which he died in 1986. Mrs Gaffney and her husband were tested for HIV and both proved positive. She died of AIDS in 1987. After her death, a 1990 Court heard that one of her units of blood came from *'a donor who had engaged in homosexual activity involving the exchange of bodily fluids'*, although he was never actually tested for HIV. The Court found that, as the United States of America was responsible for the military hospital, it was liable for the unfortunate train of events that befell Mrs Gaffney and her family, even though HIV infection had not been discovered at the time. It held that the United States was negligent in the treatment of Mrs Gaffney, that she needed to be transfused as a direct result of that negligence, and that it was foreseeable in 1981 that a communicable disease could be transmitted through blood transfusion[12].

In contrast to this was the case of Sheri Traxler, who delivered her baby in 1982. Two weeks later, she had a major postpartum hemorrhage, for which she was transfused two units of blood. Hysterectomy was considered, but it proved unnecessary. Eight years later, in 1988, it emerged that one of her blood donors had tested positive for HIV, and now she too tested positive. She sued her 1982 obstetrician on two principal grounds: (1) that he had not removed her placenta completely, and (2) that she had not specifically consented to any blood transfusion. His defence was (1) that retention of

placental fragments occurs commonly, and (2) that her written general consent to treatment provided sufficient authority for him give blood as she had lost 30–40% of her blood volume. The lower court held that there had been no negligence at the times of delivery or of the postpartum hemorrhage, and that the risk of HIV infection could not be foreseen. This decision was upheld by the Californian Court of Appeal[13].

Hepatitis C

Blood transfusion following postpartum hemorrhage may cause other blood-borne infections, such as hepatitis C. In 1988, Anita Endean delivered vaginally in British Columbia. She had a postpartum hemorrhage, and she was given a transfusion of packed red cells supplied by the Canadian Red Cross (CRC). After she went home, she had a debilitating flu-like illness. Six years later in 1994, she offered to donate blood, but she now tested positive for hepatitis C. Although its short-term effects are transient, hepatitis C carries a long-term risk of cirrhosis (10% per annum) and in those patients a further risk of hepatocellular carcinoma (5% per annum). The CRC carried out a 'traceback' procedure, and found that one of her 1988 blood donors now tested positive for hepatitis C. (Hepatitis C virus (HCV) was first identified in 1988. An antibody test for HCV was soon developed, but British Columbia did not introduce widespread testing until 1990. Nevertheless, surrogate testing for non-A non-B hepatitis had been widely available in 1988.) She took no legal action against her obstetrician, but sued the CRC who supplied the blood transfused in 1988, on the specific grounds that it had neither tested for HCV nor carried out surrogate testing, and thereby failed to prevent hepatitis C contamination of its blood supplies. She also alleged that the CRC had deliberately destroyed some of her medical records, thus disadvantaging her legal action, i.e. a separate tort known as 'spoliation'. Furthermore, together with many other patients infected with hepatitis C from blood transfusions, she joined a class action, or a mass tort action, against the Canadian Red Cross under British Columbia's Class Proceedings Act 1995. Hers proved to be a unique case of postpartum hemorrhage, as she was to become the 'representative plaintiff', or lead case, in this mass tort action. As her case raised novel legal points that were challenged by the CRC, it fell to the Supreme Court of British Columbia to grant her membership of this class action. Because the final outcome of her legal action was not reported, it is possible that the matter was settled out of court[14].

DELAY IN TRANSFUSING BLOOD (1984, 1988, 2000)

In several cases it was alleged that there was unnecessary delay in giving blood after postpartum hemorrhage.

In 1992, a Saskatchewan court considered the dangers of postpartum hemorrhage in a rural setting. In 1984, Corrine Naeth had delivered her baby uneventfully in Hospital A, but her uterus inverted when 'controlled cord traction' was used to deliver the placenta. Before replacing the uterus, the delivering doctor tried to peel the placenta off the inverted uterus, but the placenta was adherent (placenta accreta). Massive hemorrhage ensued, but there was no blood transfusion facility in the hospital. She was then transferred by ambulance to Hospital B, a traveling distance of 90 min, rather than to Hospital C, a traveling distance of only 30 min, but which only had facilities for uncross-matched blood transfusion. During transfer to Hospital B, she lost consciousness in the ambulance, and she was probably brain-dead by the time she arrived there. Hospital B had limited facilities for blood transfusion, but no obstetrician in attendance. Here blood was transfused, and the uterine inversion was corrected using normal saline as in O'Sullivan's method. She was then transferred to University Hospital in Saskatoon (Hospital D) which had full blood transfusion facilities and an obstetrician in attendance. But she was already dead by the time her ambulance arrived at Hospital D. The court recognized the additional hazards of delivery in a remote rural setting but, even so, it held that in a number of respects *'the standard of competency, skill and diligence exercised by the delivering doctor fell below the standard expected of a general practitioner practising in a rural setting'*, and it awarded her estate damages of $343 000[15].

In 2000, a Dr Gabaldoni appeared before the Maryland State Board of Physician Quality Assurance in connection with his management of a patient he had induced at term for pre-eclampsia. The birth went well, but the mother had a postpartum hemorrhage that was thought to be due to retained fragments of placenta. She deteriorated over the next 48 h and her hemoglobin level went as low as 4.7 g/dl. Dr Gabaldoni was said to be leisurely in attendance, and slow to transfuse blood. However, blood transfusion was started at 48 h postpartum, but by this time she was in severe respiratory distress, and her condition continued to deteriorate. She was admitted to the intensive care unit at 72 h postpartum, but she died there 48 h later. Two days later, Dr Gabaldoni was said to have made a series of undated additions to her notes, which suggested that she had received better care than she did. He was said to have made these additional entries in the same color ink as the original progress notes, in such a manner that his alterations to the notes would not readily be apparent. The Maryland Board of Physician Quality Assurance filed charges under the Maryland Medical Practice Act 1995. When this case was considered by the Board, there was dispute about when he had seen the patient, when he had offered a blood transfusion, and whether the medical notes as written were correct. After reviewing the evidence, the Board found he had *'failed to meet the appropriate standard for delivery of medical care'*, and so it issued a reprimand. He appealed, but in a 'deferential review' the Court of Special Appeals of Maryland dismissed his appeal[16].

In 2000, a Malaysian Court of Appeal considered whether a medical center had a duty to keep blood available for transfusion. In 1988, Pearly Choo was booked to deliver her first baby in her local medical center, which carried no stored blood. She was healthy, had an uncomplicated pregnancy, and she was considered to be at low risk. She delivered her baby uneventfully, but she then sustained a major postpartum hemorrhage. In keeping with routine practice, blood was requested from the nearby Kuala Lumpur General Hospital, and her husband was sent to collect it. By the time the husband returned with the blood, his wife had already bled to death. He took legal action against the medical center, on the grounds that it should have carried blood, and it should have transfused blood in a timely fashion. The local Sessions Court found for the defendant hospital. The case was appealed to the High Court, which reversed the decision of the Sessions Court, and it found for the husband. However, the hospital then went to the Court of Appeal, which affirmed the Sessions Court's rejection of expert medical evidence that blood must be stored before any delivery, as this *'would result in an absurd situation when one bears in mind that deliveries are also conducted by midwives in houses of the mothers where blood would not be stored before such deliveries'*. The Court of Appeal thus reversed the High Court's decision, as it held that there was no duty to hold blood for a low-risk patient in case she bled. Further, it held that in this case the postpartum hemorrhage had been managed conventionally[17].

OBSTETRICIAN ON VACATION (1961)

Obstetricians traditionally hand over the management of a complicated case to a colleague when out of town or on vacation. The case may then go wrong due to the colleague's negligence, but the vacationing obstetrician might find himself sued for negligence. In 1961, this happened following death from postpartum hemorrhage. When pregnant with her fifth child, Patricia Sturm told her obstetrician at 33 weeks that she no longer felt fetal movements. He could not detect any fetal heart beat and, as obstetric ultrasound had not yet been invented, he advised a conservative approach. He told her that she would probably deliver normally in due course, but he did discuss the possibility of fetal death. As she was upset, he did not fully discuss all the possible complications, but he did test her serum fibrinogen levels intermittently. He told her he would be on vacation at the time of her delivery, but would arrange for a colleague to look after her. However, she chose not to attend any further antenatal appointments. At 41 weeks' gestation, when her own obstetrician was away on vacation, she began to bleed vaginally. She was admitted to hospital, and the colleague delivered her of a stillborn infant. A massive postpartum hemorrhage followed for which she

had an eight-unit blood transfusion and a hysterectomy. (The court report says it was carried out vaginally, but this may be incorrect.) Unfortunately, she died despite the emergency treatment. The autopsy report attributed her death to postpartum hemorrhage due to a clotting defect that was in turn due to intrauterine death. The family sued both the delivering doctor and the vacationing doctor, on the grounds that he shared in liability for any perinatal negligence on the part of his deputy. The Supreme Court of Oklahoma rejected this argument, and the obstetrician on vacation was exculpated[18].

UNLICENSED PRACTICE OF OBSTETRICS (1963)

Only two cases of postpartum hemorrhage have been litigated where a professional attendant at delivery was not licensed to practise obstetrics. Earlier, the 1907 case of Midwife Porn was discussed. The only other reported case was in 1963. Bernhardt and Lund were two doctors of chiropractic, but they held themselves out as competent in the management of childbirth. They supervised the delivery of Ladean Stojakovich at home, but unfortunately she had a postpartum hemorrhage and she died before she could be transferred to hospital. They were charged and convicted of breach of the Business and Professions Code (for practising medicine) and of manslaughter (for causing a death that was avoidable). Surprisingly, and for complex legal reasons, the Court of Appeals of California reversed both convictions, and it denied a request for retrial[19].

DISCHARGING PATIENT HOME TOO SOON (1977)

In 1977, Patricia Hale (aged 20) delivered vaginally at term at Fannin County Hospital in Texas, under the care of Dr Sheikholeslam. Although she was still bleeding at 30 h after delivery, she was discharged home. At 8 days postpartum, she was readmitted with continued bleeding. She was given a preoperative injection (presumably of ergometrine) to contract her uterus, a blood transfusion and a uterine curettage. After her operation, she was given no injection and no antibiotics. She was discharged home after 36 h, although she felt weak and she was still bleeding. At 20 days, heavy postpartum bleeding restarted. She was then admitted to a different hospital, where a different gynecologist diagnosed an intrauterine infection. Despite a second D&C, her heavy bleeding continued, and a hysterectomy had to be carried out. She sued the first doctor and hospital for negligent care. She won her case in the lower court, which held the doctor and the hospital jointly and severally liable for damages of $100 000. However, the hospital appealed the court's decision on the grounds that the doctor was an independent contractor, and not the hospital's servant or agent and that, as the hospital was a governmental unit, it was immune from tort liability. The Court of Appeals upheld the hospital's appeal, and it reversed the lower court's decision as regards the liability of the hospital. Dr Sheikholeslam did not appeal, and thus the original liability decision against him remained unchallenged[20].

INADEQUATE STAFFING LEVELS (1981)

In 1981, Stephen Martin was born in Ontario by spontaneous vaginal delivery following a labor complicated by fetal distress. He was in poor condition, and later he was diagnosed with cerebral palsy. When the case came to trial 17 years later in 1998, Obstetrical Nurse James was found guilty of negligence in failing to give appropriate care during labor. In her defence, she said she was involved with another patient who was having a postpartum hemorrhage. This was not accepted as a valid excuse as she should have called for help. She and her hospital were each found liable for 25% of the damages of $250 000 awarded to the claimant[21].

NO AUTOPSY (1982)

In 1982, Yong Siew Yin was in labor at term with her first baby. The labor was prolonged and (on one account) she was in labor for over 24 h. She had a small intrapartum hemorrhage. As there was delay in the second stage and fetal distress, urgent delivery was needed. The fetal head was low in the pelvis, and in an occipitoposterior position, so the baby was delivered 'face-to pubes' by Neville Barnes forceps. Following this, she had a postpartum hemorrhage, and this

was attributed to vaginal tears. Whilst these were being repaired she collapsed, and a coagulation disorder became manifest. She continued to bleed heavily. An amniotic fluid embolism was suspected, but it was never proved. She was admitted to the intensive care unit where she died. Surprisingly, there was no autopsy. The judge in the lower court found the obstetrician guilty of negligence, and the hospital vicariously liable. This verdict was upheld on appeal[22].

SUING THE WRONG DOCTOR (1982)

Occasionally, a patient may sue the wrong doctor. In 1976, Jean Johnson had a normal vaginal delivery at the Wishard Memorial Hospital in Indiana. This was followed 2 weeks later by a secondary postpartum hemorrhage. She was seen by the Chief Resident, Dr Deaton, who diagnosed retained products of conception, and advised uterine curettage. He checked his diagnosis and treatment plan with Dr Padilla, a staff instructor with the Indiana University Medical School, and the operation was carried out. By 1982, it had become apparent that Jean Johnson was infertile, and this was attributed to overvigorous curettage of the endometrium in 1976 (Asherman's syndrome). She sued Dr Padilla for negligent performance of the curettage, but did not suggest that the curettage decision itself was negligent. The defence was threefold: (1) Dr Padilla did not carry out the curettage; (2) there was no doctor–patient relationship between Dr Padilla and Jean Johnson; and (3) there was no agency relationship between Dr Padilla and Dr Deaton. The Court of Appeals of Indiana accepted all three lines of defence, and dismissed the case against Dr Padilla[23].

OBSTETRICIAN WITHOUT SUFFICIENT EXPERIENCE (1986)

In 1986, Christine Steinhagen became pregnant for the third time. She had two previous Cesarean sections, the second being complicated by '*extreme and profuse bleeding*'. In her third pregnancy, she had a sudden vaginal bleed at about 20 weeks' gestation, and an anterior placenta previa was diagnosed. She was kept in hospital for 18 weeks and throughout this time given terbutaline to inhibit uterine contractions. The last dose was given on the morning she was delivered by elective Cesarean section. Her obstetrician-gynecologist had recently completed his residency training but was not yet board-certified. Moreover, he had not discussed her management with any board-certified obstetrician-gynecologist, and had no other suitably qualified surgeon in attendance. The Cesarean operation was carried out through a low transverse abdominal incision, but surgery proved to be difficult. After the baby was delivered, the uterus failed to contract, and she hemorrhaged profusely. In these circumstances, it would have been usual to give Methergine (methylergonovine) and/or Pitocin (oxytocin) to promote uterine contraction. No Methergine was given; half a dose of Pitocin may have been given, but it was not documented in the medical notes or on the drug chart. A hysterectomy was carried out, but the bleeding continued. Her bladder was damaged and she developed hematuria. A urological surgeon was then called, and he ligated the left internal iliac (or hypogastric) artery. This slowed the bleeding considerably, but it did not stop it completely. The tissues were now friable and so the abdomen was packed and closed, and she was managed overnight in intensive care. The abdomen was reopened the following day as internal bleeding continued. At the second operation, all bleeding was brought under control, but she lost her right ovary. During this episode, she was given a total of 34 units of blood, 14 of fresh frozen plasma and 10 of platelets, but she survived. Postoperatively, she developed a vesico-vaginal fistula, hepatitis, an extremely short vagina that made intercourse impossible, and severe psychological problems. As she was managed and delivered at a naval military hospital in Illinois, she took legal action against the United States of America. After hearing expert evidence, the trial judge was critical of: an obstetrician-gynecologist who was not board-certified managing this complicated case without more experienced help; his giving terbutaline immediately prior to the Cesarean section, thereby inhibiting uterine contraction after delivery; his failure to perform the operation through a midline incision which would have minimized the risk of bladder damage; his failure to give Methergine to contract the uterus; and his

failure to ligate both hypogastric arteries which might have avoided the hysterectomy and the loss of an ovary. He awarded her $300 000 in compensation[24].

NO OPERATION NOTE (1992)

In 1992, Mrs Suchorab was delivered in Saskatchewan by Cesarean section. Six weeks later, she had a postpartum hemorrhage and was readmitted to hospital. Her obstetrician took her to the operating theater, where he stabilized her condition. The operation log and the anesthetist's note both record that a dilatation and curettage operation was carried out, but no surgical operation note was ever found to confirm this. The following day, she had a further major hemorrhage, and a hysterectomy was carried out. She took legal action against her obstetrician. She argued that his care had been deficient as her bleed was due to retained products of conception, and he had failed to curette her uterus as (she claimed) was evidenced by the absence of any operation note. He claimed that he had curetted her uterus, but he had forgotten to write an operation note. Moreover, he claimed that her bleed was from a *'necrotic cervix'*, and not from the uterine cavity, and so no extra harm would have resulted from failure to curette the uterus. The court rejected her claim[25].

SHEEHAN'S SYNDROME (1977, 1995)

In 1977, Mrs Parker delivered her first child. Her obstetrician delivered the placenta by continuous cord traction. However, she had a uterine inversion and a major postpartum hemorrhage followed. She was taken to the operating theater, and in the operation note it was recorded that her *'uterus had resolved itself'*. Five months later, she was found to have *'an inverted uterus presenting well down in the vagina'*. She had various ongoing symptoms, but it was not until 1991 (14 years later) that Sheehan's syndrome was diagnosed. She then took legal action against her obstetrician of 1977. A four-person jury awarded her $960 000 in damages. Her obstetrician appealed the case on both liability and quantum. The New South Wales Court of Appeal dismissed his appeal on liability, but it ordered a new trial limited to damages, as it considered the jury award excessive[26].

In 1995, Natalie Lomeo was delivered by elective Cesarean section at her local Community Medical Center (CMC) in Pennsylvania. She had an extensive blood loss during the operation, and a postpartum hemorrhage followed. Although she exhibited signs of hemorrhagic shock, blood was not transfused until much later in the day. Over the next 3 years, she complained of fatigue, weakness, dizziness, hair loss, amenorrhea, dyspareunia, and vasomotor symptomatology. In 1998, the diagnosis of Sheehan's syndrome was made. She then took legal action against her obstetrician and the CMC. However, the defendants filed for summary judgment, asserting that her claim was time-barred under Pennsylvania law, as it had been filed more than 2 years after the allegedly negligent conduct. The Common Pleas Court denied the motion for dismissal, saying that the litigation clock only started to run when Sheehan's syndrome was diagnosed[27]. What happened next was not reported, so the case was probably settled.

MALIGNANT HYPERTENSION (1993)

In 1993, Evelyn Dybongco-Rimando had an uneventful spontaneous vaginal delivery of a healthy daughter, and she went home shortly afterwards. Some 8 years later, a judge of the Superior Court of Justice of Ontario was to say that her case *'presents a puzzle with a thousand pieces'*. The trial started in 1999, and it lasted for 33 days spread over 3 years. The judge described it as *'a challenge to bench and bar alike'*. Although her delivery was normal, 7 days later she suffered a massive postpartum hemorrhage, and she was readmitted to hospital. Over the next 2 days, she had three operations before her bleeding could be brought under control: uterine exploration, hysterectomy, and then a second-look laparotomy. She was given a large transfusion of blood, and also blood products as she developed a coagulation disorder. She became profoundly hypotensive, and required inotropic agents (principally dopamine) to support her blood pressure. However, her blood pressure then went too high, and within 33 h of readmission to hospital she had developed

malignant hypertension. Dopamine was given but discontinued when her pressure reached 237/113 mmHg. However, the maximum level of blood pressure later recorded was 256/126 mmHg. She then had a cerebral hemorrhage, and soon after this she died. Her estate started a legal action against 55 defendants, but only three defendants remained shortly after the trial started in 2000. These were her obstetrician, her internal medicine physician, and her intensivist. In his final judgment, the judge said of the internal medicine physician's testimony *'It reflects a triumph of tactics over truth. He is not credible.'* He found all three defendant doctors guilty of negligence, and he reserved judgment on the amount of damages to be awarded to the deceased patient's estate[28].

NO EXPERT MEDICAL REPORT (1995)

In 1995, Marcia Laidley had a postpartum hemorrhage after delivering her third child. A supracervical hysterectomy was performed. Later, she took legal action against her obstetrician. However, she failed to provide a timely expert medical report in support of her case by the court-imposed deadline, and so summary judgment was awarded against her. She appealed. The Court of Appeals of Ohio held that the trial court had committed a prejudicial error when it granted the defendant's motion for summary judgment without providing the opportunity for sufficient discovery on the issue[29].

POSTPARTUM HEMORRHAGE IN AN AIRCRAFT (1997)

In 1997, Gina Paone delivered her baby in Ontario, but her placenta had to be removed manually. Her uterine cavity was explored and considered to be empty. The placenta was judged to be complete. One month later, she flew to Italy, but she had abdominal pain and heavy vaginal bleeding during the flight. On arrival in Italy, she was admitted to hospital where she had a uterine curettage. She claims she was told there was further placental tissue recovered from the uterus, but there was no written confirmation of this. In 1998, she started legal proceedings in Italy by an Act of Citation naming her obstetrician, two nurses and St Joseph's Health Centre, all of whom were in Ontario. The Italian court refused to hear the case, saying it lacked jurisdiction as the medical treatment had occurred in Ontario. In 2000, she brought a similar legal action in Ontario. However, the defendants prevailed, as Ontario law requires an action against a doctor to be brought within 1 year from when the Plaintiff *'knew or ought to have known'* the material facts on which the malpractice is alleged, and against a hospital or nurse within 2 years of the patient being discharged from hospital or stopping treatment. Furthermore, the Ontario Court of Justice also found that in this case there was no genuine issue for trial as no expert reports were filed[30].

POSTPARTUM HEMORRHAGE INTO THE PLEURAL CAVITY (1997)

In 1997, an unusual case of postpartum hemorrhage occurred in California. Martha Guandique had severe pre-eclampsia at 38 weeks' gestation. Her signs and symptoms included shortness of breath, hypertension, renal malfunction, hepatomegaly and pleural effusion. Labor was induced and she delivered a male infant. She had a postpartum hemorrhage due to uterine atony, so she was given Pitocin. Blood clots were evacuated from her uterus. Shortly after delivery, she had considerable difficulty in breathing, and back pain. Various physicians were called in to see her. Pulmonary embolism and amniotic fluid embolism were in the differential diagnosis. Supportive therapy with oxygen was given and various drugs were used. Her hemoglobin fell at first to 9.5 g/dl, and it continued to fall thereafter. (Subsequent hemoglobin levels were not recorded in the court report.) A blood transfusion was started, but 20 min later she had a cardiopulmonary arrest and then she died. At autopsy, she was found to have suffered a major postpartum hemorrhage (of 1500 ml) into her right pleural cavity. The pathologist reported that *'The mechanism of production of this hemorrhage remains unknown in spite of a careful dissection of the blood vessels in the area. . . . That is why the mode of this death remains undetermined.'* In this case, much of the complicated legal argument before the Court of Appeal of California focused on which doctors might have been

liable for her death, but these legal arguments need not concern us here[31].

DISAPPEARING BABY (1999)

This too represents an unusual case, but I have seen something very similar (see below). In 1999, an unmarried mother was having an adulterous affair with a co-worker. He noticed that her abdomen was enlarging, and asked whether she might be pregnant. She said that she could be. The matter was discussed no further, neither with him nor with any other co-workers. A few weeks later, she attended her family doctor complaining of swollen feet. She told him that she was 7 months pregnant. The doctor heard the fetal heart beat and felt fetal movements, and so he pronounced the fetus healthy. This was the only medical care she sought before 12 May 1999, when she was admitted to a Texas hospital with a 2-day history of vaginal bleeding. She was said to be in shock: she was weak and pale, had a low temperature, and a tachycardia. (Her blood pressure was not mentioned in the court report.) She said that she was pregnant, but she did not know the date of her last menstrual period, nor when her baby was due. A blood test showed that she was severely anemic. Her hemoglobin level was not mentioned in the court report, but, from comments in the report, it was probably around 4–5 g/dl. Four units of blood were transfused. An obstetrician was called, and she scanned the uterus with ultrasound. She found no evidence of a baby, but she did find a placenta of a size compatible with a term baby. The placenta was then delivered, but it had no cord attached. Both the patient and her attendant family denied that any baby had been born. Therefore the police were called. They searched her home, and there they found evidence of extensive blood staining of her bed, and of her bathroom – but no baby. A grand jury was convened to determine whether any charge, such as homicide, should be brought. Under oath she said that *'I did not pass a baby'*, and she insisted that she had only passed clots of blood. She was later charged with aggravated perjury before a grand jury, convicted by a jury, and sentenced to 10 years confinement probated for 10 years. She appealed against her conviction on the grounds that the evidence was legally insufficient to support the jury's verdict, and the State had failed to prove the materiality of her alleged false statement. The Court of Appeals of Texas considered her arguments but it dismissed her appeal[32].

[In the late 1970s, I had a similar case in the UK: a 14-year-old girl who presented in shock with heavy vaginal bleeding. She had a perineal midline tear, a widely open cervix, and an enlarged uterus, but there was no baby and no placenta. Her hemoglobin level was only 4 g/dl, so she was transfused with blood. Her presentation was clearly consistent with recent childbirth followed by a major postpartum hemorrhage. Despite the overwhelming evidence, the girl and her parents firmly denied any pregnancy or recent delivery of a baby. The police were duly called in. They investigated the matter and searched the family home, but no baby was ever found. No charges were ever brought.]

ABANDONMENT (2000)

In 2000, the New York Bureau of Professional Medical Conduct considered the case of Dr Wahba, an obstetrician who was charged with professional misconduct in the treatment of seven of his patients. Two of these were at risk of postpartum hemorrhage, and here he was found guilty of negligence and/or incompetence. In both cases, he left the delivery room before the placenta was delivered. The first patient had a stillbirth, and so she was at a higher risk of postpartum hemorrhage. The second was still hemodynamically unstable; she then hemorrhaged but by this time the obstetrician had already left the hospital. Moreover, he refused the nurse supervisor's requests to return. After reviewing his management of all seven patients, the Administrative Review Board for Professional Medical Conduct revoked his licence to practise medicine in the state of New York. He then appealed to the Supreme Court of New York, but his appeal was dismissed[33].

POSTPARTUM HEMORRHAGE IN A FEMALE DOG (2006)

American courts are well known for leading the way into new areas of litigation. Therefore it may come as no surprise to learn that in

February 2006 the Court of Appeals of Texas ruled on a case involving the management of postpartum hemorrhage in a female dog in the Bureau of Animal Regulation and Care in Houston in 1999. This facility takes around 20–30 000 animals a year. One of their veterinarians was Dr Levingston. He had made a number of complaints to his employers about the inhumane treatment of animals in their care, but on one particular occasion they accused him of the negligent care of animals, and they terminated his employment. They cited his alleged mismanagement of the care of a female Rottweiler dog who had given birth to nine puppies, and who had a postpartum hemorrhage from which she exsanguinated and died. They said he should have considered the possibilities of hysterectomy or euthanasia. He appealed his termination of employment and won his case. He was awarded damages in the lower court. His employers appealed the decision, and the case went to the Court of Appeals of Texas who dismissed their appeal. The court awarded him a total of $1.24 million for past and future lost wages and compensatory damages. This amount was to include $194 000 for his lawyers' fees. If the lawyers' fees of his employers, the City of Houston, were of the same order of magnitude, then the legal bill on this case would have been around $400 000. Overall, this case ran for more than 5 years[34].

CONCLUSIONS

This account has been international in its scope, albeit confined to common law jurisdictions. It is clear that the history of litigation following postpartum hemorrhage stretches for over 100 years, from Florence Westrup of Newport, Kentucky in 1905 to the female Rottweiler dog of Houston, Texas in 2006.

In 17 of 34 cases (50%), a maternal death no doubt prompted the litigation, rather than the postpartum hemorrhage itself.

After maternal death, the second most common reason for litigation was a problem with the transfusion of blood, such as infection, delay or possible incompatibility. Such problems occurred in ten of 34 (29%) of the cases.

Equal third reasons for litigation were having a diagnosis made of Sheehan's syndrome after postpartum hemorrhage (only two cases), and having professional birth attendants who were not licensed to practise obstetrics (only two cases, one of which was litigated in 1907).

Apart from the general observation that poor obstetric practice was a typical feature of many of these cases, they were otherwise sporadic in etiology, with no common cause.

Given the millions of women who have delivered over the last 100 years across the English, Commonwealth, Irish, and American jurisdictions studied, given that the incidence of postpartum hemorrhage is around 5–10%, and given that there has been an international increase in litigation for alleged clinical malpractice, it is surprising that there have not been many more cases of postpartum hemorrhage litigated in the courts.

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Section IX

Special experiences and unusual circumstances

42

THE OBSTETRICIAN CONFRONTS POSTPARTUM HEMORRHAGE

M. E. Setchell

INTRODUCTION

Postpartum hemorrhage has been recognized as a major cause of maternal death for as long as physicians have studied and written about childbirth. Until the 20th century, however, little was possible in the way of effective treatment, and, as is apparent in many of the chapters of this book, postpartum hemorrhage is still a frequent cause of death in many parts of the world. Even in the Western world, significant numbers of deaths and morbidity from postpartum hemorrhage continue to plague obstetricians, despite considerable advances in medical care in the last half-century.

During the author's career in Obstetrics which has spanned almost 40 years, one of the most striking changes has been the one whereby the individual obstetrician no longer has to deal with the problem of postpartum hemorrhage alone, but can call on a sophisticated team of helpers, involving a whole range of other specialists. A mere glance at the contents of this book confirms that the modern management of a major postpartum hemorrhage can involve a team of anesthetists, hematologists, vascular surgeons, gynecologists and radiologists. Clearly, this change represents an advance which has saved and will continue to save countless lives, not only in the developed world where such teamwork is routine, but also in developing nations that are desperately looking for means to reduce maternal mortality as part of their efforts to comply with the United Nations Millennium Development Goals by the year 2015.

HISTORICAL PERSPECTIVE

In the middle of the 19th century, maternal mortality was around 6 per 1000 live births, and, of those deaths, about one-third were related to puerperal sepsis, and the remainder were classified as 'accidents of childbirth', which included ante- and postpartum hemorrhage and deaths from obstructed labor. Table 1 shows birth and death rates in England and Wales from 1847 until 1901. It is evident that there was no real improvement in deaths from sepsis during this period, in contrast to a relative improvement in the deaths from other causes.

The concept of Lying-In Hospitals was first adopted in the mid-18th century, and by 1904 there were 38 such hospitals in Great Britain. The stated intention was to provide a safer place for delivery and postnatal care, but any purported benefits in better obstetric care were far outweighed by the risks of death from sepsis, which, as can be seen in Table 2, amounted to 3% in the period of 1838–1860. This appalling figure improved considerably during the latter part of the 19th century, however, following the introduction of Semmelweis' observations and teachings on hygiene and antisepsis in 1861.

Francis Ramsbotham, the first Lecturer and Obstetric Physician to The London Hospital, published 'The Principles and Practice of Obstetric Medicine and Surgery in reference to the Process of Parturition' in 1841, and provided some poignant case reports, revealing what the practice of Obstetrics was like at that time. The case of a rich patient in the City of London,

Table 1 Mortality in childbirth in England and Wales 1847–1901 (a period of 55 years), in General Lying-in Hospital, London

		Deaths			*Death rate to 1000 children born alive, from*		
Year	*Registered births of children born alive*	*Puerperal septic diseases and accidents of childbirth*	*Puerperal septic diseases*	*Accidents of childbirth*	*Puerperal septic diseases and accidents of childbirth*	*Puerperal septic diseases*	*Accidents of childbirth*
1847	539 965	3226	784	2442	5.97	1.45	4.52
1848	563 059	3445	1365	2080	6.12	2.42	3.70
1849	578 159	3339	1165	2174	5.78	2.02	3.76
1850	593 422	3252	1113	2139	5.48	1.88	3.60
1851	615 865	3290	1009	2281	5.34	1.64	3.70
1852	624 012	3247	972	2275	5.20	1.56	3.64
1853	612 391	3060	792	2268	5.00	1.30	3.70
1854	634 405	3009	954	2055	4.74	1.50	3.24
1855	635 043	2979	1079	1900	4.69	1.70	2.99
1856	657 453	2888	1067	1821	4.39	1.62	2.77
1857	663 071	2787	836	1951	4.20	1.26	2.94
1858	655 481	3131	1068	2063	4.78	1.63	3.15
1859	689 881	3496	1238	2258	5.07	1.79	3.28
1860	684 048	3173	987	2186	4.64	1.44	3.20
1861	696 406	2995	886	2109	4.30	1.27	3.03
1862	712 684	3077	940	2237	4.32	1.32	3.00
1863	727 417	3588	1155	2433	4.93	1.59	3.34
1864	740 275	4016	1484	2532	5.43	2.00	3.43
1865	748 069	3823	1333	2490	5.11	1.78	3.33
1866	753 870	3682	1197	2485	4.88	1.59	3.29
1867	768 349	3412	1066	2346	4.44	1.39	3.05
1868	786 858	3503	1196	2307	4.45	1.52	2.91
1869	773 381	3283	1181	2102	4.24	1.53	2.71
1870	792 787	3875	1492	2383	4.89	1.88	3.01
1871	797 428	3935	1464	2471	4.98	1.81	3.09
1872	825 907	3803	1400	2403	4.60	1.70	2.90
1873	829 778	4115	1740	2375	4.96	2.10	2.86
1874	854 956	5927	3108	2819	6.93	3.63	3.30
1875	850 607	5064	2504	2560	5.95	2.94	3.01
1876	887 968	4142	1746	2396	4.66	1.97	2.69
1877	888 200	3443	1444	1999	3.88	1.63	2.25
1878	891 906	3300	1415	1885	3.70	1.59	2.11
1879	880 359	3340	1464	1876	3.79	1.66	2.13
1880	881 643	3492	1659	1833	3.94	1.88	2.08
1881	883 642	4227	2287	1940	4.78	2.58	2.20
1882	889 014	4524	2564	1960	5.09	2.89	2.20
1883	890 722	4508	2616	1892	5.06	2.94	2.12
1884	906 750	4647	2468	1879	4.79	2.72	2.07
1885	874 970	4449	2420	2029	4.98	2.71	2.27
1886	903 866	3877	2078	1799	4.72	2.39	1.99
1887	886 331	4160	2450	1710	4.69	2.80	1.90
1888	879 868	4160	2386	1774	4.73	2.49	2.01
1889	885 944	3585	1852	1733	4.05	2.09	1.95
1890	869 937	4255	1956	2299	4.89	2.24	2.62
1891	914 157	4787	1973	2814	5.24	2.15	3.06

continued

Table 1 *Continued*

Year	Registered births of children born alive	Deaths: Puerperal septic diseases and accidents of childbirth	Deaths: Puerperal septic diseases	Deaths: Accidents of childbirth	Death rate to 1000 children born alive, from: Puerperal septic diseases and accidents of childbirth	Death rate to 1000 children born alive, from: Puerperal septic diseases	Death rate to 1000 children born alive, from: Accidents of childbirth
1892	897 957	5194	2356	2838	5.78	2.62	3.16
1893	914 542	5950	3023	2927	6.51	3.30	3.19
1894	890 289	4775	2167	2608	5.36	2.43	2.92
1895	922 291	4219	1849	2370	4.57	2.00	2.56
1896	915 309	4561	2053	2508	4.98	2.24	2.74
1897	921 693	4250	1836	2414	4.61	1.99	2.62
1898	923 265	4074	1707	2367	4.41	1.84	2.56
1899	928 646	4326	1908	2418	4.66	2.05	2.63
1900	927 062	4454	1941	2514	4.81	2.09	2.71
1901	927 807	4394	2079	2315	4.73	2.24	2.49

Table 2 Number of deliveries, deaths and death rates during different time periods in the General Lying-in Hospital, London

Time period	Deliveries	Deaths	Average death rate from all causes
1838–1860	5833	180	1 in 32.5 or 30.85 per 1000
1861–1879	3773	64	1 in 57.875 or 16.96 per 1000
1880–1887	2585	16	1 in 161.5 or 6.18 per 1000
1888–1892	2364	9	1 in 262.67 or 3.80 per 1000

described below, illustrates how little could really be done for intra- and postpartum hemorrhage.

'Case C1V'

'I was summoned to a private patient near the Mansion House, who had been, a few minutes before, attacked with a sudden flooding in the eighth month of pregnancy, while sitting with her family at tea, in the drawing-room. Upon proceeding up stairs, tracks of blood were perceptible upon every step. In the bedroom, I found a neighbouring professional gentleman, who had been also called by the servants in their alarm at the state of their mistress; and, although this unfortunate occurrence had not happened a quarter of an hour before, it had already produced such a degree of compression as I have rarely witnessed, with its concomitant symptoms. Upon a vaginal examination a little after six, I detected the Placenta to be placed immediately over the Os Uteri; some discharge was still oozing away, but there was no tendency to pain. The urgency of the haemorrhage appeared therefore to be at present somewhat abating; and the lady for a short time seemed disposed to revive; but presently the flooding returned with its original violence. Anxiously watching its progress for a short time, and observing no diminution in the discharge, I determined on delivery; but previously I requested my professional friend to satisfy himself that the Placenta was presenting. Being answered in the affirmative, I proceeded without further loss of time to empty the Uterus. The Os Uteri was but little opened, yet it was relaxed, and permitted the passage of my hand with ease into the Uterus; but that organ showed at the moment no disposition to active contraction; having brought down the breech, the child was found to be alive; I therefore proceeded gently in its extraction; and after the child was born, the Placenta was thrown off, and was soon withdrawn. The uterine tumour proved now to be irregularly contracted, and fell flaccid under the hand. For a short time, this lady appeared comfortable; the discharge ceased, and she expressed her warmest thanks for my prompt assistance; but by-and-by she began to complain of her breath: 'Oh! my

breath! my breath!' was her urgent exclamation. My patient continued to sink, and expired soon after seven o'clock; so that in less than two hours, from an apparent state of perfect health, her valuable life was sacrificed to a sudden attack of haemorrhage, in spite of the most prompt assistance. The child was lively, and promised to do well.'

THE LONELINESS OF THE OBSTETRICIAN

Fifty years ago, and for the ensuing 20 years at least, 'Practical Obstetric Problems' by the late Professor Ian Donald, Professor of Midwifery in the University of Glasgow, was the essential and valued textbook for all young obstetricians of that generation. Nowhere is the famous dedication in the frontispiece more relevant than in relation to postpartum hemorrhage:

> 'To all those who have known doubt, perplexity and fear as I have known them,
> To all who have made mistakes as I have,
> To all whose humility increases with their knowledge of this most fascinating subject,
> This book is dedicated.'

The sense of helplessness, loneliness and fear that Dr Ramsbotham must have felt as he watched his patient expire in spite of all his good work and intentions is something that none of us ever wish to experience in our career.

As modern obstetricians, we no longer perform our tasks in isolation; we practice in hospitals which, in the majority of instances, are well or relatively well equipped, are surrounded by midwives, junior or senior colleagues, and know that various other specialists are standing by in support. Nevertheless, in dealing with postpartum hemorrhage, there comes a moment when our decisions and actions (or lack thereof) are going to determine the sequence of events. Even in complex cases of more prolonged hemorrhage, when all the support of the laboratory hematologists, the blood transfusion service, the anesthetic intensivist and other supporting clinicians has been called in, there will come a time when the only the attending obstetrician, using his or her best and most considered judgements, has to make a decision about radical treatments such as hysterectomy, laparotomy and hemostatic suturing, ligation of vessels or embolization.

The author's first 'lone' experience of postpartum hemorrhage occurred whilst working as a new Registrar at the University Hospital of the West Indies in Jamaica. Having just successfully conducted a very straightforward twin delivery, including completion of the third stage of labor with a standard dose of syntometrine, my state of calm was interrupted by a sudden gush of blood of such proportion that it seemed then (and even now) as if an old-fashioned bath tap had been turned on full pelt. The sound and sight of that hemorrhage will never leave my memory; it was a moment of absolute panic and helplessness. Miraculously, something took over, and decisions and actions were taken as if they were automatic, probably because Professor Ian Donald had been read, and re-read, in preparation for such an event. Bimanual compression, intravenous ergometrine administered by a much more experienced midwifery sister, who then made up a bottle of intravenous Syntocinon almost without being asked, and the situation was quickly under control. The young obstetrician grew significantly in maturity and experience in those few minutes, grateful that simple actions had averted what had seemed a potential disaster.

During the remaining years of my training, other dramatic postpartum hemorrhages also occurred, but the range of available interventions was limited. Intravenous or intramuscular ergometrine, intravenous Syntocinon infusions, bimanual compression, or packing the uterus with enormous packs (one teacher described putting a pillow case into the uterus first, and then filling it with as many packs as one could get hold of) were the only effective treatments. One had occasionally seen the need for postpartum hysterectomy and internal iliac artery ligation, but, in those circumstances, there had always been the welcome presence of a more senior colleague.

It is not only the trainee obstetrician who may still be faced with hard decisions. Sometimes, the presence and involvement of a large team lead to confusion of leadership. Whilst protocols, guidelines and practice 'drills' may help to coordinate teamwork and familiarize staff in how to deal with these unusual

situations, there remain numerous times when the obstetrician has to take command and make rapid or difficult decisions. In a lengthy career, one may be faced with a situation that is unique and has not been met with before. A few such cases which have faced the author are now discussed.

A patient had been admitted at 34 weeks with severe abdominal pain, a tense abdomen and absent fetal heart tones. Signs of shock and the tense, tender abdomen suggested a placental abruption, and the cardiovascular and respiratory collapse was of such severity that she was immediately transferred to the Intensive Care Unit (ITU), with a presumed diagnosis of placental abruption. Despite massive blood transfusion, her condition deteriorated, and, despite ventilation, it was difficult to maintain her PO_2. The ITU team felt that attempts to induce labor needed to be delayed until her condition improved. Eventually, ventilation resistance was so great that the ITU team was of the opinion that death was imminent. The obstetrician was therefore asked to consider carrying out a laparotomy and delivery of the dead baby in the hope that this might improve the situation. As the patient was deemed too ill to leave ITU, the operation was performed on an ITU bed. On entering the abdomen, a massive hemoperitoneum was encountered, and the first thought was of a ruptured uterus. However, the uterus was found to be intact, and, upon further exploration, it became obvious that the source of the intra-abdominal hemorrhage had been a ruptured liver. A general surgeon was called, who was able to secure hemostasis with several large hemostatic liver sutures, and the patient made a slow recovery. During the postoperative period, however, it became apparent that she also had HELPP syndrome. A stormy recovery ensued, but a year later the patient was pregnant again and delivered a healthy baby.

Another once-in-a-lifetime experience concerned a late vaginal termination at 18 weeks for a major chromosomal abnormality. During the procedure, it was apparent that the uterus had been perforated and a laparotomy was therefore carried out. A small tear was found in the caecum and a general surgeon called in. He recommended partial right colectomy, which was elegantly performed, and the perforation of the uterus closed without difficulty. A drain was left in the abdomen. An hour later, it was evident that there was major intra-abdominal hemorrhage. The drainage bottle had filled and been emptied twice, and the abdomen was distended, tense and tender. Unfortunately, the general surgeon had departed for the weekend and was not contactable. When the obstetrician returned, the patient was in a desperate condition, with major cardiovascular collapse. The anesthetist had inserted a subclavian line in order to obtain good venous access, and in doing so had inadvertently caused a pneumothorax. He was therefore inserting a chest drain. Once this had been accomplished and transfusion had restored the blood pressure, a laparotomy was carried out by the obstetrician. A small arterial bleeder was found at the ileo–colic anastomosis and was easily dealt with. The patient, who was the wife of a solicitor, made an uncomplicated recovery. The obstetrician expected that he might find a legal suit impending, but instead received a case of champagne and letter of thanks from the solicitor husband. This lady also subsequently went on to have a successful pregnancy.

On yet another occasion, the author was called in at 3 a.m. by a consultant colleague because a patient who had had a vaginal delivery with a very extensive vaginal and perineal laceration was still bleeding heavily after more than an hour of attempted suturing of the tear, and no fewer than 18 units of blood had been transfused. The operating theater looked like a battlefield theater, and the vaginal tissues appeared like wet blotting paper, with no identifiable anatomical layers. By then, the patient had major clotting deficiencies, and anesthetists and hematologists were busy attempting to correct that. Attempts were made at packing the vagina and applying pressure, but to no avail. A gynecological oncology colleague was contacted to discuss internal iliac artery ligation, and he advised that this should be done forthwith. The author had not participated in such a procedure for something like 20 years, and, although the gynecological oncologist said he would come in, he advised that time should not be wasted in getting on with the procedure. To the author's relief, the requisite details of the anatomy and necessary procedure were retrieved from the

cerebral archive almost automatically. By the time the oncologist arrived, the hemorrhage was almost completely under control, and it was then possible to complete hemostasis with a few additional vaginal sutures. After a short period of intensive care, the young woman recovered well, as did the anatomy of the vagina and perineum.

A final case involved a collapse at 36 weeks, with abdominal distension and extreme pain and tenderness. The fetal heart tones were still present, and the presumed diagnosis was placental abruption. The patient was immediately taken to theater for Cesarean section. On opening the peritoneum, a massive hemoperitoneum gushed forth, but the uterus was perfectly soft and normal in color. A Cesarean section was carried out and a healthy baby delivered. It was assumed that the source of bleeding could be a splenic artery aneurysm accident, and a four-quarter exploration of the abdomen carried out. The upper abdomen revealed no bleeding whatsoever, and eventually an arteriovenous malformation at the brim of the pelvis was found to be bleeding. A vascular surgeon was called in to check that hemostasis was satisfactory. After an 8-unit blood transfusion, the patient and baby did well.

CONCLUSION

The plethora of interventions available to the obstetrician now includes many different drugs to promote uterine contraction and hemostasis, a complex range of hematological products, and surgical interventions, including the B-Lynch stitch, the use of intrauterine pressure balloons, and early resort to hysterectomy or radiological embolization. All are described in detail in other chapters of this book. However, decisions about which intervention to try, and after how much blood loss, remain difficult, and are influenced by the likely future reproductive wishes of the woman, as well as the facilities or lack thereof available in the particular obstetric unit. Whilst much progress has been achieved in the last few decades, there remain many parts of the world where treatment options either are not much greater than they were 50 or more years ago in more developed countries or are even less, being hampered by the logistic considerations detailed in still other chapters in this volume.

The major challenge in the 21st century in this field is to narrow the inequalities of health-care provision in childbirth. It is hoped that this textbook, the first ever to discuss the topic of postpartum hemorrhage in a comprehensive manner, will go a long way in helping health-care providers to achieve this goal, for it should be obvious, even to the most neophyte reader, that the problems related to postpartum hemorrhage are not confined to one country or to one region. They are indeed world-wide, and their control will be facilitated by collaborations and partnerships, as seen in this textbook in which several chapters present details of what is being done in the developing as well as the developed world.

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43

THE MIDWIFE CONFRONTS POSTPARTUM HEMORRHAGE

A. M. Ward

INTRODUCTION

As repeatedly stated earlier in this book, postpartum hemorrhage is a major killer of women throughout the world[1] and is the second leading cause of admission of women to high-dependency units in the Western world[2,3]. Postpartum hemorrhage also causes significant morbidity for women in the Third and Western worlds[1,4,5]. Waterstone and colleagues[6] noted that two-thirds of severe maternal morbidity is related to severe hemorrhage. It stands to reason that any reduction in the frequency of postpartum hemorrhage would impact the lives of women and their families throughout the world[1]. Given these circumstances, it is essential that midwives, as first-line staff, be able to prevent, identify early and provide appropriate management during a postpartum hemorrhage[7,8].

Midwives practising in the United Kingdom (UK) are fortunate to work in a country with a relatively low maternal mortality rate[1]. At first sight, the role of midwives in the management of a postpartum hemorrhage may seem obvious, that is, they should diagnose the bleed, call for help and instigate emergency treatment[9]. The reality of the management of a postpartum hemorrhage is much more complex than this, however, and involves an ability to work effectively within a multidisciplinary team and to possess an indepth knowledge of the social, psychological and physiological processes that surround pregnancy and childbirth. Midwives should be central to the prevention, identification and management of postpartum hemorrhage and these precepts will form the focus of this chapter. The degree to which midwives can achieve these goals will obviously vary with local customs, resources and practices, but the goals should remain the same regardless.

PREVENTION OF POSTPARTUM HEMORRHAGE

Antenatal prevention

Prevention of postpartum hemorrhage should begin in the antenatal period. Midwives should assess women's risk factors at every antenatal visit and then, in partnership with the women, plan care that identifies the most appropriate lead health-care professional[10]. The antenatal risk factors, all within the midwives' domain to determine, that most commonly are reported for postpartum hemorrhage follow[11]:

- Body mass index > 30 kg/m^2
- Previous postpartum hemorrhage
- Antepartum hemorrhage
- Placental abruption
- Placenta previa
- Multiple pregnancy
- Macrosomic infant
- Previous uterine surgery
- Antenatal anticoagulation

Other risk factors include anemia, polyhydramnios, maternal age, uterine fibroids and a history of retained placenta[7]. Nulliparity has recently been identified as a possible risk factor for postpartum hemorrhage, rather than grand multiparity[12]. This is important, and it could well be that this group of women has not previously been identified as being at significant risk of postpartum hemorrhage. In the past, the management of such women may have been sub-standard as postpartum hemorrhage was not anticipated[12]. The above-mentioned risk

factors focus totally on the physical aspects of pregnancy. To ensure the optimum safety of women and their babies and to ensure holistic care, these risk factors need to be assessed in conjunction with other risk factors for severe maternal morbidity; these include maternal age > 34 years, social exclusion and non-white ethnicity[6].

Risk assessments undertaken by midwives need to carefully consider social and psychological aspects of women's lives, as there is clear evidence that women from poor areas, socially excluded groups and ethnic minorities have poorer health outcomes than other groups of women[1,13,14]. Midwives particularly need to focus care on women who book late, are poor attendees or who do not access antenatal care at all, as these are key indicators of poorer outcomes[13]. This requires effective communication links with other groups such as Public Health Nurses, General Practitioners and Social Services to ensure these special women are identified as being pregnant as early as possible and provided care in an environment appropriate for them and tailored to meet their social, cultural and psychological needs[1,13].

The National Institute for Clinical Excellence (NICE) has produced guidelines for antenatal care of healthy pregnant women in the UK[10]. These are useful in honing effective use of resources, but midwives need to be mindful that the guidelines are intended to guide the care of *healthy* pregnant women. The NICE document[15] clearly states that women should have a plan of care that is relevant to their individual physical, social and psychological needs, and the World Health Organization (WHO)[1] further indicates that this also needs to be culturally specific to women's backgrounds if it is to be truly effective.

Although midwives clearly need to know the risk factors for postpartum hemorrhage, identifying risk factors is not enough if appropriate care is not then instigated[13]. Once identified, risk factors need to be acted upon. Even where women have strong views about the type of childbirth experience they desire, open, frank discussion of identified risk factors and their implication for women and their babies, with time to assimilate and consider the information provided, leads to stronger relationships between women and midwives and reduces the potential for conflict when the safest management of care conflicts with women's wishes for their childbirth experience[15–18].

Intrapartum prevention

Intrapartum prevention of postpartum hemorrhage should begin in the antenatal period with the aim of helping women to be as healthy as possible, both physically and emotionally, and should include preparation for childbirth, focusing on strategies to keep the process normal[19]. Throughout the intrapartum period, midwives need to be with women supporting them, encouraging them to be mobile and offering alternative methods of pain relief that are less likely to interrupt the progress of labor[20,21]. Labor causes a great deal of insensible fluid loss and women need to be kept well hydrated to ensure adequate circulating volumes at delivery to enable them to cope with any excessive blood loss[22]. Women should also be provided with a quiet, private environment where they feel safe and protected to reduce the need for intervention during the process of labor[21,23]. All this is even more vital in areas where there is no direct access to intravenous fluids in the event of a postpartum hemorrhage.

Midwives need an indepth understanding of intrapartum risk factors and need to constantly reassess the woman for risk throughout labor[24]. Intrapartum risk factors for postpartum hemorrhage include:

- Prolonged labor > 12 h
- Prolonged third stage > 30 min
- Retained placenta
- Febrile illness
- Instrumental delivery
- Cesarean section, especially emergencies in late first or second stage of labor
- Amniotic fluid embolism
- Placental abruption

The first four conditions are most likely to cause an atonic uterus, whereas operative deliveries are the main cause of uterine, cervical or vaginal

trauma; embolisms and abruptions are common causes of coagulopathy, although this is the least common reason for postpartum hemorrhage[11].

The debate on whether to manage the third stage of labor actively could fill an entire text itself when considering practice in the UK and other developed countries. In the Third World, however, this is a different matter and routine active management of the third stage of labor could save many women's lives as well as saving many more from the abject misery of severe morbidity brought about by a postpartum hemorrhage[1,5,6,12]. This treatment needs to be carried out in conjunction with having in place trained birth attendants that understand women's specific cultural issues and are aware of when pregnancy and labor are not progressing normally[1].

The type of management used for the third stage of labor may be of no real consequence in a well-nourished, healthy population, but it is vitally important that midwives can clearly identify those women at increased risk of a postpartum hemorrhage, as well as understanding and carrying out expectant and active management of the third stage of labor[25]. Table 1 describes the main components of each management option for the third stage of labor.

DIAGNOSIS OF POSTPARTUM HEMORRHAGE AND POSTPARTUM PREVENTION

Definitions in themselves may not be useful, as they often involve measurement of blood loss retrospectively. As blood loss may not be entirely revealed, its estimation is notoriously inaccurate and difficult[26].

Healthy, young women can compensate for routine post-delivery blood loss very effectively, and this toleration is increased even further if there has been a healthy increase in blood volume during pregnancy[22]. Normally, plasma volume increases by 1250 ml and the red cell mass also increases, resulting in women being able to tolerate a drop in their pre-delivery blood volume of up to 25% and remain hemodynamically stable[22]. In practice, this means that midwives need to be encouraged to ignore machines and use their clinical skills of observation. They need to be alert to signs of earlier stages of shock – pallor, sweating and muscle weakness characterized by severe and rapid fatigue[22]. When women become restless and confused, shock is advancing rapidly and immediate, aggressive treatment is needed if not already instigated[22] (see also Chapter 8).

There are only two definitions for postpartum hemorrhage, primary (occurring within the first 24 h after birth) or secondary (occurring after 24 h and before 6 weeks postpartum). In contrast, experienced health-care practitioners will recognize that, in practice, there are three different presentations of postpartum hemorrhage:

(1) Rapid loss of blood at or just shortly after delivery;

(2) Constant heavy lochia that persists for a significant length of time after delivery;

Table 1 Options for the management of the third stage of labor

Active management	*Expectant management*
Oxytocic drug given at delivery of anterior shoulder	No oxytocic drug given
Cord clamped and cut immediately	Cord not clamped until pulsation ceased, then only clamped at baby's umbilicus
When uterus central and well contracted, controlled cord traction applied	No cord traction Signs of separation awaited: • Rise in fundus • Lengthening of cord • Trickle of blood at introitus
Midwife delivers placenta and membranes	Maternal effort delivers placenta and membranes

(3) Bleeding after the first 24 h following childbirth.

It is the second type of bleeding that can cause problems for health-care practitioners, because it is often the type of bleeding that is missed. Women will experience heavy lochia that they report. Their sanitary protection will be changed and then, a little while later, the same will happen and they will report it again, but this may be to another member of staff who is unaware of the previous loss. Midwives and midwifery assistants need to be encouraged to quantify the amount of blood lost and record this in the maternal notes, keeping a running total of the amount of blood lost to alert them to women who are bleeding significantly but still compensating adequately[22].

MANAGEMENT OF POSTPARTUM HEMORRHAGE

As any postpartum hemorrhage has the potential to cause maternal collapse with loss of consciousness, midwives need to be competent with basic life support (ABC algorithm)[8,22,27]. The first principle of which to be aware is that a single individual cannot effectively manage an emergency situation, and help must be urgently requested prior to commencing any treatment[27]. Midwives need to constantly ensure that women have patent airways and are breathing adequately; here, expensive technology is not required. If women do not respond when spoken to, then they potentially cannot manage their own airway and an individual with the appropriate skills and training needs to do this. Until the airway and breathing are effectively brought under control, there is little point undertaking any other task, as hypoxia can kill women much faster than hypovolemia[22]. Proper airway management needs to ensure that oxygen therapy is optimally utilized to ensure depleted hemoglobin is as well oxygenated as possible to prevent cell death[22]. Once sufficient members of the team are present, then they can move onto maintaining the circulatory system and determining the cause of the postpartum hemorrhage (see Chapter 13).

The key to reducing morbidity and mortality in the management of a postpartum hemorrhage is effective fluid resuscitation[8,22] (see also Chapter 5). Midwives may be concerned about which fluids are best, but their focus needs to be on ensuring fluid is administered quickly and is not cold. Where available, fluid warmers and pressure bags must be utilized. **Every 1 ml of blood lost needs to be replaced with 3 ml of fluid until blood is available**[8,22]. To ensure fluid can be delivered as quickly as possible, two wide-bore, short cannulae need to be used, as the volume that can be infused through a cannula is proportional to the diameter and inversely proportional to its length[22]. Midwives may also be concerned about commencing intravenous fluids without prescription or written order. However, postpartum hemorrhage is an emergency situation and, as such, midwives can administer resuscitative fluids without a prescription first[9]. Women need to be kept warm as hypothermia is a consequence of hypovolemic shock[8,22]. As the assessment of renal function is an essential part of management once the bleed is controlled, an indwelling urinary catheter should be inserted, using strict aseptic techniques to avoid infection in women who are already compromised as a result of the postpartum hemorrhage[22].

CARE FOLLOWING A POSTPARTUM HEMORRHAGE

Women who have sustained a significant postpartum hemorrhage need to be receive one-to-one care to facilitate close monitoring[4-6,12]. Initially, the focus of care will be on the woman's physical condition, observing and monitoring urinary output, fluid intake, vital signs and subsequent blood loss. Ideally, such care is best provided in an obstetric high-dependency unit if available. Any women requiring mechanical ventilation should be cared for in an intensive care unit[4-6,12].

Intensive monitoring often means that other aspects of care important to women following childbirth are neglected[3]. Care provided by midwives also needs to include the psychological well-being of women and the integration of the family unit who may be bewildered by the goings-on after the delivery[3,24]. Women who are conscious need to have contact with their babies and feel central in any decision-making around

the care of their babies[3]. Skin–skin contact is a simple procedure that can be carried out even for the sickest women and can be beneficial to women as well as their babies; it assists in the effective introduction of breastfeeding and has relaxing properties for women and babies alike[28].

Given the traumatic nature of a postpartum hemorrhage, women will need support long into the postnatal period as they recover physically and emotionally[29]. Initial debriefing may not be beneficial and may, in fact, be detrimental to these women. Later debriefing may discuss, among other things, the risk of recurrent postpartum hemorrhage. After the crisis has passed, these women need effective long-term follow-up. In larger units, it may be appropriate to have a lead midwife and obstetrician to run combined postnatal clinics for these women, where recovery can be monitored and any concerns about subsequent pregnancies can be discussed with relevant health-care professionals[29].

DOCUMENTATION

Accurate documentation is crucial during an emergency procedure and the leader of the emergency team needs to task someone by name to record events as they occur, including the times team members enter and leave the room, as well as the timing of any procedures and drugs administered, including route and dose[30]. Good records are an indication that the quality of care given to women was of a good standard[30]. Midwives have a professional duty to ensure records are kept as contemporaneously and accurately as possible[9,30]. Good practice is to ensure that the documentation completed by the named scribe is included in the maternal records and not disposed of once individual health-care practitioners have used them to complete their own notes. Accurate record-keeping is vital to reduce the risk of successful litigation, but it is also vital in the active debriefing of all team members[31] (see also Chapter 13). Simple factors can dramatically improve the quality of record-keeping and only take seconds[30]. These include:

- Dating and timing all new entries;
- Printing name and qualification alongside the first signature in any records;
- Writing legibly.

Documentation of vital signs and urine output is essential following a significant postpartum hemorrhage, but documentation itself will not ensure effective management of sick women. It is vital to ensure that trends in all important physical parameters, especially respiration, are being acted upon effectively because they can indicate the effectiveness of any treatment as well as when women are deteriorating[2,3]. Scoring tools can be developed that assist practitioners to identify women who are not responding to treatment and therefore require the expertise of senior obstetricians and anesthetists and admission to an intensive care setting.

COMMUNICATING EFFECTIVELY

In any emergency health care, professionals are relieved when help arrives, but the larger the team the more complex communication and the more difficult it can be to manage the situation effectively and utilize the team efficiently[31,32]. **Someone needs to take charge**, stand back, observe and then direct the working of the team[31,33]. The role of this lead individual is also to constantly evaluate the effectiveness of treatments instigated and to constantly be re-thinking the potential causes of postpartum hemorrhage when the treatment instigated is not being effective in controlling the bleeding[34]. Historically, this has been the most senior obstetrician on duty in an obstetric maternity unit. Both obstetricians and midwives recognize that the person co-ordinating the team at an emergency should be the most experienced clinician available[31,33]. In some circumstances, this may be the senior midwife who will be more experienced than the house officers.

An emergency situation is no time for hierarchy. Communication needs to be precise, with tasks directed to a named individual (not Mr or Mrs Somebody) and feedback requested from that individual at regular intervals. Training of teams, within individual units or the community setting, needs to be multidisciplinary, realistic to the work environment, scenario-driven and based on real timing and action to make it as

realistic as possible[33]. For example, if simulating a postpartum hemorrhage in a home setting, then paramedics need to be involved and the setting needs to reflect the equipment that would be available to midwives in those situations. For midwife-led units not attached to obstetric units, the training should involve paramedics and the ambulance service and not include the management schemes using drugs and techniques that would not be available to those midwives.

TRAINING

Team sports have recognized for decades that, to ensure that a team functions efficiently and effectively, its members must train together; such training must focus on utilizing individual skills to their greatest potential for the good of the team. In the NHS, individual professional bodies have trained their own practitioners largely in isolation of other health-care professionals and then they have been expected to work as a well-oiled machine in times of great stress, with minimal understanding of each others' strengths and weaknesses[31,35]. Happily, this trend is changing and the benefit of multidisciplinary training is being recognized[33].

In the Yorkshire Region, this has been taken one step further with many maternity units adopting a regional training program aimed at managing the first 20–30 min of obstetric emergencies effectively. As medical trainees rotate around the region, there is a systematic approach to the training for management of obstetric emergencies that they are expected to complete as early as possible into their time in a new unit. Units in the region that have adopted the training have made it mandatory for anyone involved in the intrapartum care of women, from health-care assistants to consultants.

Scenarios are run real-time using mannequins, and participants are expected to carry out procedures as if it were a real emergency. This is then videoed and the participants on the day debrief themselves, with a facilitator assisting them to focus on issues of leadership, control and communication, all of which have been highlighted as factors in suboptimal care[13]. Dedicated time is given for this training, which has been shown to improve outcomes and efficiencies and can be achieved with effective timetabling and allocation[36]. Anecdotally, the training improves communication and team work, but needs to be audited against unit guidelines considering maternal outcomes and focusing on morbidity and mortality rates, as well as adherence to the guidelines themselves.

DEBRIEFING

Part of ensuring a team learns from stressful clinical incidences is a review of their performance as close to the event as possible. The purpose of this 'debriefing' session should be to focus on what was done well. It can be used to identify what needs to be shared with team members not involved in the emergency, to aid their development and learning, as well as to provide a forum where those involved in the emergency can vocalize how they feel in a protective environment. This will enable learning whilst at the same time offering professional and emotional support, recognizing that health-care professionals are caring individuals who can be profoundly affected by traumatic situations[37]. Debriefing is a useful tool to help team members recognize that they are valued and the role they play in the effective running of the team, all of which can help increase job satisfaction and reduce the number of professionals leaving midwifery and obstetrics[37].

CONCLUSION

Midwives are central to the effective prevention, recognition and treatment of postpartum hemorrhage. They need to be aware of the risk factors for postpartum hemorrhage and take appropriate action when they are identified. They should also be skilled in basic life support and have an understanding of the pathophysiology of hypovolemic shock. This knowledge must be used in conjunction with an understanding of women's social, cultural and psychological well-being.

Training as multidisciplinary teams can be effective in improving outcomes for women and their families. The Yorkshire model may be beneficial in units that have trainees who rotate throughout their region. Effective communication and leadership are vital in the

management of any obstetric emergency and scenario-based training can be used to highlight issues of control and communication.

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44

SEPSIS AND POSTPARTUM HEMORRHAGE

B. Das and S. Clark

INTRODUCTION

Sepsis and postpartum hemorrhage are linked by common predisposing factors, especially considering that secondary postpartum hemorrhage can follow infection of retained placenta or endometrium. Depending on the extent and severity of the condition, postpartum uterine infection is designated as postpartum endometritis, endomyometritis or parametritis. Postpartum endometritis may be divided into early-onset disease, occurring within the first 48 h, and late-onset disease, presenting up to 6 weeks postpartum. This chapter reviews the causes, pathogenesis and management of uterine sepsis.

CLINICAL RISK FACTORS

The most critical factor is the route of delivery. After vaginal delivery, the incidence of postpartum endometritis varies between 0.9 and 3.9%, but can increase to 12–51% after Cesarean section. Factors such as duration of labor, bacterial vaginosis and vaginal interventions are secondary predictors of post-Cesarean endometritis. Early rupture of the membranes, mid-forceps delivery, poor maternal health and soft tissue trauma act as 'relative risk factors' for uterine sepsis, although they are not present in most patients with such infections[1]. Indigent parturients are at higher risk of developing postpartum endometritis.

ETIOLOGICAL AGENTS

Postpartum uterine sepsis is thought to arise from an ascending infection caused by colonizing vaginal flora. Etiological agents include both aerobic and anaerobic micro-organisms and may consist of peptostreptococci, bacteroides, streptococci, enterococci and *E. coli*. Group A streptococcal endometritis, a rare cause in developed countries, usually occurs in early-onset disease (within the first 48 h of delivery), often with high temperature > 39°C (102.2°F). In contrast, *Chlamydia trachomatis* is involved with late-onset disease (from 2 days up to 6 weeks postpartum) in patients who deliver vaginally.

CLINICAL FEATURES AND INVESTIGATIONS

Postpartum endometritis is diagnosed by significant pyrexia associated with uterine tenderness or abnormal lochia in absence of other obvious sources of infection. Significant pyrexia is defined as oral temperature of 38.5°C (101.3°F) or higher in the first 24 h after delivery or 38°C (100.4°F) or higher, for at least 4 consecutive hours, in the first 24 or more hours after delivery. The first manifestation of fever may occur at night[2,3]. Uterine sepsis associated with late-onset disease and secondary postpartum hemorrhage usually presents as fever on days 10–12 after delivery.

Patients with suspected postpartum endometritis should have early clinical evaluation including bimanual pelvic examination to determine size, consistency and tenderness of the uterus and to detect any adnexal mass (ultrasound study may help, if available). Cesarean section/episiotomy wounds should be assessed for evidence of surgical site infection. Unremitting pain at the operative site may indicate necrotizing fasciitis, wherein urgent debridement is life-saving[3]. A distant site of infection, e.g. urinary or respiratory tract, should be ruled out.

Laboratory investigations (where facilities are available) include full blood count, transcervical cultures (aerobic and anaerobic) and one set of blood cultures, remembering that only 10–20% of patients with postpartum endometritis have bacteremia. The presence of bacteremia does not predict severity of infection or prolonged recovery. Transcervical cultures, although difficult to interpret because of contamination with vaginal flora, are helpful in those patients in whom initial therapy fails. Whenever possible, culture/antigen tests for chlamydia should be performed in patients with late-onset disease or those who are at high risk for acquisition of such infections.

ANTIBIOTIC THERAPY AND FURTHER MANAGEMENT

The aim of the antibiotics should be to provide bactericidal cover for aerobic Gram-positive cocci, Gram-negative bacilli and β-lactamase-producing anaerobes. Those antibiotics which have been used for prophylaxis should be avoided. Empirical treatment should be commenced as soon as possible. Parental treatment with once-daily intravenous gentamicin and intravenous clindamycin is an effective combination, especially in post-Cesarean section patients and those awaiting surgical interventions, including removal of retained placenta. Gentamicin levels need to be monitored. However, other alternatives, including extended-spectrum penicillins or second-generation cephalosporins (cefoxitin), have been used, albeit with greater failure rates than the combination of gentamicin and clindamycin[4]. Alternative antibiotic regimens are shown in Table 1. Intravenous clindamycin and intravenous once-daily gentamicin are the cheapest of the antibiotic regimen options, an important issue in countries with restricted resources.

Parental therapy is continued until the patient is pain-free, afebrile for 24–48 h, the leukocyte count returns to normal, and oral liquids and solids are tolerated. There is no need to continue with oral antibiotics after stopping parental treatment. Patients with positive cultures for chlamydia should receive a 7-day course of azithromycin or doxycycline, even if there is good response to the initial empirical antibiotic regimen. Azithromycin and doxycycline, although good antichlamydial agents, are bacteriostatic drugs and should not be used as first-line antimicrobial agents to treat endometritis.

Failure to respond to the initial antibiotic regimen in 48 h or clinical deterioration requires further clinical evaluation and investigations to rule out another site of infection and complications (see Figure 1). The antibiotic regimen needs to be altered, preferably after reviewing transcervical culture and sensitivity results (see Table 2).

PREVENTION OF UTERINE SEPSIS

Strategies to prevent uterine sepsis include improved obstetric care and the use of prophylactic antibiotics in high-risk patients, as well as

Table 1 Initial antibiotic therapy[1,2,4]

Day 1
1. Clindamycin 900 mg 8-hourly + intravenous gentamicin 5 mg/kg body weight* once daily
or
2. Intravenous piperacillin–tazobactam 4.75 g 6-hourly
or
3. Intravenous metronidazole 500 mg 8-hourly + intravenous gentamicin 5 mg/kg body weight* once daily
or
4. Ampicillin–sulbactam 3.1 g 6-hourly + intravenous gentamicin 5 mg/kg body weight* once daily

*Monitor gentamicin level

Day 1

↓

Specimen collected: transcervical swab for aerobic organism and chlamydia* – blood culture	Empirical antibiotics, e.g. i.v. gentamicin + i.v. clindamycin	Surgical intervention if clinically relevent

*Specimen for *Chlamydia trachomatis* to be obtained on patients with:

(a) late onset of disease or
(b) high risk for acquisition of this infection

Day 3

Patient on empirical antibiotic

↙ ↘

Afebrile

Continue i.v. antibiotics until:

·Patient afebrile × 24–48 h

·Pain-free

·Normal cell count

Febrile

·Clinical evaluation

·Rule out other source of infection

·Urine, wound swab for culture and sensitivity (if facility available)

·Imaging ± surgical intervention

Altered antibiotic regimen (see Table 2) or specific antimicrobial therapy as per culture results, e.g. i.v. benzyl penicillin and i.v. clindamycin for Group A streptococci

Figure 1 Flow chart of treatment regimens for patient with suspected uterine sepsis and postpartum hemorrhage[1,2,4]

coverage of planned or emergency surgical interventions. In areas with limited resources, education with the emphasis on a clean environment and simple infection control measures like hand-washing, cleaning the genital area, preferably with mild detergents/disinfectant, and minimizing the number of vaginal examinations all play an important role in reducing uterine infection.

The risk of infection increases with postpartum hemorrhage especially if the blood loss is greater than 1 liter. If uterine sepsis occurs,

Table 2 Altered antibiotic regimen[1,4]. In all cases, the therapy should ideally be guided by culture results

If the patient deteriorates *or* Day 3 onwards if patient continues to be febrile on initial regimen:
Initial antibiotic regimen + another antimicrobial agent = altered regimen
1. Intravenous clindamycin + intravenous gentamicin* + intravenous ampicillin 1–2 g 6-hourly
or
2. Intravenous piperacillin–tazobactam + intravenous gentamicin 5 mg/kg* once daily)
or
3. Intravenous metronidazole + intravenous gentamicin* + intravenous ampicillin 1–2 g 6-hourly
or
4. Intravenous ampicillin–sulbactam + intravenous gentamicin intravenous metronidazole 500 mg/8 hourly
The choice of antibiotics in the altered regimen may be determined by transcervical isolates (where culture facilities are available), cost and availability of antimicrobial agents.

*Monitor gentamicin levels

such hemorrhagic consequences can be devastating: collapse can lead to death, as discussed elsewhere in this book. In many developing countries, the majority of deliveries do not occur in a facility with a skilled attendant. Traditional birth attendants (TBAs) need to recognize the consequences of delayed referral. Local and international organizations that aim to provide resources to educate TBAs, increase access to skilled attendants and to facilities for prompt care of postpartum hemorrhage and sepsis all help to decrease maternal mortality in these countries.

CASE STUDY

A 28-year-old primigravida presented at 41/40 weeks with a history of prolonged latent phase of labor. She underwent a Cesarean section as she failed to respond to 8-h oxytocin infusion, commenced after artificial rupture of the membranes. Prior to the procedure, the patient received intravenous cefuroxime and intravenous metronidazole as she was found to be pyrexial (38.7°C). At Cesarean section, she had offensive grade 1 meconium liquor; the placental membranes were found to be adherent but were successfully removed. A live baby with good Apgar score was delivered; however, the patient had primary postpartum hemorrhage due to uterine atony. The patient lost 6 liters of blood and a B-Lynch compression suture was inserted to stay the continual bleeding. The patient received a total of 7 units of blood and 4 units of fresh frozen plasma. The patient continued to be pyrexial, her white blood cell rose from 10 000 to 25 000; lochia was offensive and a transcervical swab grew *E. coli* and anaerobes. She was therefore administered an intravenous clindamycin and once-daily intravenous gentamicin regimen for uterine sepsis. Gentamicin levels were regularly monitored and the patient was discharged after 8 days intravenous therapy, having being ambulant, afebrile and pain-free for 48 h. The baby remained well.

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45

THE SINGLE-UNIT TRANSFUSION IN THE BLED-OUT OBSTETRIC PATIENT

V. Nama, M. Karoshi, M. Wac, L. G. Keith and S. A. Mujeeb

THE HISTORICAL PRACTICE OF SINGLE-UNIT TRANSFUSION

The first reported blood transfusion took place in Rome in 1492. Pope Innocent VIII suffered an apoplectic stroke, became weak and lapsed into coma. His physicians advised a blood transfusion in hopes that it would help their patient. Employing the crude methods of the day, the Pope failed to benefit from this intervention and died by the end of that year. Since then, many advances have been made, blood groups have been discovered and transfusion practices refined. Presently, blood is part of the everyday armamentarium used by physicians to treat countless diseases and conditions.

In their 2005 retrospective analysis evaluating the role of single-unit red blood cell transfusion, Ma and colleagues noted that, in the 1960s, single units were deemed insufficient to correct anemia and, therefore, useless[1]. These investigators also retold a clinical maxim from that time, i.e. the patient whose transfusion requirements could be met with one unit of red blood cells was no more in need of a transfusion than the donor who gave 500 ml of blood. Although the origins of this maxim are unclear, the prevailing attitude in the medical community was rather obvious. In the years following the 1962 Joint Blood Council call for scrutiny of blood transfusion practices in hospitals having a predominance of single-unit transfusions, one study found that 60–70% of these interventions were not indicated[2]; in addition, two studies found that all of the single-unit transfusions assessed were unnecessary or questionable[3,4], and yet another study found this practice questionable in 38% of assessed cases[5]. The very existence of these investigations documents the widespread practice of single-unit transfusions and the scrutiny to which they were subjected during the 1960s.

The debate on the usefulness of single-unit red blood cell transfusions continued with vigor in the following decades. In 1985, Grindon and associates[6] condemned the scrutiny of single-unit transfusions advocated in 1962 by the Joint Blood Council, stating that the 'administration of one unit of blood more often reflects appropriate use than misuse'. One year later, in 1986, an observational study reported that most single-unit transfusions were administered during surgery and that the indications for 62% of these were questionable[7]. Very shortly thereafter, however, a case report published in the *Journal of the American Medical Association* demonstrated that a single-unit transfusion increased the hematocrit to a safe level, especially in patients with low body mass index[8].

EVENTS LEADING TO ALTERATION OF BLOOD TRANSFUSION PRACTICES

The conflicting opinions were so numerous that the US government decided to address this issue. However, this effort only provided tangential guidelines rather than ending the debate. In 1988, the National Institutes of Health (NIH) formulated a Consensus Conference Statement, entitled 'Perioperative Red Cell Transfusion'. This document recommended the threshold of hemoglobin concentration for transfusion to be lowered from 10 g/dl to a value between 7 and 10 g/dl, depending on the clinical assessment, laboratory data, and volemia of individual patients. At the same time, it was

deemed advisable that the number of units of blood administered should be kept to a minimum, mostly to reduce the number of transmitted infections[9].

The safety concerns expressed by the NIH were amplified by additional reports associating allogenic blood transfusions with infections, transfusion-related and allergic reactions as well as adverse immunomodulatory effects[10,11]. A review published in the *British Medical Journal* in 1990[12] sought to bring an end to single-unit transfusions. Simply stated, this article opined that the single-unit transfusion significantly increased the risks of viral infection while, at the same time, offered little or no therapeutic benefit. In the immediate aftermath of this publication, a study conducted in 1992 in a West African city, also published in the *British Medical Journal*, estimated the risk of HIV infection to be between 5.4 and 10.6 per 100 units of blood administered, a substantial threat even in cases of single-unit transfusions in developing countries[13].

RE-EMERGENCE OF CONSIDERATION OF THE SINGLE-UNIT TRANSFUSION

Not surprisingly, the 1990 *British Medical Journal* publication and others condemning single-unit red blood cell transfusion did not bring the debate to a halt. At the same time, the studies from the 1960s to the 1980s warned against administering single-unit red blood cell transfusions, and clinical guidelines suggested ever-lower thresholds for transfusion as a means to preserve blood resources and increase safety[14]. Whereas some physicians became convinced that single-unit blood transfusions had no place in the treatment of anemia, others came to believe, somewhat paradoxically, that individual units of blood should be given as needed, but only when the patient's hemoglobin concentration fell below a specified threshold, which varied across guidelines. As a counterplea to those who were opposed to single-unit transfusions and in favor of low, specified thresholds of hemoglobin concentration for transfusion, one 1992 study concluded that transfusion practices should be audited for undertransfusion as well as overtransfusion[15]. This suggestion, i.e. the possibility that patients could be undertransfused, was repeated in 1998 by a study that pointed out the dangers of lowering transfusion thresholds[16].

Shortly thereafter, the 1999 multicenter Transfusion in Critical Care (TRICC) trial randomized intensive-care patients to receive 'restricted' or 'liberal' red blood cell transfusions in order to analyze overall 30-day mortality rates in patients who might be undertransfused[17]. Patients received transfusions when their hemoglobin concentrations dropped below 7 g/dl in the restricted treatment group or 9 g/dl in the liberal treatment group. Mortality rates in this Canadian trial were similar in the two groups, but mortality was significantly lower among patients who were less acutely ill in the restricted treatment group.

A more recent study (2003) conducted to assess transfusion practices in a large Scottish hospital concluded that hospital clinicians administered transfusions when their patients' hemoglobin concentrations were between 7 and 9 g/dl[18]. Not only did the clinicians not follow the available TRICC trial protocol, which proposed transfusions only when hemoglobin concentrations fell below 7 g/dl, but the study's authors reported that the Scottish practices were consistent with the findings of other recently published studies[19-21]. In 2004, hoping to finally close the argument fuelled by the TRICC trial, a Canadian review reaffirmed the 1988 NIH recommendation regarding thresholds by stating, 'The quest for a universal transfusion trigger, i.e. one that would be applicable to patients of all ages under all circumstances, must be abandoned. All RBC (red blood cell) transfusions must be tailored to the patient's needs as it arises'[22]. This statement is of particular relevance to obstetricians, who commonly deal with anemic parturients and occasionally deal with bled-out postpartum mothers.

In 2005, Ma and collaborators[1] analyzed the results of single-unit transfusions for thresholds that began at 7 g/dl, and were raised to 9 g/dl by increments of 0.5 g/dl. These investigators demonstrated that, for most patients, the transfusion of one unit of red blood cells could raise the hemoglobin concentration sufficiently to avoid the need for a second unit. When the goal of red blood cell transfusion was to maintain the

hemoglobin concentration above a threshold considered as safe, they concluded, 'the single-unit transfusions may not only be appropriate, but preferable.' Unfortunately, the circumstances leading to compliance with the premises of using a threshold level before administering a transfusion do not apply in all parts of the world and are particularly restrictive in terms of bled-out parturients in the developing world.

SINGLE-UNIT TRANSFUSIONS IN THE BLED-OUT PATIENT OF THE DEVELOPING WORLD

The only subgroup analyzed in the 2005 study by Ma and collaborators[1] consisted of orthopedic patients, and the authors did not mention whether their analysis included pregnant women who experienced postpartum hemorrhage or were anemic. In 1992, the World Health Organization (WHO) published a tabulation of its 1990 estimates of the global death burden from all forms of anemia. Women of reproductive age were determined to be at greater risk of mortality from anemia than other groups of individuals[23]. Figure 1 shows the case fatality rate in relation to maternal anemia.

Anemia during pregnancy increases the risk of death, as it may lead to rapid cardiac decompensation, even without the additional stress of a true postpartum hemorrhage. Under such circumstances, the loss of less than 500 ml of blood could represent a fatal insult in a severely anemic woman. When the hemoglobin concentration is < 8 g/l, compensatory mechanisms fail, lactic acid accumulates and patients become breathless at rest. Cardiac failure may occur when the hemoglobin concentration is < 4 g/l, especially with twin pregnancies or with splenomegaly.

Based on available evidence, the single-unit transfusion should remain a viable therapeutic option in selected obstetric patients, especially in the developing world, where many women finish their pregnancies in moderate or severe anemic states. Depending on a variety of circumstances, such patients may die within a relatively short time after a postpartum

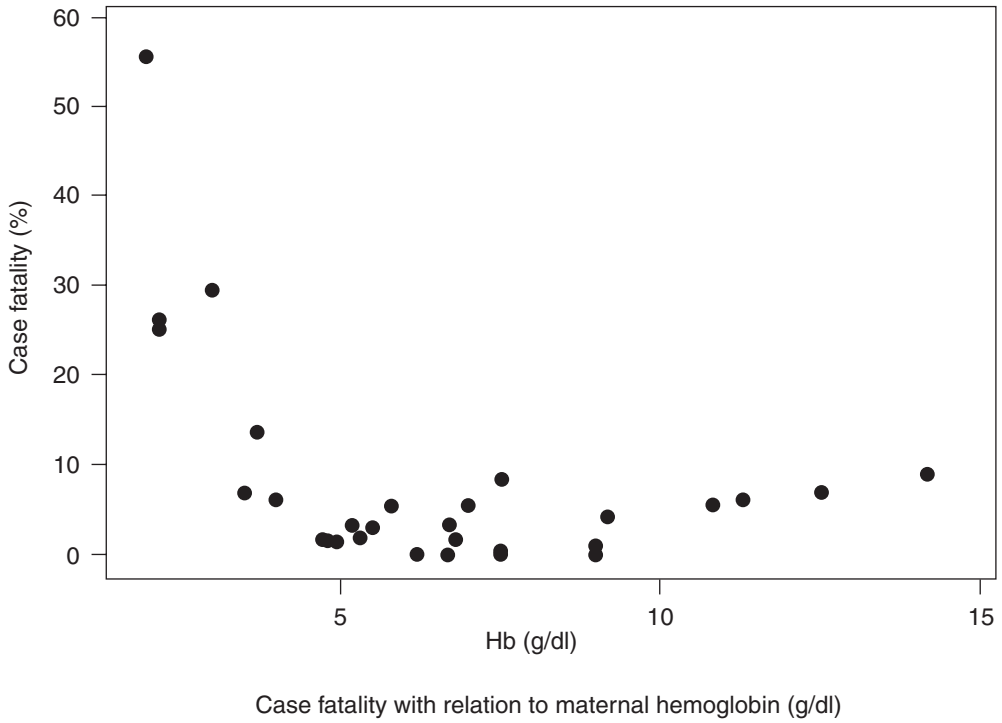

Figure 1 An analysis of anemia and pregnancy-related maternal mortality. Modified from Brabin BJ, Hakimi M, Pelletier D. *J Nutr* 2001;131:604S–14S

hemorrhage. If they do survive and if they are fortunate enough to be transported to a place where transfusion is available along with other resuscitative measures, a single-unit transfusion may make the difference between whether or not the woman can be considered sufficiently well to return home for aftercare.

Clearly, each case must be evaluated on its own merit. Sometimes, care-givers will be sufficiently satisfied with the effect of one unit that they may hold off a second planned transfusion, especially if they think that the patient has sufficiently recovered from the insult of postpartum hemorrhage. It is unlikely, however, that the effect of single-unit transfusion in women who have sustained postpartum hemorrhage will ever be examined in a randomized, controlled trial. In addition, it is highly unlikely that such a trial, if ever proposed to most western world institutional review boards, would be considered ethical.

SUMMARY

In summary, numerous studies have shown that single-unit transfusion can ameliorate symptoms of chronic anemia. Its value in obstetric emergencies when the anemia is acute has never been tested. In countries where resources are poor and the majority of women have anemia at the onset of their pregnancies, even the slightest deviation from normality during labor and delivery may lead to excessive obstetric hemorrhage that can put a woman's life at risk. In these cases, after stabilizing the patient with whatever resuscitative measures are available, transfer to a suitable center would be ideal. There, blood should be given, preferably typed and cross-matched and screened for infections. Unfortunately, such an eventuality is rare in the developing world, and patients, if they survive, arrive at the referral center in a moribund state. Some of these women, especially those who are younger and have stopped bleeding, may benefit from a single unit of blood along with other appropriate therapeutic measures. If, in the opinion of the clinician, this appears to be a reasonable course of action, then the single unit should not be denied simply in order to comply with what presently appears to be an outdated dictum[24].

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46

OUT-OF-HOSPITAL DELIVERIES

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INTRODUCTION

Out-of-hospital deliveries can be divided into planned, generally in a prepared setting and attended by medical personnel, and unplanned[1]. Unplanned out-of-hospital delivery or delivery en route to the hospital occurs when the woman is entering the active phase of labor rapidly; it can be a stressful and sometimes even hazardous experience. Unplanned out-of-hospital deliveries also carry an increased risk for adverse maternal and perinatal outcomes and specifically hemorrhage and perinatal mortality[2–14].

Bateman and colleagues[3] reported that patients who delivered out of hospital in the USA were more likely to be African-American, multigravid and to have had no or poor prenatal care. Similarly, other ethnic minorities (Asians living a long way from the hospital in Europe) are also at risk for out-of-hospital deliveries and for adverse pregnancy outcome[4–6]. Indeed, reducing out-of-hospital deliveries has been cited as an explicit health goal in the USA[15].

The two major forms of postpartum hemorrhage are early postpartum hemorrhage, which occurs within 24 h from delivery, and late postpartum hemorrhage, which takes place between 24 h and 6 weeks after delivery[16]. Definitions of each class are provided in Chapter 2; however, the validity of the definitions has not been shown by rigorous evaluation and the processes of estimation of blood loss are suspected (see Chapters 5 and 6).

In one often-quoted article, approximately 5% of all women who underwent vaginal delivery without complications lost more than 1000 ml of blood[17]. Having acknowledged this, it is generally agreed that the objective evaluation of bleeding after labor may be difficult, specifically when bleeding is slow and steady or in the presence of concomitant intra-abdominal bleeding[18]. Moreover, the clinical signs of blood loss, such as decrease in blood pressure and increased heart rate, tend to appear late, and only when the amount of blood loss reaches 1500 ml, mainly due to the high blood volume of pregnant women (see Chapter 4 on assessing loss).

Recently, our group performed a large population-based study of risk factors for early postpartum hemorrhage[16]. Although this was not the first such study[19–22], we were stimulated to characterize women at risk that warrant special attention after birth and consultation about the advisability of out-of-hospital delivery. Early postpartum hemorrhage complicated 0.43% (n = 666) of all singleton deliveries included in this study (n = 154 311). Independent risk factors for early postpartum hemorrhage, which can be of major importance during out-of-hospital deliveries, are presented in Table 1. These risk factors were drawn from a multivariate analysis and included retained placenta, labor dystocia, placenta accreta, severe lacerations, large-for-gestational age newborn and hypertensive disorders[16].

One of the largest studies regarding out-of-hospital deliveries derives from a tertiary medical center, located in the Negev region, in Israel[12,13]. In this area, most deliveries occur in the hospital, and virtually all newborns and their mothers are brought to the hospital, when delivered outside. This is done mainly because hospital deliveries are entitled to a birth payment from the government, which is also given to newborns who are brought within 24 h to the hospital. The incidence of unplanned, accidental out-of-hospital deliveries was 2% (2328/114 938). Perinatal mortality was significantly higher among out-of-hospital deliveries (odds

ratio (OR) 2.01, 95% confidence interval (CI) 1.4–2.9), as compared to in-hospital deliveries. Parturients who gave birth out of hospital had higher rates of perineal tears and retained placenta, as compared to patients delivered in hospital (Table 2). In addition, patients delivered out of hospital had a higher rate of delayed discharge from hospital, as compared to controls.

GLOBAL RATES OF OUT-OF-HOSPITAL DELIVERIES

The number of out-of-hospital deliveries in the world is not well documented (Table 3). It is important to distinguish between accidental out-of-hospital deliveries and those intended and planned to take place out of hospital, with the attendance of medical personnel. In rural and remote regions of developing countries, out-of-hospital deliveries occur mainly due to limited access to health services. Often, there is limited access not only to referral health facilities, but even to basic life-saving measures within the home and community. Such out-of-hospital deliveries are associated with high rates of perinatal morbidity and mortality[2–14,23].

In a report by the Pan American Health Organization (PAHO), currently, 79% of deliveries in the Region of the Americas take place in institutional settings, with only a few countries in the Region reporting institutional deliveries below 50%[24]. Unfortunately, the trend of increasing institutional deliveries in the Americas has not resulted in a corresponding decrease in maternal and perinatal mortality. In fact, there are even greater variations

Table 1 Independent risk factors for early postpartum hemorrhage, which can be of major importance during out-of-hospital deliveries. Results from a multiple logistic regression model. Data are expressed as odds ratio, 95% confidence interval (CI) and *p* values for statistical significance. Adapted from Sheiner *et al*. *J Matern Fetal Neonatal Med* 2005;18:149–54[16]

	Odds ratio	*95% CI*	*p*
Retained placenta	3.5	2.1–5.8	< 0.001
Labor dystocia, second stage	3.4	2.4–4.7	< 0.001
Placenta accreta	3.3	1.7–6.4	< 0.001
Lacerations	2.4	2.0–2.8	< 0.001
Large for gestational age	1.9	2.4–1.6	< 0.001
Hypertensive disorders	1.6	2.1–1.2	< 0.001

Table 3 Rates of planned and unplanned out-of-hospital deliveries in the world

Country	*Reference*	*Rate* (%)
Planned out-of-hospital deliveries		
United States and Canada	Johnson *et al*.[29]	1
Netherlands	Anthony *et al*.[32]	33
Home births in developing countries		
Ethiopia-southern	Sibley *et al*.[33]	90
India	Kodkany[34]	50
Unplanned out-of-hospital deliveries		
Israel, Negev region	Sheiner *et al*.[13]	2
UK	Scott *et al*.[27]	0.3
Finland	Viisainen *et al*.[7]	0.1
Scotland catchment	Rodie *et al*.[28]	0.6

Table 2 Pregnancy and labor complications of patients delivered out of hospital in comparison to patients delivered in hospital. Adapted from Sheiner *et al*. *J Reprod Med* 2002;47:62–30[13]

Characteristics	*Out of hospital* (*n* = 2328)	*In hospital* (*n* = 114 938)	*p*
Lack of prenatal care	809 (34.8%)	10 822 (9.4%)	< 0.001
Perineal tear grade 1–2	435 (18.7%)	16 178 (14.1%)	< 0.001
Perineal tear grade 3–4	4 (0.2%)	77 (0.1%)	0.056
Retained placenta	27 (1.2%)	693 (0.6%)	< 0.001
Small for gestational age	233 (10.0%)	6 809 (5.9%)	< 0.001
Large for gestational age	145 (6.2%)	11 774 (10.2%)	< 0.001
Perinatal mortality	29 (1.2%)	718 (0.6%)	< 0.001
Delayed discharge from hospital	911 (39.7%)	35 343 (31.1%)	< 0.001

in neonatal and maternal mortality among countries with high rates of institutional delivery. This is perhaps due to unnecessary interventions, such as Cesarean section and episiotomy, which may lead to increased morbidity and even mortality[25,26]. Efforts are being made in order to promote evidence-based interventions in these countries[24].

In a few reports from developed countries, the incidence of accidental out-of-hospital deliveries varied from 0.1 to 2%[7,13,27–29]. Factors associated with accidental out-of-hospital deliveries include multiparity and lack of prenatal care, which by themselves might increase the risk for adverse perinatal outcome[30,31].

In a large population-based study in the Negev region in Israel, the incidence of accidental out-of-hospital deliveries was 2% (2328/114 938)[13]. These deliveries were described as unattended, as opposed to deliveries that were out of hospital but attended by skilled personnel.

A report from a District General Hospital in the UK indicated a low incidence of 0.31% of unplanned out-of-hospital deliveries occurring over a 3-year period[27]. Women were multiparous, and 11 of 14 deliveries (78.6%) occurred during the night, between the hours of 20.00 and 08.00, suggesting difficulties in access to the hospital.

In a study from Finland, a trend was found towards a decrease in accidental out-of-hospital deliveries between 1963 and 1973: from 1.3 to 0.4 per 1000 births. Nevertheless, this trend was changed by the 1990s when the figures rose up to 1/1000. This change was attributed to the closing of small hospitals in remote parts of the country, leading to inconvenient access to perinatal facilities[7].

In a retrospective case-control study, women who delivered accidentally out of hospital in the catchment area in Scotland during a given study period were identified. Of all deliveries, 117 women delivered 121 babies accidentally out of hospital. The rate was 0.6% of all deliveries registered at the hospital[28].

Examples for planned home births are found in the following two studies. In a prospective study designed to evaluate the safety of home births in North America, all home births involving certified professional midwives across the United States and Canada during the year 2000 were assessed. The rate of planned home delivery was 1.6%[29].

In the Netherlands, approximately one-third of births are planned home deliveries, attended by midwives. In this cross-sectional study, maternal demographics associated with home birth included multiparity, age above 25 years and living in small as opposed to large cities[32].

The condition is quite different in undeveloped countries. In these areas, home birth with unskilled attendants is the norm, and maternal and neonatal mortality rates are high. Unfortunately, the rates and outcomes of these out-of-hospital births are grossly underreported. The causes for this situation include inadequate emergency care and home-based care by attendants who are poorly equipped or educated to respond to emergencies, leading to inappropriate or delayed action. For example, in rural southern Ethiopia, over 90% of births take place at home in the presence of unskilled attendants[33].

In most parts of the world, postpartum hemorrhage accounts for 35–55% of maternal deaths. In India, maternal mortality rates are estimated at 560/100 000 live births. In rural India, at least 50% of births occur at home[34]. These figures are reported in a recent study which presents a design for a randomized, placebo-controlled, clinical trial conducted in four primary health center areas of Belgaum District, Karnataka, India. The main goal of this study was to assess the effectiveness of misoprostol 600 μg orally in reducing the incidence of acute postpartum hemorrhage. Misoprostol would be administrated by minimally trained midwives to women randomized to receive misoprostol or placebo immediately post-delivery of the infant. A secondary goal of this study was to test the international and community collaborations necessary for the conduct of this study, so that it could serve as a model for future studies in rural settings throughout the developing world for reducing maternal mortality and morbidity.

In conclusion, the number of out-of-hospital deliveries in the world is not well documented. Although it is widely accepted that the quality of maternity care is a main determinant of maternal and fetal morbidity and mortality rates[35],

the lack of statistical information on out-of-hospital deliveries is a severe limitation for further evaluation of the relationship between out-of-hospital deliveries and maternal morbidity and mortality in general and specifically postpartum hemorrhage.

OUT-OF-HOSPITAL DELIVERY AND POSTPARTUM HEMORRHAGE

Our group[14] compared maternal and neonatal outcomes in out-of-hospital vs. in-hospital deliveries in a prospective study. Unplanned out-of-hospital deliveries resulted in a statistically significant higher rate of postpartum hemorrhage (OR 8.4; 95% CI 1.1–181.1; $p = 0.018$) (Table 4).

Postpartum hemorrhage due to uterine atony is the primary direct cause[35] of maternal mortality globally. Management strategies in developed countries involve crystalloid fluid replacement, blood transfusions, and surgery. Such definitive therapies are often not accessible in developing countries, particularly in out-of-hospital deliveries. The lack of skilled attendants at delivery who can provide even the minimum of care, long transport times to facilities that can manage uterine atony or severe lacerations of the genital tract, and unattended obstructed labor leading to a ruptured uterus, elevate postpartum hemorrhage to its position as the number one killer of women during child birth[36]. These factors are exacerbated by the prevalence of anemia, which is estimated to affect half of all pregnant women in the world[37], with this figure rising to 94% in Papua New Guinea, 88% in India, and 86% in Tanzania[38]. Anemia is rarely detected or treated during pregnancy and often exacerbated by malarial and other parasitic diseases[39].

Although the vast majority of patients with postpartum hemorrhage have no identifiable risk factor, young age at marriage[40,41] and low contraceptive use among many women in the developing world result in high total fertility rates, which result in more grand multiparous women giving birth in low-resource countries compared with more developed countries[42].

A retrospective study from Ghana compared active vs. expectant management in a rural setting at Holy Family Hospital in Berekum[43]. The study found that postpartum hemorrhage (blood loss = 500 ml) occurred less often in the actively managed group (OR 0.8; 95% CI 0.7–0.9). McCormick and colleagues[44] published a systematic review of studies that assessed the efficacy of active management of the third stage in low-resource settings. Active management of the third stage of labor, especially the administration of uterotonic drugs, reduces the risk of postpartum hemorrhage due to uterine atony without increasing the incidence of retained placenta or other serious complications. Oxytocin is preferred over syntometrine, but misoprostol also can be used to prevent hemorrhage in situations where parenteral medications are not available (see Chapters 16–19).

A 2003 Cochrane Review of active versus expectant management of the third stage of labor[45] included five randomized, controlled trials and found that, for all women, including women deemed to be at low risk for postpartum hemorrhage, active management decreased the

Table 4 Maternal outcomes of patients with unplanned out-of-hospital deliveries and the control group. Adapted from Hadar *et al. J Reprod Med* 2005;50:832–6[14]

Characteristics	*Unplanned out-of-hospital deliveries* ($n = 151$)	*Control group* ($n = 151$)	*p*
Vaginal tears	27 (17.9%)	18 (12.0%)	0.087
Postpartum hemorrhage	8 (5.3%)	1 (0.6%)	0.018
Postpartum endometritis	2 (1.3%)	0	0.157
Antibiotic treatment	2 (1.3%)	0	0.157
Sutures of vaginal tears	25 (16.6%)	18 (12.0%)	0.249
Revision of uterus cavity	6 (4.0%)	0	0.013
Hospitalization (days)	3.2 ± 0.9	2.95 ± 0.6	0.111

incidence of postpartum hemorrhage (both 500–1000 ml and > 1000 ml), shortened the third stage of labor, decreased the amount of maternal blood loss, decreased the need for blood transfusion, and decreased the need for additional therapeutic uterotonic agents. The incidence of postpartum hemorrhage of 500 ml or more was reduced in the actively managed group (relative risk 0.38; 95% CI 0.32–0.46). These figures mean that for every 12 women who are actively managed rather than expectantly managed, one case of postpartum hemorrhage (defined as blood loss = 500 ml) will be averted, whereas the number needed to treat for averting blood loss greater than 1000 ml would be 57. Women who were actively managed lost less blood, with a weighted mean blood loss of 79.33 ml less than those who were expectantly managed. The third stage was an estimated 9.77 min shorter in actively managed women. The use of routine uterotonic agents to prevent postpartum hemorrhage can reduce maternal mortality by 40%[46].

The data on the types and incidences of maternal morbidities in communities with limited access to health services are scarce[23]. Bang and colleagues found, in their prospective observational study in Gadchiroli, India, that the incidence of maternal morbidity was 52.6%, 17.7% during labor and 42.9% during puerperium. The most common intrapartum morbidities were prolonged labor (10.1%), prolonged rupture of membranes (5.7%), abnormal presentation (4.0%) and primary postpartum hemorrhage (3.2%). The postpartum morbidities included secondary postpartum hemorrhage (15.2%). In their study, mothers and the neonates were prospectively observed at home in 39 villages without interventions. It included a population of approximately one million parturients. Most deliveries in the area were conducted by traditional birth attendants and family members. This is the first reported study in a rural setting in a developing country where labor and the puerperium were prospectively observed at home in a systematic and objective manner to measure the incidence of maternal morbidities. This study had certain limitations which should be kept in mind while extrapolating the results. Their sample may underestimate the incidence of morbidities because many hospital deliveries (which may have a higher proportion of problems) were not studied.

Another randomized, controlled trial was carried out to determine whether suckling immediately after birth reduces the frequency of postpartum hemorrhage[47]. The trial participants were attended by traditional birth attendants. Traditional birth attendants recorded blood loss in the early suckling group and in the control group in 2104 and 2123 deliveries of liveborn singletons, respectively. The frequency of postpartum hemorrhage (loss greater than 500 ml) was 7.9% in the suckling group and 8.4% in the control group. Prual and colleagues reported the frequency of such morbidity as revealed in a population-based survey of a cohort of 20 326 pregnant women in six West African countries[48]. The main direct causes of severe maternal morbidity were hemorrhage (3.05 per 100 live births); in this report 23 cases involved uterine rupture (0.12 per 100). Case fatality rates were high for hemorrhage and varied from 1.9% for antepartum or peripartum hemorrhage to 3.7% for placental abruption. The high case fatality rates of several complications reflected a poor quality of obstetric care.

Walraven and colleagues[49], in their double-blind, randomized, controlled trial, sought to evaluate the impact of oral misoprostol on postpartum hemorrhage compared with standard treatment in the home birth situation in rural Gambia, with measured blood loss, postpartum hemoglobin, change in hemoglobin level between the last antenatal care visit and 3–5 days postpartum as outcome measures. The study was carried out in 26 primary health-care villages of the North Bank East Health Division, The Gambia, West Africa. Seventy-two percent of births occur at home and maternal mortality in the study area has been estimated at 424/100 000 live births in a reproductive age mortality survey, with postpartum hemorrhage as the most important direct cause of maternal mortality. There were two maternal deaths in the study population (maternal mortality ratio for study population of 163 per 100 000 live births; 95% Poisson CI 20–595), both in the misoprostol group. These deaths were attributed to postpartum hemorrhage (measured blood loss 2200 ml) and disseminated

Table 5 The risk for postpartum hemorrhage in out-of-hospital deliveries

Country	*Reference*	*Postpartum hemorrhage in out-of-hospital deliveries*
West Africa	Prual *et al.*[48]	3.1%
Malawi	Bullough *et al.*[47]	8.4%
Ghana	Geelhoed *et al.*[7]	17.4%
India	Bang *et al.*[23]	3.2%
Israel	Hadar *et al.*[14]	5.3%
Israel	Sheiner *et al.*[13]	3.2%

intravascular coagulation due to malaria (measured blood loss 300 ml), respectively.

Table 5 summarizes the existing, limited data regarding the association between out-of-hospital deliveries and postpartum hemorrhage.

CONCLUSIONS

The fact that so many women deliver in domiciliary conditions clearly affects their risk of having postpartum hemorrhage. It is widely accepted that the quality of maternity care is a main determinant of maternal mortality rates. Our research has, for the first time, established an odds ratio of 8.4[14]. This number represents an urgent call to the medical community to change this circumstance whenever possible, as is detailed in other chapters of this book. All births should be attended by adequately trained personnel. More effective strategies are needed to convince women with high-risk pregnancies to deliver in a hospital which has access to emergency referral services.

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47

INTRAOPERATIVE AUTOLOGOUS BLOOD TRANSFUSION

S. Catling and D. Thomas

INTRODUCTION

Life-saving transfusion using human blood was first described by James Blundell in 1818. He performed ten transfusions, five of which were successful; of these, four were in women suffering postpartum hemorrhage. He typically used donor blood from the patient's husband, thus showing that the technique of blood injection with a syringe-infusion was safe[1]. In one account, he is credited with the re-infusion of autologous blood[2]. It is entirely appropriate, therefore, that the subject of intraoperative autologous transfusion be described in this textbook on postpartum hemorrhage. Blundell's original report described a reasonable outcome considering the crude understanding of blood transfusion techniques in existence almost a century before Landsteiner's identification of the ABO blood groups[3].

Some of the earliest reports of intraoperative blood salvage described the life-saving technique of simply collecting spilt blood from the abdominal cavity, filtering it through a gauze swab, and re-infusing what remained. In the ensuing years, techniques to collect, filter and wash blood lost at the time of surgery have become commonplace, although refinements of the method vary widely and depend not only upon the nature of the surgical procedure but also the availability of technical resources. As might be expected, expensive apheresis machines are lacking in many, if not most parts of the world, where operative obstetrics is routine. Nevertheless, the problem of postpartum hemorrhage is so common and remains such a clinical challenge that, in these circumstances, the technique as originally described is still used out of necessity. This chapter describes various methods of autologous blood salvage and, in particular, its evolving use in obstetrics with direct reference to postpartum hemorrhage.

DEFINITION

Autologous blood salvage is the collection of spilt blood resulting from surgical or traumatic bleeding that can be undertaken intraoperatively or postoperatively. The collected blood can be filtered and re-infused or filtered, washed and then re-infused.

METHODS

The quality and constitution of re-infused blood vary depending on whether unwashed or washed systems are used. In the absence of automated cell-washing devices, simple collection, filtration and re-infusion during postpartum hemorrhage have been described and continue to be used in some areas in the world. This technique is not ideal. However, the use of unwashed blood (particularly for postoperative collection and re-infusion using a sealed postoperative collection unit with a filter) has been used extensively in total knee surgery and seems safe and effective. It is interesting that a recent report suggested that the use of unwashed blood might have properties that improve the recipient's immune response[4].

The more widely applied intraoperative cell salvage is conducted with an apparatus that has the ability to collect spilt blood at the time of operation and anticoagulate it at the tip of the suction apparatus with citrated solution or heparinized saline (25 000 IU per liter of normal saline) (Figure 1). Collected blood is then transferred to a centrifugal bowl, where spinning at 5500 revolutions per second moves

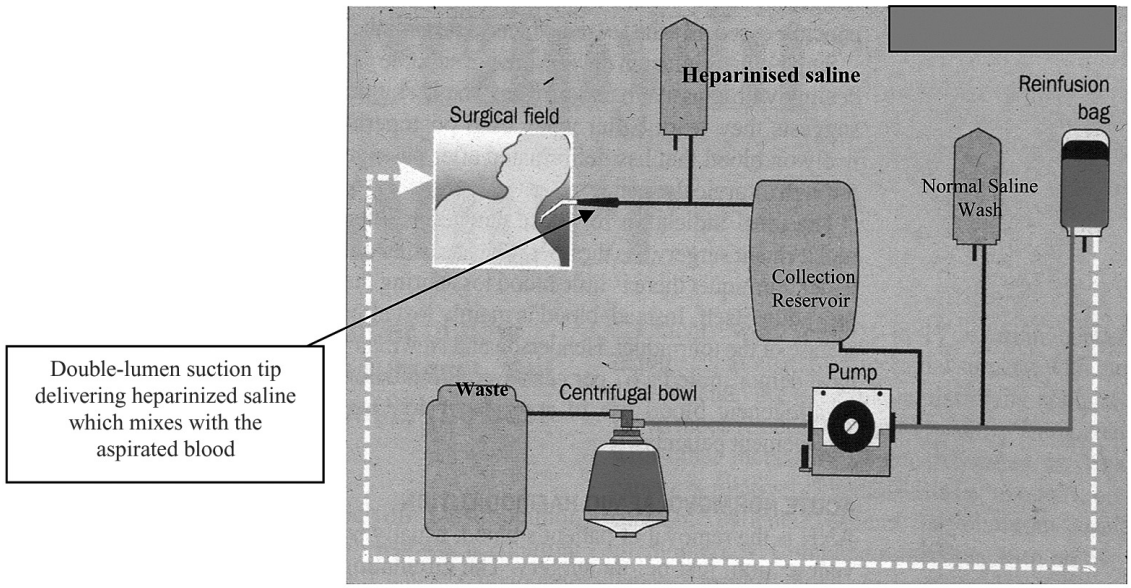

Figure 1 A diagrammatic representation of intraoperative cell salvage. (Adapted from an original drawing with the kind permission of Haemonetics Inc., Baintree). The dotted line represents infusion sent back to the patient. In the case of a Jehovah's Witness, this is primed with saline before starting to complete continuity of the circuit

the heavier red cells to the outer periphery of the bowl. As the bowl fills, the accumulation of red cells forces the plasma, platelets and other cellular debris out of a central exit, discarding waste products of the process. Special sensors identify when the bowl is full of red cells, and the fully automated machine begins to wash the collected and concentrated erythrocytes with normal saline. This process further cleanses the red blood cells. The resultant concentrate is then suspended in normal saline, producing a solution with a hematocrit of 60%. Most of the platelets and clotting factors will have been washed away at this point, however, and the fluid for re-infusion consists of autologous red cells suspended in normal saline[5].

In the presence of brisk bleeding, any of the commercially available automated cell-washing devices can produce a unit of red cell concentrate in 5–10 min. The volume of lost blood that can be processed is infinite, and reports of cell salvage in major trauma describe its successful use, the process providing approximately 50% of the required red cell transfusion[6]. Of course, in such situations, the use of cell salvage only minimizes the demand for allogeneic blood. In cases of massive hemorrhage, the cell salvage devices help to recycle transfused allogeneic blood as well as autologous blood.

As few platelets and minimal clotting factors are present in these re-infused red cells, careful assessment of coagulation parameters is required in cases of excessive bleeding where massive transfusion is required. Nowadays, this is the case in patients with massive hemorrhage anyway, as the provision of red cells suspended in a mixture of saline, adenine, glucose and mannitol (SAGM) means that only packed allogeneic red cells are being infused, and so similar provisos apply. Early consideration therefore needs to be given to platelet and fresh frozen plasma administration.

HISTORICAL COMPLICATIONS

Current machines have an extremely good safety record, but it is worthwhile dispelling some misconceptions about the technique that persist today. Air embolism is not a problem with modern equipment when it is used correctly. Free hemoglobin is almost completely removed, and the very small amounts that

remain have no significant clinical effect. Platelets are activated during salvage, but the majority are removed during the process. Leukocytes, complement and kinins are also activated during salvage, but systemic inflammatory responses have not been reported as clinically relevant.

POSSIBLE CONTRAINDICATIONS

Following a seminal report[7] supporting this technology, it now is accepted that three areas exist where the process of red cell salvage needs to be used with caution and following necessary risk–benefit analysis, depending on the clinical urgency of the situation. These involve the use of red cell salvage when spilt operative blood may contain malignant cells, or be heavily contaminated with bowel bacteria. Another area of caution is the use of red cell salvage when contaminated by amniotic fluid. It is accepted that, in the presence of any of these preconditions, cell salvage is not used unless considered necessary.

The non-availability of a safe allogeneic blood supply is clearly a situation when the use of cell salvage is justified in an attempt to preserve the patient's own blood and help oxygen carriage In the UK, current blood conservation recommendations promote the use of cell salvage[8]. The current drive for blood conservation is multifactorial, but the most topical reason is the potential decrease in the availability of donor blood resulting from the introduction of a test for the presence of abnormal prion protein. However, reduced numbers of donors is a problem that had its inception prior to the present testing concerns, as the presence of HIV and other viral pathogens have also restricted the number of potential donors.

It is against this backdrop that consideration of cell salvage in postpartum hemorrhage was made, and the remainder of this chapter examines the use of intraoperative cell salvage during postpartum hemorrhage. Fortunately, the widespread use of such devices has confirmed the safety of this process, providing there is no technical failure and the correct procedure for machine operation is practiced. The use of such devices is endorsed by national guidelines and Government directives[9,10].

SAFETY OF CELL SALVAGE IN OBSTETRICS

Two theoretical problems attend the use of cell salvage at the time of Cesarean section. First, in a Rh-negative mother, there is a risk of Rh immunization if the fetus is Rh-positive. As the cell saver cannot distinguish fetal from adult red cells, any fetal red cells suctioned from the operative field will be processed and re-infused with the maternal red cells. In practice, studies show that the degree of contamination with fetal red cells during cell salvage at Cesarean section is between 1 and 19 ml[11–13]. Applying the standard Kleihauer calculation, this would require between 500 and 2500 units (1–5 ampules) of Anti-D to avoid Rh immunization. As all Rh-negative patients require Anti-D after Cesarean section, patients receiving salvaged blood may simply require an increased dose.

The second theoretical problem is contamination with amniotic fluid, raising the specter of iatrogenic amniotic fluid embolus (AFE). This theoretical complication has been investigated by several workers, and has not been found to be a problem in practice[12–16]. The difficulty is that the precise elements of amniotic fluid, which cause the rare, and unpredictable 'anaphylactoid syndrome of pregnancy' (as AFE is more correctly called), remain unknown. To conduct a prospective, randomized, controlled trial with an 80% power to demonstrate that cell salvage does not increase the incidence of AFE by five-fold would require up to 275 000 patients, a number so enormous that the effort is unlikely ever to be undertaken. To demonstrate the absolute safety of a technique without randomized, controlled trials requires careful clinical audit of a large number of cases, supported by robust *in vitro* evidence.

IN VITRO STUDIES OF AMNIOTIC FLUID CLEARANCE:

In vitro studies have examined the clearance of α-fetoprotein[14], tissue factor[15], trophoblastic tissue[12], fetal squames and lamellar bodies[13] from maternal blood by the cell salvage process. Small molecules are removed in the plasma fraction by the centrifuge and wash process alone, and particulate material is removed by the use

of specialized leukodepletion filters. Using the combination of cell salvage and these specialized filters, every element of amniotic fluid that has been studied so far has been effectively removed from salvaged blood prior to re-transfusion[12–16].

CLINICAL CASES

Prior to 1999, approximately 300 cases in which cell-salvaged blood was administered to patients had been reported world-wide[16]. No obstetric clinical or physiological problems were encountered, despite the fact that filters were not used at this time. This means that each of these patients had some exposure to amniotic fluid, and with no ill effects. Waters and colleagues shed some light on this topic[13] by describing not only the complete clearance of squamous cells and phospholipid lamellar bodies from filtered, cell-salvaged blood, but also by clearly demonstrating the presence of both these amniotic fluid markers circulating in the maternal central venous blood at the time of placental separation. In 100% of patients in this trial, amniotic fluid was demonstrated in the circulation of healthy parturients undergoing elective Cesarean section. It is therefore probable that amniotic fluid routinely enters the maternal circulation and does no harm in the vast majority of cases. This exposure may trigger the syndrome of AFE due to an anaphylactoid reaction to an as-yet unidentified endogenous mediator in a very small number of women, the incidence of which varies between 1 in 8000 and 1 in 80 000 patients[17]. [Editor's note: since it has never been studied, there is no evidence to state that entry does not occur in an unknown number of cases of vaginal parturition.] Clearly, re-infusion of cell-salvaged blood, even if contaminated with traces of amniotic fluid, presents no extra risk to the woman from whom that blood has come, as she has already been exposed to it.

In 1999, a single report appeared describing a seriously ill Jehovah's Witness woman with severe pre-eclampsia complicated by HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) who died in Holland, after having received cell-salvaged blood[18]. It has been quoted as a 'death due to obstetric cell salvage'[19]. It should be noted, however, that a patient who is seriously ill with HELLP syndrome and who refuses platelet and coagulation factor transfusion is unlikely to survive, and that, under such circumstances, her death should logically not be related to the use of cell salvage, but rather to her refusal to accept blood component therapy.

Cell salvage in obstetrics was introduced in the UK in 1999, and its use is growing rapidly, with most major obstetric units now advocating the technique in selected circumstances. The Confidential Enquiry into Maternal and Child Health 2000–2002 (CEMACH)[20] stated that *'. . . (cell salvage) may be used in any case of obstetric haemorrhage, not just women who refuse blood transfusion'* and described the technique as *'a new development which will prove helpful in the future'*. It further stated that 'the risk of causing coagulopathy by returning amniotic fluid to the circulation is thought to be small'. Subsequent to this, the 2005 revised Guidelines for Obstetric Anaesthetic Services were published jointly by the UK Obstetric Anaesthetists Association (OAA) and the Association of Anaesthetists of Great Britain and Ireland (AAGBI)[21], stating that *'an increasing shortage of blood and blood products and growing anxiety about the use of donor blood are leading to an increasing interest in the use of cell salvage in obstetrics. Staff will have to be suitably trained, and equipment obtained and maintained. . .'*

In November 2005, the UK National Institute for Clinical Excellence (NICE) reported on Cell Salvage in Obstetrics[22], describing cell salvage as 'an efficacious technique for blood replacement, well established in other areas of medicine' and pointing out the *theoretical* concerns when used in obstetrics. NICE goes on to recommend that clinicians using it in the UK should report any side-effects to the UK Department of Health Regulatory Authority (MHRA), that patients should be fully informed prior to its use, and that cell salvage in obstetrics should be performed by multidisciplinary teams that have developed regular experience in its use.

PRACTICAL USE OF CELL SALVAGE IN OBSTETRICS

There presently exists a substantial experience with the use of cell salvage in obstetrics in the

UK; cases include major hemorrhage due to placenta previa, placenta accreta, ruptured uterus, extrauterine placentation, massive fibroids and placental abruption, as well as routine use in Jehovah's Witnesses to avoid postoperative anemia[14].

The following guidelines are in use for cell salvage in obstetric use in the Swansea NHS Trust Hospitals, UK:

(1) It may be used for any situation in which allogeneic blood is used, but in practice this has so far been confined to Cesarean sections and uterine re-exploration or laparotomy following postpartum hemorrhage. There is no reason why vaginal blood loss could not be collected and cell-salvaged, as fears about infection have proved unfounded in abdominal gunshot wounds as long as the patients are on antibiotics – but the technical problem with physically collecting vaginal blood loss has yet to be solved! [Editor's note: the routine and planned use of the BRASSS technique described in Chapter 4 would be useful to overcome this problem as well as underestimation of loss.]

(2) The machine is set up and operated according to standard operating procedure, with an 'in-continuity' set-up for Jehovah's Witnesses (this means that the whole circuit is run through with saline and the re-transfusion bag connected to the intravenous cannula before starting the salvage suction, thereby establishing a continuous circuit between the blood lost and the recipient vein).

(3) In cases where there is doubt about the extent of expected blood loss, it is economical to set up the aspiration and reservoir kit only – the decision to process and re-transfuse can be made when the degree of hemorrhage has become clear (e.g. 'expected' bleeding from placenta previa).

(4) Where practicable, amniotic fluid should be removed by separate suction prior to starting cell salvage.

(5) Suction should be via the wide-bore suction nozzle in the kit, and the surgeon should try to suction blood from 'pools' rather than 'dabbing' tissue surfaces with the suction tip, as this minimizes erythrocyte damage.

(6) Blood from swabs can be gently washed with saline and salvaged from a sterile bowl into the main reservoir.

(7) Suction pressure should be kept as low as practicable (< 300 mmHg) to avoid red cell damage, although higher vacuum can be safely used if necessary with only a minimum increase in red cell damage.

(8) It is advisable to use a leukocyte depletion filter (Leukoguard RS Pall) in the re-transfusion circuit if there is any risk of amniotic fluid contamination. This is currently the only filter that has been shown to remove all particulate elements of amniotic fluid (fetal squames, lamellar bodies). This filtration process will necessarily slow down the rate at which blood can be infused, but it is permissible to pressurize the bag of salvaged red cells up to 200 mmHg after having ensured there is no air in the bag (otherwise it may burst!), or to use a large-volume syringe and three-way tap. In situations when hemorrhage is rapid, it is possible to connect more than one suction nozzle to the reservoir, and two filters and a dual giving-set to the re-infusion bag.

(9) As with any transfusion, the patient should be carefully monitored, preferably in an obstetric 'critical care' facility for 24 h. Coagulation tests should be obtained post-transfusion, and repeated if abnormal or if clinically indicated.

(10) If the patient is Rh-negative, a Kleihauer–Braun–Betke test should be performed and Anti-D administered as appropriate within 72 h.

Units that use obstetric cell salvage should keep careful records for Audit reporting in due course – with any problems also being reported to the MHRA as per NICE Guidelines.

SUMMARY

The use of intraoperative cell salvage is a safe method of conserving operative blood loss and minimizing the need for allogeneic transfusion. In an environment where allogeneic blood is in limited supply or the demands for blood transfusion are so great, as in the case of massive postpartum hemorrhage, the use of intraoperative cell salvage may be life-saving and its use in this area is gaining clinical acceptance.

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48

TREATING HEMORRHAGE FROM SECONDARY ABDOMINAL PREGNANCY: THEN AND NOW

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INTRODUCTION

Abdominal pregnancy is an unusual but real cause of postpartum hemorrhage. The high maternal morbidity and mortality associated with abdominal pregnancy are a function of abnormal placentation which leads to intra-abdominal hemorrhage or the aftermath of retention of large amounts of dead tissue. Presently, no evidence-based guidelines have been published on this subject. This chapter begins with a series of four cases treated at the Nowrosjee Wadia Maternity Hospital in Mumbai, India, which are illustrative of the available treatment options. Wadia Hospital is a tertiary-care center with a wide referral base, both inside the city and throughout the surrounding areas. This is followed by a discussion on the technical aspects of the surgical intervention and a review of the literature on modern treatment options.

CASE 1

In 1970, a primigravida aged 24 years was referred to the hospital with an abnormal presentation. The senior author (NAD) was practicing as a junior trainee. At that time, it was routine to confirm the diagnosis of abnormal presentation with abdominal radiography. Because the radiograph was suspicious of an abdominal pregnancy, the senior consultant planned an exploratory laparotomy to deliver the woman. A male child weighing 2700 g was delivered in good condition. However, the placenta was attached to the mesentery, and an attempt to separate it set off massive hemorrhage. Local measures such as ligation of vessels and compression failed to reduce the hemorrhage, so the peritoneal cavity was packed under pressure with a large bed sheet as a last resort. She was stable for the first 6 h postoperatively, but then developed hypovolemic shock from intraperitoneal hemorrhage and died on the first postoperative day.

CASE 2

The second case occurred 4 years later at the same institute. A Cesarean delivery was undertaken to deliver a 30-year-old multiparous woman with no progress in labor. On opening the peritoneum, the amniotic sac was encountered directly. A 2400-g female child was delivered. The placenta covered the lateral pelvic wall and posterior surface of the uterus. The senior consultant was called and an attempt at placental separation was made. This effort was soon abandoned in view of the difficulty in separation and ensuing hemorrhage. The cord was then cut short and tied, the placenta left *in situ* and the abdomen closed. The abdomen was packed under pressure with large abdominal packs for control of the hemorrhage. However, the patient developed a disseminated intravascular coagulopathy and died within 48 h of the surgery.

CASE 3

In 1980, the senior author was involved in the third case of abdominal pregnancy. A 20-year-old primigravida was referred to the hospital at full term with abdominal pain thought to be of a surgical cause. There was a strong clinical suspicion of acute appendicitis which did not respond to conservative treatment. A

laparotomy was performed. A full-term abdominal pregnancy was found with the sac just below the peritoneum. A female child weighing 2600 g was delivered in good condition. The placenta was firmly adherent to the right pelvic side-wall. No attempt was made to remove it. The cord was cut short and tied and the abdomen was closed with a pelvic drain. The postoperative course was complicated by fever for the first 10 days in spite of antibiotics. She continued to have abdominal pain for 6 months after delivery. This patient had sequelae of a retained placenta but survived the pregnancy.

CASE 4

Although this is not a case of an abdominal pregnancy, it is used to illustrate the management of abnormal placentation. In 2001, the senior author performed a Cesarean section for a 25-year-old primigravida at term. She was diagnosed to have an anterior placenta previa with accreta. Blood vessels were seen invading into the bladder wall on color Doppler. After delivering a 2500-g male child in good condition, no attempt at placental separation was initiated. Rather, a decision was made to leave the placenta *in situ* followed by methotrexate therapy. The woman was monitored in hospital for 3 weeks after delivery and administered a prolonged course of antibiotics. She had an uneventful course. Further follow-up was provided on an outpatient basis with color Doppler and serum β-hCG levels. The placental mass gradually involuted over a period of 5 months and the patient resumed menstruation 7 months after delivery.

INCIDENCE

Abdominal pregnancies are rare events. In the United States, it is estimated that it occurs once in 10 000 live births and once also for every 1000 ectopic pregnancies[1]. A more recent African report provides a much higher estimate of 4.3% of ectopic pregnancies, which is probably a reflection of referral patterns in that region as well as a higher baseline rate of inherent tubal disease in the patient base of the hospital catchment area[2]. However, it also may be reasonable to presume that the incidence of abdominal pregnancies may have risen over the years, considering that the risk factors such as ectopic pregnancy, infertility from tuberculosis and endometriosis, pelvic infections and infertility treatments are more common today. Regardless, an obstetrician practicing alone may never come across an abdominal pregnancy in a career spanning decades. In the singular instance where he/she does have the need to treat such a patient, it may be in circumstances far from ideal. Although unusual, obstetricians should be aware of this potentially fatal condition, a circumstance amply illustrated by the first two cases described above.

DIAGNOSIS

A primary abdominal pregnancy presents in the first trimester in much the same fashion as an ectopic pregnancy. An advanced secondary abdominal pregnancy, on the other hand, is much more difficult to diagnose. Presenting complaints may include abdominal pain (ranging from mild discomfort to unbearable pain), painful or absent fetal movements, nausea, vomiting, abdominal fullness, flatulence, diarrhea and general malaise. On examination, there may be an abnormal lie (15–20% of cases), easily palpable fetal parts, a closed uneffaced cervix on vaginal examination, and the failure to stimulate contractions with oxytocin or prostaglandins on attempting an induction of labor[3]. Obviously, these symptoms and circumstances are far from specific. Taken together, however, they may (and should) raise a question about the location of the pregnancy. On reviewing the laboratory findings, one may also find an unexplained transient anemia in early pregnancy corresponding to the time of tubal rupture or abortion. The serum α-fetoprotein value may be abnormally elevated without explanation. Early diagnosis has been described in response to evaluation of abnormal biochemical screening results[4].

The diagnosis can be established with far greater certainty by imaging studies. Ultrasound is ubiquitously used in pregnancy, but it does not always provide an unequivocal diagnosis. Even under ideal conditions, the diagnosis is missed on ultrasound in more than half of

cases[3]. Akhan and colleagues[5] report the following criteria suggestive of abdominal pregnancy:

(1) Visualization of the fetus separate from the uterus;

(2) Failure to visualize the uterine wall between the fetus and the maternal urinary bladder;

(3) Close approximation of fetal parts to the maternal abdominal wall;

(4) Eccentric position (relation of fetus to uterus) or abnormal fetal attitude (relation of fetal parts to one another) and visualization of extrauterine placental tissue.

In the past, radiography was commonly used to establish or at least point to this diagnosis. Features such as absence of uterine shadow around the fetus, maternal intestinal shadow intermingling with fetal parts on anteroposterior view, and overlapping of the maternal spine by fetal small parts in a lateral view were all described. Today, however, radiography is largely supplanted by magnetic resonance imaging and computed tomography. Both these techniques, with their ability to produce images in different planes, have much greater accuracy and specificity than ultrasound. There is little to choose between the two imaging modalities in cases of fetal demise. If the fetus is alive, magnetic resonance imaging may be preferable since ionizing radiations are avoided.

TIMING OF INTERVENTION

Maternal mortality is about 7.7 times higher with an abdominal pregnancy as compared to a tubal ectopic pregnancy and 90 times higher as compared to an intrauterine pregnancy[1]. These risks are thought to be chiefly related to the delay in diagnosis and mismanagement of the placenta. To minimize the risk from sudden, life-threatening intra-abdominal bleeding, it seems prudent to time intervention as soon as feasible after the diagnosis is confirmed. There is no controversy if there is maternal hemodynamic instability, the fetus is dead or pre-viable (less than 24 weeks pregnancy), has oligohydramnios or gross abnormalities on ultrasound. The hypothesis that fetal death will bring about placental involution and hence reduced bleeding at laparotomy is not substantiated. Surgical intervention is mandated if any of the above conditions are present.

Some clinicians argue that, if there is an ongoing abdominal pregnancy greater than 24 weeks, a conservative approach should be taken to allow fetal maturity and improve chances of survival[6]. However, even after 30 weeks, fetal survival is only 63%, and 20% of fetuses have deformations (craniofacial and various joint abnormalities) and malformations (central nervous system and limb deficiencies)[7]. With advancing gestation, one also has to contend with the growing placenta and greater risk of bleeding. In our opinion, it would very rarely be justified to manage an abdominal pregnancy conservatively.

PREOPERATIVE PREPARATIONS

The major risk with surgery is torrential hemorrhage. When a diagnosis of abdominal pregnancy is established in advance, the opportunity to be prepared should not be lost. At least six units of blood should be cross-matched and read to transfuse in the operating room, and other blood products should also be available. Two intravenous infusion systems capable of delivering large volumes of fluids rapidly should be established. A mechanical bowel preparation should be affected if time permits. A MAST (medical antishock garment) suit has been utilized successfully in controlling intractable hemorrhage with an abdominal pregnancy[8], but these garments are not always available (see Chapter 14 for a full discussion). Kerr and colleagues[9] have advocated preoperative transfemoral catheterization and embolization of selective vessels before surgical intervention. This intervention was used successfully in three cases and the catheters can be left in place for their potential help in treating postoperative bleeding as well. The operating team should be an experienced one, and preferably should include a general, vascular and genitourinary surgeon. The anesthesia team should be comprised of senior consultants and their assistants. The operating room and nursing staffs should be fully aware of the nature of the diagnosis and its implications and schedule extra personnel in the room and as 'runners'.

SURGICAL APPROACH

A mid-line vertical approach is preferential, as it can easily be extended above the umbilicus if necessary. The amniotic sac may be adherent to the abdominal wall and viscera. It should be dissected free and opened in an avascular area away from the placenta. The fetus should be removed in such a manner as to minimize placental manipulation and avoid bleeding. If the pregnancy has been retained for a long period after fetal death, the fetus will have undergone suppuration. Bacterial contamination and abscess formation are highly likely, especially if the placenta is adherent to the intestines. There may be frank pus upon entering the peritoneal cavity. Rarely, the fetus may be mummified and calcified into a lithopedion or become converted into a yellow greasy mass called adipocere formation.

MANAGEMENT OF THE PLACENTA

The torrential hemorrhage that often ensues with surgery for abdominal pregnancy is related to the lack of constriction of the hypertrophied opened blood vessels after placental separation. Usually, the placenta is firmly attached to the parietal peritoneum, mesentery and bowel and *there is no bleeding if it is left alone*. The umbilical cord should be ligated close to the placenta, excess membranes trimmed away and the abdomen closed with drainage. Only very rarely is the placental implantation limited to the reproductive organs by a single pedicle, so that it can be easily removed[10].

In some instances, the placenta may separate spontaneously, simulating an abruption, but the situation in which hemorrhage becomes uncontrollable is more likely to arise from failed attempts at placental removal. Some clinicians advocate routine placental removal[3,8], but these papers were written before the obstetrics community appreciated the value of methotrexate in such instances. Placental separation requires complete ligation of the blood vessels supplying the placenta and manipulating it at its insertion. More importantly, placental separation is not always straightforward and fails in 40% of cases[3]. This is where the blood supply cannot be completely ligated, resulting in massive hemorrhage and shock[2]. The hemorrhage from the placenta is now torrential and rapid surgical action is essential. Various local techniques such as compression of the bleeding site, ligating the vascular pedicles, lavage with cold saline, and local and/or systemic coagulation promoting agents (tranexamic acid, plasminogen derivatives, absorbable gelatin sponge, etc.) have been described. Repair of placental lacerations may be required. The removal of the organ to which the placenta is adherent (hysterectomy and/or salpingoophorectomy, resection of the bowel and/or bladder) may be justified to control the hemorrhage. If a hysterectomy has been performed and bleeding continues, a Logothetopoulos pack brought out through the vaginal cuff can be used to exert pressure on the pelvic side-walls and bleeding vessels (see Chapter 33 for complete details). As a last resort, the abdomen may be packed tight with abdominal sponges and closed partially. The packs can be removed 48 h postoperatively or sooner if directed by hemodynamic instability.

POSTOPERATIVE CARE

Even when the placenta is left *in situ*, complications such as infection, abscesses, bowel obstruction secondary to adhesions or wound dehiscence occur in about one-half of the patients[11,12]. Although the problems associated with an abdominally retained placenta may be distressing and lead to subsequent repeat laparotomy, they are potentially less disastrous than an ill-advised attempt at removing the placenta. Prophylactic antibiotics should be administered so as to cover a substantial part of the postoperative course. Less common complications of the retained placenta include reversible maternal hydronephrosis[13] and prolonged persistent postpartum pre-eclampsia[14].

To hasten placental resorption, methotrexate as a single dose of 50 mg/m^2 can be used. This too is not without its specific problems, however. In a series of ten cases, accelerated placental destruction led to accumulation of necrotic tissue and abscess formation[15]. It is difficult to attribute this to methotrexate therapy alone, as these complications arise even without administration of methotrexate.

The patient with a retained placenta is monitored with clinical evaluation, ultrasound, color Doppler and serum β-hCG levels. Hormonal parameters drop rapidly in the postoperative period as most live cells will be destroyed early. The physical mass of the placenta is resorbed slowly over an average period of 6 months. A resorption period of 5 years has been reported[16], although this is highly unusual.

CONCLUSION

Secondary abdominal pregnancy is an uncommon and exceedingly dangerous variant of ectopic pregnancy. It is usually not diagnosed until laparotomy which leaves the obstetrician little preparation to face the prospect of torrential postpartum hemorrhage, albeit not from the usual sources. In this situation, minimizing placental handling and leaving it in the abdominal cavity can be life-saving.

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Section X

National experiences

49

COMBATING POSTPARTUM HEMORRHAGE IN INDIA: MOVING FORWARD

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INTRODUCTION

The World Health Organization (WHO) estimates that, of the 529 000 maternal deaths occurring every year, 136 000 or 25.7% take place in India, where two-thirds of maternal deaths occur after delivery, postpartum hemorrhage being the most commonly reported complication and the leading cause of death (29.6%)[1]. The unacceptably high maternal death ratio (540/100 000 live births)[1] in India during the last few decades remains a major challenge for health systems.

According to the same WHO estimates, for every maternal death about 20 women suffer from harm to general and reproductive health. In India, around 70% of the population lives in villages. Out of an estimated 25 million deliveries each year, 18 million take place in peripheral areas where maternal and perinatal services are either poor or non-existent. India's stated goal is to reduce maternal mortality (MMR) from 437 deaths per 100 000 live births that was recorded in 1991 to 109 by 2015. The MMR for 1998 is 407. Along with this improvement, the proportion of births attended by skilled health personnel has increased from 25.5% in 1992–1993 to 39.8% in 2002–2003, thereby reducing the chances of occurrence of maternal deaths[1].

The efforts to improve maternal health and reduce maternal mortality have been continuous in India since 1960 under the public health program of Primary Health Care – specifically under the Maternal and Child Health (MCH) program. In various policy documents, the government of India has listed the reduction of maternal mortality as one of its key objectives. Unfortunately, progress has been less than hoped for several reasons.

One of the critical bottlenecks for providing more high-quality emergency obstetric care (EOC) was a serious shortage of specialist staff such as obstetricians and anesthesiologists at various levels in rural areas. This deficiency was accentuated by the limited capacity for transfusion outside of the more sophisticated urban areas.

The present strategies to prevent maternal mortality in India focus on building a better and more fully functioning primary health-care system, from first referral level facilities to the community level. It is unfortunate that emergency obstetric care is not yet available for all patients in labor and this should be the main focus of the government as well as the medical profession.

Effective interventions for reducing the incidence of postpartum hemorrhage

Although training programs for traditional birth attendants (TBAs) are designed to improve the routine care for mothers and newborns at delivery, these interventions have proved ineffective in reducing maternal deaths[2–5]. Neither trained TBAs nor any other category of minimally trained community health worker can prevent the vast majority of obstetric complications from occurring. Once a complication occurs, there is almost nothing TBAs, by themselves, can do to reduce the chance of morbidity or death that can ensue.

As women at high risk for postpartum hemorrhage account for only a small percentage of all maternal deaths, the vast majority of deaths occur in women with no known risk factors. Stated another way, risk screening programs

have had little impact on overall maternal mortality levels[6–9].

Recognizing these flaws in the early recommendations of the Safe Motherhood Initiative, the present-day clear international consensus is that scarce resources should not be spent in trying to predict which women will have life-threatening complications (Safe Motherhood Initiative). Rather, maternal mortality reduction programs should be based on the principle that every pregnant women is at risk for life-threatening complications. In order to reduce the maternal mortality ratio dramatically, all women must have access to high-quality care at delivery. That care has three key elements:

(1) A skilled attendant at delivery;

(2) Access to emergency obstetric care (EOC);

(3) A functional referral system.

SKILLED ATTENDANTS AT DELIVERY

Evidence concerning the effect of skilled attendants at delivery is somewhat confused by different definitions and by variations across countries. The training of midwives and the regulations governing the procedures they are permitted to perform vary considerably. In 2004, WHO, the International Confederation of Midwives, and the International Federation of Gynecology and Obstetrics issued a joint statement with a revised definition of skilled attendant: 'A skilled attendant is an accredited health professional – such as a midwife, doctor or nurse – who has been educated and trained to proficiency in the skills needed to manage normal (uncomplicated) pregnancies, childbirth and the immediate postpartum period, and in the identification, management and referral of complications in women and newborns.'

Wide variation exists in the extent to which skilled attendants are supported and supervised in the broader health system. This is also true for the number of deliveries that skilled attendants perform annually. In a country such as Malaysia, which dramatically lowered its maternal mortality in the 1960s and 1970s, midwives became the backbone of the program, each delivering 100–200 babies per year[10]. However, in many other countries, birth attendants deliver far fewer babies. This affects their competence, because specific skills, such as manual removal of the placenta, require regular practice in order to be maintained. In Indonesia, for example, where tens of thousands of community midwives have been trained and deployed to villages around the country, each typically delivers fewer than 36 babies a year. Assessments within 3 years of placement found that confidence and competency-based skills were exceedingly low, with only 6% scoring above 70, the minimum level considered necessary for competence[11].

In addition to being properly trained for conducting routine deliveries, a second and more promising way in which skilled attendants can reduce the incidence of postpartum hemorrhage is by actively managing the third stage of labor in every delivery[12] (see Chapters 11 and 13). However, the same techniques of active management that can prevent some postpartum hemorrhages can also cause serious damage if performed incorrectly. This is not just a theoretical risk. Incorrect use of oxytocic drugs, for example, can cause the uterus to rupture, which, in the absence of surgical intervention, can lead to death.

The EOC Project in India

A project is being established to develop the capacity of general practitioners and non-specialist medical officers to provide high-quality EOC services in rural areas where skilled obstetricians are not available to prevent maternal mortality and morbidity[13].

The Federation of Obstetrics and Gynecological Societies of India (FOGSI) has established five EOC training centers in rural India that will improve the provision of EOC services by medical officers, with the ultimate goal of reducing maternal mortality and morbidity. The project has been funded by the MacArthur Foundation, Baltimore, USA and the AMDD (Averting Maternal deaths and Disability), Columbia University, New York. JHPIEGO (an international health organization affiliated with Johns Hopkins University) assists FOGSI in its endeavor to assess and strengthen selected EOC training sites, train selected trainers and strengthen FOGSI's capacity in the area of

monitoring and evaluation. During Phase 2, FOGSI and JHPIEGO will also work together to orient key stakeholders to the value of these innovations in EOC training and service delivery for feedback in order to gain consensus among stakeholders for scale-up of the approaches and technical interventions.

FOGSI members who have a keen interest in training doctors and midwives for rural areas will run these training centers. Each center will have a coordinator and three to four faculty members. These are all staff of medical colleges or well-known consultants. The District Training Centers will have one obstetrician functioning as the District Trainer.

Design and methods policy

Training centers will be set up in medical colleges where there are dedicated doctors interested in rural women's health. All master trainers will be trained in EOC at the nodal center by doctors trained by JHPIEGO. Four master trainers at medical colleges and four at district level hospitals will provide the training in a uniform manner. Each training center will offer two types of courses: a short course of 3 weeks for upgrading the skills of doctors already working in rural or under-served areas but not possessing sufficient knowledge of EOC, and a long course of 16 weeks to provide comprehensive skills including training in performing a Cesarean section. This latter course will be composed of 6 weeks of training in medical college by four master trainers and 10 weeks of practical training in a district-level hospital. Courses will be competency-based and finalized in consultation with the Department of Health and Family Welfare. These courses will be open to any doctor working in rural and under-served areas, from the government, NGO or private sectors.

The roles of FOGSI/ICOG will be, first, to coordinate with medical colleges and government hospitals to make arrangement for training, and, second, to regularly monitor the master trainers, the training program and the quality of training centers and to formalize the end assessment and certification. At the end of each course, follow-up and support activities will ensure that the trainees start to offer EOC services after going back to their work places. A Certificate will be issued at the end. Advocacy with the government and NGO heads is being negotiated to ensure that the trainee's facility is functional and to establish one training center in each state of India.

Expected outcomes

Five tertiary training centers and 20 district centers are well equipped to start the EOC Training Certification Course. Three tertiary centers and eight district centers have already started training, whilst two tertiary centers and 12 district centers will start functioning by the end of October 2006. A total of 162 doctors will be trained during the pilot project of 2 years for three centers established by FOGSI, MacArthur and JHPIEGO. FOGSI plans to develop, in a phased manner, one center per state in the future. It is expected that this pilot effort will be replicated by the government. The policy advocacy efforts will help in this direction to convince government and other stakeholders to support and develop the program so as to provide 24-h EOC services in rural areas.

Upscaling the program

The advocacy efforts of FOGSI have resulted in a significant change in the priorities of the government of India for phase II of the Reproductive and Child Health Care program. Very recently, the Indian government committed itself to the EOC training project of FOGSI. According to the preliminary discussions with the government, FOGSI has been entrusted with the task of developing 20 tertiary training centers and 160 district training centers wherein 2000 medical officers will be trained for 16 weeks of comprehensive emergency obstetric care. These medical officers will provide a skilled high-quality comprehensive EOC through the network of first referral units and community health care centers at subdistrict and Taluka places (a Taluka is an administrative block consisting of 80–100 contiguous villages). The whole program has been planned within a time frame of 5 years. During the same time period, the government will upgrade these centers with the necessary infrastructure such as an operating theater, equipment, blood storage

facilities and persons trained in anesthesia. This conceptual change in providing EOC at underserved places will take EOC to the areas where it is most needed and will bring about a significant reduction in the maternal mortality ratio.

The AOFOG PPH initiative

The Asia Oceania Federation of Obstetrics and Gynaecology (AOFOG) has launched a program called the AOFOG PPH Initiative[14]. This program focuses on the active management of the third stage of labor in areas with skilled birth attendants and in areas where misoprostol is available but without skilled birth attendants. This effort is in support of the FIGO/ICM joint statement on the management of the third stage of labor to prevent postpartum hemorrhage. The focus is on training of trainers in the national societies of those countries whose maternal mortality ratio exceeds 100/100 000 live births.

Objectives

The objectives of the AOFOG PPH initiative are:

(1) To disseminate a standard protocol for active management of the third stage of labor and to ensure uniform and safe institutional practice;

(2) To train the service providers (doctors, midwives, nurses, family welfare visitors) in the institutes to perform active management of the third stage of labor for all women giving birth;

(3) To inform the medical and nursing profession about the rational use of uterotonic drugs, such as oxytocin and ergometrine, and the role of misoprostol for preventing postpartum hemorrhage;

(4) To discuss, demonstrate and to train the service providers regarding the evidence-based management for postpartum hemorrhage;

(5) To develop an action plan to be implemented in respective institutes and to monitor the outcome.

It is expected that the participants of each individual institute will be able to state and demonstrate the standard protocol for active management of the third stage, will practice active management of the third stage and have an updated knowledge and skills for the management of postpartum hemorrhage.

ACCESS TO EMERGENCY OBSTETRIC CARE

Even under the very best of circumstances, with adequate nutrition, high socioeconomic status and good health care, approximately 15% of pregnant women experience potentially fatal complications. Fortunately, virtually all obstetric complications can be successfully treated if EOC is universally accessible and appropriately utilized. United Nations guidelines recommend a minimum of one comprehensive facility and four basic EOC facilities per 500 000 population. To reduce maternal mortality ratios by 75%, high-mortality countries must substantially improve access to emergency care.

Solution exchange for maternal and child health practitioners in India

India is a vast, powerful storehouse of knowledge. While 'expert' knowledge is well documented, valuable knowledge gained through practitioner experience is typically lost or ignored. Furthermore, practitioners cannot always access the knowledge they need, such as whether a particular idea was tried before or where to turn when facing a bottleneck. To harness this knowledge pool and help practitioners avoid reinventing the wheel, the United Nations offices in India created the *Solution Exchange* – a free, impartial space where professionals are welcome to share their knowledge and experience[15]. Members represent a wide range of perspectives from government, NGOs, donors, the private sector and academia. They are organized into Communities of Practice built around the framework of the Millennium Development Goals. Members interact on an ongoing basis, building familiarity and trust, gaining in knowledge that helps them contribute more effectively – individually and collectively – to development challenges.

Communities begin with the Solution Exchange's personalized 'Research Service'. Here individual members post questions on the Community's web-based platform about the development challenges they face; other members respond to these questions and the moderation team provides research into them. The tacit knowledge and expert knowledge are brought together in a summarized 'Consolidated Reply' which is circulated to the Community, normally within 10 working days.

The Maternal & Child Health (MCH) Community, facilitated by WHO, UNICEF and UNFPA country offices in India, focuses on implementation issues facing the attainment of the development goals and targets in the Tenth Five-Year Plan of India, the National Population Policy 2000, Rural Health Mission and Phase II of the Reproductive and Child Health Programme, which correspond most closely to the universally endorsed Millennium Development Goals and targets leading to reduction of maternal and child mortality.

The main focuses of the MCH Community are to improve maternal health and reduce maternal mortality, and to improve child health and reduce infant and child mortality. The MCH Community has now been in action for almost a year, with membership growing from 130 to 725 during this time, representing 28 states and union territories of India and a few members from outside India as well. Discussions have ranged from skilled attendance at birth, setting up a telemedicine center, exclusive breast-feeding and complementary feeding, operationalizing urban Integrated Child Development Services, medical termination of pregnancies, etc.

Safe motherhood initiative from FOGSI

'Optimizing Labor workshops' were held in 66 societies across the country, and four Workshops on postpartum hemorrhage were sponsored by AOFOG. The Federation was able to involve doctors from the government service and nurses practicing in rural areas in the workshops along with its members. Workshops were held in the Societies that cater to large rural populations such as Kalyani in Bengal, Gawhati in Assam, Rajmundhry and Vijaywada in Andhra Pradesh, Chidambaram in Tamil Nadu, Loni, Solapur and Amravathi in Maharashtra, Bijapur and Shimoga in Karnataka, Kota and Ajmer in Rajasthan, Jabalpur and Sagar in Madhya Pradesh, to name just a few[16].

The take-home messages from these workshops were, first, that actively managed and supervised labor has a better outcome with a decreased incidence of operative deliveries, and, second, that an actively managed third stage decreases the blood loss and incidence of postpartum hemorrhage.

REFERRAL SYSTEMS

Widely available, good-quality EOC is necessary but not sufficient by itself to reduce the incidence of postpartum hemorrhage. Appropriate utilization is also necessary. A helpful way to analyze the barriers to utilization is through the '*three delays model*'[17]. Once a complication occurs, the key to saving a woman's life is to provide her adequate care in time. The delays leading to death can be divided into three categories:

(1) Delay in deciding to seek care;

(2) Delay in reaching care;

(3) Delay in getting treatment at the facility.

One important element of strategies to reduce delays is the strengthening of the referral system. Widespread 'failures' in referral systems are often present, particularly for the poor and marginalized. The recent review by Murray and Pearson[18] found significant gaps in understanding how referral systems are currently functioning in addition to highlighting a fundamental problem in the literature, that is, that many studies rely on a conceptualization of an ideal referral system that has a dangerously tenuous relationship to realities on the ground.

Maternity referral systems were first conceived at a time when risk screening was thought to be an appropriate maternal mortality reduction strategy, even for high-mortality countries. This conception assumed a stepwise hierarchy of increasingly sophisticated facilities, and it assumed that high-risk women would be referred up the ladder as their pregnancy

progressed. Today, however, maternal mortality strategies concentrate on emergencies, because it is acknowledged that time is critical. An elegant model of referral from facility to facility could be worse than inefficient, it could be deadly!

Although organized ambulance services appear to be part of the referral system in every country that has achieved major maternal mortality reductions, access to transport is only one part of a far more complex problem. Maternal mortality strategies that address the 'second delay' simply by funding and organizing transport fail to grapple with perhaps even more critical systemic issues.

First and foremost is the need for referral facilities that provide 24-h 7-day-a-week care within a reasonable distance of where people live. Murray and Pearson conclude that 'Extensive pyramidal structures of referral systems with multiple tiers of facilities would seem to offer little benefit in the majority of cases for maternity care and simply delay treatment'[18]. In most countries, attention should be concentrated on referral within the district-level system. From the perspective of a district health system as a whole, it is the strength of the referral facilities and associated supervision and referral systems that should determine the level of skill that birth attendants must have in order to avert maternal deaths, not vice versa. Murray and Pearson provide the example of Yunnan, China, where accessible referral facilities, a well-functioning referral system, and a strong and very active supervision system meant that semi-skilled village doctors could successfully conduct normal births, recognize problems, stabilize patients, and refer them onward for more complex treatment of emergencies. With this system, Yunnan reduced its maternal mortality ratio from 149 to 101 in the 1990s[11].

Unfortunately, however, such results have not been documented for TBAs. A stated goal of many training programs for TBAs is to improve their referral of women experiencing obstetric emergencies to facilities that can manage them. A recent meta-analysis of studies evaluating training programs designed to improve referral practices of TBAs found little effect[19]. Other recent studies explore why TBAs often fail to refer even patients with obvious complications. They find that fear of losing prestige and future business often gets in the way.

Maternal mortality strategies should focus on building a functioning primary health-care system, from first referral level facilities to the community level. Emergency obstetric care must be accessible for all women who experience complications in pregnancy and child birth. Skilled birth attendants, whether based in facilities or communities should be the backbone of the system. Skilled attendants for all deliveries must be integrated with a functioning district health system that supplies *and* supports them adequately.

Achievements of the health department

The government of the state of Tamil Nadu is committed to providing good-quality medical care to the people in the rural areas. To achieve this, 105 primary health centers have been upgraded to 30-bed hospitals[20]. These hospitals have been equipped with X-ray machines, ECG, ultrasonography, operation theaters and laboratories. Another 180 primary health centers provide 24-h delivery care.

In addition, 62 Comprehensive Emergency Obstetric and Newborn Care (CEONC) centers have been established for providing 24-h maternal and child health-care services, including Cesarean sections. These centers have been so located as to be accessible within an hour's travel from anywhere in Tamil Nadu. In the second phase, more hospitals will be upgraded as CEONC centers so as to reduce the time to 30 min.

For the first time in India, a birth companion scheme has been introduced, permitting one female attendant to stay with the antenatal mother during labor in the labor room of all government health institutions to provide psychological support.

In this state, maternal deaths have been reduced by 25% during the last 4 years (2001–2004). An excellent network of blood banks and blood storage centers has been established in the government health institutions to ensure the supply of blood and its components (86 blood banks and 26 blood storage centers).

COMMENTS

In the safe motherhood community today, the question is often posed as whether to give highest priority to training a cadre of workers with midwifery skills who can attend every birth or to focus on strengthening emergency obstetric care services (including the human resources necessary to staff them) in order to treat the approximately 15% of pregnant women who experience complications. Under the strategy of emergency obstetric care first, therefore, emergency services need to be accessible to all (albeit not used by all). In theory, the two interventions – skilled attendants for all births and emergency obstetric care for complicated ones – do not contradict each other. But, as strategies in resource-constrained settings, they fit together less easily. Ultimately, both interventions appear to be necessary to reach very low maternal mortality levels: in every country with a maternal mortality ratio of less than 50 – or even less than 100 – a high proportion of births are attended by skilled health personnel and access to emergency obstetric care is widespread. Be that as it may, the reality in high-mortality countries today is that policymakers are indeed confronted with a choice between the two interventions, at least as a matter of emphasis or priority setting. Where should they put their scarce financial, human, and managerial resources? How should they sequence these interventions?

To look for an answer, we should look to contemporary cases of the few countries or subnational units in which maternal mortality ratios of less than 100 have been achieved. In Malaysia and Sri Lanka, a step-by-step approach, starting with coverage of basic facilities that can deliver emergency obstetric care, followed by a focus on utilization and quality, went hand in hand with the professionalization of midwifery and a governmental commitment to ensuring universal access to health services, including access by the poor and people in rural areas[10]. Over the course of several decades, both countries reduced the incidence of postpartum hemorrhage and thus halved their maternal mortality ratios every 6–12 years, going from more than 500 in 1950 to less than 30 by the early 1990s.

In a country like India, the vast majority of births (often more than 80%) take place at home, very often attended by family members or neighbors, TBAs or other kinds of minimally trained community health workers. The health system is so weak that there is no hope of providing emergency obstetric care or even a true skilled birth attendant in rural areas at any time in the foreseeable future: therefore the strategy should be to provide some additional training to community health workers or traditional birth attendants, making them, in effect, semi-skilled attendants.

The enormous pressure that concerned policy-makers feel to do something for the millions of women who give birth in these circumstances is recognized. It is also recognized that a semi-skilled worker may have the potential to save a substantial number of newborns who otherwise would die. But it must be clearly stated that a strategy of training tens of thousands of semi-skilled workers who will not be backed up by a supervision system, a supply system, or a referral system, is not a strategy that will significantly reduce maternal mortality. In fact, the proliferation of unsupported, unsupervised, semi-skilled workers ('certified' after short training courses to manage deliveries) who are deployed in the context of policies effectively that marketize and privatize health care has the potential to increase the dangers for pregnant and delivering women. In some cases where such a strategy is being considered, the explicit objective is to train such workers on the assumption that they will set up their own private practices[21]. Such private provision will be quite outside any government supervision, any effective regulatory system, or even any self-policing professional body.

It is not suggested that highly trained specialists are not necessary to reduce maternal mortality. Many categories of health personnel can be taught to provide various health services – as long as effective systems of support, supervision and supplies are established.

All the interventions necessary to save women's lives can be delivered in a district health system – at the primary care and first referral levels. This does not mean that women must give birth in facilities, nor does it mean that TBAs and other private providers have no place in a delivery system. The case studies of countries that have substantially reduced

maternal mortality demonstrate that success is possible with multiple combinations of home and institutional births, attended by different categories of health workers, as long as women have access to emergency obstetric care staffed by skilled health personnel[11].

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50

ELIMINATING MORTALITY: LESSONS FROM LUBLIN PROVINCE IN POLAND

J. Oleszczuk, B. Leszczyńska-Gorzelak, D. Szymula, M. Grzechnik, G. Pietras, J. Bartosiewicz and J. J. Oleszczuk

INTRODUCTION

Every year, over half a million women die of pregnancy, delivery and postpartum complications – equivalent to the death toll of 15 September 11th tragedies in a single year! Postpartum hemorrhage is almost always the number one cause of mortality, and in Poland it is no different. In the 10 years between 1991 and 2000, a total of 135 women died of postpartum hemorrhage, accounting for about 35% of all maternal mortality. In Lublin Province (2 181 018 inhabitants) in the south-eastern section of the country, a well-functioning regionalization system, based on three levels of perinatal care, introduced in 1993, has led to a marked reduction in perinatal mortality. A total of 25 obstetric units are part of the system – 18 in level I, five in level II and two in level III – the latter being the perinatal centers. The organizational structure is comprised of the heads of obstetric and neonatal units all of whom report to the Provincial Obstetrician-in-Chief who currently is the Head of the Department of Obstetrics and Perinatology of the Medical University in Lublin. Since 2002, no maternal death due to postpartum hemorrhage has been reported in Lublin Province.

This chapter describes the regionalization system in Lublin Province, along with a specific pathway that exists for all postpartum hemorrhage cases. In addition, the system is critically evaluated, and potential approaches to replicating this system elsewhere are provided. This effort can be viewed as a population-based, multicentric, prospective, controlled trial of an organizational system that aimed, and succeeded, in eradicating maternal mortality from postpartum hemorrhage in one of the Polish provinces. We are of the opinion that the findings from our province can be applied around the world and have immense impact on reducing unnecessary deaths.

THE SYSTEM

The regionalization system presently in place in Lublin Province is based on a very tight network of heads of obstetric and neonatal units throughout the Province. The Obstetrician-in-Chief of the Province, who is currently heading one of the perinatal centers, leads the network.

The postpartum hemorrhage pathway is based upon a centralized support system in which the Provincial Obstetrician-in-Chief acts as at all times as a 'last resort' for the most severe postpartum hemorrhage cases. If such a case occurs and the local obstetric unit decides that an intervention of this senior obstetrician is required, the unit pages the Obstetrician-in-Chief asking for immediate support. If the Obstetrician-in-Chief is unavailable (which happened four out of 33 times in the time under study), the next most senior person in the postpartum hemorrhage SWAT team is paged and attends to the patient. An ambulance is sent to pick-up a postpartum hemorrhage 'rescue kit' (containing recombinant factor VIIa, NovoSeven®, Novo Nordisk, and a set of faster absorption profile sutures for the B-Lynch operation) from the hospital of the Obstetrician-in-Chief and then takes him directly to the local obstetric unit. As the farthest unit is approximately 130 km away from the perinatal center

and the transport takes up to 1.5 hours in extreme cases, the average time from initiating the call and delivering the Obstetrician-in-Chief to the unit takes ~90 minutes.

The Obstetrician-in-Chief then takes charge of the local obstetric team, evaluates the status of the patient and makes a decision about the most appropriate management approach. After the intervention, the patient usually remains in the local obstetric unit (or is taken to the local intensive care unit) to which she was admitted but rarely is transferred to the perinatal center. During recovery, the Obstetrician-in-Chief then provides telephone consultations to the obstetric and intensive care unit teams.

RESULTS

A total of 86 237 births were recorded in Lublin Province between January 1, 2002 and March 31, 2006. During this time, no maternal mortality due to postpartum hemorrhage was reported. The numbers of maternal deaths from other direct obstetric causes are summarized in Table 1. No deaths were caused by indirect obstetric factors or non-obstetric factors.

Between January 1, 2003 and March 31, 2006, 33 cases of postpartum hemorrhage were managed in the collaborative fashion described above. In all instances, the local obstetric units did not manage to control the hemorrhage pharmacologically, and a decision was made to change the pharmacologic approach or to switch to surgical management (laparotomy or repeat laparotomy). In all cases, the Obstetrician-in-Chief was paged and took over further management. (See Chapter 22 for a US hospital-based approach to reducing mortality.)

Several types of cases can be described, depending on the status of the patient at the local obstetric unit as determined by the Obstetrician-in-Chief when he arrived on the scene (see Figure 1):

- Patient undergoing surgery with hemorrhage, difficult to manage but prior to hysterectomy;

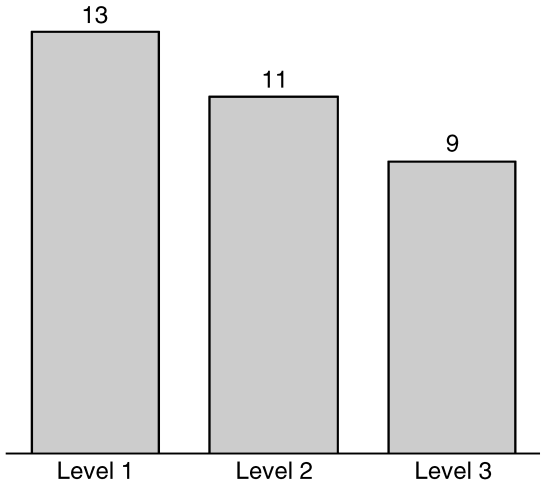

Figure 1 Level of the local obstetric unit in the 33 cases of postpartum hemorrhage managed through the regionalization system between 2003 and 2006

Table 1 Causes of maternal mortality in Lublin Province between 2002 and 2006

	Year					
	2002	*2003*	*2004*	*2005*	*2006 (1.01–31.03)*	*Total*
Deliveries	20 260	20 337	19 896	20 598	5146	86 237
Maternal deaths from:						
Postpartum hemorrhage	0	0	0	0	0	0
Infection	0	0	0	1	0	1
Embolism	0	0	0	0	0	0
Hypertensive disorders	1	1	0	0	0	2
Indirect obstetric factors	0	0	0	0	0	0
Non-obstetric factors	0	0	0	0	0	0
Total	1	1	0	1	0	3

- Patient undergoing surgery with hemorrhage, difficult to manage after hysterectomy;
- Patient after Cesarean section but repeat laparotomy needed (to perform hysterectomy or save the uterus);
- Patient after delivery – conservative management unsuccessful and a decision was required to switch to other conservative approaches or decide to operate.

Interventions were performed in six cases of vaginal delivery and in 27 cases of Cesarean section (Figure 2). Table 2 shows the various management approaches used in the 33 cases of severe postpartum hemorrhage described in this chapter.

DISCUSSION

Using coordinated and well-planned efforts, it is possible to 'eradicate' maternal mortality from postpartum hemorrhage in a large population. Even if half of these deaths could be prevented world-wide, 75 000–125 000 lives could be saved every year. In all 33 cases, patient status after surgery was satisfactory and they quickly recovered and were discharged home with no neurologic or other post-hemorrhagic complications. It is important to underline that these patients experienced the most severe postpartum hemorrhage in which the local obstetric team, usually very well trained, was helpless and required support from the Provincial Obstetrician-in-Chief. The other cases of postpartum hemorrhage which occurred in the province were less severe and responded to a variety of interventions without the need for outside assistance.

The regionalization system was critical in our success in eradicating maternal mortality due to postpartum hemorrhage in Lublin Province. The system in principle aimed at ensuring that the most complicated cases are transferred antenatally to the perinatal center, wherever such forecasting was possible (e.g. in cases of placenta previa in patients after prior Cesarean section). In acute cases, however, when patient

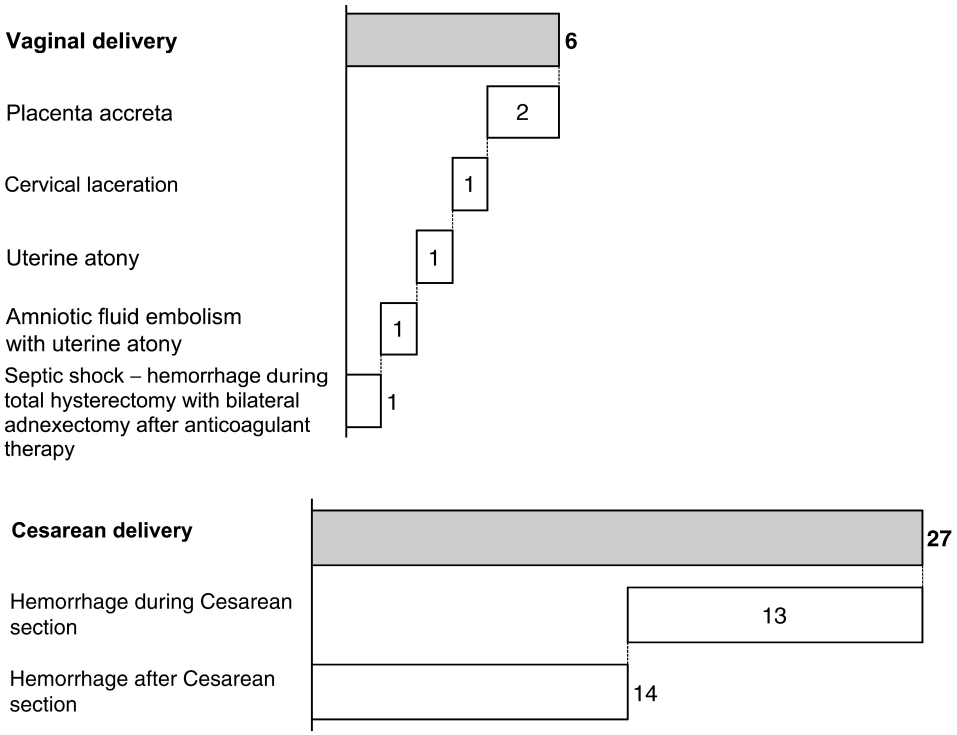

Figure 2 Underlying pathology in the 33 cases of severe postpartum hemorrhage between 2003 and 2006 in the Lublin Province

Table 2 Management approaches in the 33 cases of severe postpartum hemorrhage in Lublin Province between 2003 and 2006

Management approach	*Number of cases*
Laparotomy	3
Repeat laparotomy	9
Total hysterectomy	14
Cervical stump excision after supracervical hysterectomy	1
Unilateral adnexectomy due to bleeding or hematoma	4
Bilateral adnexectomy due to septic shock (with total hysterectomy)	1
Retroperitoneal hematoma evacuation	2
Uterine artery ligation	8
Ligation of the uterine branches of ovarian arteries	8
Bilateral hypogastric artery (internal iliac) ligation	20
Unilateral hypogastric artery ligation	1
Repair of cervical laceration	1
B-Lynch suture	1
Hayman suture	1
NovoSeven	7
Uterus saved	8

transport was not possible, it was critical that an appropriately trained senior obstetrician from the perinatal center be taken to the patient at the remote location, along with specialist supplies that the local hospital did not have. In order to provide appropriate coverage at all times every day of the year, a team of highly trained and skilled obstetricians is ready and available in the perinatal center (a postpartum hemorrhage SWAT team). Because severe postpartum hemorrhage is rare, every member of the postpartum hemorrhage SWAT team should take every opportunity to observe and/or perform most, if not all, of these operations as well as the simpler interventions to get the appropriate training and familiarity with the surgical technique.

With regard to management approaches, a number of methods were used, including a combination of the well-known surgical ligation methods of the uterine artery, uterine branch of the ovarian artery and the hypogastric artery. The latter method should, however, only be performed by the highest skilled surgeons who are comfortable with retroperitoneal space surgery, as these approaches carry a high risk of vascular or ureteral complications. For example, in one of the cases, the hypogastric vein was damaged and subsequently required suture closure. In addition, if these conservative surgical methods are not successful, hysterectomy is the method of choice, and it is critical to time this decision appropriately. In such cases, the uterus is excised with the cervix (total hysterectomy) but without the adnexa.

We see two potential risks with our approach and potential replicas of our approach elsewhere: reimbursement and legal/malpractice. In Poland, reimbursement is on a quasi-DRG (diagnosis-related groups) basis, but the full payment goes to the admitting hospital, without specific breakdown of doctor fees from hospital fees. Thus, our entire system is essentially performed on a *pro bono* basis by the postpartum hemorrhage SWAT team. Unfortunately, this is not sustainable for the long term, and the hospital administration of the perinatal center is currently negotiating appropriate remuneration for these services with the Polish national payor. Legal/malpractice is another risk. In Poland, physicians are covered by a hospital malpractice insurance contract, but theoretically this covers services provided only within the premises of the hospital. Thus, our postpartum hemorrhage SWAT team is not covered by malpractice insurance while performing the intervention in a remote location. Again, this is not sustainable on a long-term basis, as these cases are the most difficult ones and legal proceedings are more likely than after a physiologic delivery. Attempts are now being made to resolve this issue and introduce a malpractice insurance scheme similar to that of the ambulance services or the Good Samaritan Act in the United States.

CONCLUSIONS

(1) It is possible to 'eradicate' maternal mortality from postpartum hemorrhage in a large population.

(2) Programs aiming to 'eradicate' maternal mortality from postpartum hemorrhage in

large populations should encompass the following:

- medical staff – one to several highly experienced surgeons
- Availability at all times every day of the year of an ambulance or other means of medical transport.
- Therapeutic aids – recombinant Factor VIIa (e.g. NovoSeven®) and faster absorption profile sutures for the B-Lynch operation in a ready 'Post-partum hemorrhage kit'.
- Appropriate support – reimbursement contract and malpractice.

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51

POSTPARTUM HEMORRHAGE IN IRAN

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Iran, located in the Middle East, is one of the world's oldest cultures. Although Iran is presently considered to be amongst the so-called developing countries, it was once a renowned center of wisdom and science, boasting such famous names as Avecenna whose thoughts and works influenced much of the world for centuries.

In 2005, the official 'Statistical center of Iran' cites Iran's population as 60 055 488. The number of registered live births 961 572 in 2005[1]. During these years, approximately two-thirds of births took place in urban areas and one-third in rural communities, villages or in the countryside. The 1996 live birth rate per 100 000 population was 37.4, placing Iran in a transitional zone between developing countries (200 per 100 000) and industrialized nations (20 per 100 000).

Due to the desire of Iran's government to achieve the United Nations Millennium Development Goals and to identify the main causes of mortality among neonates and mothers which would affect strategies toward public health promotion, a National Committee of Maternal & Neonatal Mortality Reduction was formed in 1995. In addition, a Reproductive Age Mortality Survey (RAMOS) was designed by the Maternal Health Unit of Iran's Ministry of Health & Medical Education to deal with every reported case of death related to obstetric complications. Some of the information collected and disseminated by this committee is presented below.

During 1996, a total of 382 deaths were recorded as being directly related to obstetric complications. The main causes for these deaths were hemorrhage, eclampsia, cardiovascular disorders and puerperal infections. Most hemorrhagic events occurred during the intrapartum or postpartum periods, highlighting the importance of essential obstetric care. These observations are entirely compatible with those from other developing countries, where poor availability and access to medical services are considered the primary causes of maternal mortalities.

Between 1997 and 2000, the annual numbers of reported obstetric deaths were 162, 170, 214 and 212, respectively. Because these numbers are considerably less than those reported in the 1996 survey, they suggest, but do not prove, a possible inadequacy of that survey system and the potential for underreporting. In any event, the main causes of deaths had equal proportions in the years under consideration.

Despite these limitations, the surveys yielded the following findings:

(1) During 2000, 24.5% and 31.5% of deaths, respectively, occurred among women older than 35 years of age and those with at least four pregnancies.

(2) As many as 57% of the women who died in 2000 had either basic or no education whatsoever, a circumstance that was more prominent in rural populations.

(3) Approximately two-thirds of deaths during 2000 took place among the rural population, a figure which accentuates the importance of creating health-care facilities in underprivileged regions.

(4) Despite a decrease from 44% in 1996 to 19.5% in 2000, delivery by inexperienced and less than fully trained birth personnel ('Ghabele' in the local language) remains an important factor associated with maternal mortality and morbidity during this time interval.

(5) Whereas 43% of deaths occurred in the hospitals in 1996, this number reached 68.5% in 2000, a change which might be indicative of either declining quality of services in hospitals or increased hospital admissions.

The shortcomings of the survey system between 1996 and 2000 led to the evolution of a revised national system called the National Maternal Mortality Surveillance System in 2000, which was a dynamic surveillance system of inputs, interpretations and feedbacks. The main characteristics of this system included a standard definition of pregnancy-associated deaths, regional surveillance systems, reliance on national registration systems that recorded every death, questionnaires regarding the circumstance of every death, acquiring data from multiple sources, timely gathering of information, precise recognition of causes of death (especially preventable), dissemination of results and feedback and, finally, the design and use of appropriate interventions to resolve shortcomings.

Utilizing the new surveillance system, the total number of reported deaths between 2001 and 2004 showed a significant increase compared to previous reports, a change which may be indicative of a higher adequacy and reliability of the new system. During 2001, 2002, 2003 and 2004, a total of 222, 308, 332 and 278 cases of maternal mortality were reported. Table 1 shows the main results of this survey.

The main causes of maternal deaths were as follow: hemorrhage (34.8%), eclampsia (16.7%), embolic events (10%), infection (9.1%), cardiovascular events (6.2%), other causes (12.5%), and unknown (10.7%)[2].

As mentioned previously, these statistics (extracted from Maternal Health Unit of Iran's Ministry of Health & Medical Education publications) only represent registered cases of maternal mortality and the actual rates might be higher. Moreover, deaths due to hemorrhagic events are primarily attributable to poor access or unavailability of health-care facilities or delayed referral, which usually happens in the rural and underprivileged areas. Deaths due to obstetric hemorrhagic events in urban areas, where appropriate medical services are readily available, are rare and are primarily due to delayed referral from underprivileged areas.

One more important factor in the areas with poor access or unavailability of medical services is the high prevalence of puerperal infections as a leading cause of maternal death. Delayed diagnosis and limited access to antibiotics are possible contributing factors. Moreover, in a survey between 1998 and 2000, tetanus vaccination coverage among pregnant women was only 80%[2]. So, in the deprived areas, it is estimated that maternal mortality due to infectious etiologies is only second to hemorrhagic events and surpasses eclampsia. Moreover, these patients usually carry a more unfavorable prognosis as compared to those with hemorrhagic events due to late referral and limited therapeutic options.

Hemorrhagic events have been the most common cause of maternal mortality in Iran and the postpartum hemorrhage is the most frequent type. Unfortunately, there are no official population-based statistics about postpartum hemorrhage, and only two cross-sectional studies in university-based hospitals described postpartum hemorrhage. Although these studies might not reflect an exact view of postpartum hemorrhage in Iran, they might be helpful in some aspects.

In the first study by Sadeghi and colleagues, among 18 134 women undergoing delivery, 141 patients with postpartum hemorrhage were identified in Tehran's Akbarabadi and Firoozgar hospitals in 1993. This represents a frequency of 1%. Of these occurrences, 90% occurred in patients undergoing normal spontaneous vaginal delivery and 10% in patients undergoing Cesarean section. About two-thirds of cases of postpartum hemorrhage occurred in the first and second pregnancies. While 91% of cases were early cases of postpartum hemorrhage, 9% were late. Approximately two-thirds of cases of postpartum hemorrhage were mild, and one-third was either moderate or severe.

The etiologies of postpartum hemorrhage in this study were uterine atony (38%), retained products of conception (38%), lacerations (8%), prolonged stage 3 of labor (4%), puerperal infection (1.4%), uterine rupture (1.4%), placenta accreta/increta (1.4%), hematoma (1.4%), etc.

Table 1 Characteristics of maternal mortality in Iran, 2000–2004

	Percentage of women			
	2001	*2002*	*2003*	*2004*
Age				
> 18 and < 35 years	76	71	77	71
< 18 years	1	2	3	2
> 35 years	20	25	20	27
Residency of mother				
Urban	42	44	45	44
Rural	58	56	55	56
Timely report of death	36	80	92	88
Proposing a plan to prevent similar deaths	32	76	62	57
Applying the plan to prevent similar deaths	n/a	53	45	50
Identifying preventable causes of death	n/a	76	66	63
Number of pregnancies ≥ 5	29	30	20	24
Pregnancy interval < 3 years	10	16	20	23
High-risk mother since start of pregnancy	60	73	67	71
Death during pregnancy	15	16	18	9
Death during delivery	4	8	4	9
Death after delivery	80	75	76	78
Mother delivered at home	36	22	20	15
Mother delivered at hospital	61	73	78	78
Maternal death at home	19	11	9	9
Maternal death on way to hospital	10	11	13	10
Maternal death in hospital	69	75	73	80
Mother delivered by obstetrician	46	56	56	69
Mother not delivered by obstetrician	36	36	40	25
Mother delivered by herself	17	7	4	6
Mother delivered by normal spontaneous vaginal delivery	57	48	52	43
Mother delivered by Cesarean section	42	50	48	55
Delayed family decision causing death	19	38	37	36
Delayed referral causing death	5	23	29	32
Delayed hospital treatment causing death	74	37	39	37

No predisposing factor was found in 62% of patients, but in 13% and 9%, respectively, induction and multiparity were recognized as predisposing factors, especially in those with uterine atony. Approximately two-thirds of patients received more than one treatment. Most patients with uterine atony were successfully treated with uterine massage and oxytocin, whereas most of those with retained products of conception were treated with dilatation and curettage (D&C). Six patients (4.2%) who underwent emergency hysterectomy included two cases of placenta accreta, two cases of uterine rupture, one case with uterine atony and one case with placenta accreta and uterine rupture[3].

It is important to note that this study was conducted 13 years ago; at that time, ultrasonography was not available in the centers, and those suspected of having retained products of conception would undergo D&C without imaging documentation. In addition, poor management of the third stage of labor may have been a contributing factor.

The second study by Beigi and colleagues investigated 74 cases of early moderate to severe

postpartum hemorrhage among 5601 patients undergoing delivery in Tehran's Arash hospital between 2001 and 2002[4]. Here, a frequency of 1.3% postpartum hemorrhage was observed over 3 years. The most common etiologies were uterine atony (60%), lacerations (23%) and retained products of conception (16%). Of those patients with postpartum hemorrhage, 77% and 70%, respectively were between 20 and 35 years of age and between 38 and 40 weeks of gestational age. Nulliparity and multiparity were almost evenly distributed, and two-thirds of patients underwent normal spontaneous vaginal delivery, in contrast to 32% who underwent Cesarean section. Four patients delivered macrosomic babies (5.4%). Multiple gestation was present in two patients (2.7%) but polyhydramnios was present in only one of them. One patient had a previous history of postpartum hemorrhage. The duration of labor was normal in 88% of patients, prolonged in 11% and short in 1%. One-third of patients were induced by oxytocin and no induction method was used in the remaining two-thirds.

Approximately 40% of the cases of postpartum hemorrhage in this study were referred patients, primarily from satellite districts. Although no maternal mortality was observed, referred patients usually carried a more unfavorable prognosis[4].

Whereas it is recognized that neither of these studies reflect an exact picture of postpartum hemorrhage in Iran, they reflect the presence of postpartum hemorrhage in three university-based hospitals of the capital. In this regard, they complement literature from other parts of the world where population-based statistics are absent. They also reflect the actual problems that exist in developing countries in the recent past that are continuing to the present day.

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52

POSTPARTUM HEMORRHAGE AND MATERNAL MORTALITY IN NIGERIA

I. A. O. Ujah and I. S. Ejeh

INTRODUCTION

Although specific studies on postpartum hemorrhage in Nigeria are scanty, the contribution of postpartum hemorrhage to maternal mortality is well documented. Almost four decades ago, a study conducted by Balachandran[1] in Kaduna, Northern Nigeria documented postpartum hemorrhage as the most common cause of maternal mortality, accounting for 25% of all maternal deaths. Many patients were admitted in a moribund state having delivered their babies several hours previously at home. Adewunmi's 1986 study from Ibadan reported that postpartum hemorrhage contributed 18.7% to maternal mortality[2]. A more recent study from Eastern Nigeria reported 2.72% incidence and a case fatality rate of 3.25% for postpartum hemorrhage[3].

In the most recent report (2003), Ijaiya and colleagues reported an incidence of 4.5% for postpartum hemorrhage in Ilorin. The risk factors in this study included advanced maternal age of over 35 years and grand multiparity[4]. Uterine atony was the most common cause of postpartum hemorrhage, accounting for 183 (53.8%) of the cases, the same as was noted in a study from the same center a decade earlier[5].

Similar data are reported from diverse locations within the country. At the University of Nigeria Teaching Hospital, Enugu, south-east Nigeria, hemorrhage was second only to obstructed labor as the cause of maternal mortality[6], and the most recent study from north central Nigeria revealed that hemorrhage was responsible for 34.6% of maternal mortality[7,8].

FACTORS CONTRIBUTING TO POSTPARTUM HEMORRHAGE IN NIGERIA

In Nigeria, as in other parts of the world, postpartum hemorrhage is most commonly caused by uterine atony. Other causes include retention of placenta or placental fragments, trauma to the genital tract, prolonged second stage of labor, multiple gestations or hydramnios, past history of postpartum hemorrhage, antepartum hemorrhage, uterine fibroids, mismanaged third stage of labor, and Cesarean section. All are recounted in detail in later chapters of this book. However, poverty, illiteracy, and unavailability of trained medical personnel combine to accentuate these problems in Nigeria, as do dwindling health resources as a result of bad governance.

MANAGEMENT OF POSTPARTUM HEMORRHAGE

The prevention of postpartum hemorrhage is predicated on its anticipation, and active management of the third stage of labor. Several strategies have prevented or reduced postpartum blood loss and decreased the incidence of severe postpartum hemorrhage and hence maternal mortality. Active management of the third stage of labor with the use of oxytocics with or without ergometrine is beneficial. The use of oxytocic drugs reduces postpartum hemorrhage by about 40%. The effective use of contraception also reduces the risk of high parity and consequently reduces the incidence of maternal deaths due to postpartum hemorrhage.

Here also, these concepts are dealt with in detail in chapters that follow. Ideally, every woman in labor must be closely monitored after childbirth for symptoms and/or signs of postpartum hemorrhage, although this is not yet possible in Nigeria. In addition, steps should be taken to eliminate the unnecessary procedures that contribute to the high incidence of postpartum hemorrhage such as episiotomy or operative vaginal delivery without clear indications. Apart from medical management of postpartum hemorrhage, the surgical approach is well documented and discussed in detail elsewhere.

PREVENTION OF POSTPARTUM HEMORRHAGE

Because postpartum hemorrhage is unpredictable, it is pertinent in countries such as Nigeria to advocate for the promotion of the routine active management of the third stage of labor with oxytocin and the availability and use of misoprostol when oxytocin is not available. Training and re-training of skilled birth attendants on active management of labor will help to reduce maternal hemorrhage-related morbidity and mortality. Extensive governmental campaign efforts should be directed at sensitizing the community to institutional deliveries where adequate monitoring is ensured such that prolonged labor is avoided

CONCLUSION

Postpartum hemorrhage remains a major cause of obstetric morbidity and mortality in Nigeria. Active management of the third stage of labor for high-risk pregnancies is advocated to reduce the incidence of postpartum hemorrhage due to uterine atony. A medical audit of cases of postpartum hemorrhage should be introduced with the aim of identifying the factors associated with postpartum hemorrhage, in order to determine the preventive measures necessary.

In many ways, Nigeria exemplifies many other countries in the developing world where the factors working against the hoped for reductions in maternal mortality outnumber those that actually reduce the problem.

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53

POSTPARTUM HEMORRHAGE IN ASIAN COUNTRIES: AVAILABLE DATA AND INTERPRETATION

S. J. Duthie

INTRODUCTION

Asia is one of the world's largest continents, stretching from the Arctic Ocean to the Equator and from Sumatra and Borneo in the south-east to the Suez Canal in the south-west. Its north-western boundary comprises the Ural Mountains and the Ural River. As such, Asia is home to approximately two-thirds of the world's population, contains its two largest nations (China and India), is home to three of the longest rivers in the world (Ob, Yangtze and Amur) and comprises deserts as well as paddy fields and coconut plantations.

Within Asia, postpartum hemorrhage is a significant cause of maternal mortality and morbidity, although sharp differences exist across Asian countries in the maternal mortality ratio, which is itself a measure of socioeconomic well-being[1]. The major causes of maternal mortality and the manner in which the maternal mortality ratio has fallen also vary between Asian countries. Obstetric hemorrhage is often the most common cause of maternal deaths within Asia. The recognition of this fact and improvements in care, targeted at the management of women with hemorrhage, are both important challenges facing governments as well as medical authorities.

A striking feature about Asia in recent decades is the increase in the gross domestic product of most nations, and the fact that this advance was not always accompanied by a decrease in maternal deaths from hemorrhage. Even in Japan, which has a modern and mature economy, obstetric hemorrhage is the most common cause of maternal mortality, and inadequate obstetric services have been blamed for maternal deaths[2]. In stark contrast, the gross domestic product of Hong Kong increased 14-fold between 1966 and 1985[3], while the maternal mortality ratio dropped nine-fold between 1961 and 1985[4].

In September 2000, representatives from 189 nations met at the United Nations Millennium Summit in New York and endorsed the Millennium Declaration with its eight goals. The Millennium Declaration represents a global agenda for the start of the twenty-first century to promote human development and to reduce global inequalities. Goal number 5 was to improve maternal health. Some Asian countries, such as Thailand and China, have already published progress reports on their achievement of the Millennium Development goals[5,6]. Since that time, there have been encouraging signs in the management of postpartum hemorrhage in Asia. Two issues are very clear. First, Asian countries are making strident efforts to control maternal mortality due to postpartum hemorrhage. Second, it is clear that both the Asian gross domestic product and population numbers will continue to rise. How these obviously intertwined phenomena will affect maternal deaths from hemorrhage will depend on factors other than the gross domestic product alone.

KEY ISSUES

The definition of postpartum hemorrhage varies. The standard definition is blood loss in excess of 500 ml or more within 24 h after delivery. However, *Global Burden of Disease 2000* defines postpartum hemorrhage only when the blood loss exceeds 1000 ml or more[7]. In Thailand, Prasertcharoensuk and colleagues studied 228 pregnant women and reported that

the actual incidence of primary postpartum hemorrhage (defined as a blood loss in excess of 1000 ml) was 3.51% by direct measurement of the blood loss[8]. Other authors, however, report that visual estimation of blood loss would have identified postpartum hemorrhage correctly in only 0.44% of patients[8]. An earlier report from Asia demonstrated significant differences between measured and estimated blood loss at normal deliveries[9]. In a study on normal patients who received standard antenatal care in Hong Kong, blood loss during normal delivery was measured in 37 primiparas and 25 multiparas. In primigravidas, the mean estimated blood loss was 260 ml and the mean measured blood loss was 401 ml. In multiparas, the mean estimated blood loss was 200 ml and the mean measured blood loss was 319 ml. In both groups, the mean estimated blood loss was significantly lower ($p < 0.05$) than the mean measured blood loss. The size of the discrepancy between measured and estimated blood loss was proportional to the measured blood loss (Figure 1). This study highlights the fact that blood loss during a so-called normal delivery may be considerable. Using the standard definition of primary postpartum hemorrhage, 11 out of 62 patients (17.4%) had unnoticed primary postpartum hemorrhage and six women (10%) developed postpartum anemia.

Studies on postpartum hemorrhage are limited by variations in the definition, differences between visual estimation and measured blood loss, and (in many countries) the sheer difficulty of collecting data from widespread and remote areas. Many papers report the incidence and management of obstetric hemorrhage, but include antepartum hemorrhage, postpartum hemorrhage and secondary postpartum hemorrhage. The widespread lack of a confidential system of enquiry into maternal death with published findings adds to the difficulty of ascertaining accurate figures in many Asian countries.

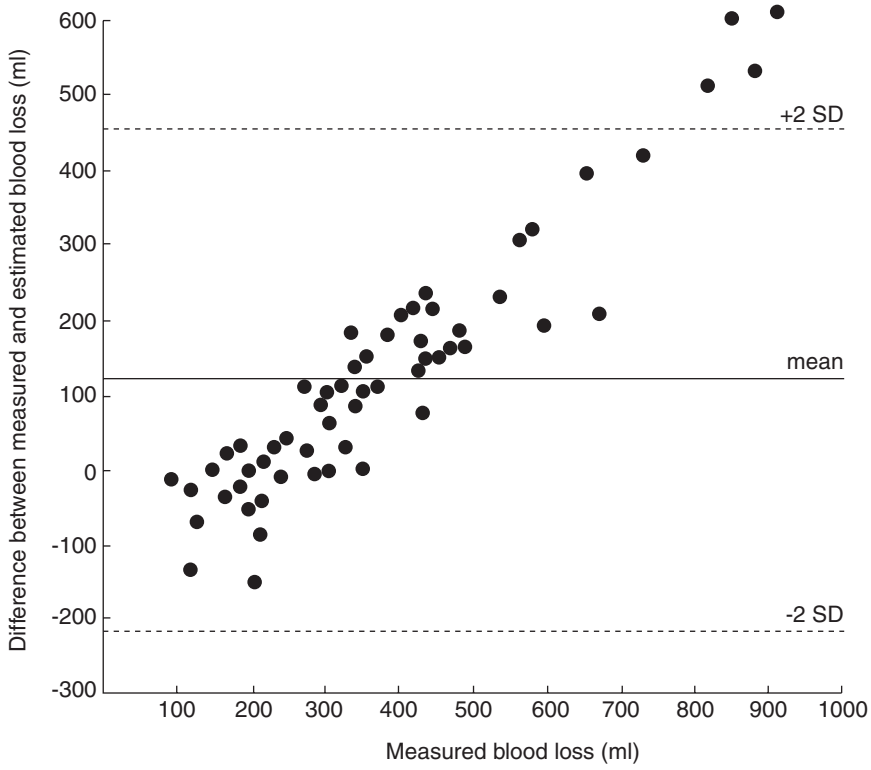

Figure 1 Plot of the difference between measured and estimated blood loss against the measured blood loss. Reprinted from Duthie SJ *et al. Eur J Obstet Gynaecol Reprod Biol* 1990;38:119–24, with kind permission of Elsevier[9]

ASIAN DATA

As postpartum hemorrhage continues to be a major cause of maternal death in the developing and the developed world[10], this section details available data (in no particular order).

Japan

Japan has the largest and most sophisticated economy in Asia and a medical system that was substantially revised after World War II. Despite these advantages, the number of maternal deaths from postpartum hemorrhage increased in number from four to 17 between 1995 and 2003[11]. More importantly, as a percentage of causes of maternal mortality, postpartum hemorrhage increased from 4.7% to 24.6% between 1995 and 2003 (Figure 2). During the same period of time, obstetric embolism (amniotic fluid, air and septic embolism as well as pulmonary embolism) decreased in incidence as a cause of maternal mortality.

Nagaya and colleagues studied 219 cases of maternal death in Japan between 1991 and 1992[2]. The purposes of this study were to identify causes of maternal mortality, examine attributes of treating facilities associated with maternal mortality and assess the presence of preventable factors. Of the 230 maternal deaths

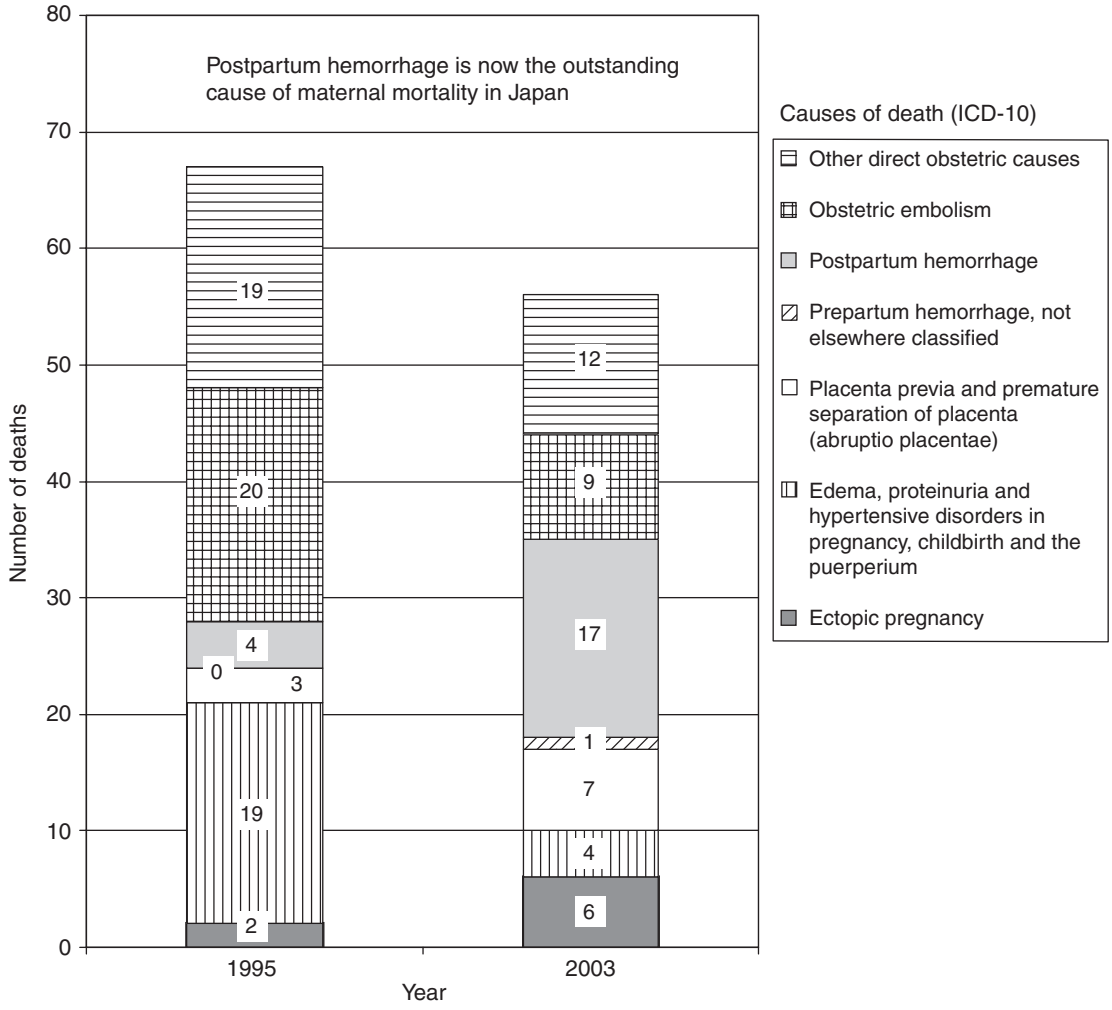

Figure 2 Maternal deaths and percentages by main causes, 1995–2003 (Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labor and Welfare of Japan)

which were identified, 197 women died in the hospital and had medical records available for review, 22 died outside of a medical facility but medical records were also available, and, for 11 women, no records were available. Hemorrhage was identified as the most common cause of these deaths, occurring in 86 (39%) of the 219 women for whom records were available. The overall maternal mortality ratio was 9.5 per 100 000 total births, a figure more than double that reported from Hong Kong for the period 1986–1990 (4 per 100 000 total births[12]). Nagaya and colleagues found that 37% of the maternal deaths occurring in health-care facilities were deemed preventable and another 16% possibly preventable. Among the preventable deaths, most were attributed to the fact that only one physician worked both as the obstetrician and anesthetist. Nagaya and colleagues conclude that inadequate obstetric services are associated with maternal mortality in Japan.

Hong Kong

Data from Hong Kong covering the period 1961–1985 show that the major cause of maternal death was hemorrhage during pregnancy and childbirth (ICD Ninth Revision 640,641,666). Of the 438 maternal deaths during the study period, 150 (34%) were due to hemorrhage. This compares with 89 (20%) due to gestational proteinuric hypertension and 60 (14%) due to ectopic pregnancy. Comparison of the distribution of maternal deaths by cases between two periods (1961–1965 (inclusive) and 1981–1985 (inclusive)) showed an 86% reduction in deaths due to hemorrhage[4]. Pulmonary embolism was not a major cause of maternal mortality between 1981 and 1985. Further data from Hong Kong on obstetric hemorrhage and pulmonary embolism reveal an interesting observation (Figure 3). During the time period 1986–1990 (inclusive), the most common cause of maternal death was pulmonary embolism[12]. Although hemorrhage during pregnancy and childbirth accounted for the same proportion (34%) of maternal deaths during both time periods, it was no longer the most common cause of maternal mortality in Hong Kong. However, it is still a cause for concern that the proportion of deaths due to hemorrhage had not diminished.

These are important lessons for the rest of Asia, and indeed for the rest of the world. The experience in Hong Kong between 1961 and 1985 clearly shows that, as the gross domestic

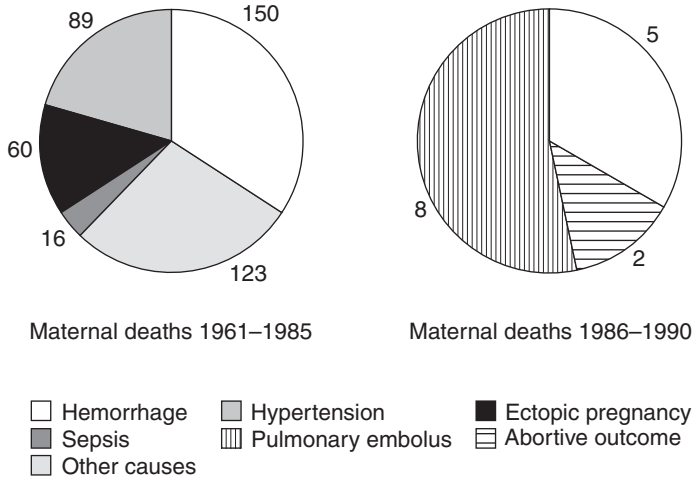

Figure 3 There were no maternal deaths from either hypertension or ectopic pregnancy between 1986 and 1990 in Hong Kong. This is a significant achievement compared with the previous 25 years. Hemorrhage during pregnancy and childbirth (ICD 640, 641, 666) remains a significant cause of maternal mortality, whereas the most common cause of maternal mortality during the study period was obstetric pulmonary embolism (ICD 673). Reproduced from Duthie SJ *et al. Br J Obstet Gynaecol* 1994;101:906–7, with the kind permission of the Royal College of Obstetricians and Gynaecologists

product of Hong Kong rose, the maternal mortality ratio fell. The exact number of deaths due to pulmonary embolism during 1961–1985 was unavailable[4], but it was recognized as a significant cause of maternal mortality in Hong Kong, indeed more common than hemorrhage between 1986 and 1990[12]. It is important to ask why pulmonary embolism has overtaken hemorrhage as the main cause of maternal mortality in Hong Kong. Part of the answer may well be due to a change in civil practice. Since 1986, all maternal deaths were investigated by a coroner's post-mortem. In many parts of Asia, this is not possible, and thus it is very difficult to obtain a perspective on individual cases of fatal postpartum hemorrhage.

India

Chhabra and Sirohi studied trends in maternal mortality specifically due to hemorrhage over 20 years in rural India[13]. Obstetric hemorrhage was the contributory cause of maternal mortality in 19.9% of the cases, and the leading cause of fatal hemorrhage was postpartum hemorrhage due to an atonic uterus. Other causes included ruptured uterus, placental abruption and retained placenta. It is reasonable to ask why so many women died due to an atonic uterus. The answer could be as simple as the high number of home births (60%) and the lack of medical attention and/or use of uterotonic agents.

A study carried out in Calcutta, India between 1995 and 1997 (inclusive) identified a maternal mortality ratio of 686.67 per 100 000 births, and hemorrhage was the second most common cause (16.75%), with toxemia as the leading cause (53.2%) of maternal mortality[14].

Several reports from India describe hemorrhage as the leading cause of maternal death in specific regions of the country. Comparison of two quinquennia, 1987–1991 and 1992–1997, shows that the number of deaths due to hemorrhage has increased and hemorrhage has increased as a proportion of direct causes of maternal mortality[15]. The data from a government hospital in Peninsular India show that the main causes of maternal death were hemorrhage and sepsis. Between 1987 and 1991, sepsis accounted for 47 out of 105 maternal deaths (31%), whereas hemorrhage accounted for 36 out of 105 (25.4%). However, in the succeeding quinquennium, 1992–1997, sepsis only accounted for 22 out of 107 deaths (13.5%) and hemorrhage increased to 45 out of 107 (28%). Hemorrhage was also shown to be the leading cause of maternal mortality at a hospital in West India, where 24.6% of maternal deaths were due to hemorrhage[16]. Data from north-eastern India, covering a 5-year time period between June 1998 and June 1993, also identified hemorrhage as the most common cause of maternal mortality, accounting for 27.65% of deaths[17]. In a detailed and critical analysis, Mukherji and colleagues show that 58.0% of the cases of maternal death due to hemorrhage were actually due to postpartum hemorrhage, mainly stemming from the lack of provision of emergency transport at community level[17].

Pakistan

Evidence from Pakistan identifies hemorrhage as being the most common cause of maternal mortality in many regions. In one study, direct causes of maternal death accounted for 78.1% of cases and the most common cause was hemorrhage[18]. A study in a tertiary care hospital in Pakistan also identified hemorrhage as the most common cause of maternal mortality[19]. One-third of the cases of maternal mortality were due to hemorrhage (nine out of 26), and the authors conclude that most maternal deaths were preventable.

Thailand

Data from Thailand show that the maternal mortality ratio in a government hospital in Thailand was 19.18 per 100 000 births between 1985 and 1998 (inclusive). The most common cause of death was identified as hemorrhage and the authors concluded that a significant number of maternal deaths were preventable[20].

Indonesia

Between 1995 and 1999, a district-based audit of maternal deaths in South Kalimantan, Indonesia demonstrated that 41% of cases of maternal death were due to hemorrhage[21]. Supratikto and colleagues provide a searching discussion of

some of the key issues. Their audit of maternal death in South Kalimantan led to changes in the quality of obstetric care in the district, by developing the concept of accountability of both health providers and policy-makers. Supratikto and colleagues also underlined the need to incorporate scientific evidence to the review process. These are important points as there is ample evidence from some parts of Asia that maternal mortality is not always investigated robustly[22].

Malaysia

A report from Malaysia with a 10-year study period between 1981 and 1990 demonstrated a maternal mortality rate of 74 per 100 000 births[23]. The most common cause of maternal death was hemorrhage. Other causes included hypertension, embolism and sepsis during the decade between 1981 and 1990. Risk factors from maternal deaths were lack of antenatal care, maternal age above 40 years, grand multiparty, and Indian ethnic origin. A postmortem examination was performed in only 8.2% of the women who died.

Similarly, a report from Malaysia describes postpartum hemorrhage, obstetric embolisms, trauma and hypertensive disorders of pregnancy as the main causes of 131 sudden maternal deaths[23]. The sudden maternal deaths comprised 20.6% of all maternal deaths. Twenty mothers died after a Cesarean section and the need for training in the emergency care of women who collapse is emphasized.

China

Data from China also underline the contribution of postpartum hemorrhage to maternal mortality. A case-controlled study of maternal mortality that was conducted in two rural provinces of China (Henan and Jiangsu) identified postpartum hemorrhage as the major cause of maternal death in both provinces[24]. Here, the large proportion of deaths occurred during the journey between the woman's home and the health-care facility, a fact not well emphasized in reports from other countries. A study carried out in Myiun County in China estimated that 27.3% of maternal deaths were unreported[25]. The leading causes of maternal deaths were hemorrhage followed by postpartum infections and pregnancy-induced hypertension. Over the 3 years between 1985 and 1988, improvements in the health-care system were achieved in terms of strengthening referrals between village health stations and township hospitals, establishment of case management procedures for caring for women with postpartum hemorrhage, severe pregnancy-induced hypertension, amniotic fluid embolism, shock and neonatal asphyxia. These improvements were followed by significant reductions in the maternal mortality ratio in pilot areas[25].

Saudi Arabia

In Saudi Arabia, the leading cause of maternal death was hemorrhage in 43.75% of patients at a university hospital between 1983 and 2002[26]. The authors carried out a detailed analysis of the underlying cause of each maternal death and analyzed potentially avoidable factors. Risk factors for maternal death were maternal age in excess of 35 years, a parity of 5 or greater, and iron deficiency anemia[26]. The main avoidable factors were identified as the failure of patients to seek timely medical advice and to follow medial advice.

Sri Lanka

Although hemorrhage is the leading cause of maternal death in several Asian reports, it must be emphasized that it is not always the major cause of maternal mortality. In Sri Lanka, for example, a study covering an 11-year period identified 103 maternal deaths and the main causes were genital tract sepsis (26%), hypertension in pregnancy (24%) and obstetric hemorrhage (20%)[27]. Care was considered to be substandard in 79% of the deaths, and the substandard care was felt to have influenced the outcome of maternal deaths in 7% of the cases.

Bangladesh

Here also, hemorrhage did not head the list of causes of maternal death. Eclampsia (34.3%) was first and hemorrhage (27.9%) second in a study of 8562 maternal deaths[28].

Singapore

The situation in Singapore is encouraging, in that a close scrutiny of maternal deaths in that highly industrialized and compact country shows that most maternal deaths were not due to the traditional direct causes of hemorrhage, sepsis, embolism or hypertensive disease[29]. Over a 7-year period between 1986 and 1992, the maternal mortality rate at the National University Hospital in Singapore was 34.4 per 100 000 births, including incidental deaths. Most of the women who died had underlying medical disorders that placed them at high risk of mortality.

INTERPRETATION

Postpartum hemorrhage is a significant cause of maternal mortality in Asia, regardless of occasional exceptions. The numbers are large and generally on a downward trend. However, some regions still have an extremely high maternal mortality ratio. A direct comparison between different countries and the regions within each country is not feasible for the following reasons:

(1) There is a variation in the definition of postpartum hemorrhage;

(2) Different data are not necessarily matched over the same time frame;

(3) There are major differences in the sizes of the study group in different papers;

(4) Obstetric hemorrhage is not divided into antepartum, postpartum and secondary postpartum hemorrhage in many papers;

(5) Some studies rely on indirect observations and verbal autopsies, whereas other studies involve detailed analysis of individual maternal deaths;

(6) The depth of discussion on preventable factors varies between reports.

The study from Japan[2] investigated preventability of maternal deaths as determined by a 42-member panel of medical specialists. This was a well-organized and robust study. On the other hand, several reports rely on estimates and speculation. In Hong Kong, the total number of births per annum and birth rate dropped, whereas the population size and the number of legal abortions rose over the period 1961–1985. Therefore, parity among Hong Kong women fell during this period[4]. Studies carried out in Hong Kong showed that maternal mortality rates vary greatly by parity, i.e. 41 per 100 000 total births if the parity was zero, and 82 per 100 000 total births if the parity was more than 5[30]. These observations support the speculation that the fall in parity contributed to the fall in maternal mortality rate, but the available data cannot show that it was the high-parity women who were the major group who died from hemorrhage in 1961, and who were no longer present in 1985[4].

Once a maternal death takes place, significant differences in practice are present in different parts of Asia. In Hong Kong, for example, all maternal deaths have been investigated by a coroner's post-mortem since 1986[12]. By contrast, Abdullah and Raj-Hasim pointed out that a post-mortem examination (of any type) was carried out in only 8.2% of cases of maternal death in a university obstetric unit in Malaysia over a 10-year study period between 1981 and 1990[22]. It is also important to note that the data from many countries are already several years old. Medical practice, changes in gross domestic product and the health of individual women have altered in recent years and all these issues have an impact on postpartum hemorrhage and its consequences.

A common theme in most of the Asian papers is that postpartum hemorrhage and its sequelae are preventable. Education of both the health-care workers and the women themselves is emphasized. This leads to two questions:

(1) How can matters be improved further?

(2) Once postpartum hemorrhage is controlled as a cause of maternal death, will other causes of maternal death become more significant?

In order to reduce the incidence and consequences of postpartum hemorrhage, it is essential to obtain precise data. It is of concern that a significant number of women die outside the medical facility and a significant number of maternal deaths did not have records available for scrutiny in a country as technologically

advanced as Japan[2]. Japan has a low maternal mortality ratio, a high gross domestic product and a high rate of female literacy. Although the data indicate that Japan is ahead of most other Asian countries, there is still room for improvement. The rise in maternal deaths due to postpartum hemorrhage in Japan is a major cause for concern. In Hong Kong and Singapore, the maternal mortality rates have fallen to admirably low levels. However, a system of confidential enquiries into maternal deaths is long overdue in Hong Kong[12].

Thailand reported a large reduction in maternal mortality ratio between 1990 and 1999[6]. The proportion of deaths due to hemorrhage has also fallen sharply. Similarly, China has reported a sharp reduction in the maternal mortality ratio between 1990 and 2001, thereby demonstrating China's progress to achieving Goal number 5[5]. Nevertheless, the report from China highlights the differences in the maternal mortality ratio between western China, with a relatively low stage of development, and the more advanced eastern provinces, including Hong Kong. In India, the maternal mortality ratio and proportion of deaths due to postpartum hemorrhage remain unacceptably high.

In Hong Kong, hemorrhage was the most common cause of maternal mortality between 1961 and 1985. However, pulmonary embolism was the most common cause of maternal mortality between 1986 and 1990[12]. This leads to the interesting question as to whether or not other Asian countries that follow Hong Kong's development would face a similar change in the causation of maternal mortality.

RECOMMENDATIONS

It is crucial that progress be made beyond the stage of simply acknowledging the problem, describing it and emphasizing that the problem must be resolved. In practical terms, the first step is to provide adequate training and education of health-care personnel in each country. The systems that provide emergency obstetric care to women with postpartum hemorrhage must be in place within the frame work of clinical governance. Professional responsibility and accountability must be established. The next step would be to ensure that each and every maternal death is certified, investigated and discussed. Analysis of death certificates is useful, but is simply not enough. The practice in Hong Kong whereby the coroner investigates maternal deaths is an example to follow. Once an adequate investigation is carried out, each maternal death (whether due to postpartum hemorrhage or other causes) must be the subject of a multidisciplinary meeting. The appropriate conclusions and areas for improvement must be disseminated within the health-care system. Journals that publish articles on maternal mortality and postpartum hemorrhage must be encouraged to do so only if the authors meet strict criteria of definition, sources of data and an analysis of preventable factors with robust recommendations for change. There is no doubt that the problem of postpartum hemorrhage has been tackled throughout Asia. However, there remains a need for education, certification of deaths, uniformity of definition and critical incident review. There is a significant rise in the gross domestic product of most Asian counties and the benefits should be seen in terms of a reduction in the incidence and fatal consequences of postpartum hemorrhage. The progress achieved so far shows that we need not despair but we should not be complacent.

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Index