



MATERNAL-FETAL MEDICINE

High-Risk Pregnancy Care, Research, and Education for Over 35 Years

From The Society for Maternal-Fetal Medicine and the SMFM Foundation

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First recognized by the American Board of Obstetrics and Gynecology in 1973, the subspecialty of Maternal-Fetal Medicine (MFM) grew from a need to care for increasingly complicated pregnancies and from emerging technologies that provided greater opportunity to evaluate and treat problems involving the fetus.

Maternal-fetal medicine specialists are the leaders in high-risk obstetric care and serve as consultants to general obstetricians, family practitioners, nurse practitioners and midwives. With additional years of subspecialty training after completion of residency, maternal-fetal medicine specialists care for pregnant women who have illnesses such as diabetes, hypertension, and heart disease. Maternal-fetal medicine specialists also utilize new diagnostic tools and treatments to optimize care and pregnancy outcomes. Technologic advances such as obstetric ultrasonography have revolutionized the management of pregnancy by providing a window into the womb and allowing identification of previously unknown problems in the fetus. The field of prenatal genetic diagnosis has evolved rapidly, and the application of knowledge from this arena requires an increasingly in-depth understanding. Even more challenging and exciting has been the opportunity to perform procedures directly on the fetus to improve the chance of survival or avoid serious complications following birth. In addition to caring for women with high-risk pregnancies, maternal-fetal medicine specialists are leaders in medical education in obstetrics and in research that identifies better ways to evaluate and care for pregnant women and their fetuses.

This monograph was written to provide a clearer understanding who maternal-fetal medicine specialists are and what we do. It offers examples of the kinds of patients cared for by maternal-fetal medicine specialists and what is done for them. This monograph highlights important research that has emerged to improve the outcomes of mothers and babies and describes the challenges that face us as we strive to provide optimal pregnancy outcomes for mothers and their babies.



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MATERNAL-FETAL MEDICINE

Maternal-fetal medicine specialists, also known as MFM specialists, perinatologists, and high-risk pregnancy physicians, are highly trained obstetrician/gynecologists with advanced expertise in obstetric, medical, and surgical complications of pregnancy and their effects on the mother and fetus.

In the United States, maternal-fetal medicine physicians are fully trained and qualified obstetrician/gynecologists who, upon fulfilling the requirements of a three-year fellowship and satisfactorily completing written and oral examinations, are certified as subspecialists by the American Board of Obstetrics and Gynecology (ABOG). In addition, the American Osteopathic Board of Obstetrics and Gynecology (AOBOG) confers subspecialty certification in Maternal-Fetal Medicine to physicians who have primary certification in Obstetrics and Gynecology, have successfully completed a three year fellowship and research requirements, and have passed the subspecialty clinical examination. Outside the United States, subspecialty certification in Maternal-Fetal Medicine may be offered on successful completion of training and examination requirements by national bodies (e.g., The Royal College of Physicians and Surgeons of Canada).



The Society for Maternal-Fetal Medicine is an international Society dedicated to the optimization of pregnancy and perinatal outcomes. The Society provides leadership for the advancement of women's and children's health through pregnancy care, research, and education. Its mission is to improve maternal and child outcomes and raise the standards of prevention, diagnosis, and treatment of maternal and fetal disease by focusing on the advancement and dissemination of knowledge through research, education, training, and support for the practice of maternal-fetal medicine. The Society is also an advocate for improving public policy and expanding research funding opportunities in the area of maternal-fetal medicine. The Society was established in 1977 and has more than 2,000 active members. Since 1980 the Society has annually hosted educational meetings at which peer-reviewed research and postgraduate courses in the area of maternal-fetal medicine are presented.

The Society for Maternal-Fetal Medicine Foundation was created to support the development of research and clinical skills in maternal-fetal medicine. The Foundation receives contributions from SMFM members, a Corporate Council, and grateful patients to support fundamental research and help maternal-fetal medicine specialists develop cutting-edge clinical skills. Thanks to these generous donors, the SMFM Foundation, in association with the American Association of Obstetricians and Gynecologists Foundation, annually selects an SMFM/AAOGF Scholar and supports three additional years of mentored research for this individual to further develop his or her skills as a physician scientist. In addition, the Foundation funds a Mini-Sabbatical Grant to provide additional training for physicians already in practice who want to bring new skills or knowledge to their practice or institution.

QUICK Q & A

1. What is a high-risk pregnancy?

A high-risk pregnancy is one in which some condition puts the mother or the developing fetus, or both, at an increased risk for complications during or after pregnancy and birth.

2. What is the range of care provided by maternal-fetal medicine specialists?

Also known as “MFM” specialists, maternal-fetal medicine physicians specialize in the diagnosis, treatment, and care of expectant mothers and their unborn babies who may be at high risk for health problems. Some women require a single consultation before or during pregnancy to help them prepare and to provide guidance to their obstetrician, family practitioner, or nurse-midwife who is less familiar with managing concurrent illnesses or complications of pregnancy. Others may warrant ongoing MFM specialist care, such as monitoring their condition through regular prenatal visits, performing fetal assessments with ultrasound and/or invasive procedures, and participating in delivery. Following delivery, MFM specialists may be consulted to diagnose or manage adverse or unusual pregnancy or postpartum events.

3. What are common medical illnesses and obstetric high-risk conditions managed by maternal-fetal medicine specialists?

The most common medical illnesses include hypertension, diabetes, seizure disorders, autoimmune diseases, and blood clotting disorders. Certain infectious diseases that can affect both mother and child, such as HIV, cytomegalovirus, and parvovirus are often managed by MFM specialists as well. MFM specialists provide care for women who are at increased risk for preterm birth, including multiple gestations, women with cervical insufficiency who may require a surgery to prevent preterm birth, and women with placental problems such as bleeding from premature separation (placental abruption). In addition, MFM specialists are often responsible for the management of preterm labor, premature rupture of membranes, and other complications

during labor that have the potential to impact newborn and long-term infant outcomes.

4. What are the common fetal illnesses managed by maternal-fetal medicine specialists?

Numerous fetal illnesses and abnormalities are managed by MFM specialists. These include structural malformations (birth defects), chromosomal abnormalities, genetic syndromes, cardiac arrhythmias, blood disorders, congenital infections, and intrauterine growth abnormalities. MFM specialists are specially trained in diagnostic ultrasound and can play an important role in screening for fetal chromosome abnormalities and birth defects. For optimal care, certain birth defects, such as neural tube defects (spina bifida) and congenital heart defects require a multidisciplinary approach, and MFM specialists often coordinate this in preparation for delivery. Pregnancies complicated by fetal illness may require specialized care that can include fetal testing, interventions, and determining the timing and route of delivery to optimize neonatal outcome.



5. What procedures do maternal-fetal medicine specialists perform?

In addition to common obstetric procedures (e.g., external cephalic version, cerclage, amniocentesis, operative vaginal and cesarean delivery), many MFM physicians have specialized training in chorionic villus sampling (CVS), percutaneous umbilical cord sampling, fetal transfusion, fetal biopsy, diagnostic fetoscopy, and procedures specific to multiple gestations such as multifetal pregnancy reduction and laser photocoagulation of placental anastomoses in twin-twin-transfusion syndrome. MFM specialists are highly trained in obstetric ultrasound and perform both screening and diagnostic examinations of the fetus, placenta, uterus, and cervix at key times during gestation. MFM specialists may also

be involved in procedures related to critically ill patients, including cesarean hysterectomy, placement of central lines, intubation, and ventilation.

6. Are there other specialties that maternal-fetal medicine specialists work with?

MFM specialists often coordinate the care of the high-risk pregnant woman working hand in hand with the woman's obstetrician to develop a plan of care that is tailored to her needs and those of her unborn child. As experts in understanding and balancing the risks to the mother and the fetus, they also work directly with other adult medical and surgical subspecialists, anesthesiologists, and critical care team members if the maternal condition warrants. MFM specialists communicate and work directly with the neonatologist and/or other pediatric subspecialists to ensure an optimal plan for newborn care.



7. When during pregnancy does a woman see a maternal-fetal medicine specialist?

Before pregnancy, MFM specialists can help women think about and prepare for the risks of pregnancy, especially when the patient has medical conditions such as diabetes or hypertension. Similarly, if a woman has had a poor pregnancy outcome before, consultation can be helpful in planning for the subsequent gestation.

During pregnancy, MFM specialists care for women with preexisting health problems, conditions that arise during the pregnancy (e.g., gestational diabetes and hypertension, placental bleeding, preterm labor, and early rupture of membranes), and those who have complications relating to the fetus itself. As these complications occur, MFM specialists develop a plan of care with their doctor. Sometimes, the MFM specialist will need to assume responsibility for care if this is beyond the expertise of her obstetric caregiver.

Complications can occur even after a pregnancy is over (e.g., postpartum hypertension, excessive bleeding, resistant infection), and some complications in pregnancy can have long-term implications for the woman's health. The MFM

specialist can provide care for the immediate problem and help these patients establish a plan to prevent or limit future complications.

8. What kind of research does a maternal-fetal medicine specialist do?

In general, MFM specialists aim to discover how to improve the health of pregnant women and/or that of their unborn child. These studies encompass many types of investigations such as laboratory studies of the smallest molecules that govern the development of pregnancy, clinical studies of medicines or interventions to improve pregnancy outcomes, and public health studies of systems that can assist pregnant women in getting the most effective and efficient care.

9. What role do maternal-fetal medicine specialists play in education?

MFM specialists play a crucial role in educating the next generation of obstetric providers and teaching the fellows who will become future MFM specialists. MFM specialists contribute to the teaching of medical students and resident physicians and play a key role in continuing education for physicians, nurses, midwives, and other healthcare providers involved in the care of women during pregnancy. In many communities MFM specialists are also involved in quality reviews regarding serious maternal and newborn complications, with a goal of helping all clinicians and institutions to provide up-to-date patient care.

10. How does a woman find a maternal-fetal medicine specialist?

The easiest way to find an MFM specialist is for women to ask their primary caregiver for a reference or referral. Most large maternity hospitals have MFM specialists affiliated with the institution. MFM specialists can also be found through the Society for Maternal-Fetal Medicine website (www.SMFM.org).

QUICK FACTS

Preterm birth

- The rate of preterm birth (before 37 weeks) in the United States has steadily increased over the last two decades; reaching 1 in 8 babies in 2007 (12.7%). There are over 500,000 preterm births each year in the United States.
- African American women are almost twice as likely to deliver preterm (18.3%) compared with white (11.6%) and Hispanic (12.1%) women, regardless of socioeconomic status and education level.
- The annual cost to society (medical, educational, and lost productivity) of preterm birth in the United States is at least \$26 billion (in 2005 dollars).
- The average first-year inpatient and outpatient medical care cost for a preterm infant is 10 times more than for a term infant (\$32,325 vs. \$3,325 in 2005 dollars).
- The 34-week human brain is one-third smaller and significantly less developed than that of a term infant. Late preterm infants, born at 34–36 weeks, are 3.4 times more likely to develop cerebral palsy and 1.3 times more likely to have cognitive impairment than are term babies.
- Severe neuro-developmental disability including cerebral palsy occurs in approximately 34% of infants surviving after birth at 23–25 weeks (the threshold of viability).
- Intramuscular 17 alpha-hydroxyprogesterone caproate, given weekly from 16–20 weeks through 36 weeks has been found to decrease recurrent preterm birth by one-third in women with a prior spontaneous preterm birth.
- To date, there is no treatment that consistently prevents preterm birth once preterm labor occurs.
- A single course of antenatal corticosteroids (betamethasone or dexamethasone) before preterm birth offers significant neonatal health benefits, including reduction of neonatal death, respiratory distress syndrome, cerebroventricular hemorrhage, and necrotizing enterocolitis.
- Antenatal magnesium sulfate is associated with a 31% decrease in the rate of cerebral palsy in surviving infants when given to women at risk of delivering preterm.

Multiple gestations

- Preterm birth complicates 95%, 93%, and 60% of quadruplet, triplet, and twin pregnancies, respectively. Early preterm birth (before 32 weeks' gestation) affects 1 in 63 singleton, 1 in 8 twin (12%), 1 in 3 triplet (36%), and 4 in 5 quadruplet (79%) pregnancies.
- Intrauterine growth restriction complicates up to 25% of twin and 50–60% of triplet and quadruplet pregnancies.
- One-fourth of twin, three-fourths of triplet, and virtually all quadruplet newborns require neonatal intensive care unit (NICU) admission, with average NICU stays of 18, 30, and 58 days, respectively.
- The infant mortality rate for twins and higher-order multiples is 5-fold higher than for singletons (32 versus 6 per 1,000).
- Matched for gestational age at birth, twin and multifetal pregnancy infants have a nearly 3-fold higher risk of cerebral palsy than do singleton infants.



Hypertensive diseases in pregnancy

- Chronic hypertension complicating pregnancy is associated with an 8-15% risk of fetal growth restriction and a 12-34% risk of preterm birth. Placental abruption and perinatal death are 2- and 2 to 4-fold more common in pregnancies complicated by chronic hypertension.
- Hypertension in pregnancy is the 2nd leading cause of maternal death in the United States, accounting for 15% of all deaths.
- One in four women with chronic hypertension will also develop preeclampsia.
- Some serious complications of preeclampsia include pulmonary edema (2-5%), kidney failure (1-2%), cerebral hemorrhage (<1%), and eclampsia (seizures: <1%).
- In the developed world, the risk of maternal death in cases of eclampsia is 1-2%, and the risk of perinatal mortality is 6-12%.

Diabetes in pregnancy

- Over 8 million women in the United States have pregestational diabetes. It complicates 1% of all pregnancies.
- Major birth defects are the leading cause of perinatal mortality in pregnancies complicated by pregestational diabetes, with the risk being proportionate to 1st trimester control of blood sugar as reflected by hemoglobin A1c values. With very high levels, the risk of major birth defects can be as high as 20% or more.
 - Diabetic ketoacidosis occurs in 5-10% of pregnant women with type 1 diabetes, and stillbirth can occur in up to 10% of cases when this occurs.
 - Up to 200,000 pregnancies are affected by gestational diabetes each year.
 - Approximately 50% of women with gestational diabetes will develop diabetes later in life.



Other medical complications

- Asthma affects 1-4% of pregnant women, with hospitalization needed in 2% with mild, 7% with moderate, and 27% with severe asthma.
- Uncontrolled maternal hypothyroidism is associated with increased risks of preeclampsia (44%), placental abruption (19%), stillbirth (12%), as well as more frequent preterm birth and impaired psychomotor function in the child.
- Women with systemic lupus erythematosus are at increased risk for preeclampsia (20-50%), preterm birth (20-30%), and pregnancy loss (10-20%).
- Of women with moderate and severe renal insufficiency, 43% will have deterioration of renal function, and this will not resolve after delivery in 10% of these women.
- Women requiring dialysis during pregnancy have more frequent perinatal complications, including stillbirth (8-50%), preterm birth (48-84%), severe preeclampsia (11%), and fetal growth restriction (50-80%).
- About 25-30% of women with epilepsy have an increase in seizure frequency during pregnancy.

Cesarean delivery

- In 2007, the cesarean delivery rate increased to 32%, marking the 11th annual increase. This rate has climbed by more than 50% since 1996.
- The risk of an abnormally adherent placenta (placenta accreta) increases with the number of prior cesarean deliveries: from 3% to 11% to 40% for women with one, two, and three prior cesarean deliveries, respectively. This condition can result in severe hemorrhage and usually requires hysterectomy.
- Hysterectomy is needed in 10%, 45%, and 67% of women with placenta previa when they have had 1, 2, or 4 or more prior cesarean deliveries, respectively.
- The rate of primary cesarean delivery was 21 per 100 live births in the United States in 2006. During the same time period, 92.4% of women with a prior cesarean underwent a repeat cesarean delivery.



- Of women who attempt a vaginal birth after cesarean delivery, 75% will be successful. Uterine rupture will complicate only 0.7 to 1% of attempts.

Fetal and infant mortality

- Stillbirths account for 58% of all perinatal deaths before 28 days of life, and 48% of all deaths in the first year of life in the United States.
- One in six stillbirths (17.5%) occurs at term.
- The rate of stillbirth equals the rate of death due to preterm birth and sudden infant death syndrome combined.
- The 10 leading causes of infant death (death in the first year of life) in the United States in 2006 were birth defects, preterm birth and low birth weight (absent another cause), sudden infant death syndrome (SIDS), maternal complications, accidents, umbilical cord and placental complications, newborn respiratory distress, newborn sepsis, neonatal hemorrhage, and circulatory system diseases. Birth defects account for about 1 in 5 infant deaths.
- In 2009 the CIA World FactBook ranked the United States 45th among 224 countries for infant mortality, a higher rate than in most developed countries. Much of this is because of the high rate of preterm birth, which is responsible for about one-third of U.S. infant deaths.

- Infant mortality is over two times more common among non-Hispanic black infants than non-Hispanic white or Hispanic infants (13.6 versus 5.8 and 5.6 per 1,000 live births, respectively).

Fetal growth and well-being

- Infants born small for gestational age at term have a 5-fold higher risk of death than normal-weight infants.
- Intrauterine growth restriction (IUGR) accounts for 50% of stillbirths and 20% of neonatal deaths.
- There is a 10-30% increase in minor and major birth defects among IUGR fetuses.
- Fetal infection (e.g., cytomegalovirus, rubella, and toxoplasmosis) accounts for 5-10% of IUGR cases.
- Maternal vascular disease and subsequent utero-placental insufficiency accounts for 25-30% of IUGR cases.
- Use of antenatal fetal surveillance decreases the rate of perinatal mortality from 8.8 to 1.3 deaths per 1,000 births.

Maternal mortality

- Maternal mortality declined 50-fold in the United States between 1915 and 2006, from 608 to 13 deaths per 100,000 live births. In 2006, one maternal death complicated every 7,500 live births.
- The leading causes of maternal death in the United States are hemorrhage, hypertension, thrombosis and thromboembolism, infection, stroke, amniotic infection, stroke, amniotic fluid embolism, and cardiac disease.
- Black women have a substantially higher risk of maternal death than white or Hispanic women (32.7 deaths per 100,000 live births in 2006 for black women, versus 9.5 and 10.2 for white and Hispanic women)

KEY CLINICAL ISSUES

PRETERM BIRTH

Preterm birth (delivery before 37 weeks' gestation) is common, is associated with increased risks of death in the immediate newborn period as well as in infancy, and can cause long-term complications including devastating disabilities. About 20% of premature babies die within the first year of life, and although the survival rate is improving, many preterm babies have lasting disabilities, including cerebral palsy, mental retardation, respiratory problems, and hearing and vision impairment. Preterm birth occurs in nearly 13% of all deliveries in the United States, a higher rate than in other developed countries (5–9%). Although very preterm

infants born before 32 weeks' gestation represent only 2% of births, they account for over half of all infant deaths. Considerable racial disparity exists, with a preterm birth rate of 18.3% among U.S. black women and 11.5% among white women (2007 rates). For all of these reasons, research to prevent preterm birth and reduce its related morbidity and mortality is a top priority.

Most people are unaware of the magnitude of the problem of preterm birth, even though problems directly related to prematurity account for more than one third of all infant deaths within the first year of life as well as a significant proportion of long-term disabilities. In addition to the impact on the child, there is a significant emotional and financial burden for the family, and preterm birth has considerable societal implications for health insurance, education, and social support systems. The total cost of preterm birth in the United States is \$26 billion a year, according to a 2006 report of the Institute of Medicine.

Most preterm births occur in women with no known risk factors. However, women who have already had a preterm birth are two to three times more likely to deliver preterm in a subsequent pregnancy. Multiple gestation (twins, triplets,

etc.) increases preterm birth risk substantially—nearly 60% of twins are born preterm. A short cervix (which can be identified with ultrasound in mid-pregnancy); vaginal bleeding; and previous cervical surgery are other risk factors for preterm birth. Uterine infection is a significant risk factor, with microbiology studies suggesting that it might account for 25–40% of preterm births. A number of risk factors for preterm birth are modifiable, including smoking, illicit drug use, low pre-pregnancy weight, poor nutritional status, and a short interval (six months or less) between pregnancies.

Medically indicated preterm delivery, initiated because of problems such as preeclampsia or diabetes, is responsible for about one-third of preterm births and some of the recent rise in their frequency. The decision as to whether it is better to deliver or to try to prolong the pregnancy entails balancing the risks from prematurity for the newborn against the increasing risk of fetal and maternal morbidity associated with prolonging the pregnancy. For example, in a pregnancy complicated by preeclampsia, early delivery may be warranted to avoid maternal organ damage, stroke, and fetal loss, but early delivery carries risks for the newborn. Research is needed to develop predictors and tools to help weigh the risks and benefits for both mother and baby of delivery versus continued pregnancy when pregnancy complications occur.

Over the past two decades there has been a significant increase in our understanding of the multiple mechanisms that result in preterm birth. These mechanisms can be grouped into four major categories: infection or inflammation, physical or psychological stress, uterine bleeding, and stretching of the uterus. A pregnancy can be affected by one or more risk factors. This complexity adds to the difficulty in pinpointing the cause of threatened preterm birth in individual cases so that appropriate interventions can be made.



Over 500,000 babies are born preterm each year in the U.S.

Markers for risk

Measured in samples from the amniotic fluid; urine, cervical and vaginal secretions; blood; or saliva, various biomarkers may identify women at higher or lower risk of preterm birth. No individual biomarker is effective in identifying all women at risk for preterm birth. One biomarker that holds promise for pregnancy management is a protein called fetal fibronectin, a protein that is found at higher levels in vaginal secretions before delivery. A negative fetal fibronectin test has a high predictive value—99% of women with a negative test will not deliver in the following week. Such a result can provide useful guidance for clinical management. For example, if a woman with early contractions tests negative for fetal fibronectin, unnecessary interventions can be avoided. For women with early contractions, a positive fetal fibronectin test is associated with early delivery, so a positive test could provide guidance for administration of antenatal corticosteroids for fetal maturation (see below) and transfer to a facility capable of caring for preterm infants. But for women with a positive test who are not having contractions, interventions have not been shown to prevent preterm births. Another biomarker, estriol in the saliva, is predictive of late preterm birth, but it is not as useful for predicting earlier births, where the potential for newborn complications is highest.

Cervical length measurement in asymptomatic women can also provide information regarding the risk of preterm birth. The association between cervical length and preterm birth is a continuum, with progressively shorter length being associated with higher risk. This relationship holds true for women with prior preterm births, and even for women in their first pregnancy. Measured by transvaginal ultrasound, a cervical length below the 10th percentile is associated with a 6.5- and 7.7-fold increase in the risks of preterm birth before 35 and 32 weeks' gestation, respectively. Because cervical length shortens during labor, measurement of ultrasound cervical length for women presenting with preterm contractions has also been used to identify those more likely to deliver preterm. In this scenario, the information obtained has similar utility to that obtained from fetal fibronectin screening.

Progesterone to prevent preterm delivery

A major advance in the prevention of preterm birth has been the use of progesterone in the second and third trimesters. Following a series of studies in the 1970s and 1980s, a national clinical trial with 19 participating institutions showed that progesterone treatment (17 alpha-hydroxyprogesterone caproate) resulted in a substantial reduction in the rate of preterm delivery among women who had a previous preterm birth, and also reduced the risk of newborn complications. These findings were confirmed by others and in meta-analyses of published literature. A recent analysis, which used 2002 national birth certificate data, suggested that nearly 10,000 spontaneous preterm births could be averted each year and that the overall preterm birth rate in the United States would decline by 2% if this therapy were given to women at risk for recurrent preterm birth. The annual savings of preventing recurrent preterm delivery by progesterone treatment in the United States has been estimated at more than \$2 billion. Research into progesterone use in women with other risk factors is continuing. So far, studies have shown that progesterone treatment is not effective in twin or triplet pregnancies, but it may reduce the rate of preterm birth in women with a short cervix. If effective for this indication, progesterone treatment would be particularly helpful for identifying women at risk in their first pregnancy. Ongoing study is needed to identify the optimal populations for treatment and the best treatment regimens.

Antenatal corticosteroids to prevent complications after preterm birth

A significant development in clinical care, antenatal corticosteroid administration promotes fetal lung maturity. It is one of the most effective means of preventing newborn complications, including respiratory distress, intraventricular hemorrhage, and death, when preterm birth occurs. Maternal-fetal medicine specialists have led the way in providing clinical guidance regarding the use of antenatal corticosteroids and in conducting research to evaluate the optimal

The estimated annual cost of preterm birth in the U.S. is over \$26 billion



dosage and timing of their administration. Though a single course of treatment is effective if given before preterm birth, the effect appears to decline over time if the pregnancy remains undelivered. Research over the past decade has shown that repeated doses of antenatal corticosteroids, either weekly or on alternate weeks, is associated with negative effects on fetal growth that could potentially outweigh their benefits. Current research is evaluating the potential benefits of a single “rescue course” of corticosteroids for undelivered women who have a second episode of threatened preterm delivery.

Preterm Birth Research Targets

- Biological mechanisms that trigger preterm labor
- New methods to characterize, stratify, and quantify risks
- Causes of racial disparity in preterm birth rates
- Role of maternal viral infections in preterm birth
- Prevention strategies to use before conception
- Effective interventions during pregnancy
- How progesterone works to prevent preterm birth
- Optimal timing of medically indicated delivery

Magnesium sulfate for fetal neuroprotection

In response to retrospective studies that found infants with cerebral palsy were less likely to have been exposed to magnesium sulfate than preterm babies without cerebral palsy, three recent large randomized controlled trials have suggested that magnesium sulfate treatment, given when preterm delivery is expected before 32–34 weeks, results in a reduction in cerebral palsy. Because cerebral palsy is the most prevalent chronic motor disability, with an estimated lifetime cost of nearly \$1 million per individual, its prevention is of great significance to patients, their family and to society. While current evidence is encouraging, further study is needed to determine the optimal treatment regimen and which pregnancies would benefit most from this intervention.

Research to understand the mechanisms of labor and how the presence of risk factors re-

lates to preterm birth is crucial if the incidence of preterm birth is to be significantly reduced. The unexplained racial disparity in preterm birth rates is an important area for further study. How infection is related to preterm birth is not well understood, and the role of maternal viral infections has had little study.

Not all hospitals are equipped to provide the level of intensive newborn care needed when preterm birth is anticipated. It is important that women at high risk for premature birth be treated and delivered in a hospital that has adequate resources. New public policies, education campaigns (such as those developed by the March of Dimes), and health care programs are needed to address gaps in knowledge and implement strategies to reduce risks before conception and during pregnancy. The field of cancer offers numerous examples of how effective such programs can be. For instance, increased public awareness about the risks of smoking has led to the development of diverse strategies to reduce the smoking rate—smoking cessation campaigns, public and private nonsmoking policies, and taxes on cigarettes, to name a few. The changes that resulted from education about smoking risk are now paying off in reduced lung cancer rates.

It is clear that premature delivery is an end point that results from many different causes, much like cancer is not just one disease but a myriad of diseases with multiple causes. Preterm birth will remain one of the most pressing problems in obstetrics until new options are created for identifying those at risk and developing cause specific interventions. Maternal-fetal medicine specialists and researchers continue to peel away the layers of this complex problem which has such devastating consequences. In the meantime, obstetric caregivers look to maternal-fetal medicine specialists to provide guidance and care for patients at risk for premature birth.

MULTIPLE GESTATIONS (TWINS, TRIPLETS, AND BEYOND)

Pregnancy for women with a multiple gestation carries significant risks, and the statistics regarding outcomes are sobering. Twins are five times more likely than singletons to die before their first birthday, and triplets have a tenfold risk of dying before one year of age. Multiples

that survive are more likely to have long-term mental and physical handicaps than those born after a singleton pregnancy. For example, the rate of cerebral palsy among twins is 12 times that of children born as singletons, mainly due to more frequent preterm birth. All of the complications listed for twins are even more common for pregnancies with three or more fetuses.

Largely due to the increased use of fertility treatments, the rate of multiple gestations increased dramatically in the 1980s and 1990s, with twin births up 70% and births of triplets or more surging approximately 400%. Fortunately, the birth rate for twins leveled off at 3.2 per 100 live births in 2004–2006, and the birth rate of triplets and higher reached a plateau after the American Society of Reproductive Medicine issued guidelines in 1998 to limit the number of embryos transferred in assisted fertilization processes. Still, at 15.3 per 1,000 births, the birth rate for triplets or more is twice as high as it was in 1990 and four times higher than in 1980. Women considering assisted reproduction should be counseled about the pregnancy complications and adverse outcomes associated if a multiple gestation occurs.

In a pregnancy with multiple fetuses, complications occur more often, begin earlier, and are more severe than in singleton pregnancies. Preterm birth, the single greatest threat to the health of newborns, is the most frequent complication in multiple gestations. Of most concern is the high rate of births before 32 weeks, when risk of death and long-term disability is highest. Some studies have found that the likelihood of adverse outcomes also increases in twins when delivery occurs after 37 weeks (after 35 weeks in triplets), but each pregnancy must be evaluated individually.

Pregnancies with multiple fetuses warrant heightened prenatal monitoring and specialized clinical management. Maternal-fetal medicine specialists are trained to offer the needed high level of prenatal surveillance and specialized care. Early in pregnancy it should be determined with ultrasound whether the twins share one placenta (monochorionic) because the risk of most complications is greater in monochorionic twins, and

Complications in Twins Compared with Singletons

- *Premature delivery*: at least five times more frequent
- *Pregnancy-induced hypertension*: two to four times more frequent
- *Anemia*: two times more frequent
- *Gestational diabetes*: two to three times more frequent
- *Placental abruption*: three times more frequent
- *Restricted fetal growth*: three times more frequent
- *Excessive bleeding after delivery*: four times more frequent
- *Birth defects such as spina bifida, stomach abnormalities, and heart defects*: twice as frequent
- *Fetal loss before 24 weeks*: three times more frequent
- *Infant death in the first year after birth*: five times more common

the intensity of needed monitoring is greater. Counseling regarding appropriate nutrition is especially important with multiple gestations. One study of twin pregnancies found that participation in a program that included nutrition education and monitoring was associated with significant improvement in pregnancy outcomes. The increased risk of intrauterine growth restriction, which can result in fetal death, calls for regularly scheduled ultrasound exams to assess fetal growth. If the ultrasound reveals intrauterine growth restriction, more frequent monitoring is needed to determine the best time for delivery.

A serious complication in monochorionic twin pregnancies is twin-twin transfusion syndrome, a life-threatening condition in which blood and nutrients are shared unequally between the fetuses because they have unsafe connections between their blood vessels within the shared placenta. One of the twins develops complications of too much circulating blood, while the other has problems from not having enough.



Untreated severe twin-twin transfusion syndrome often results in the death of both fetuses before birth, and 25% of those who do survive will have brain damage. The complexity of this condition requires advanced training and experience in its evaluation and treatment. In the 1990s, maternal-fetal medicine specialists pioneered the use of laser surgery through endoscopes inserted into the womb to close the connecting blood vessels between the fetuses so that they no longer share placental blood. This treatment, called laser photocoagulation, presented a major breakthrough in therapy and outcomes. With this treatment, both twins can survive in 80% of cases, and in another 10% of cases one twin survives; fewer than 5% of all surviving twins have brain damage. Laser photocoagulation is available at only a few specialized perinatal centers in the United States.

Further study is needed to determine the optimal approaches to reproductive technologies to allow successful pregnancies in infertile couples while minimizing the chance that multifetal pregnancies will occur. Studies regarding optimal nutrition, monitoring, and timing of delivery in uncomplicated multifetal pregnancies are also needed to provide the best opportunity for long-term health in these complex pregnancies.

OBSTETRIC ULTRASONOGRAPHY AND ANEUPLOIDY SCREENING

Since its initial use as a window into the womb less than 40 years ago, ultrasound has become an increasingly important tool in the evaluation and care of pregnancy. Ultrasound examinations have proven useful in establishing gestational age, identifying and guiding care of multifetal gestations, assessing fetal growth and placentation, and in identifying fetal malformations. Ultrasonography also provides guidance for invasive procedures, including amniocentesis, chorionic villus sampling, fetal blood sampling and transfusion, fetal bladder drainage, and assessment of fetal renal function for urinary tract obstruction.



Advances in ultrasound technology have continued to change obstetric practice over the last decade. An ultrasonographic evaluation of fetal anatomy performed at 18–20 weeks' gestation can detect the majority of major fetal structural anomalies; 85% of heart defects can be detected by 22 weeks' gestation. The ability of ultrasound to identify fetal abnormalities varies widely with operator expertise, machine quality, maternal obesity and prior abdominal surgery, fetal position, and the type of anomaly present. Ultrasound exams performed at tertiary centers are more accurate in detection of fetal anomalies. When a fetal abnormality is suspected, a detailed ultrasound can provide additional information and guide treatment. For example, when ultrasound markers for Down syndrome are found, there is an increased risk for other birth defects even if the baby does not have Down syndrome.

Ultrasound resolution has continued to improve, making earlier pregnancy evaluation possible. Recent studies of fetal anatomy evaluation at 14–16 weeks of gestation have been able to detect 60% of heart defects. Unfortunately, much of this technological gain is negated if the mother is obese. Visualization of fetal anatomy can be completed only 50% of the time in obese women.

Ultrasonography has allowed identification of fetal conditions that may be amenable to surgery in the womb before birth. Though fetal surgery remains largely restricted to research protocols, ultrasound can provide needed information to determine if in-utero surgery may be appropriate. A current randomized clinical trial involving 200 women carrying babies with spina bifida, the Management of Myelomeningocele Study (MOMS), is comparing outcomes of infants who have in-utero repair with those who receive surgery after birth.

3- and 4-dimensional ultrasound

The recent advent of 3- and 4-dimensional ultrasonography has facilitated further evaluation of suspected fetal abnormalities, and 3-D images can help parents understand a structural problem, giving a better idea of what the baby will look like. Evaluation of facial anomalies, particularly facial clefts, neural tube defects, and skeletal malformations, is especially enhanced by 3-D ultrasound. For neural tube defects, 3-D imaging

can help clarify the extent and level of the defect, providing detail for pediatric neurologists or neurosurgeons who will care for the infant after birth. Similarly, 3-D images of hand or foot abnormalities can provide useful information to the pediatric surgeon for consulting with parents about surgical options for their child. Real-time 4-D ultrasound has potential for evaluation of cardiac anatomy and function, brain structure, and as an adjunct to invasive fetal procedures.

Doppler ultrasound for fetal anemia

In addition to traditional ultrasound “imaging” of the fetus, Doppler ultrasound can measure blood flow through major fetal arteries or veins. Doppler ultrasonography is used in the evaluation of pregnancies complicated by fetuses with suspected intrauterine growth restriction (see Fetal Growth). Previously, invasive techniques such as amniocentesis or direct fetal blood sampling had to be performed every few weeks in pregnancies at high risk for severe fetal anemia that could result in stillbirth (e.g., Rh disease or parvovirus infection). In the late 1990s, maternal-fetal medicine specialists found that Doppler ultrasonography could accurately diagnose moderate to severe fetal anemia by measuring blood flow in the baby’s brain. This novel and noninvasive approach has revolutionized monitoring of pregnancies at risk for severe fetal anemia and has made invasive fetal testing for this indication generally unnecessary.

Screening for aneuploidy

Fetuses with some chromosome abnormalities may have birth defects that become evident with ultrasound only later in pregnancy, or are not even apparent until birth. Traditionally, women have relied on risk factors, such as age over 35 years or a positive family history of abnormalities, to guide their decision making. This approach resulted in many women being considered high-risk even though they carried normal babies, and led to unneeded testing in many cases. Further, most babies with chromosome abnormalities such as Down syndrome are born to younger women, and these women were not routinely offered testing because of their age.

The increasing ability of obstetric ultrasound to identify subtle birth defects and “markers” for

aneuploidy has allowed us to offer early screening to all pregnant women regardless of pre-existing risk factors. In 2005, the results of a large U.S. clinical study (“FASTER”: First- and Second-Trimester Evaluation of Risk) were published. In this study and others, an increase in the size of the fluid space at the back of the fetal neck (known as nuchal translucency) was confirmed to be more common in fetuses with Down syndrome. This study evaluated how well Down syndrome was detected using ultrasound findings combined with maternal blood screening tests in the first trimester (PAPP-A and hCG) and also the second trimester (AFP, hCG, Inhibin, Estriol) and determined the accuracy of various combinations of screening. First-trimester combined screening (blood work plus nuchal translucency measurement) had a higher Down syndrome detection rate (87%, 85%, and 82% at 11, 12, and 13 weeks, respectively) than did second-trimester blood screening alone (81%), allowing earlier testing to confirm whether the fetus was affected. Combining both first-trimester and second-trimester screening results had the highest detection rate of all (95%) but delayed the final result until the second trimester. Pregnant women now have several screening strategies available depending on their desire for screening or definitive testing, how early they begin prenatal care, and local resources.

When the association between increased nuchal translucency on specialized first trimester ultrasound and the risk of Down syndrome was first demonstrated in the early 1990s, detection rates varied considerably because of the lack of systematic training and measurement guidelines. The Society for Maternal-Fetal Medicine took the lead in developing a training curriculum and quality assessment program for nuchal translucency assessment and invited other stakeholder professional societies to collaborate in this venture. Together these organizations established the Nuchal Translucency Quality Review program that provides both training and ongoing quality assessment. Through its training programs, this program has contributed significantly to the



availability of this testing for pregnant women and is a model for ongoing quality assessment in ultrasound practice.

Considerable effort continues toward the development of noninvasive approaches to prenatal diagnoses of genetic abnormalities. Research is focused on obtaining and analyzing fetal cells circulating in maternal blood, but the scarcity of fetal cells is one of several significant challenges. Another approach is microarray analysis of fetal DNA or RNA that can be found in the mother's bloodstream. Newer approaches to directly evaluating free fetal DNA and RNA in the maternal circulation hold great promise for detecting genetic problems without the need for amniocentesis or CVS. With the introduction of technologies such as these into clinical practice, pregnant women will be able to obtain even more accurate information about their pregnancy without the risks incurred by invasive testing.



Hypertension is the 2nd leading cause of maternal death in the U.S.

HYPERTENSIVE DISEASES

High blood pressure (hypertension) during pregnancy endangers the health of both the mother and the baby and is increasingly common as women delay pregnancy until they are older, and as they are more frequently overweight. Hypertension can be present before or develop for the first time during pregnancy (see Box). Preeclampsia occurs only in pregnant women and affects approximately 7% of pregnancies, but resolves within days to weeks after delivery.

For the mother, hypertension is associated with early delivery, increased need for labor induction because of pregnancy complications, stroke, pulmonary or heart failure, and death. The likelihood and severity of these complications increases as the severity of the hypertension increases, and if preeclampsia develops.

For the baby, hypertension increases the chance of preterm birth and its complications, poor fetal growth, intrauterine asphyxia from poor placental function, early separation of the placenta from the wall of the uterus (placental abruption), and fetal death.

Preeclampsia can develop in any pregnancy. Chronic hypertension significantly increases the chance of this happening. The cause or causes of preeclampsia remains one of the greatest mysteries in obstetrics. One of the top three causes of maternal death in the United States, preeclampsia is a major cause of maternal, fetal, and neonatal mortality worldwide. The diagnosis of preeclampsia (new onset hypertension and proteinuria, sometimes accompanied by headache, abnormal liver tests, low platelets, overt liver, kidney or heart failure, seizures, or stroke) may be difficult when chronic hypertension is also present. When preeclampsia becomes evident preterm, a balance must be achieved between the risks of progressive disease to the mother and fetus as opposed to the risks of preterm birth. Both mother and fetus must be carefully monitored; delivery may be required if she or the fetus shows signs of worsening disease. Maternal-fetal medicine specialists have training and broad experience in diagnosis and management of hypertensive diseases in pregnancy, especially the most severe and very early onset cases of preeclampsia. They can provide needed advice regarding medications, fetal evaluation, ongoing management, and the timing of delivery. In cases of preterm or severe preeclampsia, monitoring should take place in a facility equipped to deal with maternal emergencies and intensive neonatal care.

Types of Hypertensive Diseases in Pregnancy

- *Chronic hypertension:* High blood pressure existing before and after pregnancy.
- *Gestational hypertension:* High blood pressure that develops after 20 weeks of pregnancy and goes away after delivery.
- *Preeclampsia:* A pregnancy-specific multi-organ system disease whose most common signs are hypertension and protein in the urine that usually presents after 20 weeks of pregnancy.
- *Chronic hypertension with superimposed preeclampsia:* This condition develops in at least 25% of pregnant women with chronic hypertension.

Antihypertensive medication therapy for severe hypertension can reduce the chance of maternal stroke, cardiopulmonary complica-

tions, and placental abruption, but lowered blood pressure can decrease blood flow to the placenta and reduce the transfer of needed nutrients to the fetus. Although no antihypertensive medications have received FDA approval for use in pregnancy, several have a history of successful use. Research regarding the optimal antihypertensive medications and their optimal administration is needed, as current guidelines are based largely on small studies and expert opinion. In the United States, magnesium sulfate has been used for many years to reduce the chance of maternal seizures (eclampsia) when preeclampsia occurs. A recent trend in some centers has been to use magnesium sulfate only in cases of severe preeclampsia where its effectiveness as an anticonvulsant has been proven in clinical trials. In the past, women with preeclampsia were almost always hospitalized for the duration of the pregnancy, allowing close monitoring and rapid intervention if needed. Outpatient management is becoming more common for selected patients when preeclampsia is not severe. Randomized clinical trials are needed to determine criteria for safe home monitoring, and markers are needed to provide guidance regarding the optimal timing for delivery to maximize fetal outcomes and minimize maternal risks when preeclampsia occurs preterm.

Currently, there is no test or biomarker that can reliably predict whether and when preeclampsia will occur. However, studies have suggested that maternal blood levels of the proteins endoglin and sFLT might be predictive of preeclampsia weeks before its onset. Specific placental proteins that are involved in angiogenesis—the development of new blood vessels—can interact abnormally with endothelial cells that line placental blood vessels and result in preeclampsia. Most exciting for the future is the potential of developing therapeutic interventions that could mitigate the effects of these proteins, thereby preventing preeclampsia or decreasing its severity. Potential candidates, including antioxidants vitamin E and vitamin C, calcium supplementation, and low-dose aspirin therapy have been studied, but none has yet been consistently shown to be effective.

The long-term implications of preeclampsia are now becoming more widely recognized. Studies have shown that women who have had preeclampsia are more likely to develop chronic hyper-

tension, to die from cardiovascular disease, and to require cardiac surgery later in life. Studies regarding the molecular mechanisms that trigger preeclampsia suggest that this condition is more likely to occur in women who have a genetic predisposition to develop vascular disease. Whatever the association may be, pregnancy can be considered a stress test of the cardiovascular system, providing a window into lifelong health. Knowing this, patients and caregivers can prepare for future pregnancies, take measures to reduce long-term cardiovascular risk and monitor for developing chronic hypertension and cardiovascular disease.

PREGESTATIONAL AND GESTATIONAL DIABETES

The hormonal changes of pregnancy often bring about a diabetic state (gestational diabetes) in predisposed women or can seriously worsen preexisting diabetes. Whether diabetes mellitus existed before conception or gestational diabetes develops during pregnancy, maternal glucose intolerance can have significant medical consequences. Poorly controlled diabetes is associated with miscarriage, congenital malformations, abnormal fetal growth, stillbirth, obstructed labor, increased cesarean delivery, and neonatal complications such as hypoglycemia. In contrast, when diabetes is well controlled before and during pregnancy, the risk of birth defects is similar to that of women without diabetes, and there is an excellent chance of having a healthy baby.

When diabetes is present before pregnancy, preconceptional and early prenatal care is of great importance. The fetal organs form primarily during the first two months of pregnancy, often before a woman knows she is pregnant. Poorly controlled maternal blood sugar during this time can result in miscarriage or serious birth defects, most frequently involving the brain, spine, or heart. In fact, hyperglycemia (high blood sugar) at the time of conception is one of the worst known teratogens. Women with pregestational diabetes are also more likely to have underlying vascular disease, kidney disease,



and hypertension, and to develop gestational hypertension and preeclampsia.

Optimally, glucose control should be achieved before pregnancy through the combination of diet, exercise, and medical therapy with the goal of reaching normal glucose control before conception. During pregnancy, more stringent glucose control (fasting glucose <95 mg/dl and 1-hour postprandial glucose values <130 mg/dl or 2-hour glucose postprandial values <120 mg/dl are recommended) is needed to maximize the opportunity for the best outcomes. Maternal-fetal medicine specialists are experienced in providing intense monitoring and care needed for pregnant

women with diabetes. In addition to monitoring glucose and adjusting insulin or oral hypoglycemic therapies throughout pregnancy, the maternal-fetal medicine specialist supervises glucose monitoring during labor and delivery to reduce the risk of hypoglycemia in the newborn.

For most women with gestational diabetes, glucose levels return to normal after delivery. However, they are at high risk for gestational diabetes in future pregnancies and have at least a seven-fold higher risk of developing type 2 diabetes later in life. Because of these risks, formal assessment for diabetes should be performed six or more weeks after delivery and then repeated at least every three years.

The lack of scientific evidence based on well-designed studies has contributed to decades-long controversy over screening techniques, diagnostic criteria, and treatment options for gestational diabetes. Several recent multicenter studies have provided needed evidence about pregnancy outcomes relative to glucose control and aggressive treatment of even mild gestational diabetes, and their findings are likely to change clinical practice. The HAPO study (Hyperglycemia and Adverse Pregnancy Outcome) showed that adverse outcomes increased with rising maternal glucose levels, even when the level was in the normal range. There was no specific cutoff that marked the point where adverse outcomes were more likely. With the influx of new data, guidelines to revise

screening and diagnostic criteria for gestational diabetes are being developed. In 2005 the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) trial found that treatment of gestational diabetes reduced serious perinatal complications, and a multicenter U.S. trial reported in 2009 that treatment of even the mildest form of gestational diabetes had significant clinical benefits; reducing the incidence of large babies by 50% as well as reducing the rates of shoulder dystocia, cesarean delivery, and gestational hypertension.

There have been a number of advances in diabetes management in recent years. Oral antidiabetic agents (glyburide and metformin) have been introduced into clinical practice as an alternative to insulin therapy. Though insulin therapy remains the treatment of choice in pregnancy, oral antidiabetic agents are sometimes preferred by patients because they are cheaper than insulin and do not have to be injected. Insulin administered to the mother does not cross the placenta and thus acts on the fetus only through its effect on lowering maternal glucose levels. Small studies have suggested that metformin and glyburide are effective and safe in pregnancy, but the extent of transfer across the placenta to the fetus is the subject of ongoing study. Well-designed long-term studies are still needed to verify that oral antidiabetic medications do not adversely affect the fetus.

During pregnancy, insulin is given by subcutaneous injection anywhere from one or two times daily for the mildest forms of gestational diabetes, to four or more times daily for those with diabetes that is difficult to control. Subcutaneous insulin pumps can deliver medicine continuously 24 hours a day through a catheter placed under the skin. The pump delivers insulin more precisely and evenly than can be done with separate injections, and it can be programmed to give different amounts of insulin at different times of the day, or extra insulin if the patient has a large meal.

The last decade has seen the introduction insulin analogs that have potential advantages over regular insulin. Lispro is a fast-acting form of insulin that affects glucose levels almost immediately. It eliminates the need to inject insulin 30 minutes before meals and is less likely to produce a big drop in glucose after meals. A long-acting insulin analog, glargine, can help reduce glucose fluctua-



Half of women with gestational diabetes will develop diabetes later in life.

tions over a 24-hour period. Glargine insulin use during pregnancy has had limited study.

Glucose monitoring meters are now smaller, faster, and allow use of sites other than the fingertip for testing, making it easier for women to track their glucose levels throughout the day. A newly developed technology allows continuous glucose monitoring using a sensor inserted just under the skin. The device detects and transmits the glucose level to a device worn at the waist, and data collected can be uploaded to a computer. The patient also inputs data about her insulin intake, exercise, and food eaten, and the system creates a report showing how these factors affected her glucose levels over a three-day period. This system may prove useful in particularly difficult cases and will help improve our understanding of glucose metabolism throughout the day during pregnancy.

The epidemic of obesity is having serious repercussions on the rate of diabetes in pregnancy, and this may impact future generations. Obese women are more likely to have type 2 diabetes before pregnancy and are more likely to develop gestational diabetes during pregnancy. The potential problems of diabetes during pregnancy do not end when the baby is born. Recent research has shown that when the mother is obese, the fetus can develop insulin resistance in utero. Children of obese women are more likely to develop diabetes, and children from pregnancies with poorly controlled diabetes are at increased risk for developing obesity and diabetes later in life.

While research about diabetes treatment continues, more attention to diabetes prevention is needed. Public health educators need effective strategies for changing lifestyle behaviors involving diet and exercise to both treat and prevent obesity and diabetes. Preconception counseling should be part of the basic health information given to women with diabetes in their reproductive years. Research about the most effective ways to convey such information to women and providers is needed.

OTHER MEDICAL COMPLICATIONS

Advances in medicine have increased the complexity of pregnancy management. Many women with serious medical conditions are now able to go through pregnancy and birth with

conditions that would have made pregnancy inadvisable in the past. Repair of congenital heart defects, organ transplantation, HIV therapy, and cystic fibrosis and cancer treatments are just a few examples of major medical advances that have allowed women to survive, thrive, and begin their families. Lifestyle changes and increasing substance abuse/addiction are also making obstetric care more complex. Increasing obesity rates, prescription narcotic addiction, expanded use of prescribed antidepressants, and a rising rate of amphetamine use require careful and skilled management in pregnancy.

In pregnancies with medical complications, consideration must be given to the effect the disease or condition has on the pregnancy, the effect the pregnancy has on the disease, and the effects of the disease on the fetus and newborn. Their advanced training and experience makes maternal-fetal medicine specialists well suited to care for and coordinate care of pregnancies for women with medically complicated pregnancies. This is particularly true in the critical care setting, when a multidisciplinary team of obstetricians, medical, surgical and anesthesiology specialists may be needed. In this circumstance, the maternal-fetal medicine specialist's understanding of the physiology of pregnancy and impact of disease and its treatment on the pregnancy (and vice versa) may substantially alter treatment from that given to non-pregnant patients for the same condition.

A detailed review of all medical complications of pregnancy is not practical in this monograph. Several conditions are briefly described as examples of the potentially complex situations faced in high-risk obstetric care.

Congenital heart disease

Pregnancy increases the demands on the cardiovascular system, with an increased cardiac output seen early in pregnancy to deliver oxygen and nutrients to the fetus. The demands on the cardiovascular system rise again during childbirth. Women with repaired heart defects can be at



increased risk for cardiovascular complications during pregnancy, and they have increased risk for obstetric complications such as preterm birth. Treating these complications can aggravate the underlying cardiac disease. The presence of a maternal heart defect also increases the risk of a similar problem in her child. Such defects can often be diagnosed prenatally by ultrasound, thus allowing assessment of fetal well-being and newborn evaluation and treatment. Women who have ongoing cardiac conditions (e.g., pulmonary hypertension or severe heart valve abnormalities) are particularly at increased risk for stillbirth, maternal heart failure, and death.

Women with cardiac diseases can benefit from preconception counseling that incorporates current information about pregnancy outcomes and available treatments. As with many medical diseases complicating pregnancy, a collaborative team approach is helpful. Regular visits with a cardiologist and a maternal-fetal medicine specialist can allow early identification and intervention for medical or pregnancy complications. Involvement of a perinatal and/or cardiac anesthesiologist can facilitate development of a plan for labor, delivery, and the early postpartum period, which are times of maximum risk.



Obesity

In addition to diabetes, obese women are at increased risk for a variety of complications, including miscarriage, hypertension, cardiovascular disease, pulmonary hypertension, sleep apnea, and cesarean delivery. If cesarean delivery is required, obese women are at a higher risk for surgical complications such as failed intubation, increased blood loss, postoperative infections, blood clots, and poor wound healing.

Obesity also increases the risk of stillbirth and of birth defects such as spina bifida, cardiac abnormalities, and facial clefts.

With the current epidemic of obesity in the United States, obese and morbidly obese women are now commonly seen in obstetric practice, and an increasing number have had prior bariatric surgery. The good news is that those who have

lost weight following such surgery are at lower risks for diabetes, hypertension, sleep apnea, preterm delivery, and low birth weight. However, these women may experience nutritional problems as a direct result of their surgery. Nutritional supplementation is difficult because of the limited ability to take in adequate amounts of food and because of poor absorption of certain vitamins after bariatric surgery. Although rare, intestinal obstruction can also occur from scarring after bariatric surgery.

Organ transplantation

Pregnancy after organ transplant is increasingly common, with kidney transplantation being the most frequent type encountered in pregnancy. Liver, pancreas, heart, lung, bowel, and combined transplants (such as pancreas-kidney and heart-lung) are also now seen more commonly in obstetric practice. Pregnant transplant recipients are at greater risk for hypertension, preeclampsia, diabetes, urinary tract infections, anemia, preterm birth, low birth weight, and stillbirth.

Preconception counseling after transplantation is of paramount importance to discuss risks, optimize management of pre-existing conditions, and determine the options for maintaining immunosuppression medication levels to prevent transplant rejection during pregnancy. Anti-rejection medications have steadily improved outcomes after transplantation, but data about safety during pregnancy is often not available for the newer drugs. Nevertheless, the benefits of immunosuppressive therapy in transplant recipients generally outweigh the slightly increased risk of adverse pregnancy outcomes. Pregnancies in transplant recipients are high-risk and should be managed by a multidisciplinary team.

The National Transplantation Pregnancy Registry has documented pregnancy outcomes in different types of transplant recipients since 1991. This registry now includes data from more than 1,743 pregnancies among 1,094 recipients, and also 1,128 pregnancies fathered by transplant recipients. Because of the rarity of transplantation in pregnancy, registries such as this are critical to provide information that will guide pregnancy counseling and management.

Drugs in pregnancy

Most drugs approved by the FDA have not undergone study regarding their safety in pregnancy. Drug companies are often reluctant to develop new drugs or test established drugs for use during pregnancy, likely because of the increased liability related to potential adverse effects on the fetus. With the pharmacokinetics of drugs in pregnancy largely unknown, optimal treatment regimens to maximize efficacy and minimize maternal and fetal toxicity have not been developed for many medications. The physiologic changes in pregnancy, including increased blood volume and alterations in binding proteins, can substantially alter the optimal dosing from that in the non-pregnant state. A research network sponsored by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development is conducting studies to improve our understanding of drugs used during pregnancy and breastfeeding. Established in 2004, the Obstetrical Pharmacology Research Units network is studying a broad range of drugs, such as antibiotics, oral hypoglycemic agents, antidepressants, and tocolytic drugs that reduce uterine contractions. Studies like these are critical to the introduction of safe treatments for pregnant women and their fetuses.

Medical Complications Research Targets

- Evaluation and care of critically ill women (e.g., Apache-2 scoring for prediction of outcomes in pregnancy, tidal-volume ventilation in pregnant patients)
- Effects of obesity and of bariatric surgery on nutrition in pregnancy and pregnancy outcome
- Incidence and prevalence of sleep apnea and its effect on maternal-fetal outcomes
- Short and long-term maternal and fetal outcomes following organ transplantation
- Criteria for testing and treatment of women with thrombophilias
- Pharmacokinetics, efficacy and safety of medications during pregnancy

CESAREAN DELIVERY AND VBAC

Cesarean delivery is the most common surgical procedure performed in the United States. The percentage of births delivered by cesarean

has risen significantly in the last 10 years, from 21% in 1996 to 32% in 2007. While there is no known optimal rate, the climbing rate of cesarean delivery is concerning. Though uncommon, the risk of a number of serious maternal complications, including blood loss, damage to nearby organs, and death, are increased with cesarean delivery. Subsequent pregnancies after cesarean delivery have higher risks of uterine rupture, hysterectomy, need for transfusion, and perinatal mortality regardless of delivery method. The rates of abnormal placental attachment into the uterine muscle and surrounding organs (placenta accreta), hysterectomy, blood transfusions, intestinal obstruction, intensive care unit admission, and injury to the bladder, bowel, or ureters all increase as the number of cesareans a woman has increases. In addition, the time spent in surgery increases directly with the number of previous cesareans. Being prepared for the possibility of complications is an important part of the management of women requiring a repeat cesarean delivery.

Collaboration between multiple services (anesthesiology, blood bank, and sometimes other surgical specialties) is important when placenta accreta is suspected, as severe bleeding during surgery and hysterectomy are common, and surrounding organs can be involved. Special considerations may include preoperative ureteric stent placement, ultrasound mapping of the placental location to guide the uterine incision, and use of peri-operative pelvic artery embolization through internal iliac balloon catheters. When placenta accreta is diagnosed prenatally, delivery should be planned to occur in an institution that has adequate blood banking resources for potential massive bleeding and has surgical personnel with expertise in dealing with complications related to this condition.

Women commonly lose 3,000 to 5,000 mL of blood if hysterectomy is required during cesarean delivery, and this can rapidly use up the body's clotting factors. Timely replacement of red blood cells and maternal clotting factors is

Nearly 1 in 3 babies in the U.S. is born by cesarean section, a 50% increase in that past decade.



important when heavy bleeding occurs. A recent advance is the use of recombinant activated factor VIIa, which has been shown to be effective when other measures fail to stem bleeding. However, this treatment carries the risk of vascular thrombosis and thromboembolic complications.

Vaginal Birth After Cesaraen

The escalation in the cesarean delivery rate has been fueled by a steep decline in the number of vaginal birth after cesarean (VBAC) attempts. Once a woman has a cesarean delivery, there is a 92% chance that she and her physician will opt for cesarean delivery for her next delivery. Increasing the number of VBAC attempts would reduce the overall cesarean delivery rate and the complications

associated with repeated cesarean deliveries. VBAC is appropriate for most women whose cesarean delivery was through a low transverse uterine incision. Although VBAC is associated with some risks, a large multi-institution study of over 39,000 women with prior cesarean showed that the risks were uncommon—around 0.74% for uterine rupture and 0.5% for neonatal complications such as hypoxic ischemic encephalopathy. Research has found a number of factors predictive of a successful VBAC attempt, including vaginal delivery

before or after the earlier cesarean, and cesarean delivery for a reason that is not expected to occur again in the next pregnancy. Predictive models can be useful in guiding decision making as to whether a VBAC attempt is appropriate. Because of the potential risks and concomitant liability, some hospitals that do not have 24-hour availability of surgical personnel (including an obstetrician and anesthesia staff available to perform an emergent cesarean delivery) will not allow VBAC attempts. Under this circumstance, referral of appropriate candidates to a center capable of offering a VBAC attempt should be considered.

While cesarean delivery and VBAC attempts are performed by both general obstetricians and maternal-fetal medicine specialists, much of the research in this area is done by the latter. These studies impact the choices made as to whether a

cesarean is needed or VBAC attempt is appropriate, and also how and when these are performed.

FETAL GROWTH

Intrauterine growth restriction (IUGR), or fetal growth restriction, is a serious condition in which the fetus is not growing adequately and is smaller than expected for its age. IUGR is present in almost half of all stillbirths. IUGR babies are at increased risk for serious complications such as meconium aspiration, difficulty maintaining normal body temperature after birth, and perinatal death. Surviving infants with severe IUGR are at risk for long-term developmental delay and neuromotor disabilities such as cerebral palsy. Epidemiologic studies have linked low birth weight with the development of adult chronic diseases including hypertension, diabetes, and heart disease.

A number of conditions have been associated with IUGR, though the mechanism in any given case is not always evident. Abnormalities of the placenta, infection, multiple gestation, and chromosomal anomalies are all associated with IUGR, as are maternal hypertension, diabetes, malnutrition, and substance abuse. The most significant modifiable risk factor for IUGR is smoking. When compared with nonsmokers, smokers are 3.5 times more likely to have an infant that is growth restricted. Women are often more willing to stop smoking during pregnancy than at other times, and obstetric providers should encourage smoking cessation and assist in long-term cessation efforts.

At the other end of the growth continuum, excessive fetal growth (large for gestational age, LGA) can also lead to complications, including birth injuries, cesarean delivery, and metabolic disorders such as hypoglycemia and hyperbilirubinemia. LGA infants are more common in pregnancies of diabetic and obese mothers, and the babies themselves are more likely to become obese and to develop diabetes as they get older.

Diagnosis and evaluation of IUGR

In pregnancies at risk for IUGR, or when measurements of the mother's pregnant abdomen suggest that fetal growth may be lagging, ultrasonography can be performed to estimate fetal weight. Repeated estimation of fetal weight, generally done four or more weeks apart, has



Over 3 out of 4 of VBAC attempts will be successful.

considerable value in confirming or excluding the diagnosis of IUGR and determining if the fetus is growing appropriately.

Maternal-fetal medicine specialists are often consulted to either perform the initial diagnostic ultrasounds or to confirm the diagnosis and recommend the best course for continuing prenatal care and delivery for IUGR fetuses. Additional tests, typically performed to confirm the diagnosis, include measuring amniotic fluid volume and blood assessment. IUGR fetuses are more likely to have less amniotic fluid, and in many cases Doppler studies of blood flow to the placenta will suggest increased resistance. Ultrasound can also be used to assess fetal well-being through evaluation of fetal body and breathing movements in addition to the amniotic fluid volume. Frequent fetal heart rate monitoring is used in many cases. Developments in ultrasound technology and our understanding of fetal physiology have led to continuing refinement of the use of Doppler studies in obstetric care. Largely limited to studies of the umbilical and uterine arteries in the 1980s, modern Doppler techniques can include not only studies of fetal arteries but also venous blood flow to help identify fetuses at the highest risk for stillbirth and serious complications (see Assessment of Fetal Well-Being, page 25)

Though obstetricians rely on ultrasound fetal weight estimates, these are not accurate in all circumstances. Current research is evaluating the utility of incorporating fetal measurements from 3-dimensional ultrasound to improve our accuracy.

Individualized fetal growth potential

The diagnosis of suspected IUGR has been traditionally made when the estimated fetal weight is below the 10th percentile (smaller than 9 of 10 fetuses) on standard growth charts for gestational age. Many of these fetuses are simply small but normal, and use of this criterion as the threshold can lead to undue anxiety, testing, and even early delivery of a normal baby. More stringent cutoffs, such as the 5th and 3rd percentiles, are much more likely to identify fetuses that truly have IUGR and who may have complications before or after birth. However, these criteria can miss some babies who are actually having trouble growing but are larger. Standard growth charts that are created from large population-based

databases do not take into account factors such as maternal and paternal size, preexisting maternal medical conditions, or racial, environmental, or genetic factors that can affect fetal size. Several research groups have pursued the study and development of customized growth curves that identify the growth potential for an individual fetus based on some of these characteristics. These studies are examining the value of customized growth curves to identify fetuses at risk for complications because of abnormal growth.

New Fetal Growth Research Targets

- Refinement of the definition of normal fetal growth
- Optimal methods of assessing fetal growth, including customized growth curves
- Role of genetics, the environment, and demographic characteristics in fetal growth
- Molecular mechanisms involved in fetal growth
- Biomarkers, including DNA markers, to identify fetuses at risk for abnormal growth
- Interventions that increase blood flow and nutrient delivery to the fetus
- Integration of multi-vessel Doppler studies and biophysical fetal assessment for improved diagnosis and management of IUGR
- Correlation of fetal growth with short- and long-term health outcomes
- Optimal timing of delivery in cases of abnormal fetal growth

Fetal body composition

Like adults, newborns come in all shapes and sizes. Some are very lean, and some already have significant extra fat at birth. Advances in ultrasound technology have increased our ability to evaluate fetal body composition by measuring both fetal fat and lean body mass. Measurements of the fat of the fetal arm, thigh or abdomen, for example, could allow us to better understand which fetuses are undernourished versus those that are small but normal. In diabetic pregnancies the presence of additional fat stores might suggest that glucose control is not adequate.

Fetal programming

Because it has been shown that low birth weight is associated with high blood pressure and cardiac disease decades later, and fetal obesity is associated with an increased risk for later obesity and diabetes, it has been suggested that the intrauterine environment programs the fetus to develop these complications. A standard for normal fetal growth that leads to a life course that is as healthy as possible has never been established. Defining this standard and improving the accuracy of estimating fetal weight are primary goals of the National Standard for Normal Fetal Growth project, launched by the National Institutes of Health in 2009. The study will develop individualized growth standards that incorporate factors including race/ethnicity and maternal characteristics. An international multicenter study with similar objectives is planned by the World Health Organization.

STILLBIRTH

Stillbirth, defined as the death of a fetus at 20 or more weeks of gestation, complicated nearly 26,000 pregnancies in the United States in 2005; a rate of 6.2 per 1,000 live births (1 in 160). Considerable racial disparity exists—stillbirth is more than twice as common among African-Americans than Caucasian women (11.1 versus 4.8 per 1,000). Other maternal risk factors for stillbirth include advanced age, obesity, and coexisting medical disorders such

as diabetes or hypertension. The possible impact of environmental exposures on stillbirth risk remains unknown. Of known stillbirth causes, the most common are genetic abnormalities, alterations in the number or structure of the chromosomes, maternal infection, hemorrhage, and problems with the umbilical cord or placenta. However, the cause remains unknown in about half of all stillbirths. Knowledge about the causes and prevention of stillbirth has been hampered because postmortem investiga-

tions are often not done, and the evaluations that are done are not uniform.

A detailed postmortem evaluation after stillbirth is important not only to determine the cause but also for developing strategies to prevent a recurrence. One of the most useful evaluations is an autopsy, as this can identify birth defects, abnormalities that likely have a genetic cause, and other potential causes such as infection, anemia, or lack of oxygen. Despite its importance, autopsy is done after only about one-third of stillbirths. Parents often decline an autopsy because of misconceptions about what is done, concerns about how it might affect a planned burial, or concerns about the cost. Because discussing autopsy is difficult for both the doctor and the parents during this emotionally devastating time, autopsy may not be offered, its value may not be explained, and the parents' concerns about the procedure may not be addressed. For families that decide against an autopsy, x-rays or magnetic resonance imaging can sometimes provide useful information and may be an option that is acceptable to them.

The second most important assessment to determine the cause of a stillbirth is examination of the placenta. Through this assessment information can be obtained about possible contributing factors such as intrauterine infection, thrombosis in the blood vessels, local placental abnormalities and infarction, and early placental separation from the uterus.

Fetal karyotype assessment is also recommended to identify chromosomal abnormalities. Amniocentesis before delivery can be a valuable tool to obtain fetal cells for chromosome analysis. This approach is particularly important if the stillborn is not delivered right away.

To address the gaps in knowledge about stillbirth risks and causes, the Stillbirth Collaborative Research network was established in 2003 by the National Institutes of Health. With the participation of 58 rural and urban hospitals in five states, researchers are studying stillbirth causes and risk factors using standardized protocols for interviews with parents, autopsies, and other postmortem tests. The knowledge gained by this network will inform future research to determine opportunities and appropriate fetal testing strategies for prevention of stillbirth.

Half of all perinatal deaths are stillbirth.



Stillbirth Research Targets

- New technologies to identify genetic abnormalities in stillborn fetuses
- Reasons for racial disparity in stillborn rates
- The role of infection and environmental exposures in stillbirth
- Development of clinical assessment tools to identify women at risk for stillbirth
- Fetal monitoring strategies to prevent stillbirth based on risk factors

ASSESSMENT OF FETAL WELL-BEING

Evaluation of the condition of the baby before birth has been a challenge in obstetrics since recorded time. The first description of a stethoscope specifically designed for listening to the fetal heart dates back to the 1700s. The advent of biochemical tests to assess placental function in the 1960s and electronic fetal heart rate monitoring (EFM) to allow real time evaluation of fetal heart rate patterns in the 1970s marked the beginning of fetal medicine and in many ways heralded the new subspecialty of maternal-fetal medicine. Many of the investigators who developed these technologies were also the founders of this subspecialty.

Fetal assessment can be performed both before (antepartum) and during (intrapartum) labor, but the specific technologies used during these times vary. More than half of stillbirths before labor occur in women who are at increased risk for stillbirth. Antepartum monitoring of these women can potentially prevent fetal death by identifying those fetuses who can benefit from either improving their condition in the womb (e.g., by fetal blood transfusion in severely anemic fetuses) or from early delivery to remove them from a sub-optimal intrauterine environment. Before the advent of EFM, fetal death during labor was a relatively common event, occurring about once in 300 births. With EFM now widely used during labor, intrapartum fetal death has become extremely uncommon. Because EFM can identify the fetus that may be developing an abnormal acid-base status as a result of decreased oxygenation in labor, there was great hope that this technology would also reduce cerebral palsy and neurologic injuries. This hope has not yet been realized.

The techniques that are used to evaluate the fetus before labor vary depending on the high-

risk condition of the fetus or mother. One of the most common tests used to assess fetal well-being is the non-stress test, which is EFM of a fetus in a mother with no provoked contractions. A contraction stress test is used to evaluate the fetal response to uterine contractions. Ultrasound is used to evaluate the amount of amniotic fluid around the fetus, which often decreases before stillbirth, and other biophysical parameters including fetal movement, tone, and breathing movements. Doppler ultrasound can be used to evaluate the blood flow in the umbilical cord and arteries within the fetal brain. Such testing can be useful in evaluating deteriorating fetal condition and placental function in the former case and also fetal anemia in the latter. As the technology to evaluate fetal blood flow has improved, changes in venous blood flow in the fetus have been studied to identify critical fetal compromise. Most recently, ultrasound research has focused on direct evaluation of fetal heart function. Studies evaluating the phases of the cardiac cycle suggest that worsening heart function can be identified before heart failure or stillbirth occur. Advances in 4-dimension ultrasound technology may further improve our ability to evaluate fetal heart function and wellbeing. Because antepartum testing provides only a brief window to the fetus, and because maternal and fetal condition can change over time, ongoing effort is focusing on how best to incorporate the broad range of antepartum testing options into specific clinical situations.

In an effort to improve the consistency and performance of EFM in the United States, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the American College of Obstetricians and Gynecologists, and the Society for Maternal-Fetal Medicine co-sponsored a workshop in 2008 to revisit the recommendations for intrapartum EFM. The conference resulted in recommendations to use a system to differentiate those patterns predictive of normal (Category I), intermediate (Category II), and abnormal (Category III) fetal acid-base status. The group recommended



studies regarding the epidemiology of and outcomes related to intermediate EFM tracings, the effectiveness of EFM education programs, and the value of supplementary monitoring techniques such as computerized fetal heart rate pattern interpretation and fetal EKG monitoring to improve our ability to evaluate the fetus. Maternal-fetal medicine specialists will continue to lead efforts to overcome challenges in evaluating the fetus by developing new techniques, refining present ones, and improving the day-to-day care of high-risk pregnancies through performance of this testing.



PATIENT SAFETY

Pregnancy, particularly around the time of delivery, provides numerous challenges for ensuring patient safety. The environment of care has much in common with both Intensive Care Units and Emergency Departments. Like Emergency Departments, the Labor and Delivery Unit provides care for unscheduled patients who present with a broad range of acuity that often cannot be anticipated, has peaks and valleys of activity, has patients who often require care over two or more shifts including medical, nursing, and ancillary staff, and has a high rate of patient turnover. Most patients are in the Labor and Delivery Unit for less than 24 hours before being moved to the postpartum unit. As in Intensive Care Units, women with a high-risk pregnancy often have acute conditions requiring complex care and may need coordination of care by providers from several disciplines. Obstetricians themselves must master a broad range of diagnostic, medical, and surgical skills. Women in labor are monitored closely because their condition can change quickly and unexpectedly. Even low-risk patients can suddenly develop serious and potentially life-threatening problems. Significantly, there are two patients at risk, not just one, to monitor and care for.

Maternal-fetal medicine specialists play a key role in enhancing safety for patients with high-risk pregnancies. In complex cases that require multidisciplinary care, maternal-fetal medicine specialists have the greatest

understanding of maternal and fetal physiology, can coordinate care, and can provide information to other specialists about the risks and benefits of diagnostic tests, interventions and medications in pregnancy. For example, concerns of patients and radiologists about fetal exposure to needed x-ray testing can be knowledgeably addressed. Because tertiary care perinatal centers are typically staffed by maternal-fetal medicine specialists, they are often asked to provide advice about the need for transfer, putting high-risk mothers and fetuses in the right place at the right time for delivery. In most cases, if transport to a higher-level perinatal facility is needed, it is best to transfer the mother before delivery, as neonatal intensive care facilities may not be available at the referring hospital. Health care systems and insurers can enhance patient safety by ensuring that primary care obstetric facilities have policies and plans in place for maternal or newborn transfer as needed.

Patient Safety Research Targets

- Identification and validation of relevant quality indicators
- Measurement of the effects of quality improvement programs
- Comparison of effectiveness between patient simulator and traditional training methods

Measuring and improving quality of care

Numerous markers of quality have been proposed and/or incorporated into practice to track and improve the quality of obstetric care. Examples of such indicators have been rates of cesarean delivery and VBAC, the frequencies of low Apgar scores, excessive maternal blood loss, birth injury, cesarean delivery for uncertain fetal status, and preterm delivery before 32 weeks in non-tertiary care institutions. These rates have not generally been adjusted for factors that might appropriately mitigate these outcomes. These markers have typically been established by consensus rather than evidence that they correspond with quality, or that changing these rates improves overall obstetric quality at the institutional or practitioner level.

Recognizing the need for evidence-based quality measures, in 2008 the *Eunice Kennedy Shriver* National Institute of Child Health and

Human Development launched a three-year study to identify and validate measures of quality in obstetric care. Data related to 120,000 deliveries at 25 hospitals will be analyzed to evaluate the relationships between hospital, provider, and patient characteristics and specific obstetric outcomes including thromboembolism after cesarean delivery, uterine hemorrhage, and maternal infection. The Centers for Medicare and Medicaid Services has also funded initiatives to collect data and share resources to improve birth outcomes. A number of states are using this funding to initiate or enhance collaboratives that include a wide range of stakeholders such as hospitals, health care plans, nonprofits, public health agencies, and providers from multiple disciplines. In addition to performing research regarding monitoring and implementation of practices to improve patient safety, an important function of these collaboratives is the dissemination of information to institutions and providers about approaches to patient safety that have proven effective.

Preparing for emergencies

Team drills that simulate emergency clinical situations may decrease medical errors by clarifying expectations, identifying and correcting obstacles, and reducing confusion or miscommunication that can occur during uncommon emergencies regardless of the presence of appropriate policies and protocols. One approach to such drills is the use of simulators in which real-life scenarios are practiced using robotic patients programmed to mimic symptoms, react to medications, and go into cardiac arrest, for example. Patient simulators enable the caregiver to learn and practice procedures as often as needed to become comfortable with the emergency scenario and its variations. Like team drills, patient simulators can help clinicians gain experience and maintain their management skills for conditions they may rarely encounter. While the use of patient simulators has been well established in other industries (e.g., flight simulators in the aviation industry), are relatively new to obstetrics. Further research is needed to determine the optimal approaches to simulation and the impact of such training on continuing practice and patient outcomes.

EVOLVING MOLECULAR RESEARCH TECHNOLOGIES

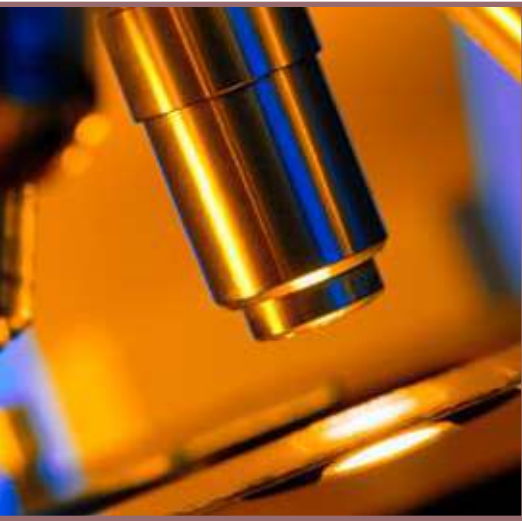
Many medical and obstetric complications represent the final common outcome from a complex set of pathways and causes (e.g., preterm labor, premature rupture of the membranes, preeclampsia, asthma, fetal growth restriction, placental abruption). Genetic and environmental factors may play a role in the development of these complications and can also affect how women respond to treatments or preventive efforts. Because treatment is often directed at the final common pathway (e.g., the contractions of preterm labor or the hypertension associated with preeclampsia) rather than the underlying cause(s), these interventions may have limited or no effect. Advances in our understanding of gene regulation and the availability of new biotechnologies and bioinformatics tools are improving our ability to understand pregnancy complications and may result in targeted treatments. These “-omics” technologies evaluate the contributions of the genes and their products that predispose to (or protect against) disease, and they also assess the effect of the environment on these genes and their products.

Genomics

DNA is the blueprint that provides needed information for each cell to develop and function. An individual's genome, which includes his or her entire genetic make up (all DNA), is responsible for the tremendous diversity in the way people look and function (phenotype), and in their susceptibility to diseases and complications. The Human Genome Project successfully sequenced and mapped the roughly 70,000 genes in the human genome. In genomics, genes are studied together to determine how they interact and influence biologic pathways. Large-scale structural variations in the genome (e.g., large insertions or deletions, “copy number variants,” and balanced chromosomal rearrangements) have recently been detected in disease susceptibility studies. New technologies, such as microarray-based comparative genomic



hybridization (CGH), allow screening of the entire genome for small deletions and imbalances that are not visible through traditional chromosome analysis and can eliminate the need for culturing and growth of biological specimens. Whole-genome amplification technologies paired with sensitive DNA isolation methods allow analysis of samples with only a small amount of available genetic material (e.g., after stillbirth). Array CGH has become a powerful technique for the study of human genetic syndromes, birth defects, stillbirth, and fetal growth restriction.



Epigenomics

Environmental exposures can significantly affect the likelihood of individuals developing a disease as well as the severity of their disease. Epigenomics is the study of heritable changes in gene expression that are unrelated to changes in the DNA sequence. The study of environmental influences on the mechanisms of gene expression, stability, and heredity is an exciting new field. Together with classical genetics, epigenomics will help us understand the mechanisms behind heritable diseases that don't have a strictly genetic explanation.

Transcriptomics

Messenger RNA (mRNA) is built directly from DNA in a process called "transcription" and then serves as the backbone for protein synthesis (translation). Transcriptomics involves evaluation of all of the RNA present in a tissue sample to evaluate which parts of the DNA blueprint are being actively expressed. A variety of techniques (e.g., oligo nucleotide microarrays, serial analysis of gene expression, and massive parallel signature sequencing) are available to assist in evaluation of the RNA transcriptome, and data from these can be integrated with genome studies to monitor genomic activity. This allows identification of genes that are actively reacting to physical or environmental conditions.

Proteomics

Proteomics involves evaluation of proteins present in tissues or body fluids. As with genomics and transcriptomics, the focus is on many proteins at once rather than the study of individual proteins. By doing this, groups of proteins that are more or less abundant under certain circumstances (e.g., active preeclampsia, preterm labor, or asymptomatic women destined to have pregnancy complications) can be evaluated simultaneously. While this technique can allow the study of proteins that are likely to be involved in a condition, it also can identify previously unrecognized proteins or groups of proteins that are also involved.

Metabolomics

The above-mentioned new technologies that allow us to study a person's DNA blueprint (genomics), its expression (epigenomics and transcriptomics), and protein products (proteomics) are changing the way we look at the biology and causes of pregnancy complications. However, even these don't provide the whole story of the complex processes involved in pregnancy. A whole set of small-molecule metabolites (such as hormones and other signaling molecules and secondary metabolites) can be found in biologic samples, and this "metabolome" can change rapidly within minutes. Over 50,000 metabolites have been identified in plants, and the number of these identified in humans is rapidly increasing. The new field of metabolomics will improve our understanding of how DNA expression and protein levels impact the body's metabolic processes, both in normal pregnancy and when complications or diseases occur.

The promise of all of these new technologies is that a better understanding of the biologic processes involved in pregnancy and pregnancy complications will lead to improved prediction, prevention, and treatment strategies that will improve maternal and infant health.

SOCIETY ACTIVITIES

The Society for Maternal-Fetal Medicine works actively to create awareness of the importance of maternal-fetal medicine research that will improve the care of our patients. The Society has built strong relationships with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the Centers for Disease Control and Prevention (CDC), and other national organizations that are dedicated to improving the health of pregnant women and their babies.

Identifying and working with key members of Congress with an interest in maternal-fetal medicine, members of the Society for Maternal-Fetal Medicine have highlighted the importance of preventing preterm birth and the work of the NICHD Maternal-Fetal Medicine Units (MFMU) network in the Congressional Record. Society members have testified before the House Appropriations Committee in support of NICHD and have requested policy guidance language in House and Senate reports directing NICHD to place as priorities such areas as the MFMU and the Stillbirth Collaborative Research networks, reduction of preterm birth and other adverse pregnancy outcomes, assisted reproductive technology, genomics and proteomics research, and first pregnancy complications.

The Society for Maternal-Fetal Medicine played a major role in crafting the recommendations for the Surgeon General's 2008 Conference on the Prevention of Preterm Birth. The Society has organized Capitol Hill days and a congressional briefing to educate members of Congress and their staff about the research advances made by the NICHD-MFMU network that have changed obstetric practice and have had an immediate impact on patient care, and also to garner support for ongoing funding of the research network.

Recently, the Society collaborated with the CDC to identify programmatic barriers and research needs related to the expanded use of 17 alpha-hydroxyprogesterone caproate, which has been shown to decrease the risk of repeated preterm birth. Society representatives served as invited members of a CDC advisory committee to assist in the review and planning of CDC's research agenda for the prevention of preterm birth.

The Society for Maternal-Fetal Medicine develops white papers that address issues related to the practice of maternal-fetal medicine. In conjunction with the American College of Obstetricians and Gynecologists, the Society for Maternal-Fetal Medicine responded to a Center for Medicare and Medicaid Services proposal that would require physician practices to enroll as Independent Diagnostic Testing Facilities in order to bill for imaging services. This proposal would have restricted patient access to imaging services and impose a significant administrative burden on physician practices. Society leadership met with members of Congress, urging them to reject policies that would restrict the ability of physician specialists to provide office-based imaging services to their patients. The Society developed a white paper on why maternal-fetal medicine specialists should have discretionary ability to perform ultrasound procedures, and this document was used during congressional visits, in testimony submitted to the House Ways and Means Committee, and in a letter submitted to the Medicare Payment Advisory Commission, which is charged with making recommendations to Congress on access to care and quality of care issues. The Society believes that office-based obstetric ultrasound procedures by qualified individuals can provide patients with clinically appropriate and high-quality care, as well as access to timely imaging services in an efficient and effective setting.

The Society for Maternal-Fetal Medicine continues to support increased funding for the National Institutes for Health, in particular the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and its programs focusing on maternal health, pregnancy, fetal well-being, and labor and delivery. The Society supports ongoing CDC programs such as the Safe Motherhood and Infant Health Program with a focus on preterm birth (the Pregnancy Risk Assessment Monitoring System) and fetal death. The Society encourages timely access for pregnant women to high-quality obstetric care and imaging services, the development of enhanced birth certificate reporting and monitoring, and the development of electronic health records systems aimed at improving the quality and efficiency of health care and patient safety.

RESEARCH THAT IS CHANGING OBSTETRICS

Basic and clinical research is the cornerstone for improving our understanding of the physiology and pathophysiology of pregnancy, the interrelationships between the mother and fetus, the impact of medical conditions on pregnancy, and the impact of medical diseases and pregnancy outcomes on the long-term health of both mother and child. Bench-based and clinical research provides the evidence needed to inform pregnancy management and guides the evolution of clinical practice toward improved maternal, newborn, and long-term health.



PubMed (<http://pubmed.gov>) provides access to MEDLINE, a database that includes citations for papers from approximately

5,200 biomedical journals from more than 80 countries worldwide in over 37 languages. PubMed currently has over 670,000 citations for papers regarding pregnancy, including over 493,000 human studies, 135,000 clinical studies, and 11,000 reports from randomized clinical trials. The number of pregnancy studies is increasing rapidly. Over half of these have been published in the past 20 years, and 16,000 to 22,000 papers are currently published each year.

Listed here are some of the articles published in the last 10 years that represent groundbreaking research that has affected the way we think about or practice obstetric care. The studies cited here represent just a few of those important to pregnancy and its complications. Each is a reflection of many other studies by numerous investigators that laid the groundwork allowing them to be performed. Additional key studies and publications that have served as the basis for this monograph are available at www.SMFM.org (under "Publications").

A prospective, randomized, multicenter trial of amnioreduction vs selective fetoscopic laser photocoagulation for the treatment of severe twin-twin transfusion syndrome.

Crombleholme TM, Shera D, Lee H, Johnson M, D'Alton M, Porter F, Chyu J, Silver R, Abuhamad A, Saade G, Shields L, Kauffman D, Stone J, Albanese CT, Bahado-Singh R, Ball RH, Bilaniuk L, Coleman B, Farmer D, Feldstein V, Harrison MR, Hedrick H, Livingston J, Lorenz RP, Miller DA, Norton ME, Polzin WJ, Robinson JN, Rychik J, Sandberg PL, Seri I, Simon E, Simpson LL, Yedigiarova L, Wilson RD, Young B. *Am J Obstet Gynecol.* 2007;197:396.e1-9.

This five-year multicenter randomized controlled trial is one of several that have increased our understanding of the risks and benefits of selective fetoscopic laser photocoagulation versus serial amnioreduction in the treatment of severe twin-twin transfusion syndrome.

Neonatal respiratory distress syndrome after repeat exposure to antenatal corticosteroids: a randomised controlled trial.

Crowther CA, Haslam RR, Hiller JE, Doyle LW, Robinson JS. Australasian Collaborative Trial of Repeat Doses of Steroids (ACTORDS) Study Group. *Lancet.* 2006;367:1913-9.

This study is the largest of a series of multicenter randomized controlled trials that found weekly doses of antenatal corticosteroids, administered to women at high risk for preterm birth, offered only limited improvements in newborn pulmonary outcomes while to reducing fetal growth.

Amnioinfusion for the prevention of the meconium aspiration syndrome.

Fraser WD, Hofmeyr J, Lede R, Faron G, Alexander S, Goffinet F, Ohlsson A, Goulet C, Turcot-Lemay L, Prendiville W, Marcoux S, Laperrière L, Roy C, Petrou S, Xu HR, Wei B. Amnioinfusion Trial Group. *N Engl J Med.* 2005;353:909-17.

This clinical trial refuted the belief that amnioinfusion, administered intrapartum to women with documented meconium stained fluid, prevented neonatal meconium aspiration syndrome.

Planned caesarean section versus planned vaginal birth for breech presentation at term: a randomised multicentre trial.

Hannah ME, Hannah WJ, Hewson SA, Hodnett ED, Saigal S, Willan AR. Term Breech Trial Collaborative Group. *Lancet*. 2000;356:1375-83.

This international multicenter trial found that planned cesarean delivery for breech presentation reduced the likelihood of adverse infant outcomes when compared with planned vaginal delivery by an experienced clinician.

Maternal and perinatal outcomes associated with a trial of labor after prior cesarean delivery.

Landon MB, Hauth JC, Leveno KJ, Spong CY, Leindecker S, Varner MW, Moawad AH, Caritis SN, Harper M, Wapner RJ, Sorokin Y, Miodovnik M, Carpenter M, Peaceman AM, O'Sullivan MJ, Sibai B, Langer O, Thorp JM, Ramin SM, Mercer BM, Gabbe SG. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. *N Engl J Med*. 2004;351:2581-9.

This large multicenter observational study quantified the outcomes for delivery after prior cesarean and led to a series of publications that have provided current and objective information regarding the benefits and risks of repeat cesarean delivery and attempted vaginal birth after cesarean.

A comparison of glyburide and insulin in women with gestational diabetes mellitus.

Langer O, Conway DL, Berkus MD, Xenakis EMJ, Gonzales O. *N Engl J Med* 2000;343: 1134-8.

This study demonstrated adequate glucose control with the oral antidiabetic glyburide and led the way for the incorporation of oral hypoglycemic therapy in pregnancy into clinical practice.

Soluble endoglin and other circulating anti-angiogenic factors in preeclampsia.

Levine RJ, Lam C, Qian C, Yu KF, Maynard SE, Sachs BP, Sibai BM, Epstein FH, Romero R, Thadhani R, Karumanchi SA. CPEP Study Group. *N Engl J Med*. 2006;355:992-1005.

This multicenter observational study found preeclampsia could be predicted by circulating anti-angiogenic factors in maternal blood remote from delivery and enhanced our understanding of the pathophysiology of preeclampsia.

Broad-spectrum antibiotics for spontaneous preterm labour: the ORACLE II randomised trial.

Kenyon SL, Taylor DJ, Tarnow-Mordi W. ORACLE Collaborative Group. *ORACLE Collaborative Group. Lancet*. 2001;357:989-94.

This large multicenter randomized controlled trial found no improvements in newborn outcomes among fetuses exposed to antibiotics in utero for treatment of preterm labor with intact membranes, and a follow-up evaluation found increased long-term neurologic morbidities in these infants.

First- and Second-Trimester Evaluation of Risk (FASTER) Research Consortium.

First-trimester or second-trimester screening, or both, for Down's syndrome.

Malone FD, Canick JA, Ball RH, Nyberg DA, Comstock CH, Bukowski R, Berkowitz RL, Gross SJ, Dugoff L, Craigo SD, Timor-Tritsch IE, Carr SR, Wolfe HM, Dukes K, Bianchi DW, Rudnicka AR, Hackshaw AK, Lambert-Messerialian G, Wald NJ, D'Alton ME. *N Engl J Med*. 2005;353:2001-11.

This multicenter study provided U.S. data and stimulated the introduction of first-trimester serum and ultrasound screening for fetal aneuploidy and cardiac abnormalities into practice.

Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization.

Mari G, Deter RL, Carpenter RL, Rahman F, Zimmerman R, Moise KJ Jr, Dorman KF, Ludomirsky A, Gonzalez R, Gomez R, Oz U, Detti L, Copel JA, Bahado-Singh R, Berry S, Martinez-Poyer J, Blackwell SC. Collaborative Group for Doppler Assessment of the Blood Velocity in Anemic Fetuses. *N Engl J Med*. 2000;342:9-14.

In this multicenter study, noninvasive middle cerebral artery Doppler blood flow studies were highly predictive of severe fetal anemia, resulting in this technology largely replacing more risky invasive fetal blood sampling to evaluate for fetal anemia

Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate.

Meis PJ, Klebanoff M, Thom E, Dom-browski MP, Sibai B, Moawad AH, Spong CY, Hauth JC, Miodovnik M, Varner MW, Leveno KJ, Caritis SN, Iams JD, Wapner RJ, Conway D, O'Sullivan MJ, Carpenter M, Mercer B, Ramin SM, Thorp JM, Peaceman AM, Gabbe S. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. *N Engl J Med.* 2003;348:2379-85.

This multicenter trial found that 17 alpha-hydroxyprogesterone caproate reduced preterm and early preterm birth, as well as newborn complications, among women with a previous spontaneous preterm birth, and led to incorporation of this therapy into clinical practice.

Hyperglycemia and adverse pregnancy outcomes.

Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, Hadden DR, McCance DR, Hod M, McIntyre HD, Oats JJ, Persson B, Rogers MS, Sacks DA. HAPO Study Cooperative Research Group. *N Engl J Med.* 2008;358:1991-2002.

This international multicenter study demonstrated a direct relationship between maternal glucose levels and adverse pregnancy outcomes, including macrosomia, cesarean delivery, neonatal hypoglycemia, and c-peptide levels, and is redefining our approach to gestational diabetes.

A randomized, controlled trial of magnesium sulfate for the prevention of cerebral palsy.

Rouse DJ, Hirtz DG, Thom E, Varner MW, Spong CY, Mercer BM, Iams JD, Wapner RJ, Sorokin Y, Alexander JM, Harper M, Thorp JM Jr, Ramin SM, Malone FD, Carpenter M, Miodovnik M, Moawad A, O'Sullivan MJ, Peaceman AM, Hankins GD, Langer O, Caritis SN, Roberts JM. Eunice Kennedy Shriver NICHD Maternal-Fetal Medicine Units Network. *N Engl J Med.* 2008;359:895-905.

This multicenter study is the largest randomized clinical trial to confirm that magnesium sulfate, given for neuroprotection before anticipated preterm birth, can reduce the risk of cerebral palsy in surviving infants.

Active Bacterial Core Surveillance Team. A population-based comparison of strategies to prevent early-onset group B streptococcal disease in neonates.

Schrag SJ, Zell ER, Lynfield R, Roome A, Arnold KE, Craig AS, Harrison LH, Reingold A, Stefonek K, Smith G, Gamble M, Schuchat A. *N Engl J Med.* 2002;347:233-9.

This observational study is one of several regarding the approach to screening for and prevention of newborn group B streptococcus sepsis, that resulted in widespread adoption of routine screening at 36-37 weeks into obstetric practice.

The practice of medicine continues to evolve and individual circumstances will vary. This document reflects information available at the time of publication and is not intended to establish an exclusive standard of perinatal care. This publication is not expected to reflect the opinions of all members of the Society for Maternal-Fetal Medicine.

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Bibliography & Links

Articles, texts, and websites used in the preparation of this monograph, and additional research papers that have changed the way we think about or practice obstetric care can be found at www.SMFM.org

QUICK LINKS

The Society for Maternal-Fetal Medicine: www.SMFM.org

American Board of Obstetrics and Gynecology: www.abog.org

American College of Obstetricians and Gynecologists:
www.acog.org

American Academy of Pediatrics: www.aap.org

Agency for Healthcare Research and Quality: www.ahrq.gov

American Institute of Ultrasound Medicine: www.aium.org

American Osteopathic Board of Obstetrics And Gynecology:
www.aobog.org

Centers for Disease Control and Prevention: www.cdc.gov

National Center for Health Statistics: www.cdc.gov/nchs

Cochrane Collaboration and Database of Systematic Reviews:
www.cochrane.org

Food and Drug Administration: www.fda.gov

March of Dimes: www.marchofdimes.com

National Institutes of Health: www.nih.gov

The Eunice Kennedy Shriver National Institute of Child and Health and Human Development:
www.nichd.nih.gov

National Library of Medicine: www.nlm.nih.gov

World Health Organization: Gender, Women and Health:
www.who.int/gender/en



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