UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF IDAHO
SOUTHERN DIVISION

UNITED STATES OF AMERICA, Plaintiff, v. THE STATE OF IDAHO, Defendant.	Case No. 1:22-cv-329

DECLARATION OF LEE A. FLEISHER, M.D.

I, Lee A. Fleisher, M.D., of the Centers for Medicare & Medicaid Services (CMS), declare that the following statements are true and correct to the best of my knowledge and belief, and that they are based on my personal knowledge as well as information provided to me in the ordinary course of my official duties.

1. I am employed by the United States Department of Health and Human Services (HHS) in CMS. I am the Chief Medical Officer and Director of the Center for Clinical Standards and Quality for CMS. In this capacity, I am responsible for executing all national clinical, quality, and safety standards for all Medicare and Medicaid-certified healthcare facilities and providers, as well as establishing coverage determinations for items and services that improve health outcomes for Medicare beneficiaries.

2. I am also currently a Professor Emeritus of Anesthesiology and Critical Care at the University of Pennsylvania Perelman School of Medicine and continue to provide anesthesia care approximately three times per month at the Hospital of the University of Pennsylvania. From 2004 until 2020, I was the Robert D. Dripps Professor and Chair of Anesthesiology and Critical Care

and Professor of Medicine at the University of Pennsylvania and Chair of the Department of Anesthesiology and Critical at the Hospital of the University of Pennsylvania (HUP) and Penn Presbyterian Medical Center. Prior to joining the University of Pennsylvania, I was an attending anesthesiologist at The Johns Hopkins Hospital (JHH) from 1992-2003, where I provided obstetrical anesthesia and anesthesia for emergency surgical procedures. While at JHH, I was appointed in 1999 as the Clinical Director of Operating Rooms, a position I held until I moved to the University of Pennsylvania in 2004.

3. In addition, I have held a number of other faculty, hospital, and administrative appointments, which are set forth in my curriculum vitae, which is attached hereto as Ex. A. Among other appointments listed on my CV, since 2007 I have served as an elected member of the National Academy of Medicine (NAM) (formerly Institute of Medicine), and between 2016 and 2018, I served as a member of NAM's Committee on Reproductive Health Services for Assessing the Safety and Quality of Abortion Care, and was an author of the 2018 report on The Safety and Quality of Abortion Care in the United States, available at https://www.ncbi.nlm.nih.gov/books/NBK507236/. My work with this committee on safety of abortion services was focused on risks to women both from the abortion procedure itself and from delays in obtaining abortion procedures. I was also the President of the Medical Board of HUP from 2014-16 and a member of the Board of Trustees of HUP from 2012-16, in which capacity I oversaw the review and approval of hospital policies and procedures including those pursuant to EMTALA. Additionally, I was Chair of the Credentials Committee of HUP from 2008-14, in which capacity I oversaw the evaluation and credentialing of all medical providers on the staff.

4. I graduated with a B.A. from the University of Pennsylvania in Molecular Biology in 1981. I earned an M.D. from the State University of New York at Stony Brook in 1986. I

completed an internship in surgery at the University of Minnesota from 1986 to 1987, and a residency in anesthesiology at Yale University from 1987 to 1990.

5. In my thirty-plus years as a medical doctor, I have had extensive experience providing anesthesia for obstetrical care, including through the provision of anesthesia for the treatment of pregnancy-related conditions that threaten the life and/or health of pregnant patients as well as review of complications of care in my role as Chair of the Department. For example, in my practice at JHH from 1992-2003, I provided emergency obstetrical care approximately 3 times per month. In my role as Clinical Director of the Operating Rooms at JHH, I evaluated and determined the urgency of proceeding to surgery for all emergency surgical cases, including ectopic pregnancies, and provided anesthetic care for many pregnant individuals requiring emergent care including vaginal bleeding and preeclampia/eclampsia.

6. In addition, through my official duties at CMS, I am familiar with federal Medicare and Medicaid requirements, as well as data and other information collected by CMS and HHS regarding medical risks related to pregnancy. And based on my role at CMS, my roles as a medical practitioner, and my leadership roles in several hospitals and medical organizations, I am experienced with the requirements of the Emergency Medical Treatment and Labor Act (EMTALA), 42 U.S.C. § 1395dd, including how they arise in the actual practice of medicine.

IDAHO LAW AND EMTALA

7. I understand that, if the Idaho law goes into effect on August 25, 2022, "[e]very person who performs or attempts to perform an abortion . . . commits the crime of criminal abortion" and that the crime of criminal abortion is a felony that is punishable by up to five years in prison and loss of medical license. Idaho Code § 18-622(2). I further understand that Idaho law defines "abortion" as "the use of any means to intentionally terminate the clinically diagnosable

pregnancy of a woman with knowledge that the termination by those means will, with reasonable likelihood, cause the death of the unborn child." Idaho Code § 18-622. This definition of "abortion" in the Idaho Code covers some procedures that would not be characterized as an abortion in the medical community. In some circumstances in which a pregnancy is nonviable and/or termination of pregnancy is necessary to treat a pregnant patient's medical condition, physicians may not consider that treatment to be properly characterized as an abortion.

8. I further understand that Idaho law includes an "affirmative defense" allowing physicians to avoid criminal liability only if they can prove, among other things, that an abortion was "necessary to prevent the death of the pregnant woman." Idaho Code § 18-622(3)(a)(ii).

9. In addition, I am aware of EMTALA's requirements for hospitals participating in Medicare. In particular, EMTALA requires that "[i]f any individual . . . comes to a hospital and the hospital determines that the individual has an emergency medical condition, the hospital must provide either—(A) with the staff and facilities available at the hospital, for such further medical examination and such treatment as may be required to stabilize the medical condition, or (B) for transfer of the individual to another medical facility" in accordance with certain requirements in subsection (c) of the statute. 42 U.S.C. § 1395dd. A hospital may not discharge or otherwise transfer a person with a medical condition who has not been stabilized unless the individual requests a transfer or a physician certifies that the benefits of a transfer to another medical facility outweighs the increased risks to the patient. 42 U.S.C. § 1395dd(c).

10. I am aware that EMTALA defines "emergency medical condition" as: "(A) a medical condition manifesting itself by acute symptoms of sufficient severity (including severe pain) such that the absence of immediate medical attention could reasonably be expected to result in—(i) placing the health of the individual (or, with respect to a pregnant woman, the health of the

woman or her unborn child) in serious jeopardy, (ii) serious impairment to bodily functions, or (iii) serious dysfunction of any bodily organ or part; or (B) with respect to a pregnant woman who is having contractions—(i) that there is inadequate time to effect a safe transfer to another hospital before delivery, or (ii) that transfer may pose a threat to the health or safety of the woman or the unborn child." 42 U.S.C. § 1395dd(1).

11. I am aware that EMTALA defines "to stabilize" to mean "to provide such medical treatment of the condition as may be necessary to assure, within reasonable medical probability, that no material deterioration of the condition is likely to result from or occur during the transfer of the individual from a facility." 42 U.S.C. § 1395dd(e)(3).

EMERGENCY MEDICAL CONDITIONS IMPLICATED BY IDAHO LAW

12. Based on my experience as a medical practitioner and as the Chief Medical Officer at CMS, I know that pregnant patients experience a number of medical conditions that fall within the definition of "emergency medical condition" set forth in EMTALA. This is because for these medical conditions, "in the absence of immediate medical attention," which can include monitoring, treatment, or both, the condition "could reasonably be expected to result in" the patient's health being "plac[ed] . . . in serious jeopardy," "serious impairment to [the patient's] bodily functions," or "serious dysfunction of any bodily organ or part [of the patient]," as described more fully below. I also know that the appropriate stabilizing treatment that is necessary to avoid "serious jeopardy," "serious impairment," and "serious dysfunction," which would otherwise result from those conditions, is very frequently—and in some cases nearly always—a form of treatment that is covered by the definition of "abortion" set forth in the Idaho Code. EMTALA requires providing such care independent of whether doing so is, or well before doing so becomes, necessary to prevent the patient's death. As explained further below, in some cases where the

patient's health is unambiguously threatened, it may be less clear whether there is also a certainty of death without stabilizing treatment—and a physician may not ever be able to confirm whether death would result absent immediate treatment. EMTALA does not allow leaving the patient untreated when doing so would irreparably risk or harm their health, as with the conditions discussed below.

13. For example, a pregnant individual may present to an emergency department with bleeding, pelvic pain or severe abdominal pain that, when evaluated, is determined to be caused by an ectopic pregnancy. An ectopic pregnancy is when an embryo or fetus grows outside of the uterus, frequently in a fallopian tube. An ectopic pregnancy in a fallopian tube is an emergency medical condition that places the patient's life in jeopardy because it will cause the fallopian tube to rupture and in the vast majority of cases cause significant and potentially fatal internal bleeding. In most cases, the physician cannot reasonably know when that rupture will occur—it could happen within minutes, hours or days of the physician's examination—but without immediate treatment it is reasonably probable that the patient's condition will continue to deteriorate. Accordingly, given this serious risk of unknown imminence, where a patient suffers from an ectopic pregnancy, especially in a fallopian tube, the appropriate stabilizing treatment is nearly always emergency surgery and removal of the involved fallopian tube, including the embryo or fetus, or administration of a drug to cause embryonic or fetal demise. One of these two treatments is necessary because of the inevitability that the fallopian tube will rupture absent surgery or intervention with medication that causes embryonic or fetal demise. There is an extremely high risk that such rupture would result in the patient bleeding to death. Because a physician can determine with reasonable certainty that an ectopic pregnancy exists and that, depending upon the location, a rupture will occur as a result, but the physician cannot discern with reasonable certainty

the time at which that rupture will occur, it is necessary that an ectopic pregnancy be treated immediately or else the patient's life and health will likely continue to deteriorate and remain at constant and ongoing risk.

14. Even though a physician at a hospital where EMTALA applies could conclude that this treatment is required for an ectopic pregnancy, particularly one involving a fallopian tube, Idaho law prohibits this treatment. Idaho's definition of abortion would include both the medical and surgical treatment described in ¶ 13, because both cause embryonic or fetal demise in a clinically diagnosable pregnancy. This treatment would be prohibited by Idaho law even though an ectopic pregnancy has no chance of maturing into a viable child. Additionally, despite the extremely serious risks posed by an ectopic pregnancy, particularly in a fallopian tube, and the inevitability of a rupture, which are apparent at the time when treatment is required to address those risks, a physician may not be able to establish or know, with certainty, that termination of the pregnancy is "necessary to prevent the death of the woman." However, that does not change the fact that the patient's condition will very likely deteriorate without the necessary treatment, and that failure to provide the necessary treatment will seriously jeopardize the patient's health and/or life in the process.

15. As another example, a pregnant individual may present to the emergency room with chest pain and severe shortness of breath, requiring supplemental oxygen to keep their blood oxygen levels in reasonable range. The patient may be early in or mid-pregnancy and during the evaluation may be diagnosed with severe heart failure related to long-standing pulmonary hypertension (i.e., elevated blood pressure in the vessels to the lungs), or a massive pulmonary embolism (i.e., a blood clot to the lungs). For some patients, pregnancy can substantially exacerbate the heart failure and initially cause the patient to have difficulty breathing at rest that

can then turn into further complications from a lack of oxygen as well as a drop in blood pressure. Some pregnant patients may present to the emergency room when they are in extremis, and a physician will need to place the patient on a ventilator and prescribe medications to maintain the blood pressure. Severe heart failure, especially from pulmonary hypertension or a pulmonary embolism, can be an emergency medical condition because if left untreated, the patient's condition will continue to deteriorate and cardiac arrest or inability to oxygenate the patient could result, which places the patient's life, health, and bodily organs in jeopardy. In some circumstances, the appropriate stabilizing treatment for a patient suffering from severe heart failure is treatment of the heart and blood vessels through medications. In severe cases, the physician may determine that, despite other medical treatment, the patient continues to have worsening deterioration of blood oxygenation and maintenance of blood pressure. In such circumstances, the physician could conclude that termination of the pregnancy is medically necessary because, by virtue of the severity of the symptoms, there is a high probability of the pregnant patient's death or impairment or severe dysfunction of bodily organs (such as the lungs, heart, and kidneys) absent that termination.

16. Even though a physician at a hospital where EMTALA applies could conclude that this treatment is required for severe heart failure, Idaho law prohibits this treatment because it would cause embryonic or fetal demise. This treatment would be prohibited by Idaho law even though the pregnant individual with this condition would most likely not survive to carry the pregnancy materially further. Additionally, despite the extremely serious risks posed by severe heart failure, which are apparent at the time when treatment is required to address those risks, a physician may not be able to establish or know, with certainty, that termination of pregnancy is "necessary to prevent the death of the woman." However, that does not change the fact that the

patient's condition will very likely deteriorate without the necessary treatment, and that failure to provide the necessary treatment will seriously jeopardize the patient's health and/or life in the process.

17. As a third example, a pregnant individual may present to the emergency department with nausea and shortness of breath, which an initial evaluation may diagnose as resulting from new onset of high blood pressure. Pre-eclampsia is when high blood pressure and high levels of protein in the urine develop in a pregnant individual, usually midway through the pregnancy. Pre-eclampsia can quickly progress to eclampsia with the onset of seizures, and a physician cannot discern when that progression to seizures will occur with reasonable medical certainty in all cases, especially when the blood pressure cannot be controlled. Pre-eclampsia and eclampsia are emergency medical conditions because they place the patient's life in jeopardy or can cause serious impairment to bodily functions. Without treatment for severe pre-eclampsia/eclampsia, the patient's condition is reasonably likely (indeed nearly certain) to deteriorate. Specifically, the seizures that characterize the transition from pre-eclampsia to eclampsia can cause coma, pneumonia from the aspiration of stomach contents, kidney failure, stroke and even cardiac arrest. While the only curative treatment for pre-eclampsia or eclampsia is delivery of the fetus, in most and many cases, the pregnant patient with pre-eclampsia will respond reasonably promptly to medications to control their blood pressure, reduce their chances of seizures, and mature the fetus' lungs to allow delivery as soon as possible. However, in some cases in which high blood pressure and/or the seizures of severe pre-eclampsia/eclampsia cannot be controlled, termination of the pregnancy is medically necessary. In such cases, absent termination of the pregnancy, death or severe bodily dysfunction of the pregnant patient is the reasonably probable outcome.

18. Even though a physician at a hospital where EMTALA applies could conclude that this treatment is required for severe pre-eclampsia or eclampsia, Idaho law prohibits this treatment because the treatment would cause fetal demise. This treatment would be prohibited by Idaho law even though the pregnant individual with this condition would most likely not survive to carry the pregnancy materially further. Additionally, despite the extremely serious risks posed by this severe preeclampsia/eclampsia, which are apparent at the time when treatment is required to address those risks, a physician may not be able to establish or know, with certainty, that termination of pregnancy is "necessary to prevent the death of the woman." However, that does not change the fact that the patient's condition will deteriorate without the necessary treatment, and that failure to provide the necessary treatment will seriously jeopardize the patient's health and/or life in the process.

19. As a fourth example, a pregnant individual may present to the emergency department with a life-threatening infection of the uterine contents. Such an infection may occur when there is premature rupture of the membranes (PROM), which is when the amniotic sac surrounding the embryo or fetus ruptures and the uterus or embryo/fetus can become infected. The infection can progress to sepsis wherein multiple body organs and functions can start failing including the heart, lungs and blood pressure, which could lead to death. Sepsis can progress quickly, and a physician cannot discern with reasonable medical certainty if or when the sepsis will resolve or result in organ failure or death without immediate treatment. Septic infection is an emergency medical condition because it places the patient's life and health in jeopardy or can cause serious impairment to bodily functions; if untreated, it can lead to kidney failure and even cardiac arrest. In many cases, the pregnant patient can respond to treatment with antibiotics and concurrently be administered medications to support their blood pressure. However, if the

antibiotics cannot control the infection, then removal of the source of the infection is necessary—and in circumstances in which the embryo or fetus is infected and is causing the sepsis, that necessary treatment could include removal of the embryo or fetus, which may result in embryonic or fetal demise. Absent this treatment for severe sepsis unresponsive to antibiotics and blood pressure support, the patient's condition will deteriorate, and death or severe bodily dysfunction of the pregnant patient is the reasonably probable outcome.

20. Even though a physician at a hospital where EMTALA applies could conclude that this treatment is required for severe sepsis, Idaho law prohibits this treatment because the treatment would cause embryonic or fetal demise. This treatment would be prohibited by Idaho law even though the pregnant individual with this condition would most likely not survive to carry the pregnancy materially further. Additionally, despite the extremely serious risks posed by severe sepsis, which are apparent at the time when treatment is required to address those risks, a physician may not be able to establish or know, with certainty, that termination of pregnancy is "necessary to prevent the death of the woman." However, that does not change the fact that the patient's condition will deteriorate without the necessary treatment, and that failure to provide the necessary treatment will seriously jeopardize the patient's health and/or life in the process.

21. As a fifth example, a pregnant individual may present to the emergency department with vaginal bleeding. Vaginal bleeding may occur in some of the previously described conditions, but it can also be a result of a placental abruption, which occurs when the placenta partly or completely separates from the inner wall of the uterus. Placental abruption with uncontrolled and catastrophic bleeding is an emergency medical condition that places the patient's life in jeopardy or can cause serious impairment to bodily functions. This is because catastrophic and/or uncontrolled bleeding can lead to shock, which can result in organ dysfunction such as kidney

failure, and even cardiac arrest. The placental abruption can be diagnosed in the emergency department by examination, including ultrasound, to check the location of the bleeding. If bleeding will not stop, then a physician could conclude that the necessary stabilizing treatment for the uncontrolled and catastrophic bleeding includes removal of the fetus or the entire uterus (*i.e.* a hysterectomy, which also results in termination of the pregnancy), which could result in fetal demise. Absent this treatment for placental abruption where indicated, the patient's condition will deteriorate and death or severe bodily dysfunction of the pregnant patient is the reasonably probable outcome.

22. Even though a physician at a hospital where EMTALA applies could conclude that this treatment is required for placental abruption, Idaho law prohibits this treatment because termination would cause fetal demise. This treatment would be prohibited by Idaho law even though the pregnant individual with a placental abruption would most likely not survive to carry the pregnancy materially further. Additionally, despite the extremely serious risks posed by placental abruption with catastrophic or uncontrolled bleeding, which are apparent at the time when treatment is required to address those risks, a physician may not be able to establish or know, with certainty, that termination of pregnancy is "necessary to prevent the death of the woman." However, that does not change the fact that the patient's condition will deteriorate without the necessary treatment, and that failure to provide the necessary treatment will seriously jeopardize the patient's health and/or life in the process.

23. The emergency medical conditions described in paragraphs 13-22 above are just some examples of those that present in pregnant patients, as to which the treating physician could, in the exercise of their professional medical judgment, determine that the stabilizing treatment would include termination of pregnancy. Myriad other medical conditions that present in pregnant

patients may cause acute symptoms that place the health of the pregnant patient in serious jeopardy, or else risk serious impairment to the pregnant patient's bodily functions or dysfunction of a bodily organ or part. How emergency conditions present in a pregnant patient will often vary depending on the patient's specific circumstances, and termination of pregnancy may be a necessary treatment to stabilize the patient based on their physical circumstances.

24. For each of the medical conditions described above (as well as other emergency medical conditions that present in pregnant patients), in some cases, termination of pregnancy would be the only option to ensure that a pregnant patient will not die, or suffer a serious impairment to their bodily functions, or serious dysfunction of any bodily organ or part as a result of their emergency medical condition. In that regard, a physician could conclude that termination of the pregnancy is the only way to stabilize the pregnant patient as required by EMTALA.

25. In other words, pregnancy termination may be necessary to ensure that "no material deterioration of the patient's condition is likely to result from or occur during the transfer [including discharge] from a facility," as is required by EMTALA. 42 U.S.C. § 1395dd(e)(3). Yet, under the Idaho abortion ban, physicians at hospital emergency rooms could be prosecuted for administering necessary stabilizing treatment to patients with these conditions despite knowing that the patients will suffer severe bodily impairment or serious jeopardy to their health without such treatment.

26. Indeed, under the definition of "criminal abortion" in the Idaho law, this is true even in cases in which the physician knows that there is no chance that the pregnancy will result in a live birth. Because the Idaho law prohibits termination of any pregnancy that would "cause the death of the unborn child," a physician would be forbidden from administering treatment even if: (1) a patient presents with an emergency medical condition; (2) which will render it impossible

for the pregnancy to result in a live birth; but (3) embryonic or fetal demise has not yet occurred at the time the patient arrives at the hospital. Under those circumstances, a physician following Idaho law would be required to wait for embryonic or fetal demise before stabilizing the pregnant patient, causing the pregnant patient to suffer through the emergency medical condition, often with great pain and increased risk to their health and/or life.

27. When stabilizing treatment is provided at a hospital that includes termination of the pregnancy (including "abortion" as defined under Idaho law), that procedure may require the participation of numerous personnel—not just the physician performing the procedure, but also frequently nurses, operating room technicians, anesthesiologists or certified registered nurse anesthetists, pharmacists, physician's assistants, or other medical health professionals.

PREVALENCE OF EMERGENCY PREGNANCY CONDITIONS

28. Based on my role at CMS and my experience in public health, I am aware of statistics regarding the prevalence of emergency pregnancy conditions, and I am experienced in identifying reliable data about those conditions. Data relating to health risks associated with pregnancy confirms that a significant percentage of pregnant patients experience emergency health conditions, including conditions as to which termination of pregnancy is the appropriate stabilizing treatment.

29. According to the Centers for Disease Control and Prevention (CDC), the overall maternal mortality rate in the United States in 2020 was 23.8 maternal deaths per 100,000 live births. *See* Donna L. Hoyert, CDC, *Maternal Mortality Rates in the United States*, 2020 (Feb. 23, 2022), https://www.cdc.gov/nchs/data/hestat/maternal-mortality/2020/maternal-mortality-rates-2020.htm. That represents an increase from 17.4 and 20.1 maternal deaths per 100,000 live births

in 2018 and 2019, respectively. *See id.* The maternal mortality rates for Black women are significantly higher and have similarly increased between 2018 and 2020. *See id.*

30. According to CDC, for each maternal death, more than 50 pregnant women suffer significant short- or long-term consequences to their health. *See* CDC, *Severe Maternal Morbidity: Rate per 10,000 Delivery Hospitalizations* (Feb. 10, 2020), https://www.cdc.gov/reproductivehealth/maternalinfanthealth/smm/rates-severe-morbidity-indicator.htm. These consequences include heart attacks, sepsis, eclampsia, and kidney failure. *Id.*

31. Pregnant patients regularly come to hospitals with emergency medical conditions, including the conditions discussed above.

32. I am aware that the American College of Obstetricians and Gynecologists (ACOG) has reported, for instance, that ectopic pregnancies account for approximately two percent of all pregnancies, though the incidence could be significantly higher given the lack of recent national surveillance data. *See* ACOG Practice Bulletin No. 193 (Mar. 2018) (attached as Exhibit B). I am also aware that data from 2011 to 2013 shows that ruptured ectopic pregnancies account for 2.7 percent of all pregnancy-related deaths and are the leading cause of hemorrhage-related maternal deaths. *See id.*

33. I am also aware that CDC estimates that pre-eclampsia happens in 1 in 25 pregnancies. *See* CDC, *High Blood Pressure During Pregnancy* (May 6, 2021), https://www.cdc.gov/bloodpressure/pregnancy.htm I am further aware that ACOG has reported that the rate of pre-eclampsia in the United States increased by 25 percent between 1987 and 2004. *See* ACOG Practice Bulletin No. 222 (June 2020) (attached as Exhibit C).

34. I am also aware that ACOG has reported that cardiovascular disease— including as a result of hypertension—affects approximately one to four percent of pregnancies in the United

States per year and that cardiovascular disease accounts for 26.5 percent of pregnancy-related deaths in the United States. *See* ACOG Practice Bulletin No. 212 (May 2019) (attached as Exhibit D). ACOG additionally reports that hypertensive disorders affect up to ten percent of pregnancies and that, in those affected pregnancies, pregnant persons are eight to thirteen times more likely to suffer a myocardial infarction (heart attack).

35. Further, I am aware that ACOG has reported that premature rupture of membranes (PROM) complicates two to three percent of pregnancies in the United States. *See* ACOG Practice Bulletin No. 217 (Mar. 2020) (attached as Exhibit E). ACOG has also reported that intraamniotic infection occurs in 15 to 25 percent of preterm PROM cases and postpartum infection occurs in 15 to 25 percent of cases, with the risk higher in cases involving earlier gestational ages.

36. As described above, these conditions frequently require emergency care, including abortion, and given these nationwide numbers, it is not surprising that pregnant patients in Idaho are among persons who require treatment for medical conditions that frequently present as medical emergencies. For example, Idaho providers made claims to Medicaid and the Children's Health Insurance Program ("CHIP") for payment for: 98 ectopic pregnancies that were treated with pregnancy termination in 2018; 72 ectopic pregnancies were treated with pregnancy termination in 2019; 103 ectopic pregnancies were treated with pregnancy termination in 2020; and 108 ectopic pregnancies were treated with pregnancy termination in 2021. Notably, these numbers are based only on patients who are Medicaid or CHIP beneficiaries, not all patients in Idaho—which means the number of patients who presented with ectopic pregnancies in Idaho during those years is likely even higher overall.

37. As discussed above, similar treatment for ectopic pregnancy will no longer be available under Idaho's new abortion law. Based on the consistent historical data, it is a near-

certainty that patients with ectopic pregnancies will continue to require emergency medical treatment that qualifies as a prohibited "abortion" under Idaho law—just like the hundreds of patients who have needed that treatment in recent years. Without access to that treatment, the inevitable result for those patients will be substandard care and dire consequences for their health.

38. With respect to other emergency pregnancy conditions, including those described above in paragraphs 15-22, there is not similar readily available Medicaid/CHIP data. This does not reflect an absence of those conditions for patients in Idaho, but rather only the realities of how hospitals and other providers track diagnose/s and treatments, and how the federal government and private insurance companies reimburse for the costs of health care. However, based on my experience practicing medicine for more than 30 years, it is virtually certain that pregnant persons in Idaho present themselves in emergency rooms across the state each year with these emergency conditions and that the proper treatment in at least some cases would be termination of the pregnancy. Under the Idaho law, that treatment would be unavailable, and the consequence of denying that care to those patients will be tragic.

I declare under penalty of perjury that the foregoing is true and correct. Executed this 8th day of August, 2022 in Philadelphia, PA.

Lee A. Fleisher, M.D.

FLEISHER DECLARATION: EXHIBIT A

UNIVERSITY OF PENNSYLVANIA - PERELMAN SCHOOL OF MEDICINE
Curriculum Vitae

Date: 10/16/2021

Lee A. Fleisher, M.D.

Address: Chief Medical Officer
Director, Center for Clinical Standards and Quality
Center for Medicare and Medicaid Services
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Professor of Anesthesiology and Critical Care
Professor of Medicine
Perelman School of Medicine of the University of Pennsylvania
Philadelphia, PA 19104 USA

If you are not a U.S. citizen or holder of a permanent visa, please indicate the type of visa you have:
none (U.S. citizen)

Education:

1981	B.A.	University of Pennsylvania (Molecular Biology)
1986	M.D.	State University of New York at Stony Brook (Medicine)
2024	M.Law	University of Pennsylvania Carey School of Law (Law)

Postgraduate Training and Fellowship Appointments:

1986-1987	Intern in Surgery, University of Minnesota
1987-1990	Resident in Anesthesiology, Yale University

Faculty Appointments:

1990-1992	Assistant Professor of Anesthesiology, Yale University School of Medicine
1992-1996	Assistant Professor of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine
1993-2003	Joint Appointment in Medicine, Johns Hopkins University School of Medicine
1996-2002	Affiliate Faculty, Program for Medical Technology Assessment and Practice, Johns Hopkins University School of Medicine
1996-2002	Associate Professor of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine
1996-2003	Joint Appointment in Health Sciences Informatics, Johns Hopkins University School of Medicine
1997-2003	Joint Appointment in Health Policy and Management, Johns Hopkins University School of Public Health
1997-2003	Affiliate Faculty, Center for Evidence Based Medicine, Johns Hopkins University School of Medicine

2002-2003	Professor of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine
2004	Professor of Anesthesiology and Critical Care, University of Pennsylvania School of Medicine
2004-2010	Adjunct Professor of Health Sciences Informatics, Johns Hopkins University
2004-2015	Consulting Professor of Anesthesiology, Duke University
2004-2017	Professor of Medicine, University of Pennsylvania School of Medicine (Secondary)
2004-2020	Robert Dunning Dripps Professor of Anesthesia, University of Pennsylvania School of Medicine
2019-present	Professor of Medicine, University of Pennsylvania School of Medicine (Secondary)
2020-present	Professor of Anesthesiology and Critical Care, University of Pennsylvania School of Medicine

Hospital and/or Administrative Appointments:

1990-1992	Director, Division of Peripheral Vascular Anesthesia, Yale New Haven Hospital
1990-1992	Attending Physician, Critical Care Anesthesia Service, Yale New Haven Hospital
1990-1992	Attending Physician, Liver Transplantation Team, Yale New Haven Hospital
1992-2003	Attending Physician, Department of Anesthesiology and Critical Care Medicine, Johns Hopkins Hospital
1997-2003	Anesthesia Coordinator, General Operating Room, Johns Hopkins Hospital
1998-2001	Director of Manpower and Program Development Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine
1998-2001	Chief, Division of Perioperative Health Services Research Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine
1999-2003	Clinical Director of Operating Rooms Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine
2001-2003	Vice Chair for Clinical Investigation Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine
2002-2003	Director, Program for Medical Technology Assessment and Practice, Johns Hopkins University School of Medicine
2004-present	Chair, Department of Anesthesiology and Critical Care, University of Pennsylvania Health System
2004-present	Member, Medical Board of the Hospital of the University of Pennsylvania (Vice-Chair, 2012-2014; Chair, 2014-2016)
2007	Vice-Chair, Search Committee for Chair of Medicine,

	University of Pennsylvania
2008-2014	Chair, Credentials Committee, Hospital of the University of Pennsylvania
2008-present	Chair, Committee on Professional Liability, Clinical Practices of the University of Pennsylvania
2010-2012	1st Vice-President, Medical Board, Hospital of the University of Pennsylvania
2010-2012	Chair, Bylaws Committee of the Medical Board of the Hospital of the University of Pennsylvania
2011-2014	Member, Advisory Committee for Medical Education (ACME), University of Pennsylvania School of Medicine
2012-2014	President-elect, Medical Board of the Hospital of the University of Pennsylvania
2012-2014	Chair, Committee on Clinical Effectiveness and Quality Improvement, Hospital of the University of Pennsylvania
2012-2016	Member, Board of Trustees, Hospital of the University of Pennsylvania
2012-2015	Co-Chair, Perelman School of Medicine Information Technology Committee
2012-present	Member, Contracting team with Blue Cross, University of Pennsylvania Health System
2014-2016	President, Medical Board, Hospital of the University of Pennsylvania
2015-2016	Member, Leadership and OversightCommittee, Penn Medicine License Committee on Medical Education (LCME) reaccreditation
2016-present	Member, Advisory Council for the Office of Inclusion and Diversity, Penn Medicine
2017-present	Member, IBC/Penn Medicine Delegated Care Mgmt Workgroup, IBC/UPHS Product Deep-Dive Workgroup, IBC/Penn Medicine Episodes Workgroup
2018-present	Clinical Program Lead, Penn Med-Vinmec Alliance

Other Appointments:

2004-present	Senior Fellow, Leonard Davis Institute for Health Economics (Member, Executive Committee)
2011-present	Member, Managed Care Contracting Advisory Committee of the Clinical Practices of the University of Pennsylvania Health System, Vice-Chair (2014-present)
2014-present	Member,, Medical Alumni Advisory Committee(MAAC), Perelman School of Medicine, University of Pennsylvania
2014-present	Affiliated Faculty, Quattrone Center for the Fair Administration of Justice of the University of Pennsylvania Law School
2020-present	CMS Chief Medical Officer and Director, Center for Clinical Standards and Quality, Centers for Medicare and Medicaid

Services

Specialty Certification:

1991	American Board of Anesthesiology

Licensure:

1991-2004	Maryland - D42689
2004-present	Pennsylvania MD423444

Awards, Honors and Membership in Honorary Societies:

1981	Benjamin Franklin Scholar University of Pennsylvania
1981	Magna cum laude with Distinction in Biology University of Pennsylvania
1986	M.D. with Distinction in Research State University of New York at Stony Brook
1989	Burroughs Wellcome Resident Scholar
1990	Young Investigator Award American Society of Critical Care Anesthesiologists
1995-1996	Richard S. Ross Clinician Scientist
2005-present	John Morgan Society
2007	Member, National Academy of Medicine (formerly Institute of Medicine)
2007	John C. Oakley Pioneer in Pain Medicine Award
2009	Foundation for Anesthesia Education and Research Hononary Research Lecturer
2011	2011 Distinguished Alumni Award, State University of New York at Stony Brook School of Medicine
2011	Eliasberg Medal for Anesthesiology Accomplishments from Mt. Sinai Medical School
2011	Foundation for Anesthesia Education and Research Academy of Mentors
2012	Member (Honorary), Chinese Society of Anesthesiologists
2013	C. William Hanson, Jr., M.D. Service Award, Hospital of the University of Pennsylvania
2015	2015 Innovations in Criminal Justice award, Quattrone Center for the Fair Administration of Justice: Using Root Cause Analysis To Instill a Culture of Self-Improvement (, Association of Prosecuting Attorneys
2015	Chinese Society of Anesthesiologists Distinguished Service Award
2016	Christian R. and Mary F. Lindback Award for Distinguished Teaching, University of Pennsylvania
2018	Honorary Fellow, Chinese College of Anesthesiology, Chinese Society of Anesthesiology
2020	Foundation of Anesthesia Education and Research (FAER)

Mentoring Excellence in Research Award

Memberships in Professional and Scientific Societies and Other Professional Activities:

International:

1990-Present	International Anesthesia Research Society
1990-1996	International Society for Ambulatory Monitoring - Founding Fellow
1990-Present	Society of Cardiovascular Anesthesiologists ((Research Committee, Member 1993-1997, 2003-2004, Chair 1997-2003) (Board of Directors, Member 1995-2001) (Taskforce on Practice Guidelines, Chair 2003-2005))
1993-2000	Association of Pharmacoeconomic and Outcome Research (Education Committee, Member 1997)
1995-2003	International Society for Technology Assessment in Health Care
2000-2004	International Society of Pharmacoeconomics and Outcome Research
2005-Present	Society for Perioperative Assessment and Quality Improvement (Member, Board of Directors)

National:

1987-Present	American Society of Anesthesiologists ((Committee on Acute Medicine, Adjunct Member 1992-1994) (Committee on Refresher Courses, Member 1994, 2003-2008) (Committee on Guidelines for Preoperative Evaluation, Consultant 1994-1997, Member 1999) (Subcommittee on Clinical Circulation, Member 1996-2000, 2005, 2006, 2007, Chair 2001-2004) (Committee on Performance and Outcomes Measurement, Member 2005-present; Chair 2008-2011) (Committee on Regional and Metropolitan Refresher Courses, Adjunct Member 1997-1998) (Committee on Outreach Education, Member 1997-1999) (Committee on Scientific Papers, Member 1997, 2001-2004) (Committee on Annual Meeting, Member 1997, 2001-2004) (Committee on Practice Parameters, Member 2003-present) (Representative to the Surgical Care Improvement Project 2003-present) (Committee on Research, Member 2007-2010, 2011-present) (Representative to American Medical Association Physician Consortium for Performance Improvement 2011-Present); Chair, Patient Safety Initiative Perioperative Brain Health Initiative 2015-Present)
1991-1992	American Society of Critical Care Anesthesiologists (Program Committee, Member

	1991)
1992-1993	National Institute of Mental Health (Biological Psychopharmacology Study Section, Ad-hoc Reviewer)
1993-Present	American Heart Association- Fellow (ACC/AHA Task Force for Perioperative Cardiovascular Evaluation for Noncardiac Surgery (Member 1993-2002, Chair 2003-present) Anesthesiology, Radiology and Surgery Study Committee (Member 1996-2001), Fellow 2007; Executive Database Committee (member 2007-2011); Member, Guideline Transformation & Optimization Advisory Group 2016-Present)
1994-Present	American College of Cardiology - Fellow (Member, ACCF/AHA Task Force on Practice Guidelines (2014-2020))
1994	National Heart, Lung, Blood Institute (SCOR Study Section, Ad-hoc Reviewer)
1995-Present	Society for Medical Decision Making
1998-Present	Society of Ambulatory Anesthesia ((Committee on Annual Meeting, Member 1999-2003) (Committee on Research, Member 2003-present, Chair 2005-2008) (Committee on Development, Member 2003-2004) (Task Force on Benchmarking Project, Member 2006))
1999-Present	Association of University Anesthesiologists (Member (1996-present), Councilor-at-Large (1999-2001), President-elect (2011-2012), President (2012-2014), Past President (2014-2016))
1999-Present	Center for Medicare and Medicaid Services (Technical Expert Panel evaluating applications for the Cardiovascular Demonstration Project 1999, Innovation Advisors Program (2012-2013); Hospital-Acquired Condition (HAC) Reduction Program Technical Expert Panel (2014); Member, Care Transformation Forum, an Initiative of the Health Care Payment Learning & Action Network (2019-2020))
1999	Society for Obstetric Anesthesia and Perinatology
2002-present	Association of American Medical Colleges (Council of Faculty and Academic Specialties (Representative from AUA 2013-present, Member, Administrative Council (2013-2016), Council of Academic Specialties (Representative from AUA 2002-present, Ex-officio member of Administrative Board 2011-2013), , CAS Initiative to Highlight Faculty Innovations (Chair 2010-2013), CAS Leadership Development Task Force (2009-2010);)
2003-2010	Surgical Care Improvement Project (sponsored by the Centers for Medicare and Medicaid Services, Agency for Healthcare Policy and Research, Centers for Disease

	Control and 10 other partners) (Member, Steering Committee; Member, Communications Subcommittee, Member, Technical Expert Panels on Surgical Site Infection and Cardiovascular Disease; Chair, Publications Committee)
2004-2008	American Medical Association (Member, AMA Physician Performance Improvement Committee)
2004-2008	Association of Anesthesiology Program Directors (Council member 2005-6)
2005-present	Morton Society (President (2016-2018))
2006-2015	Foundation for Anesthesia Education and Research (Member, Board of Directors; Member 2006-2015, Development Committee; Member 2006, Grant Awards Review Committee; Member, Geriatric Research Council; Member 2006, Cerebral Functioning Monitoring Task Force)
2007-Present	Academy Health (Member, Committee on Advocacy and Public Policy (2018))
2007-Present	National Academy of Medicine (formerly Institute of Medicine) (Member, IOM Priority Assessment Inventory Working Group (2009); Reviewer, Accounting for Social Risk Factors in Medicare Payment: Identifying Social Risk Factors (2016); Member, Committee on Reproductive Health Services: Assessing the Safety and Quality of Abortion Care (2016-Present); Planning Committee and Presenter, Building the Evidence Base for Improving Health Care: Contributions, opportunities and priorities (2017-8))
2007	Rand Corporation/Assistant Secretary of Health for Planning and Evaluation (Member, Technical Expert Panel)
2008-2014	AAAHC Institute for Quality Improvement (Member, Board of Trustees; Member, Measurement Development Task Force 2009-2011)
2008-Present	National Quality Forum (Ex-oficio member (2015-6), Member (2019-2022), Treasurer (2019-21) Board of Directors; Member, Perioperative Care Steering Committee 2008-2009; Co-Chair, Main Patient Outcomes Steering Committee 2009-2011; Member 2012-2018, Vice-Chair 2014-2015, Chair 2015-2016 Consensus Standards Advisory Committee; Member, Measure Evaluation Committee 2013; Co-Chair, Surgery Standing Committee 2014-7; Measurement and Use Advisory Panel 2015-2016; Member, Measures Application Partnership Hospital Workgroup 2016-2019; Member, Measure Feedback Committee 2018-2019)
2012	Physician Quality Reporting System Program (Preoperative Beta-Blocker in Patients with Isolated CABG Surgery Technical Expert Panel (TEP))
2012	Yale New Haven Health Services Corporation/Center for Outcomes Research and Evaluation (YNHHSC/CORE)/ The Society of Thoracic

	Surgeons (STS)/ CMS (Member, Technical Expert Panel (TEP) for the Coronary Artery Bypass Graft (CABG)outcomes measures)
2013-2019	Physicians Consortium for Performance Improvement (Member, Quality Improvement Advisory Council)
2014-2016	American Institutes for Research (Member, Advisory Board, Gordon and Betty Moore Foundation funded project developing a coordinated approach to measuring patient and family engagement in the hospital setting)
2014-Present	Blue Cross Blue Shield Association (Member, Medical Advisory Panel, Technology Evaluation Center)
2016-Present	American Society for Enhanced Recovery (Member, Advisory Board 2016-Present)
2016-Present	Physician Leadership Academy (joint venture of Deloitte Consulting and Wharton School) (Member, Board of Advisors 2016-Present)
2016-Present	Yale/YNHH Center for Outcomes Research and Evaluation (CORE) (Member, Hospital-Wide Mortality Technical Working Group 2016-present; Member, 90-day CABG Mortality Bundled Payment Technical Evaluation Panel 2018-present; member, Star Ratings Provider Leadership Work Group; member, Technical Expert Panel (TEP) for the Reevaluation of Inpatient Claims-Based Outcome Measure 2019-2020)
2017-2023	Accreditation Council for Graduate Medical Education (Member, Standing Panel for Accreditation Appeals in the specialty of Anesthesiology)
2018-Present	Leapfrog Group (Chair, Ambulatory Surgery Expert Panel)
2019-Present	Health Care Payment Learning and Action Network (LAN) (member, Care Transformation Forum (CTF))
2019	Department of Health and Human Services - Value Based Transformation - June Sepsis Planning Meeting

Editorial Positions:

1994-Present	Ad hoc Reviewer, Anesthesia & Analgesia
1995-Present	Ad hoc Reviewer, Journal of Clinical Anesthesia
1995-2000	Ad hoc Reviewer, Journal of Clinical Monitoring
1996-Present	Editorial Board Member, Journal of Cardiothoracic and Vascular Anesthesia
1996-2001	Co-Editor In-Chief, Problems in Anesthesia
1996-1998	Expert Analyst, Vascular Anesthesia, The Cardiovascular and Thoracic Anesthesia Journal Club Journal

1997-Present	Question Writer, In-Training Council, American Board of Anesthesiology
1999-2002	Editorial Board Member, American Journal of Anesthesiology
1999-Present	Editorial Board Member, Anesthesiology News
1999-2000	Section Editor, Practice Management, Economics and Technology Assessment, Current Anesthesiology Reports
2000-2003	Associate Editor, Anesthesiology
2000-Present	Ad hoc Reviewer, Circulation
2000-Present	Ad hoc Reviewer, American Journal of Physiology
2000-Present	Editorial Board Member, Current Opinion in Anesthesiology
2001-Present	Ad hoc Reviewer, New England Journal of Medicine
2001-Present	Ad hoc Reviewer, Chest
2001-Present	Ad hoc Reviewer, Journal of the American College of Cardiology
2001-Present	Ad hoc Reviewer, Medical Care
2001-Present	Ad hoc Reviewer, Journal of Nuclear Cardiology
2001-2002	Executive Committee Member, American Journal of Anesthesiology
2001-Present	Consulting Editor, Anesthesiology Clinics of North America
2001-Present	Ad hoc Reviewer, Journal of the American Medical Association
2002-Present	Section Editor, Pro/Con, Journal of Cardiothoracic and Vascular Anesthesia
2002-Present	Ad hoc Reviewer, Veterans Administration Clinical Trials Study Section
2002-Present	Ad hoc Reviewer, Urology
2005-Present	Ad-hoc reviewer, Medical Care
2011-present	Perioperative Medicine, Co-Editor-in-Chief (2017-present)
2012-present	Annals of Surgery, Member, Editorial Board

Academic and Institutional Committees:

1990-1992	Member, Residency Review Committee Department of Anesthesiology Yale University School of Medicine
1994-1999	Member, Outpatient General Clinical Research Center Protocol Review Subcommittee Johns Hopkins University School of Medicine
1994-2003	Member, Education Committee Department of Anesthesiology and Critical Care Medicine Johns Hopkins University School of Medicine
1994-1995	Member, Patient Satisfaction Task Force Department of Anesthesiology and Critical Care Medicine Johns Hopkins Hospital
1994-1999	Member, Presurgical Work Group Surgical Services Design Team Johns Hopkins Hospital
1995	Member, Ambulatory Surgery Task Force Johns Hopkins Hospital
1998-2003	Member, Service Executive Committee

	Department of Anesthesiology and Critical Care Medicine Johns Hopkins University School of Medicine
1998-2003	Member, Executive Manpower Committee Department of Anesthesiology and Critical Care Medicine Johns Hopkins University School of Medicine
1998-1999	Member, Operating Room Posting Task Force Johns Hopkins Hospital
1999-2003	Member, Vice-Chairman Committee Department of Anesthesiology and Critical Care Medicine Johns Hopkins University School of Medicine
1999-2003	Member, Minimally Invasive Surgery Focus Group Johns Hopkins Hospital
1999-2003	Member, Operating Room Executive Committee Johns Hopkins Hospital
1999-2003	Member, General Operating Room Subcommittee Johns Hopkins Hospital
2000-2001	Participant, Leadership Development Program Johns Hopkins University School of Medicine
2000-2003	Member, Clinical Competence Committee Department of Anesthesiology and Critical Care Medicine Johns Hopkins University School of Medicine
2000-2002	Member, Office of Technology Licensing Advisory Committee Medical School Council Johns Hopkins University School of Medicine
2000-2003	Member, Government Affairs Committee Clinical Practice Association Johns Hopkins University School of Medicine
2000-2003	Member, Innovations in Patient Care - Long Term Strategies Committee Johns Hopkins Medicine
2000-2003	Member, Simulation Center Committee Johns Hopkins Hospital
2000-2003	Member, Outpatient Surgery Operating Room Committee Johns Hopkins Hospital
2002-2003	Member, Ophthalmology Chair Search Committee Johns Hopkins University School of Medicine
2002-2003	Member, Budget and Finance Committee Clinical Practice Association Johns Hopkins University School of Medicine
2002-2003	Member, Board of Advisors for the Johns Hopkins Biostatistics Center Johns Hopkins School of Hygiene and Public Health
2004-2005	Member, Steering Committee of the Standing Committee Department Chairs, University of Pennsylvania School of Medicine
2004-2020	Member, Clinical Practices of the University of Pennsylvania Board of Directors

2004-2006	Member, Clinical Practices of the University of Pennsylvania Executive Committee
2004-2005	Member, Steering Committee of the Standing Committee of Department Chairs, Centers and Institutes
2004-2020	Member, Standing Committee of Department Chairs, Centers and Institutes
2004-2020	Operating Room Executive Committee, Hospital of the University of Pennsylvania
2004-2005	Chair, Internal Review Committee of the Leonard Davis Institute, University of Pennsylvania
2004-2012	Member, Clinical Practices of the University of Pennsylvania Finance Subcommittee
2005-2007	Member, Clinical Practices of the University of Pennsylvania Clinical Effectiveness and Quality Improvement Committee
2005-2006	Member, Clinical Practices of the University of Pennsylvania Finance Committee
2005-2006	Member, Tenure Track Review Committee, University of Pennsylvania School of Medicine
2005-2006	Chair, Review Committee of the Department of Neurosurgery, University of Pennsylvania School of Medicine
2005-2006	Member, Steering Committee, Magnet Designation, Hospital of the University of Pennsylvania
2006	Member, Tia Sophia Review Committee
2006-2007	Member, Committee to Review the Clinical Transplant Institute Proposal
2006-2020	Member, Penn Advisory Board, Robert Wood Johnson Clinical Scholars Program
2006-2008	Member, 2008 LCME Review Steering Committee (Chair, Medical Student Task Force), University of Pennsylvania School of Medicine
2006-2015	Member, Steering Committee, Comprehensive Neurosciences Center
2007	Co-chair, Department of Medicine Chair Search Committee
2007-2020	Chair, Clinical Practice of the University of Pennsylvania Professional Liability Subcommittee
2008-2009	Member, Chair of Surgery Search Committee, University of Pennsylvania
2008-2009	Member, Search Committee for Chair of Ophthamology
2009-2010	Member, Chair of Dermatology Search Committee
2010-2011	Chair, Seach Committee for the Chair of the Department of Medical Ethics and Health Policy
2010-2020	Vice-Chair, Managed Care Contracting Subcommittee, Clinical Practices of the University of Pennsylvania; Physician representative to UPHS Contracting Committee with Independence Blue Cross (2012, 2016)
2012-2013	Member, Search for Chair of Department of Pediatrics, Perelman School of Medicine

2012-2013	Member, Integrating Knowledge Working Group (IKWG) for the Middle States Reaccreditation Self Study, University of Pennsylvania
2013	Chair, Search for Chair of Department of Biostatics and Epidemiology, Perelman School of Medicine
2014	Chair, Distinguished Alumni Award Committee
2014-2015	Chair, Orthopedic Review Committee
2015-2016	Chair, Department of Ophthalmology Review Committee
2016-2017	Chair, Pathology Review Committee
2016-2020	Member, Advisory Council for the Office of Diversity and Inclusion
2017-2018	Chair, Committee to review the Department of Health Policy and Medical Ethics
2017	Member, Search Committee for Senior Vice Dean for Education
2017	Member, Advisory group: search committee training project
2018-2019	Member, Search Committee for Director of Leonard Davis Institute of Healthcare Economics

Major Academic and Clinical Teaching Responsibilities:

1994-1999	Section Leader, Clinical Decision Making Course Medical Student Curriculum 2nd Year Johns Hopkins University School of Medicine
1996-2003	Course Instructor, Medical Technology Assessment Johns Hopkins University School of Public Health
1997-2003	Course Instructor, Decision Analysis, Summer Institute Johns Hopkins University School of Public Health
1997-2003	Director, Anesthesia Case Conference Department of Anesthesiology and Critical Care Medicine Johns Hopkins University School of Medicine
1999-2003	Instructor, Physician in Society Medical Student Curriculum 2nd Year Johns Hopkins University School of Medicine
1999-2003	Course Instructor, Decision Analysis Johns Hopkins University School of Public Health
2005-2008	"Cost-effectiveness and decision analysis" in Epidemiology for 1st year medical students
2006-2016	Preceptor, Doctoring Course
2007-2008	Guest Lecturer, Health Care Management Undergraduate course
2008-2020	Course Director, Frontiers Course for 4th year medical students, "Science of Quality"
2016-2020	Small Group Preceptor, Health Care Systems, Perelman School of Medicine,

Lectures by Invitation:

Jan, 1999	"Preoperative cardiac evaluation" - Department of Anesthesia, Mount Sinai School of Medicine, New York, NY
Jan, 1999	"Risk of anesthesia" - Department of Anesthesia, Jefferson Medical

	College, Philadelphia, PA
Feb, 1999	"Risk of anesthesia" - Department of Anesthesia, University of Michigan, Ann Arbor, MI
Mar, 1999	"Cardiac risk of noncardiac surgery" - Mini-Course, American College of Cardiology 48th Annual Scientific Session, New Orleans, Louisiana
Apr, 1999	"Outcomes evaluation/measurement in cardiac surgery" - Scientific Program Committee, Society of Cardiovascular Anesthesia Annual Meeting, Chicago, IL
Apr, 1999	"Outcome measure for ambulatory anesthesia" - Society for Ambulatory Anesthesia Annual Meeting, Chicago, IL
May, 1999	"Meet the experts: coronary disease and surgical emergencies" - 33a Jornada Paulista de Anestesiologia by the Sociedade de Anestesiologia do Estado de Sao Paulo, Sao Paulo, Brazil
May, 1999	"Preoperative assessment of the patient with cardiovascular disease" - 33a Jornada Paulista de Anestesiologia by the Sociedade de Anestesiologia do Estado de Sao Paulo, Sao Paulo, Brazil
May, 1999	"Preoperative cardiac evaluation" - Department of Anesthesia, Sunnybrook Health Science Center, Toronto, Canada
Jun, 1999	"Perioperative aschemia: is it a bad thing?" - 2nd Annual Cardiothoracic Update, Hilton Head, SC
Sep, 1999	"Risk of anesthesia" - Department of Anesthesia, Emory University, Atlanta, GA
Nov, 1999	"Preoperative assessment" - 1999 Survey of Current Issues in Surgical Anesthesia, Cleveland, OH
Dec, 1999	"Impact of economic pressures on anesthesia training and practice" - Winter College Lecture, Royal College of Anaesthetists, Dublin, Ireland
Jan, 2000	"Evidence based anesthesia care: the high risk cardiac patient" - Department of Anesthesia, New York University, New York, NY
Feb, 2000	"Evidence based anesthesia care: the high risk cardiac patient" - Department of Anesthesia, SUNY at Stony Brook, Stony Brook, NY
Mar, 2000	"Heart rate variability as a measure of system complexity" - Japanese Society of Intensive Care Management, Nagoya, Japan
Mar, 2000	"Anesthetic management of the cardiac patient undergoing noncardiac surgery" - Japanese Society of Intensive Care Management, Nagoya, Japan
May, 2000	"Risk of readmission after ambulatory surgery by location of care: analysis of Medicare claims" - Society of Ambulatory Anesthesia Annual Meeting, Washington, D.C.
Jun, 2000	"Strategies to reduce cardiac risk of noncardiac surgery" - Department of Anesthesia, Duke University, Durham, NC
Jul, 2000	"Does anything reduce cardiac complications of noncardiac surgery" - Georgia Society of Anesthesiology, Amelia Island, FL
Sep, 2000	"Preoperative cardiac evaluation" - Department of Anesthesia, SUNY at Buffalo, Buffalo, NY

Sep, 2000	"Risk of anesthesia" - Yale Anesthesia Alumni Foundation Lecture, New Haven, CT
Sep, 2000	"Preoperative cardiac evaluation" - Department of Anesthesia, Campus University Hospital Gasthuisberg, Leuven, Belgium
Sep, 2000	"Strategies to reduce cardiac risk of noncardiac surgery" - Department of Anesthesia, Yale University, New Haven, CT
Oct, 2000	"Data mining: Medicare and beyond." - Panel for the Foundation for Anesthesia Education and Research, American Society of Anesthesiologists Meeting, San Francisco, CA
Oct, 2000	"Strategies to reduce the risk of anemia" - Symposium on Hemostatis and Transfusion, Graz, Austria
Oct, 2000	"Risk of outpatient surgery: analysis of Medicare claims" - Panel on Risk of Anesthesia, American Society of Anesthesiologists meeting, San Francisco, CA
Nov, 2000	"Strategies to reduce cardiac risk of noncardiac surgery" - Department of Anesthesia, University of Rochester, Rochester, NY
May, 2001	"Patients with CAD" - Panel on Difficult Medical Patients, Society of Ambulatory Anesthesia, Palm Desert, CA
Jun, 2001	"Strategies to reduce cardiac risk of noncardiac surgery" - Department of Anesthesia, Washington University in St. Louis, St. Louis, MO
Sep, 2001	"Strategies to reduce cardiac risk of noncardiac surgery" - Department of Anesthesia, University of Medicine and Dentistry of New Jersey, Newark, NJ
Sep, 2001	"Strategies to reduce cardiac risk of noncardiac surgery" - Department of Medicine, University of Medicine and Dentistry of New Jersey, Newark, NJ
Nov, 2001	"Preoperative cardiac evaluation" - University of Chicago, Department of Anesthesiology and Critical Care Medicine Annual Meeting, Chicago, IL
Nov, 2001	"Risks of outpatient surgery" - University of Chicago, Department of Anesthesiology and Critical Care Medicine Annual Meeting, Chicago, IL
Dec, 2001	"Does preoperative screening improve anesthetic outcome?" - Panel on Preoperative Testing - Are There Any Standards?, Postgraduate Assembly in Anesthesiology, New York, NY
Dec, 2001	"Perioperative management of the high risk patient for non-cardiac surgery" - Panel on How has Research Changed Your Clinical Practice?, Postgraduate Assembly in Anesthesiology, New York, NY
Apr, 2002	"Recent developments in perioperative stress protection in non-cardiac surgery" - Symposium at the 10th ESA Anniversary Meeting, 24th EAA Annual Meeting, Nice, France
Apr, 2002	"Application of the AHA/ACC guidelines to the elderly ambulatory patient" - Society of Ambulatory Anesthesia Annual Meeting, Orlando, FL

Apr, 2002	"The patient with ischemic heart disease undergoing arthroscopic surgery" - PBLD at the Society of Ambulatory Anesthesia Annual Meeting, Orlando, FL
May, 2002	"Strategies to reduce cardiac risk of noncardiac surgery" - Department of Anesthesia, Western Pennsylvania Hospital, Pittsburgh, PA
May, 2002	"Strategies to reduce cardiac risk of noncardiac surgery" - Department of Anesthesia, Northwestern University Medical Center, Chicago, IL
Aug, 2002	"Strategies to reduce cardiac risk of noncardiac surgery" - Department of Anesthesia, University of Illinois at Chicago, Chicago, IL
Aug, 2002	"Strategies to reduce cardiac risk of noncardiac surgery" - Department of Anesthesia, Rush-Presbyterian Medical Center, Chicago, IL
Sep, 2002	"Strategies to reduce cardiac risk of noncardiac surgery" - Department of Anesthesia, University of California at Los Angeles, Los Angeles, CA
Oct, 2002	"Preoperative assessment of the patient with cardiac disease" - American Society of Anesthesiologists Annual Meeting, Orlando, FL
Oct, 2002	"Preoperative testing: how should I apply the update to the AHA/ACC perioperative cardiovascular evaluation guidelines and the ASA advisory on preanesthetic evaluation?" - Panel Moderator, American Society of Anesthesiologists Annual Meeting, Orlando, FL
Oct, 2002	"Risk of anesthesia (and surgery) in the outpatient setting: the importance of patient, surgery and location of care" - Keynote lecture, Society of Ambulatory Anesthesia Annual Meeting, Orlando, FL
Oct, 2002	"Risk of undertransfusion" - American Academy of Blood Bankers, Orlando, FL
Nov, 2002	"The role of searching and evaluating the literature to ensure patient safety in clinical research: practices and protocol" - Panel, AMIA 2002 Symposium, San Antonio, TX
Dec, 2002	"Cost analysis in cardiac surgery" - Panel, New York State Society of Anesthesiologists Postgraduate Assembly, New York, NY
Dec, 2002	"Evidence-based medicine: perioperative beta-blockers" - Robertazzi Memorial Panel, 56th Postgraduate Assembly in Anesthesiology, New York, NY
Dec, 2002	"Evidence-based medicine: perioperative beta blockers" - Rovenstein Panel, New York State Society of Anesthesiologists Postgraduate Assembly, New York, NY
Jan, 2003	"Strategies to reduce cardiac risk of noncardiac surgery" - Department of Medicine, University of Florida, Gainesville, FL
Jan, 2003	"Strategies to reduce cardiac risk of noncardiac surgery" -

	Departments of Surgery and Anesthesia, University of Florida, Gainesville, FL
Mar, 2003	"Optimizing perioperative outcomes" - Refresher Course, IARS 77th Clinical and Scientific Congress, New Orleans, LA
Mar, 2003	"Operating room management" - Panel, IARS 77th Clinical and Scientific Congress, New Orleans, LA
Jun, 2003	"Risk of anesthesia" - Department of Anesthesia, Oxford University, Oxford, UK
Sep, 2003	"Strategies to reduce cardiac risk of noncardiac surgery" - Department of Anesthesia, University of Colorado, Boulder, CO
Sep, 2003	"Risk of Anesthesia: Does location of care matter?" - Department of Anesthesiology, The Geffen School of Medicine at UCLA, Los Angeles, CA
Sep, 2003	"Cardiac patient presenting for aortic aneurysm resection." - Department of Anesthesiology, The Geffen School of Medicine at UCLA, Los Angeles, CA
Sep, 2003	"Risk of anesthesia: Are we still safe in outpatient surgery?", Colorado Society of Anesthesiologists, Denver, CO.
Oct, 2003	"How old is too old? Risk in the geriatric patient" - Society of Ambulatory Anesthesia Mid-Year Meeting, San Francisco, CA
Oct, 2003	"Tailoring the preop to the procedure: the evidence" - SAMBA Breakfast Panel on Whom Do We Invite to Our Party?: How and why the preoperative evaluation of surgical outpatients is different., American Society of Anesthesiologists Annual Meeting, San Francisco, CA
Oct, 2003	"Differences in outcomes from surgery performed in physicians offices and ambulatory surgery centers" - Panel on the Surgeon Anesthesia Supervisor: How much do they need to know, how is it evaluated, and why do we care?, American Society of Anesthesiologists Annual Meeting, San Francisco, CA
Oct, 2003	"Which patients need what coronary evaluation before carotid endarterectomy?" - Panel on Carotid Endarterectomy: What preoperative evaluation?; What anesthetic technique (regional or GA)?; What neurologic monitoring?, American Society of Anesthesiologists Annual Meeting, San Francisco, CA
Oct, 2003	"Evidence based medicine: perioperative interventions" - Panel on Evidence-Based Medicine in Anesthesiology, American Society of Anesthesiologists Annual Meeting, San Francisco, CA
Oct, 2003	"Preoperative assessment of the patient with cardiac disease" - American Society of Anesthesiologists Annual Meeting, San Francisco, CA
Oct, 2003	"What do I do with a positive stress test result" - Panel Moderator on High-Risk Patients Undergoing Noncardiac Surgery: What do I do about the results of preoperative testing, perioperative testing, perioperative beta-blockers and pacemakers?, American Society of Anesthesiologists Annual Meeting, San Francisco, CA

Dec, 2003	"Vascular Surgery" - Focus Session on What should change our clinical practice? Evidence based medicine: Here to stay., 57th Postgraduate Assembly in Anesthesiology, New York, NY
Dec, 2003	"What should change our clinical practice? Evidence based medicine: Here to stay.", Panel Moderator, 57th Postgraduate Assembly in Anesthesiology, New York, NY
Apr, 2004	"Preoperative cardiac risk assessment and risk reduction" - Royal College of Physicians and Surgeons of Canada, Toronto, Canada
Apr, 2004	"Strategies to reduce cardiac risk of noncardiac surgery"- Meet the experts. World Congress of Anesthaesiologists. Paris, Fr.
Apr, 2004	"What is the most appropriate monitoring for perioperative myocardial ischaemia ?"- World Congress of Anaesthesiologists. Paris, Fr
May, 2004	"Strategies to reduce cardiac risk of noncardiac surgery"- British Cardiac Society. Manchester, England
Jun, 2004	"Risk of anesthesia: importance of location of care"- Ali Gharib Lecture. Department of Anesthesia. Case Western Reserve University School of Medicine
Sep, 2004	"Strategies to reduce cardiac risk for vascular surgery" - Vascular Anaesthesia Society of Great Britain and Ireland. Cambridge, England
Sep, 2004	"Strategies to reduce cardiac risk for vascular surgery"- Vascular Anaesthesia Scoiety of Great Britain and Ireland, Oxford, England
Oct, 2004	"When is Preoperative Testing Worth the Money?" for Panel on The Economics of the Preoperative Process- American Society of Anesthesiologists Annual Meeting, Las Vegas, NV
Oct, 2004	"Current State of the Evidence of Beta-Blockers" for Panel on So the Hospital Mandates a Beta-blocker Protocol, but How do I Implement One?- American Society of Anesthesiologists Annual Meeting, Las Vegas, NV
Oct, 2004	"Preoperative Assessment of the Patient with Cardiac Disease" - ASA Refresher Course, American Society of Anesthesiologists Annual Meeting, Las Vegas, NV
Oct, 2004	"Preoperative Cardiac Evaluation of the Endovascular Stent" for Panel on New Fronteirs in Vascular Surgery: Not Office-based ... Yet- American Society of Anesthesiologists Annual Meeting, Las Vegas, NV
Dec, 2004	"Improving perioperative outcomes: what's the role of the government and other specialty societies?" Panel on To Err is Human: are our patients safe? Postgraduate Assembly of the New York State Society of Anesthesiologists. New York, NY
Mar, 2005	"Is outcome research a waste of time?" - 25th Myron B. Laver International Postgraduate Course, Basel, Switzerland
Mar, 2005	"Preoperative patient evaluation" - 25th Myron B. Lavar International Postgraduate Course, Basel, Switzerland
Mar, 2005	"Cardiovascular risk of vascular surgery" - International Anesthesia

	Research Society Annual Meeting, Honolulu, HI
Apr, 2005	"Cardiac Risk and Beta-Blockade" - Controversies in Adult and Pediatric Anesthesia, HUP/CHOP Symosium, Philadelphia, PA
Apr, 2005	"Strategies to Reduce Cardaic Risk of Noncardiac Surgery"- Lancaster General Hospital, Lancaster, PA
Apr, 2005	"Is Outcomes Research a Waste of Time? Debunking dogma with data"- SUNY at Downstate, Brooklyn, NY
May, 2005	"Surgical Risk Reduction" at Society of Ambulatory Anesthesia Annual Meeting, Scottsdale, AZ
May, 2005	"Academic Practice" on Panel for Resident Component - Society of Ambulatory Anesthesia Annual Meeting, Scottsdale, AZ
May, 2005	"Strategies to Reduce Cardiac Risk of Noncardiac Surgery"- Reading Hospital, Reading, PA
Oct, 2005	"Clinical Forum on cards consult? Revascularization or just beta blockers"- American Society of Anesthesiologists Annual Meeting, Atlanta, GA
Oct, 2005	Preoperative evaluation, Panel on Diabetes Update: The Inpatient, the Outpatient and the Non-Patient"- American Society of Anesthesiologists Annual Meeting, Atlanta, GA
Oct, 2005	"Perioperative beta-blockade- Panel on Strategies to reduce cardiac risk of noncardiac surgery- but I thought we knew the answers!"- American Society of Anesthesiologists Annual Meeting, Atlanta, GA
Oct, 2005	"Preoperative Cardiac Assessment"- American Society of Anesthesiologists Annual Meeting, Atlanta, GA
Oct, 2005	Preoperative evaluation, Panel on Diabetes Update: The Inpatient, the Outpatient and the Non-Patient"- American Society of Anesthesiologists Annual Meeting, Atlanta, GA
Oct, 2005	"Is outcomes research a waste of time?" Orkin Memorial Lecture, Montefiore Hospital, Bronx, NY
Dec, 2005	"Strategies to reduce cardiac risk of noncardiac surgery"- Department of Anesthesiology, University of Virginia, Charlottesville, VA
Dec, 2005	"Risk of anesthesia: importance of location of care"- Department of Anesthesiology, University of Virginia, Charlottesville, VA
Dec, 2005	"Wading through the American Colleg of Cardiology/American Heart Association Algorithm", Panel of Using practice guidelines to improve outcome: what the clinician needs to know. Postgraduate Assembly of Anesthesiology. New York, NY
Dec, 2005	"How can I imporve organ protection during surgery?: Protecting the heart" Postgraduate Assembly in Anesthesiology, New York, NY
Feb, 2006	"Preoperative cardiac evaluation and management" Neurosurgical Grand Rounds, University of Pennsylvania
Apr, 2006	"Strategies to reduce cardiac risk of noncardiac surgery" Pennsylvania Association of Nurse Anesthetists Annual Meeting.

	Hershey, PA
Apr, 2006	"Risk of anesthesia in the outpatient setting" Pennsylvania Association of Nurse Anesthetists Annual Meeting. Hershey, PA
May, 2006	"Pharmacologic management to reduce perioperative myocardial infarction" Panel on Best practices in cardiac surgery. Society of Cardiovascular Anesthesiologists Annual Meeting. San Diego, CA
May, 2006	"From student to mentor and chair: _my journey to return to the University of Pennsylvania" Duke Anesthesiology Academic Evening. Duke University. Durham, NC
May, 2006	"Strategies to reduce cardiac risk of noncardiac surgery"- Department of Anesthesiology, Duke University, Durham, NC
May, 2006	"Strategies to reduce cardiac risk of noncardiac surgery" Departments of Anesthesiology, Surgery and Cardiology. University of Cincinnati. Cincinnati, OH
May, 2006	Guidelines, P4P, and Improving Care. University of Cincinnati Department of Anesthesiology, Cincinnati, OH
Jun, 2006	"Multicenter trials to improve care- noncardiac surgery" European Society of Anesthesiologists, Madrid, Spain
Jun, 2006	"Guidelines, P4P, and improving care". Department of Anesthesia and Perioperative Care, University of California San Francisco, San Francisco, CA
Sep, 2006	"Cardiac Risk Stratification and Risk Reduction for Non-Cardiac Surgery in 2006", 2nd Annual Perioperative Medicine Summit, Cleveland, OH
Sep, 2006	"Strategies to reduce cardiac risk of noncardiac surgery", Department of Medicine Grand Rounds, University of Pennsylvania School of Medicine, Philadelphia, PA
Oct, 2006	"Preoperative cardiac evaluation"- American Society of Anesthesiologists, Chicago, IL
Nov, 2006	"Strategies to reduce cardiac risk of noncardiac surgery"- University of California at San Diego, San Diego, CA
Feb, 2007	"Strategies to reduce cardiac risk of noncardiac surgery"- Department of Anesthesiology and Critical Care, University of Miami, Miami, FL
Feb, 2007	"Guidelines, P4P and Improving Perioperative Care"- Department of Anesthesiology and Critical Care, University of Miami, Miami, FL
Feb, 2007	"Strategies to reduce cardiac risk of noncardiac surgery"- Englewood Hospital, Englewood, NJ
Mar, 2007	"Analyzing retrospective data: the clinical implications of statistical methods"- International Anesthesia Research Society Annual Meeting, Orlando, FL
Apr, 2007	"The new AHA/ACC Guidelines on Beta-Blockade" Society of Cardiovascular Annesthesiologists Annual Meeting. Montreal
May, 2007	"Guidelines, P4P and improving perioperative outcome" Beth-Israel Deaconess Medical Center, Boston, MA
Jun, 2007	"Pharmacologic reduction in perioperative myocardial infarction",

	European Society of Anesthesiologists Annual Meeting, Munich, Germany
Jun, 2007	"Strategies to reduce cardiac risk for noncardiac surgery", Department of Anesthesiology and Perioperative Medicine, Oregon Health Sciences University
Jun, 2007	"How will clinical trials influence practice guidelines and pay for performance", European Society of Anesthesiologists, Munich, Germany
Jun, 2007	"The cardiac risk patient-what is new?" European Society of Anesthesiologists, Munich, Germany
Nov, 2007	"Strategies to reduce cardiac risk for noncardiac surgery" Department of Anesthesiology, Washington University in St. Louis, St. Louis, MO
Nov, 2007	"Risk of outpatient surgery: analysis of medicare claims" Department of Anesthesiology, Washington University in St. Louis, St. Louis, MO
Nov, 2007	"Strategies to reduce cardiac risk of noncardiac surgery" Departments of Anesthesiology and Surgery, Atlantic City Regional Medical Center, Atlantic City, NJ
Nov, 2007	"Did the AHA/ACC Guidelines really say that?" EM Papper Annual Lecture. Columbia University School of Medicine Department of Anesthesiology, New York, NY
Nov, 2007	"Risk of anesthesia in the outpatient setting: Using of claims data" Columbia University School of Medicine Department of Anesthesiology, New York, NY
Dec, 2007	"Outcome-Measures" Focus session on How do we demonstrate quality?. Postgraduate Assembly in Anesthesiology, New York, NY
Dec, 2007	"Outcomes" in Panel on Practice management issues: P4P and other things I better know about. Postgraduate Assembly in Anesthesiology, New York, NY
Jan, 2008	"Strategies to reduce cardiac risk of noncardiac surgery", Detroit Medical Center Department of Anesthesiology
Feb, 2008	"Strategies to reduce cardiac risk of noncardiac surgery", Yale University School of Medicine Department of Anesthesiology, New Haven, CT
Feb, 2008	"Guidelines, P4P, and Improving Perioperative Care", Yale University School of Medicine Department of Anesthesiology, New Haven, CT
Mar, 2008	"Perioperative beta-blockade", Panel of Guidelines on Perioperative Cardiovacular Evaluation, American College of Cardiology Annual Meeting, Chicago, IL
Mar, 2008	"Rolling the Dice: the wise use of statistics", Panel on Publication Roulette, IARS Annual Meeting, San Francisco, CA
Mar, 2008	"Did the AHA/ACC Guidelines really say that?" IARS Annual Meeting, San Francisco, CA

Apr, 2008	"Perioperative cardiovascular evaluation guidelines"
Apr, 2008	"Perioperative Cardiac Guidelines", Society of Hospital Medicine Annual Meeting, San Diego, CA
May, 2008	"Have we pushed office-based surgery too far?", Society of Ambulalatory Anesthesia Annuall Meeting, Miami, FL
Jun, 2008	"Strategies to reduce cardiac risk of noncardiac surgery", Seoul National Hospital 50th Department of Anesthesiology and Pain Medicine Anniversary Meeting, Seoul, Korea
Jun, 2008	"Strategies to reduce cardiac risk of noncardiac surgery" Departments of Anesthesiology and Surgery Grand Rounds, Medical University of South Carolina, Charleson, SC
Jul, 2008	"ACC/AHA Guidelines on Perioperative Cardiovascular Evaluation", Evidence Based Perioperative Medicine Meeting 2008, London, England
Jul, 2008	"Pay-4-Performance, the US perspective", Evidence Based Perioperative Medicine Meeting 2008, London, England
Oct, 2008	"Preoperative assessment of the patient with cardiac disease", American Society of Anestheisologists Annual Meeting, Orlando, FL
Oct, 2008	"Who gets revascularization and how? Update on the Guidelines for preoperative evaluation of the noncardiac surgical patient" American Society of Anestheisologists Annual Meeting, Orlando, FL
Oct, 2008	"The diabetic patient undergoing noncardiac surgery: what should we do from a cardiac evaluation standpoint?" Panel on Management of the diabetic patient. American Society of Anestheisologists Annual Meeting, Orlando, FL
Oct, 2008	"Can we really improve performance?" Panel on Avoiding performance anxiety. American Society of Anestheisologists Annual Meeting, Orlando, FL
Oct, 2008	"From student to mentor and chair: _my journey to return to the University of Pennsylvania" Foundation for Anesthesia Education and Research Scholar Presentation
Nov, 2008	"Postoperative care for the bariatric surgery patient" Panel on The Morbidly Obese Patient. American Heart Association Annual Meeting, New Orleans, LA
Nov, 2008	"Heart disease in the cardiac patient before noncardiac surgery." Panel on Clinical Challenges in Daily Practice and Case-Based Applications of Recent Guidelines I, American Heart Association Annual Meeting, New Orleans, LA
Nov, 2008	"Strategies to reduce cardiac risk for noncardiac surgery", St. Joseph Medical Center, Towson, MD
Jan, 2009	"Strategies to reduce cardiac risk of noncardiac surgery" University of Maryland, Baltimore, MD
Jan, 2009	"Guidelines, P4P and improving perioperative care" University of Maryland, Baltimore, MD

Jan, 2009	"Strategies to reduce cardiac risk of noncardiac surgery: Update on the AHA/ACC Guidelines", Department of Anesthesiology, University of Miami School of Medicine, Miami, FL
Feb, 2009	"Strategies to reduce cardiac risk of noncardiac surgery: Update on the AHA/ACC Guidelines", 4th Annual Perioperative Medicine Summitt, Miami Beach, FL
Mar, 2009	"How do different forms of anesthesia play a role", Panel on Preoperative Cardiac Evaluation, American College of Cardiology Annual Meeting, Orlando, FL
Mar, 2009	"Choice of Anesthesia and Outcome", Panel on perioperative cardiovascular care for noncardiac surgery, American College of Cardiology Annual Meeting, Orlando, FL
Mar, 2009	"Improving perioperative care: Guidelines, P4P, and Quality Measures", Department of Anesthesiology, University of Michigan School of Medicine, Ann Arbor, MI
Mar, 2009	"Strategies to reduce cardiac risk of noncardiac surgery", Department of Anesthesiology, Cardiovascular Medicine Institute, University of Michigan School of Medicine, Ann Arbor, MI
Apr, 2009	"Perioperative cardiovascular evaluation before noncardiac surgery", Cardiology Update 2009, University of Pennsylvania School of Medicine, Absecon, NJ
Apr, 2009	"Evidence based medical management of the patient undergoing noncardiac surgery", Society of Cardiovascular Anesthesiologists Annual Meeting, San Antonio, TX
Apr, 2009	"Surgical Care Improvement Project: Target for the CT anesthesiologist", Society of Cardiovascular Anesthesiologists Annual Meeting, San Antonio, TX
May, 2009	"Strategies to reduce cardiac risk of noncardiac surgery" Stengart Lecture, University of California at Davis, Sacramento, CA
Jun, 2009	"Strategies to reduce cardiac risk of noncardiac surgery", Canadian Anesthesiologists' Society Annual Meeting, Vancouver, Canada
Jul, 2009	"Improving Perioperative outcomes: risk assessment, patient preferences and performance measures", Evidence Based Perioperative Outcomes Meeting, London, England
Jul, 2009	"Improving Perioperative outcomes: risk assessment, patient preferences and performance measures", Massachussets General Hospital, Boston, MA
Jul, 2009	"Strategies to reduce cardiac risk of noncardiac surgery: An update to the AHA/ACC Guidelines" Massachussetts General Hospital, Boston, MA
Aug, 2009	"Strategies to reduce cardiac risk of noncardiac surgery", University of Alabama Department of Anesthesiology, Birmingham, AL
Oct, 2009	Preoperative cardiac assessment for noncardiac surgery" American Society of Anesthesiologists Annual Meeting. New Orleans, LA
Oct, 2009	"Preoperative cardiac evaluation for noncardiac surgery" in Panel on Preparing the cardiac patient for noncardiac surgery. American

	College of Surgeons Annual Meeting, Chicago, IL
Oct, 2009	"Improving perioperative outcomes: my journey into Risk Assessment, Patient Preferences and Performance Measures" Foundation for Anesthesia Education and Research Honorary Research Lecture. American Society of Anesthesiologists Annual Meeting. New Orleans
Nov, 2009	"How to deal with sudden death in your department", Society of Academic Anesthesiology Assocations Annual Meeting, Boston, MA
Dec, 2009	"Anesthesiologist: Measure thyself", Rovenstine Honorary Lecture at the PGA, New York, NY
Apr, 2010	"New insights: the latest data on perioperative outcome and anesthesiology practice". Society of Cardiovascular Anesthesiologists Annual Meeting. New Orleans, LA
Apr, 2010	"Strategies to reduce cardiac risk for noncardiac surgery." Australia and New Zealand College of Anaesthetists Annaul Meeting. Christchurch, NZ
Apr, 2010	"Risks of outpatient surgery". Day Surgery Conference, Australian and New Zealand College of Anaesthetists, Christchurch, NZ
Apr, 2010	"The Institute of Medicine Evidence for limiting resident duty hours". Association of University Anesthesiologists Annual Meeting. Denver, CO
May, 2010	"Improving perioperative outcomes". Day Surgery Conference, Australian and New Zealand College of Anaesthetists, Christchurch, NZ
Jul, 2010	"Risks of Outpatient Surgery", Evidence Based Perioperative Outcomes Meeting, London, England
Sep, 2010	"Strategies to reduce cardiac risk for noncardiac surgery." Walters Visiting Professor, University of Wisconsin, Madison, WI
Sep, 2010	"Development of EB Guideline into Practice: AHA/ACC Guideline" International Congress of Cardiovascular and Vascular Anesthesia, Beijing, CN
Oct, 2010	"Preoperative cardiac evaluation for noncardiac surgery" American Society of Anesthesiologists Annual Meeting, San Diego, CA
Oct, 2010	"Evidence supporting performance measurement and outcome". IN Panel on Performance Anxiety. American Society of Anesthesiologists Annual Meeting, San Diego, CA
Nov, 2010	"Clinical research in anesthesiology" Beijing, Shanghai, Guongzhou, Chonquin, CN
Nov, 2010	"Preoperative cardiac evaluation" University of Florida, Gainseville, FL
Mar, 2011	"Preoperative Cardiac Risk Assessment: Implementing the Guidelines into Practice" Perioperative Medicine Summitt 2011, Miami, FL
Mar, 2011	Panel on "Faculty leaders: how we were prepared for the leadership challenges we face; the leadership skills our successors will need"

	Council of Academic Specialties Annual meeting, American Association of Medical Colleges, Providence, RI
Mar, 2011	"Optimizing perioperative outcomes: my journey into guidelines, patient preferences and measurement", Crawford Long Lecture, Emory University
Apr, 2011	"Evidence-based medicine: how it should inform research and care",International Anesthesia Research Forum, Xi'An, CH
Apr, 2011	"How to look at data", "Is my paper important", "What reviewer and editors are looking for", Workshop on how to write a clinical paper, Xi'an, CH
Apr, 2011	"Strategies to reduce cardiac risk of noncardiac surgery", Anesthesiology and Critical Care Forum, Xi'An, CH
May, 2011	"Optimizing Perioperative Outcomes: Risk Assessment, Patient Preferences and Performance Measures", Shields Lecture, University of Toronto, Toronto, CA
May, 2011	"Cardiac risk stratification for non cardiac surgery: an update", Simposio Mostra Anestesia Rianimazion E Terapia Intensiva, Milan, IT
May, 2011	"Cardiac risk stratification for non cardiac surgery: an update", Simposio Mostra Anestesia Rianimazion E Terapia Intensiva, Milan, IT
May, 2011	"Cardiac risk stratification for non cardiac surgery: an update", Simposio Mostra Anestesia Rianimazion E Terapia Intensiva, Milan, IT
May, 2011	"Perioperative medicine and perioperative outcomes: a personal overview ", Simposio Mostra Anestesia Rianimazion E Terapia Intensiva, Milan, IT
May, 2011	"Perioperative strokes and beta-blockade ", Simposio Mostra Anestesia Rianimazion E Terapia Intensiva, Milan, IT
Jul, 2011	"Biomarkers", Evidence Based Perioperative Medicine Annual Meeting, London, England
Jul, 2011	"Improving Perioperative Outcomes", Evidence Based Perioperative Medicine Annual Meeting, London, England
Oct, 2011	"Improving Perioperative Outcomes", University of California, Irvine, CA
Oct, 2011	"Preoperative cardiac evaluation for noncardiac surgery" American Society of Anesthesiologists Annual Meeting, Chicago, IL
Oct, 2011	"The future of perioperative quality measurement in the landscape of health reform" in Panel on Quality mesurement and reporting in anesthesiology and perioperative care: current controversies and future directions. American Society of Anesthesiologists Annual Meeting, Chicago
Mar, 2012	"Care in the era of Healthcare reform: our role in the value proposition" Eliasberg Lecture, Department of Anesthesiology, Mount Sinai School of Medicine, New York, NY
Mar, 2012	"Strategies to reduce cardiac risk of noncardiac surgery: an update"

	Perioperative Medicine Summit, Miami, FL
Apr, 2012	"Academia and HCR: What does it mean for all 3 missions?" in Panel on Practice Management: From Private to Academics: Advice from the Top in Healthcare Reform Climate. Society of Cardiovascular Anesthesiologists, Boston, MA
May, 2012	"A personal journey into improving outcome" Keynote lecture at Cardiac Disease and Anaesthesia Symposium, Royal College of Anaesthetists, London, England
May, 2012	"Strategies to reduce cardiac risk of noncardiac surgery" Kampine Honoary Lecture, Medical College of Wisconsin, Milwaukee, WI
May, 2012	"Care in the era of Healthcare reform: _our role in the value proposition", Medical College of Wisconsin, Milwaukee, WI
Jun, 2012	"Preoperative Cardiac Evaluation for Noncardiac Surgery" Brigham & Women's Hospital, Boston, MA
Jul, 2012	"Care in the era of Healthcare reform: _our role in the value proposition", Massachusetts General Hospital, Boston MA
Aug, 2012	"Care in the era of U.S. Healthcare reform: _what will drive anesthesia staffing?" in University of Pennsylvania-Chinese Society of Anesthesiologists Communication Forum, Chongqing, China
Sep, 2012	"Guidelines and performance measures: How do you apply the evidence?". UCSF The Changing Practice Of Anesthesia 2012. San Francisco, CA
Sep, 2012	"Value from anesthesia care: where do we influence the outcome/cost equation in medicine?: UCSF The Changing Practice Of Anesthesia 2012. San Francisco, CA
Oct, 2012	"How we improve quality" on FAER Panel on The Science of Quality Improvement: What Leads to Improvement. American Society of Anesthesiologists Annual Meeting. Washington, DC
Oct, 2012	"AHA/ACC Guideline Update for Preoperative Evaluation and Testing in Non-cardiac Surgery" on Panel on Cardiovascular Guidelines: Update for the Patient with Cardiac Disease. American Society of Anesthesiologists Annual Meeting. Washington, DC
Oct, 2012	"Preoperative Cardiac Evaluation for Noncardiac Surgery". American Society of Anesthesiologists Annual Meeting. Washington, DC
Oct, 2012	"Pro: Beta-blockers P4P" on Pro/Con for Does Preoperative Beta-blockade help and should be a P4P Measure. American Society of Anesthesiologists Annual Meeting. Washington, DC
Apr, 2013	"PRO: PERFORMANCE MEASUREMENT: DOES IT MATTER?", Association of University Anesthesiologists, Miami, FL
Apr, 2013	"Bundled care and cardiac surgery:_what does it mean?", Society of Cardiovascular Anesthesiologists, Miami, FL
May, 2013	"Preoperative cardiac evaluation-should we bother?", Keynote lecture, Irish Congress of Anaesthesia 2013, Dublin
May, 2013	"Perioperative beta-blockers and statins- what do we really know?",

	Irish Congress of Anaesthesia 2013, Dublin
Jul, 2013	"Learning valuable lessons from large datasets!", Evidence-Based Perioperative Medicine (EBPOM), London
Jul, 2013	"Preoperative cardiac risk evaluation-where do we stand now?", Evidence-Based Perioperative Medicine (EBPOM), London
Oct, 2013	"Aspirin" on Panel on Perioperative cardiovascular and anti platelet agents: which to take, which to stop? an update. American Society of Anesthesiologists, San Francisco, CA
Oct, 2013	"Perioperative cardiac arrests: what is the evidence". Journal Symposium: cardiac arrest and resuscitation. American Society of Anesthesiologists, San Francisco, CA
Oct, 2013	"Implementation science" on FAER Panel: clinical research in anesthesia. American Society of Anesthesiologists, San Francisco, CA
Oct, 2013	"The Economic Imperative for perioperative medicine" in Panel on Perioperative medicine as the future of anesthesiology: why, who and how. American Society of Anesthesiologists, San Francisco, CA
Oct, 2013	"One chair's perspective: using measures for departmental reporting to CMS and other quality entities: leveraging the process to facilitate resident's and faculty's understanding and involvement in quality" in Panel on Performance measures, academic anesthesiology departments and MOCA: Is there a way to synergize the impact? American Society of Anesthesiologists, San Francisco, CA
Oct, 2013	"PRO: Raising both the stakes and the bar: anesthesiologists and surgeons sharing joint accountability for patient outcomes", American Society of Anesthesiologists, San Francisco, CA
Nov, 2013	"Preparing Felllows to be Faculty", Association of Anesthesiology Specialty Program Directors, Philadelphia, PA
Nov, 2013	"Importance of Health Policy Research to Academic Departments", Society of Academic Anesthesiology Associations, Philadelphia, PA
Feb, 2014	"Value in anesthesia: _when do we make a difference?", Asian Australasian Congress of Anesthesiologists, Aukland, NZ
Feb, 2014	"Evaluation of the cardiac patient for non-cardiac surgery", Asian Australasian Congress of Anesthesiologists, Aukland, NZ
Feb, 2014	"Beta-blockers and statin", Asian Australasian Congress of Anesthesiologists, Aukland, NZ
Apr, 2014	"The new guidelines on perioperative management of patients with heart disease undergoing non cardiac surgery", Oxford University, Oxford, England
Apr, 2014	"The new guidelines on perioperative management of patients with heart disease undergoing non cardiac surgery", Royal College of Anaesthetists, London, England
Jul, 2014	"Cardiac risk for non cardiac surgery", University of New Mexico, Albuquerque, NM
Oct, 2014	"Preoperative Cardiac Evaluation for Noncardiac Surgery",

	American Society of Anesthesiologists, New Orleans, LA
Oct, 2014	"Why Are Process Measures Fading into the Night?", American Society of Anesthesiologists Annual Meeting, New Orleans, LA
Oct, 2014	"PRO: Performance Metrics are an Efficient Way to Promote Enhanced Recovery", ERAS meeting at the ASA Annual Meeting, New Orleans, LA
Jan, 2015	"Improving perioperative outcomes: _Do we just need to apply the evidence?", University of California at Los Angeles, Los Angeles, CA
Mar, 2015	"Improving Medical Care: The Importance of Measuring Outcomes", Penn Wharton China Center Opening Symposium, Beijing, China
Mar, 2015	"The New AHA Guidelines", International Anesthesia Research Society, Honolulu, Hawaii
Mar, 2015	"The Economic Imperative for the Perioperative Surgical Home", International Anesthesia Research Society, Honolulu, Hawaii
Mar, 2015	"Performance_Measurement and new models of determining quality" University of Utah Biomedical Informatics, Salt Lake City, UT
Mar, 2015	"Preoperative cardiac evaluation for non cardiac surgery", Perioperative Medicine Summit 2015, Phoenix, AZ
May, 2015	"Preoperative cardiac evaluation for non cardiac surgery", World Congress of Enhanced Recovery After Surgery and Perioperative Medicine, Washington D.C.
Jul, 2015	"Measuring outcomes in perioperative care: new approaches and paradigms", EBPOM, London
Jul, 2015	"The impact of the ACC/AHA guidelines on reducing perioperative harm", EBPOM, London
Sep, 2015	"Measuring Perioperative Outcomes" Brigham and Women's Hospital, Boston, MA
Sep, 2015	"Strategies to reduce Cardiac Risk of Noncardiac Surgery" Brigham and Women's Hospital, Boston, MA
Sep, 2015	"The future of academic anesthesiology: leading change", Chinese Society of Anesthesiology Annual Meeting, Xi'An, China
Oct, 2015	"Strategies to Reduce Cardiac Risk for Noncardiac Surgery", Japanese Society of Cardiovascular Anesthesia, Fukuoka, Japan
Jan, 2016	"Performance measurement and new ways to measure performance", Penn State Hershey Anesthesiology and Perioperative Medicine, Hershey, PA
Jan, 2016	"Strategies to reduce cardiac risk of non cardiac surgery", Penn State Hershey Anesthesiology and Perioperative Medicine, Hershey, PA
Apr, 2016	"Impact of respiratory compromise in US Healthcare", Becker's Healthcare, Chicago, IL
Apr, 2016	"Does the use of Regional Anesthesia Impact Outcome in Patients with Cardiac Disease Undergoing Non-cardiac Surgery?" Indian Society of Anesthesiologists Delhi Chapter, Delhi, India

Apr, 2016	"Root cause analysis in anaesthesia: Why?" Indian Society of Anesthesiologists Delphi Chapter, Delphi, India
Apr, 2016	"Assessing the patient with CAD for non-cardiac surgery: what's new?", Indian Society of Anesthesiologists Delhi Chapter, Delphi, India
Apr, 2016	"Measuring Outcomes in Perioperative Care: New Approaches and Paradigms", American Society of Enhanced Recovery, Washington, DC
May, 2016	"Health Policy Research: University of Pennsylvania Health System", Association of University Anesthesiologists, San Francisco, CA
May, 2016	"Strategies to reduce cardiac risk of non cardiac surgery", Yale University Department of Anesthesiology, New Haven, CT
May, 2016	"Measuring Outcomes in the Era of Healthcare Reform", Yale University Department of Anesthesiology, New Haven, CT
May, 2016	"Preoperative Exercise Testing and Prehabilitation", International Anesthesia Research Society, San Francisco, CA
Jul, 2016	"Choosing wisely", Evidence based Perioperative Medicine Annual Meeting, London, England
Jul, 2016	"General Anaesthesia - A well tried solution", Evidence based Perioperative Medicine Annual Meeting, London, England
Aug, 2016	"Cost and quality containment", World Congress of Anaesthesiologists, Hong Kong
Aug, 2016	"Achieving value of perioperative care in the elderly", World Congress of Anaesthesiologists, Hong Kong
Aug, 2016	"Anesthesiologists in the value equation: beyond preventing anesthesia related complications", Chinese Society of Anesthesiologists Annual Meeting, Guangzhou, China
Aug, 2016	"Strategies to reduce cardiac risk of non cardiac surgery", Chinese Society of Anesthesiologists Annual Meeting, Guangzhou, China
Aug, 2016	"Improving health and transforming care through measurement: science and policy", Massachusetts General Hospital Department of Anesthesia, Boston, MA
Oct, 2016	"The Brain Health Initiative: What does the patient want to know and what do we want them to know", American Society of Anesthesiologists Annual Meeting, Chicago, IL
Oct, 2016	"Is the Perioperative Surgical Home a viable option for anesthesiology?: Con", American Society of Anesthesiologists Annual Meeting, Chicago IL
Oct, 2016	"Risk stratification tools from the preoperative to the postoperative period", American Society of Anesthesiologists Annual Meeting, Chicago, IL
Nov, 2016	"Panel on Why health is no one's business: economic incentive barriers to improving health" Global Action Summit, Nashville, TN
Mar, 2017	"The place for PhDs in the Medical Schools of Tomorrow: Clinical Department Perspective" Council for Faculty and Academic

	Societies, AAMC, Orlando, FL
Mar, 2017	"Aspirin should be continued preoperatively" in Debate on Perioperative Aspirin Therapy, Perioperative Medicine Summit, Fort Lauderdale, FL
Mar, 2017	"Evaluation Prior to Noncardiac Surgery: ACC/AHA Update", Perioperative Medicine Summit, Fort Lauderdale, FL
Sep, 2017	"Perioperative Brain Health Initiative: Anesthesiologist leadership in improving population health". Chinese Society of Anesthesiologists, Zhengzhou, CN
Sep, 2017	"Leading An Academic Departmentï¼šThe US Perspective On Demonstrating Value". Chinese Society of Anesthesiologists. Zhengzhou, China
Sep, 2017	"Strategies to reduce cardiac risk for non cardiac surgery". Polish Society of Anesthesiology and Intensive Care. Bydgoszcz, Poland
Sep, 2017	"Guidelines and Performance Measures: How do you apply the evidence?" Polish Society of Anesthesiology and Intensive Care. Bydgoszcz, Poland
Oct, 2017	"Strategies to reduce cardiac risk for non cardiac surgery", Boston, MA
Oct, 2017	"Quality Anesthesia: Medicine Measures, Patients Decide", Rovenstine Lecture, American Society of Anesthesiologists, Boston, MA
Oct, 2017	"Brain Health- A Global Safety Challenge", International Forum on Perioperative Safety and Quality, Boston, MA
Oct, 2017	"Quality Anesthesia: Medicine measures, patients decide", University of Kentucky, Lexington, KY
Nov, 2017	"The American perspective: The perioperative surgical home", Perioperative Medicine Special Interest Group of the Australian Society of Anesthesiologists, 6th Annual Australasian Symposium of Perioperative Medicine, Manly, Australia
Nov, 2017	"Value based care: A system overhaul", Perioperative Medicine Special Interest Group of the Australian Society of Anesthesiologists, 6th Annual Australasian Symposium of Perioperative Medicine, Manly, Australia
Nov, 2017	"Research Directions in Perioperative Medicine", Perioperative Medicine Special Interest Group of the Australian Society of Anesthesiologists, 6th Annual Australasian Symposium of Perioperative Medicine, Manly, Australia
Nov, 2017	"Quality Anesthesia: Medicine Measures, Patients Decide", Henry Ford Hospital, Detroit, MI
Dec, 2017	"The Cardiac Patient Presenting for Non-Cardiac Surgery Sub-Topic: Is there Any Value to Cardiology Consults During the Perioperative Period?", Postgraduate Assembly in Anesthesiology, New York, NY
Feb, 2018	"Strategies to reduce cardia risk of noncardiac surgery", University of Pittsburgh, Pittsburgh, PA

Mar, 2018	"Auditing, Reporting to the C-Suite", American Society of Enhanced Recovery, Ft. Lauderdale, FL
Mar, 2018	"Brain Health Initiative", Perioperative Medicine Summit, Ft. Lauderdale, FL
Mar, 2018	"CV Risk Assessment", Perioperative Medicine Summit, Ft. Lauderdale, FL
Mar, 2018	"Postoperative Care has to be Delivered by the Surgeon", American Society of Enhanced Recovery, Ft. Lauderdale, FL
Apr, 2018	"Payment reform, MACRA, Physician-Focused Payment Model update", EBPOM-USA Masters Course. A Perioperative Care Practicum; Atlanta, GA
Jul, 2018	"Perioperative brain health initiative: A population health safety initiative", Evidence Based Perioperative Medicine Symposium, London, England
Oct, 2018	"Perioperative Brain Health", Uniformed Services Society of Anesthesiologists (USSA)/Association of Veterans' Affairs Anesthesiologists (AVAA) Academic Meeting, San Francisco, CA
Oct, 2018	"Preparation of the elderly patient undergoing surgery: when do we need a preoperative consultation as opposed to skipping a clinic visit?", ICAA-CSA symposium, San Francisco, CA
Nov, 2018	"Quality of Perioperative care: using measurement to improve outcome", Asian Australasian Congress of Anaesthesiologists/Chinese Society of Anesthesiology Annual Meeting, Beijing, CN
Apr, 2019	"Patient decision making and engagement: How can we measure and improve it?", American Society of Enhanced Recovery Annual Meeting, Fort Lauderdale, FL
Apr, 2019	"Auditing, Reporting to the C-Suite", American Society of Enhanced Recovery Annual Meeting, Fort Lauderdale, FL
May, 2019	"Findings from the Perioperative Brain Health Initiative and Their Impact on Day-to-Day Practice", Harvard Anesthesiology Update 2019, Boston, MA
May, 2019	"Measuring Patient Outcomes in the Perioperative Period", Harvard Anesthesiology Update 2019, Boston, MA
Jul, 2019	"Brain Health (Peri-Operative Quality Initiative: POQI 6) - what can we do tomorrow?", Evidence-based Perioperative Medicine, London
Jul, 2019	"Decision making for elective and end of life care", Trainees with an Interest in Peri-Operative Medicine Annual Meeting, London
Jul, 2019	"Communication and Decision-Making in Perioperative Care", Cambridge University THIS Institute, Cambridge, England
Sep, 2020	"From Data to Policy: _My 30 year Journey", Eckenhoff Lecture, Department of Anesthesiology and Critical Care, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA
May, 2021	"The future of the specialty: how the pandemic and policy changes should influence", International Anesthesia Research Society. T.H. Seldon Lecture

May, 2021 "Preoperative cardiac evaluation for non cardiac surgery", Michael E. DeBakey Veterans Medical Center Grand Rounds, Houston, TX

Organizing Roles in Scientific Meetings:

1991 Meeting of Investigators of Heart Rate Variability
Unknown

1992 Meeting of Investigators of Heart Rate Variability
Unknown

1993 Meeting of Investigators of Heart Rate Variability
Unknown

1994 Meeting of Investigators of Heart Rate Variability
Unknown

Oct, 2012 Organizer, Investigators in Perioperative Health Services Research
Washington, DC

Jan, 2018 Planning Committee Member, Building the Evidence Base for Improving Health Care
Contributions, opportunities, and priorities, National Academy of Sciences
Washington, DC

Grants:

Current:

Assessing Hospital Quality of Care for Patients with Multimorbidity, NIH, 11/2019-6/2022 (Jeffrey Silber, PI), $79,433/annual direct costs (Role in grant: Co-I)

Outcomes in Patients with Multimorbidity at Ambulatory Surgical Centers, NIH, 7/2019-6/2022 (Jeffrey Silber, PI: Lee Fleisher, Co-Investigator), $43,300/annual direct costs (Role in grant: Co-I)

Neurocognitive Disorder after Appendectomy in the Elderly: A Natural Experiment , NIA, 4/2017-3/2022 (Jeffrey Silber, PI), $500,000/annual direct costs (Role in grant: Co-I)

A Practical Intervention To Improve Patient-Centered Outcomes After Hip Fractures Among Older Adults (Regain Trial), Patient Centered Outcomes Research Institute (Pcori), 10/2015-7/2022 (Mark D. Neuman, PI), $57,660/annual direct costs (Role in grant: Co-I)

Training In Critical Care Health Policy Research, National Heart, Lung, And Blood Institute/Nih/Dhhs, 5-T32-HL-098054-10, 5/2015-4/2020 (Scott Halpern, PI), $537,348/annual direct costs (Role in grant: Co-PI)

Past:

A matching Study of Outcomes and Costs at Teaching and Non-teaching Hospitals, Association of American Medical Colleges, 1/2016-12/2018 (Jeffrey Silber, M.D., Ph.D., PI: Lee A. Fleisher, M.D., Co-Investigator), $100,000/annual direct costs, 2% effort

(Role in grant: co-P.I.)

Understanding Multimorbidity through Multivariate Template Matching, NIA, 9/2015-9/2016 (Jeffrey Silber, M.D., Ph.D., PI), $238,095/annual direct costs, 1.25% effort (Role in grant: Co-I)

Support For Pharmacoepidemiology Training, Pfizer Inc., N/A, 1/2014-12/2015 (SEAN HENNESSY, PI), $39,352/annual direct costs (Role in grant: Co-PI)

Role Of Hif1a In Inflammation, Tissue Repair, And Cancer Of The Pancreas, American Association For Cancer Research, N/A, 7/2013-6/2016 (M. Celeste Simon, PI), $122,727/annual direct costs (Role in grant: Co-PI)

Mixed-Methods Assessment Of Faer'S Investments In Career Development, Foundation For Anesthesia Education And Research, IMPACT ANALYSIS, 7/2013-12/2014 (LEE A. FLEISHER, PI), $57,402/annual direct costs (Role in grant: PI)

Understanding Racial Disparities in Surgical Outcomes , NIH, 9/2012-8/2015 (Jeff Silber, PI), $387,785/annual direct costs, 5% effort (Role in grant: Co-investigator)

Chronic Disease Clinical Epidemiology Training In Guatemala And Peru, Fogarty International Center/Nih/Dhhs, 5-D43-TW-008317-05, 7/2010-6/2016 (Charles C. Branas, PI), $199,884/annual direct costs (Role in grant: Co-PI)

Improving process measurement, AHRQ, 1 R01 HS018338, 7/2010-6/2013 (Jeffrey H. Silber, PI), $375,000/annual direct costs, 2.5% effort (Role in grant: Co-I)

Training In Critical Care Health Policy Research, National Heart, Lung, And Blood Institute/Nih/Dhhs, 5-T32-HL-098054-05, 5/2010-4/2015 (DAVID A ASCH, PI), $483,132/annual direct costs, 2% effort (Role in grant: Co-PI)

Inspiratory Work Of Breathing During Proportional Assist Ventilation Compared With Assist Control Ventilation (Acv) In Acute Lung Injury (Ali), Tyco Healthcare, #2, 12/2007-8/2009 (Maurizio F. Cereda, PI), $8,829/annual direct costs (Role in grant: Co-PI)

A Prospective, Randomized, Double-Blinded Study Of The Effect On Improved Recovery Using The Sedline For The Titration Of Sevoflurane In Elderly Patients Undergoing Non-Cardiac Surgery After Beta-Adrenergic Blockade, Hospira, CP-09-003, 11/2007-9/2008 (JONATHAN W TANNER, PI), $31,683/annual direct costs (Role in grant: Co-PI)

Plan for Extracting Intraoperative Anesthesia Data to the ACS NSQIP Database, NLM, 8/2007-7/2009 (Clifford Ko, PI), $149,820/annual direct costs (Role in grant: Co-Investigator)

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Of Intravenous Methyinaltrexone (Moa-728) For The Treatment Of Post Operative Ileus, Wyeth-Ayerst Research, 3200L2-300-WWW, 3/2007-3/2009 (ASHISH C. SINHA, PI), $20,147/annual direct costs (Role in grant: Co-PI)

Use Of The Sedline Monitor In Gastrointestinal Endoscopy Cases, Hospira, SEDLINE, 9/2006-9/2007 (JONATHAN W TANNER, PI), $37,736/annual direct costs (Role in grant: Co-PI)

Obesity and Surgical Outcomes, NIDDK, 1 R01 DK073671-01A1, 7/2006-6/2011 (Jeffrey Silber, M.D., Ph.D., PI), $511,407/annual direct costs, 5% effort (Role in grant: Investigator)

Cltr: Aprepitant For The Prevention Of Postoperative Nausea And Vomiting, Merck & Co., Inc., 6/2004-3/2005 (LEE A. FLEISHER, PI), $2,869/annual direct costs (Role in grant: PI)

Evaluating patient information prescriptions in different service environments, National Library of Medicine, 10/2003-9/2006 (Nancy Roderer, M.D., PI), $150,000/annual direct costs, 5% effort (Role in grant: Co-Investigator, Single-center)

FOCUS, NIH, 5U01HL073958-02, 9/2003-8/2008 (Jeffrey Carson, PI), $1,000,000/annual direct costs (Role in grant: Consultant/Steering Committee, A randomized trial of two different transfusion triggers in patients with hip fractures to determine return of functional status.)

Phase III, multi-center, placebo-controlled, randomized, double-blind study to evaluate the efficacy of zoniporide administered perioperatively to subjects undergoing vascular surgery, Pfizer, 1/2002-6/2003 (Lee A. Fleisher, PI), $150,000/annual direct costs, 5% effort (Role in grant: PI)

Relationship between discharge hemoglobin level and patient-oriented outcomes during recovery from surgery, Advanced Transfusion Practices and Blood Research, 7/2001-6/2002 (Lee A. Fleisher, PI), $70,429/annual direct costs, 10% effort (Role in grant: PI)

Evidence review of management of atrial fibrillation in the post-coronary artery bypass patient, American College of Chest Physicians, 6/2001-11/2001 (Lee A. Fleisher, PI), $99,863/annual direct costs, 10% effort (Role in grant: PI)

Cost-effectiveness of ambulatory blood pressure monitoring, Agency for Healthcare Quality and Research, 9/2000-9/2001 (Larry Appel, PI), $250,000/annual direct costs, 2.5% effort (Role in grant: Co-Investigator)

Impact of location of care and patient factors on the rate of complication and readmissions after outpatient surgery: a claims analysis, Society of Ambulatory Anesthesia (SAMBA), 7/2000-6/2002 (Lee A. Fleisher, PI), $100,000/annual direct costs,

5% effort (Role in grant: PI)

A cost-findings study of the use of the hemosonic noninvasive cardiac output monitor compared to routine care in whipple surgery, Arrow International, 6/2000-12/2001 (Lee A. Fleisher, M.D., PI), $120,000/annual direct costs, 5% effort (Role in grant: PI)

A randomized study of esmolol versus nitroglycerin in high risk lower extremity procedures, Baxter Pharmaceutical, 6/2000-5/2001 (Lee A. Fleisher, M.D., PI), $100,000/annual direct costs, 5% effort (Role in grant: PI)

An open label, pharmacokinetic study to evaluate the pharmacokinetics, pharmacodynamics, toleration and safety of CP-597,396 administered for 24 hours in subjects undergoing coronary artery bypass (CABG) surgery, Pfizer, 4/2000-12/2001 (Lee A. Fleisher, PI), $200,000/annual direct costs, 5% effort (Role in grant: PI)

Phase II, multi-center, placebo-controlled, randomized, double-blind, dosing regimen optimization and dose-escalation study to evaluate the safety, toleration and clinical pharmacology of CP-597,396 administered in subjects undergoing vascular surgery, Pfizer, 4/2000-12/2001 (Lee A. Fleisher, PI), $300,000/annual direct costs, 5% effort (Role in grant: PI)

Phase III trigger study: A3181007 a double blind, placebo-controlled, parallel group study of the effects of Zoniporide on perioperative cardiac events in high risk subjects undergoing noncardiac vascular surgery, Pfizer, 4/2000-12/2000 (Lee A. Fleisher, PI), $300,000/annual direct costs, 5% effort (Role in grant: PI)

Cost effectiveness of preoperative evaluation before vascular surgery (CEPEVS), Maryland American Heart Association Grant-in-Aid, 1/2000-12/2001 (Lee A. Fleisher, PI), $60,000/annual direct costs, 10% effort (Role in grant: PI)

Perioperative anemia recovery from surgery trial (PARST), International Anesthesia Research Society, 1/2000-12/2001 (Lee A. Fleisher, M.D., PI), $75,000/annual direct costs, 5% effort (Role in grant: PI)

Anesthesia for cataract surgery, Agency for Health Care Policy & Research/Evidence Based Center, 1/2000-12/2000 (Lee A. Fleisher, PI), $249,000/annual direct costs, 10% effort (Role in grant: Co-PI)

Bayesian communication of clinical trials, National Library of Medicine, 10/1999-9/2002 (Harold Lehmann, PI), $249,211/annual direct costs, 1% effort (Role in grant: Evaluator)

Cost-effectiveness of perioperative ROMI protocols, Dade Pharmaceuticals, 1/1999-12/1999 (Lee A. Fleisher, PI), $108,000/annual direct costs, 5% effort (Role in grant: PI)

Pharmacologic modulation of cocaine effects, NIH, 1/1999-12/1999 (George Bigelow, PI), $331,935/annual direct costs, 5% effort (Role in grant: Co-Investigator)

Analysis of the medicare database to assess morbidity and mortality after outpatient anesthesia, Anesthesia Patient Safety Foundation, 1/1998-12/1998 (Lee A. Fleisher, PI), $42,800/annual direct costs, 10% effort (Role in grant: PI)

Remifentanil in microsuspension laryngoscopy, Glaxo Pharmaceuticals, 1/1997-12/1998 (Lee A. Fleisher, PI), $24,902/annual direct costs, 5% effort (Role in grant: PI)

Analysis of short- and long-term costs of cardiovascular disease in patients undergoing major vascular surgery: Analysis of medicare claims data, DuPont Pharmaceuticals, 1/1995-12/1996 (Lee A. Fleisher, PI), $20,000/annual direct costs, 5% effort (Role in grant: PI)

The effect of enalaprilat on heart rate variability, Merck Pharmaceuticals, 1/1995-12/1996 (Lee A. Fleisher, PI), $16,500/annual direct costs, 5% effort (Role in grant: PI)

ACR: A mechanism for disseminating information and improving patient satisfaction, Society of Ambulatory Anesthesia, 1/1994-12/1995 (Lee A. Fleisher, PI), $10,000/annual direct costs, 1% effort (Role in grant: PI)

Outpatient laparoscopic surgery trial, Glaxo Pharmaceuticals, 1/1994-12/1995 (Lee A. Fleisher, PI), $35,000/annual direct costs, 5% effort (Role in grant: PI)

Utilization of information from preoperative cardiac evaluation, Dupont Pharma, CG#94019, 1/1994-12/1995 (Lee A. Fleisher, PI), $15,000/annual direct costs, 5% effort (Role in grant: PI)

Anesthesia as a stress test, Caliber Medical, 1/1993-12/1994 (Lee A. Fleisher, PI), $25,000/annual direct costs, 1% effort (Role in grant: PI)

CAD mechanisms in high risk families: racial differences, NIH, NIH-92-HL-1-H, 1/1992-12/1996 (Lewis Becker, PI), $273,815/annual direct costs, 5% effort (Role in grant: Co-Investigator)

Methods of anesthesia and analgesia for aortic surgery, NIH, GM38177-05, 1/1992-12/1996 (Richard Traystman, PI), $248,355/annual direct costs, 5% effort (Role in grant: Co-Investigator)

Amlodipine and heart rate variability, Pfizer Pharmaceutical, 1/1992-12/1993 (Lee A. Fleisher, PI), $35,000/annual direct costs, 5% effort (Role in grant: PI)

Perioperative body temperature myocardial ischemia trial, Mallinckrodt Medical, 1/1992-12/1993 (Steve Frank, PI), $108,863/annual direct costs, 5% effort (Role in grant: Co-Investigator)

Power spectral analysis and reflex sympathetic activation in high risk patients undergoing

regional anesthesia, Society of Cardiovascular Anesthesiologists Starter Grant, 1/1991-12/1991 (Lee A. Fleisher, PI), $10,000/annual direct costs, 20% effort (Role in grant: PI)

Power spectral analysis and reflex sympathetic activation in high risk patients undergoing regional anesthesia, Foundation of Anesthesia Education and Research Young Investigator Award, 1/1991-12/1991 (Lee A. Fleisher, PI), $20,000/annual direct costs, 20% effort (Role in grant: PI)

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Research Publications, peer reviewed (print or other media):

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2. Fleisher, L. A., Rosenbaum, S. H., Nelson, A. H., Barash, P. G.: The predictive value of preoperative silent ischemia for postoperative ischemic cardiac events in vascular and nonvascular surgery patients. Am Heart J 122(4 Pt 1): 980-6, 1991.

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9. Deutschman C, Harris A, Fleisher LA: Changes in heart rate variability under propofol anesthesia: a possible explanation for propofol induced bradycardia. Anesth Analg 79: 373-377, 1994.

10. Fleisher LA, Frank SM, Shir Y, Estafanous M, Kelly S, Raja SN: Cardiac sympathovagal balance and peripheral sympathetic vasoconstriction: epidural vs. general anesthesia. Anesth Analg 79: 165-171, 1994.

11. Fleisher LA, Skolnick ED, Holroyd K, Lehmann H: Coronary artery revascularization before abdominal aortic aneurysm surgery: A decision analytic approach. Anesth Analg 79: 661-669, 1994.

12. Frank SM, Shir Y, Raja SN, Fleisher LA, Beattie C: Core hypothermia and skin surface temperature gradients: epidural vs. general anesthesia and the effects of age. Anesthesiology 80: 502-508, 1994.

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bayesian model for perioperative cardiac risk assessment in vascular surgery patient. J Am Coll Cardiol Page: 779-786, 1996.

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FLEISHER DECLARATION: EXHIBIT B

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

INTERIM UPDATE

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Committee on Practice Bulletins—Gynecology. This Practice Bulletin was developed by the Committee on Practice Bulletins—Gynecology in collaboration with Kurt T. Barnhart, MD, MSCE; and Jason M. Franasiak, MD, TS (ABB).

INTERIM UPDATE: This Practice Bulletin is updated as highlighted to clarify the guidance on the assessment of hCG levels after uterine aspiration in women with a pregnancy of unknown location.

Tubal Ectopic Pregnancy

Ectopic pregnancy *is defined as a pregnancy that occurs outside of the uterine cavity. The most common site of ectopic pregnancy is the fallopian tube. Most cases of tubal ectopic pregnancy that are detected early can be treated successfully either with minimally invasive surgery or with medical management using methotrexate. However, tubal ectopic pregnancy in an unstable patient is a medical emergency that requires prompt surgical intervention. The purpose of this document is to review information on the current understanding of tubal ectopic pregnancy and to provide guidelines for timely diagnosis and management that are consistent with the best available scientific evidence.*

Background

Epidemiology

According to the Centers for Disease Control and Prevention, ectopic pregnancy accounts for approximately 2% of all reported pregnancies (1). However, the true current incidence of ectopic pregnancy is difficult to estimate because many patients are treated in an outpatient setting where events are not tracked, and national surveillance data on ectopic pregnancy have not been updated since 1992 (1). Despite improvements in diagnosis and management, ruptured ectopic pregnancy continues to be a significant cause of pregnancy-related mortality and morbidity. In 2011–2013, ruptured ectopic pregnancy accounted for 2.7% of all pregnancy-related deaths and was the leading cause of hemorrhage-related mortality (2). The prevalence of ectopic pregnancy among women presenting to an emergency department with first-trimester vaginal bleeding, or abdominal pain, or both, has been reported to be as high as 18% (3).

Etiology

The fallopian tube is the most common location of ectopic implantation, accounting for more than 90% of cases (4). However, implantation in the abdomen (1%), cervix (1%), ovary (1–3%), and cesarean scar (1–3%) can occur and often results in greater morbidity because of delayed diagnosis and treatment (4). An ectopic pregnancy also can co-occur with an intrauterine pregnancy, a condition known as heterotopic pregnancy. The risk of heterotopic pregnancy among women with a naturally achieved pregnancy is estimated to range from 1 in 4,000 to 1 in 30,000, whereas the risk among women who have undergone in vitro fertilization is estimated to be as high as 1 in 100 (5, 6).

Risk Factors

One half of all women who receive a diagnosis of an ectopic pregnancy do not have any known risk factors (3). Women with a history of ectopic pregnancy are at increased risk of recurrence. The chance of a repeat ectopic pregnancy in a woman with a history of one ectopic pregnancy is approximately 10% (odds ratio [OR] 3.0; 95% CI, 2.1–4.4). In a woman with two or more prior ectopic pregnancies, the risk of recurrence increases to more than 25% (OR, 11.17; 95% CI, 4.0–29.5) (3). Other important risk factors for ectopic pregnancy include previous damage to the fallopian tubes, factors secondary to ascending pelvic infection, and prior pelvic or fallopian tube surgery (3, 7). Among women who become pregnant through the use of assisted reproductive technology, certain factors such as tubal factor infertility and multiple

embryo transfer are associated with an increased risk of ectopic pregnancy (8, 9). Women with a history of infertility also are at increased risk of ectopic pregnancy independent of how they become pregnant (7). Other less significant risk factors include a history of cigarette smoking and age older than 35 years (7).

Women who use an intrauterine device (IUD) have a lower risk of ectopic pregnancy than women who are not using any form of contraception because IUDs are highly effective at preventing pregnancy. However, up to 53% of pregnancies that occur with an IUD in place are ectopic (10). Factors such as oral contraceptive use, emergency contraception failure, previous elective pregnancy termination, pregnancy loss, and cesarean delivery have not been associated with an increased risk of ectopic pregnancy (3, 7, 11, 12).

Clinical Considerations and Recommendations

▶ *How is an ectopic pregnancy diagnosed?*

The minimum diagnostic evaluation of a suspected ectopic pregnancy is a transvaginal ultrasound evaluation and confirmation of pregnancy. Serial evaluation with transvaginal ultrasonography, or serum hCG level measurement, or both, often is required to confirm the diagnosis.

Women with clinical signs and physical symptoms of a ruptured ectopic pregnancy, such as hemodynamic instability or an acute abdomen, should be evaluated and treated urgently. Early diagnosis is aided by a high index of suspicion. Every sexually active, reproductive-aged woman who presents with abdominal pain or vaginal bleeding should be screened for pregnancy, regardless of whether she is currently using contraception (13, 14). Women who become pregnant and have known significant risk factors should be evaluated for possible ectopic pregnancy even in the absence of symptoms.

Transvaginal Ultrasonography

Ultrasonography can definitively diagnose an ectopic pregnancy when a gestational sac with a yolk sac, or embryo, or both, is noted in the adnexa (15, 16); however, most ectopic pregnancies do not progress to this stage (15). The ultrasound findings of a mass or a mass with a hypoechoic area that is separate from the ovary should raise suspicion for the presence of an ectopic pregnancy; however, its positive predictive value is only 80% (15) because these findings can be confused with pelvic structures, such as a paratubal cyst, corpus luteum, hydrosalpinx, endometrioma, or bowel. Although an early intrauterine gestational sac may be visualized as early as 5 weeks of gestation (17), definitive ultrasound evidence of an intrauterine pregnancy includes visualization of a gestational sac with a yolk sac or embryo (16). Visualization of a definitive intrauterine pregnancy eliminates ectopic pregnancy except in the rare case of a heterotopic pregnancy. Although a hypoechoic "sac-like" structure (including a "double sac sign") (18) in the uterus likely represents an intrauterine gestation, it also may represent a pseudogestational sac, which is a collection of fluid or blood in the uterine cavity that is sometimes visualized with ultrasonography in women with an ectopic pregnancy (19, 20).

Serum Human Chorionic Gonadotropin Measurement

Measurement of the serum hCG level aids in the diagnosis of women at risk of ectopic pregnancy. However, serum hCG values alone should not be used to diagnose an ectopic pregnancy and should be correlated with the patient's history, symptoms, and ultrasound findings (21, 22). Accurate gestational age calculation, rather than an absolute hCG level, is the best determinant of when a normal pregnancy should be seen within the uterus with transvaginal ultrasonography (23, 24). An intrauterine gestational sac with a yolk sac should be visible between 5 weeks and 6 weeks of gestation regardless of whether there are one or multiple gestations (25, 26). In the absence of such definitive information, the serum hCG level can be used as a surrogate for gestational age to help interpret a nondiagnostic ultrasonogram.

The "discriminatory level" is the concept that there is a hCG value above which the landmarks of a normal intrauterine gestation should be visible on ultrasonography. The absence of a possible gestational sac on ultrasound examination in the presence of a hCG measurement above the discriminatory level strongly suggests a nonviable gestation (an early pregnancy loss or an ectopic pregnancy). In 50–70% of cases, these findings are consistent with an ectopic pregnancy (27–29). However, the utility of the hCG discriminatory level has been challenged (24) in light of a case series that noted ultrasonography confirmation of an intrauterine gestational sac on follow-up when no sac was noted on initial scan and the serum hCG level was above the discriminatory level (30–32). If the concept of the hCG discriminatory level is to be used as a diagnostic aid in women at risk of ectopic pregnancy, the value should be conservatively high (eg, as high as 3,500 mIU/mL) to avoid the potential for misdiagnosis and possible interruption of an intrauterine pregnancy that a woman hopes to continue (24, 32). Women with a multiple gestation have higher hCG levels than those with a single gestation at any given gestational age and may have hCG levels above traditional discriminatory hCG levels before ultrasonography recognition (24).

Trends of Serial Serum Human Chorionic Gonadotropin

A single hCG concentration measurement cannot diagnose viability or location of a gestation. Serial hCG concentration measurements are used to differentiate normal from abnormal pregnancies (21, 22, 33, 34). When clinical findings suggest an abnormal gestation, a second hCG value measurement is recommended 2 days after the initial measurement to assess for an increase or decrease. Subsequent assessments of hCG concentration should be obtained 2–7 days apart, depending on the pattern and the level of change.

In early pregnancy, serum hCG levels increase in a curvilinear fashion until a plateau at 100,000 mIU/mL by 10 weeks of gestation. Guidelines regarding the minimal increase in hCG for a potentially viable intrauterine pregnancy have become more conservative (ie, slower increase) (21, 22) and have been demonstrated to be dependent on the initial value (35). There is a slower than expected increase in serum hCG levels for a normal gestation when initial values are high. For example, the expected rate of increase is 49% for an initial hCG level of less than 1,500 mIU/mL, 40% for an initial hCG level of 1,500–3,000 mIU/mL, and 33% for an initial hCG level greater than 3,000 mIU/mL (35). In early pregnancy, an increase in serum hCG of less than a minimal threshold in 48 hours is suspicious of an abnormal pregnancy (ectopic or early pregnancy loss) because 99% of normal intrauterine pregnancies will have a rate of increase faster than this minimum. However, even hCG patterns consistent with a growing or resolving gestation do not eliminate the possibility of an ectopic pregnancy (36).

Decreasing hCG values suggest a failing pregnancy and may be used to monitor spontaneous resolution, but this decrease should not be considered diagnostic. Approximately 95% of women with a spontaneous early pregnancy loss will have a decrease in hCG concentration of 21–35% in 2 days depending on initial hCG levels (34). A woman with decreasing hCG values and a possible ectopic pregnancy should be monitored until nonpregnant levels are reached because rupture of an ectopic pregnancy can occur while levels are decreasing or are very low.

Pregnancy of Unknown Location

A pregnant woman without a definitive finding of an intrauterine or ectopic pregnancy on ultrasound examination has a "pregnancy of unknown location" (37). A pregnancy of unknown location should not be considered a diagnosis, rather it should be treated as a transient state and efforts should be made to establish a definitive diagnosis when possible (16). A woman with a pregnancy of unknown location who is clinically stable and has a desire to continue the pregnancy, if intrauterine, should have a repeat transvaginal ultrasound examination, or serial measurement of hCG concentration, or both, to confirm the diagnosis and guide management (22, 37). Follow-up to confirm a diagnosis of ectopic pregnancy in a stable patient, especially at first clinical encounter, is recommended to eliminate misdiagnosis and to avoid unnecessary exposure to methotrexate, which can lead to interruption or teratogenicity of an ongoing intrauterine pregnancy (16, 38, 39). The first step is to assess for the possibility that the gestation is advancing.

When the possibility of a progressing intrauterine gestation has been reasonably excluded, uterine aspiration can help to distinguish early intrauterine pregnancy loss from ectopic pregnancy by identifying the presence or absence of intrauterine chorionic villi. Choosing the appropriate time and intervention should be done through shared decision making, incorporating the patient's values and preferences regarding maternal risk and the possibility of interrupting a progressing pregnancy. If chorionic villi are found, then failed intrauterine pregnancy is confirmed and no further evaluation is necessary. If chorionic villi are not confirmed, hCG levels should be monitored, with the first measurement taken 12–24 hours after aspiration. A plateau or increase in hCG postprocedure suggests that evacuation was incomplete or there is a nonvisualized ectopic pregnancy, and further treatment is warranted. Although the change at which hCG is considered to have plateaued is not precisely defined, it would be reasonable to consider levels to have plateaued if they have decreased by less than 10–15%. Large decreases in hCG levels are more consistent with failed intrauterine pregnancy than ectopic pregnancy. In two small series of women undergoing uterine aspiration for pregnancy of unknown location, nearly all women with a decrease in hCG levels of 50% or greater within 12–24 hours after aspiration had failed intrauterine pregnancies (29, 40). Patients with a decrease in hCG of 50% or greater can be monitored with serial hCG measurements, with further treatment reserved for those whose levels plateau or increase, or who develop symptoms of ectopic pregnancy. Management of patients with an hCG decrease of less than 50% should be individualized, as while failed intrauterine pregnancy is more frequent, ectopic pregnancy risk is appreciable. One study (29) noted 55.6% of patients with ectopic pregnancies had an hCG decrease of more than 10%, 23.5% had a decrease of more than 30%, and 7.1% had a decrease of more than 50%. In a series of patients who had an initial decrease of hCG levels between 15% and 50% 12–24 hours after office uterine aspiration for pregnancy

of unknown location who were monitored with serial hCG measurement, 3 of 46 patients had rising or plateauing hCG levels necessitating treatment for ectopic pregnancy (41). The other patients had resolving hCG levels, and were presumed to have failed intrauterine pregnancies. Patients with an hCG decline between 15% and 50% 12–24 hours after aspiration require at least close follow-up with serial hCG measurement, with consideration of treatment for ectopic pregnancy based on clinical factors such as plateau or increase in hCG, development of symptoms, or high clinical suspicion or strong risk factors for ectopic pregnancy (29, 40, 41).

There is debate among experts about the need to determine pregnancy location by uterine aspiration before providing methotrexate (42, 43). Proponents cite the importance of confirming the diagnosis to avoid unnecessary exposure to methotrexate and to help guide management of the current pregnancy and future pregnancies (37, 42). Arguments against the need for a definitive diagnosis include concern about the increased risk of tubal rupture because of delay in treatment while diagnosis is established and the increased health-care costs associated with additional tests and procedures (43). However, with close follow-up during this diagnostic phase, the risk of rupture is low. In one large series with serial hCG measurement of women with pregnancies of unknown location, the risk of rupture of an ectopic pregnancy during surveillance to confirm diagnosis was as low as 0.03 % among all women at risk and as low as 1.7% among all ectopic pregnancies diagnosed (22). In addition, presumptive treatment with methotrexate has not been found to confer a significant cost savings or to decrease the risk of complications (44). The choice of performing a uterine aspiration before treatment with methotrexate should be guided by a discussion with the patient regarding the benefits and risks, including the risk of teratogenicity in the case of an ongoing intrauterine pregnancy and exposure to methotrexate.

▶ *Who are candidates for medical management of ectopic pregnancy?*

Medical management with methotrexate can be considered for women with a confirmed or high clinical suspicion of ectopic pregnancy who are hemodynamically stable, who have an unruptured mass, and who do not have absolute contraindications to methotrexate administration (45). These patients generally also are candidates for surgical management. The decision for surgical management or medical management of ectopic pregnancy should be guided by the initial clinical, laboratory, and radiologic data as well as patient-informed choice based on a discussion of the benefits and risks of each approach. Women who choose methotrexate therapy should be counseled about the importance of follow-up surveillance.

Methotrexate

Methotrexate is a folate antagonist that binds to the catalytic site of dihydrofolate reductase, which interrupts the synthesis of purine nucleotides and the amino acids serine and methionine, thereby inhibiting DNA synthesis and repair and cell replication. Methotrexate affects actively proliferating tissues, such as bone marrow, buccal and intestinal mucosa, respiratory epithelium, malignant cells, and trophoblastic tissue. Systemic methotrexate has been used to treat gestational trophoblastic disease since 1956 and was first used to treat ectopic pregnancy in 1982 (46). There are no recommended alternative medical treatment strategies for ectopic pregnancy beyond intramuscular methotrexate. Although oral methotrexate therapy for ectopic pregnancy has been studied, the outcomes data are sparse and indicate that benefits are limited (47).

Contraindications

Box 1 lists absolute and relative contraindications to methotrexate therapy (45). Before administering methotrexate, it is important to reasonably exclude the presence of an intrauterine pregnancy. In addition, methotrexate administration should be avoided in patients with clinically significant elevations in serum creatinine, liver transaminases, or bone marrow dysfunction indicated by significant anemia, leukopenia, or thrombocytopenia. Because methotrexate affects all rapidly dividing tissues within the body, including bone marrow, the gastrointestinal mucosa, and the respiratory epithelium, it should not be given to women with blood dyscrasias or active gastrointestinal or respiratory disease. However, asthma is not an exclusion to the use of methotrexate. Methotrexate is directly toxic to the hepatocytes and is cleared from the body by renal excretion; therefore, methotrexate typically is not used in women with liver or kidney disease.

Relative contraindications for the use of methotrexate (Box 1) do not serve as absolute cut-offs but rather as indicators of potentially reduced effectiveness in certain settings. For example, a high initial hCG level is considered a relative contraindication. Systematic review evidence shows a failure rate of 14.3% or higher with methotrexate when pretreatment hCG levels are higher than 5,000 mIU/mL compared with a 3.7% failure rate for hCG levels less than 5,000 mIU/mL (48). Of note, studies often have excluded patients from methotrexate treatment when hCG levels are greater than

Box 1. Contraindications to Methotrexate Therapy

Absolute Contraindications

- Intrauterine pregnancy
- Evidence of immunodeficiency
- Moderate to severe anemia, leukopenia, or thrombocytopenia
- Sensitivity to methotrexate
- Active pulmonary disease
- Active peptic ulcer disease
- Clinically important hepatic dysfunction
- Clinically important renal dysfunction
- Breastfeeding
- Ruptured ectopic pregnancy
- Hemodynamically unstable patient
- Inability to participate in follow-up

Relative Contraindications

- Embryonic cardiac activity detected by transvaginal ultrasonography
- High initial hCG concentration
- Ectopic pregnancy greater than 4 cm in size as imaged by transvaginal ultrasonography
- Refusal to accept blood transfusion

Modified from Medical treatment of ectopic pregnancy: a committee opinion. Practice Committee of American Society for Reproductive Medicine. Fertil Steril 2013;100:638–44.

5,000 mIU/mL based on expert opinion that these levels are a relative contraindication to medical management. Other predictors of methotrexate treatment failure include the presence of an advanced or rapidly growing gestation (as evidenced by fetal cardiac activity) and a rapidly increasing hCG concentration (greater than 50% in 48 hours) (48–50).

▶ ***What methotrexate regimens are used in the management of ectopic pregnancy, and how do they compare in effectiveness and risk of adverse effects?***

There are three published protocols for the administration of methotrexate to treat ectopic pregnancy: 1) a single-dose protocol (51), 2) a two-dose protocol (52), and 3) a fixed multiple-dose protocol (53) (Box 2). The single-dose regimen is the simplest of the three regimens; however, an additional dose may be required to ensure resolution in up to one quarter of patients (54, 55). The two-dose regimen was first proposed in 2007 in an effort to combine the efficacy of the multiple-dose protocol with the favorable adverse effect profile of the single-dose regimen (55). The two-dose regimen adheres to the same hCG monitoring schedule as the single-dose regimen, but a second dose of methotrexate is administered on day 4 of treatment. The multiple-dose methotrexate regimen involves up to 8 days of treatment with alternating administration of methotrexate and folinic acid, which is given as a rescue dose to minimize the adverse effects of the methotrexate.

The overall treatment success of systemic methotrexate for ectopic pregnancy, defined as resolution of the ectopic pregnancy without the need for surgery, in observational studies ranges from approximately 70% to 95% (55). Resolution of an ectopic pregnancy may depend on the methotrexate treatment regimen used and the initial hCG level. However, there is no clear consensus in the literature regarding the optimal methotrexate regimen for the management of ectopic pregnancy. The choice of methotrexate protocol should be guided by the initial hCG level and discussion with the patient regarding the benefits and risks of each approach. In general, the single-dose protocol may be most appropriate for patients with a relatively low initial hCG level or a plateau in hCG values, and the two-dose regimen may be considered as an alternative to the single-dose regimen, particularly in women with an initial high hCG value.

Single-Dose Versus Multiple-Dose

Observational studies that compared the single-dose and multiple-dose regimens have indicated that although the multiple-dose regimen is statistically more effective (92.7% versus 88.1%, respectively; P=.035) (single-dose

Box 2. Methotrexate Treatment Protocols

Single-dose regimen*

- Administer a single dose of methotrexate at a dose of 50 mg/m^2 intramuscularly on day 1
- Measure hCG level on posttreatment day 4 and day 7
  - If the decrease is greater than 15%, measure hCG levels weekly until reaching nonpregnant level
  - If decrease is less than 15%, readminister methotrexate at a dose of 50 mg/m^2 intramuscularly and repeat hCG level
  - If hCG does not decrease after two doses, consider surgical management
- If hCG levels plateau or increase during follow-up, consider administering methotrexate for treatment of a persistent ectopic pregnancy

Two-dose regimen†

- Administer methotrexate at a dose of 50 mg/m^2 intramuscularly on day 1
- Administer second dose of methotrexate at a dose of 50 mg/m^2 intramuscularly on day 4
- Measure hCG level on posttreatment day 4 and day 7
  - If the decrease is greater than 15%, measure hCG levels weekly until reaching nonpregnant level
  - If decrease is less than 15%, readminister methotrexate 50 mg/m^2 intramuscularly on day 7 and check hCG levels on day 11
  - If hCG levels decrease 15% between day 7 and day 11, continue to monitor weekly until reaching nonpregnant levels
  - If the decrease is less than 15% between day 7 and day 11, readminister dose of methotrexate 50 mg/m^2 intramuscularly on day 11 and check hCG levels on day 14
  - If hCG does not decrease after four doses, consider surgical management
- If hCG levels plateau or increase during follow-up, consider administering methotrexate for treatment of a persistent ectopic pregnancy

Fixed multiple-dose regimen‡

- Administer methotrexate 1 mg/kg intramuscularly on days 1, 3, 5, 7; alternate with folinic acid 0.1 mg/kg intramuscularly on days 2, 4, 6, 8
- Measure hCG levels on methotrexate dose days and continue until hCG has decreased by 15% from its previous measurement
  - If the decrease is greater than 15%, discontinue administration of methotrexate and measure hCG levels weekly until reaching nonpregnant levels (may ultimately need one, two, three, or four doses)
  - If hCG does not decrease after four doses, consider surgical management
- If hCG levels plateau or increase during follow-up, consider administering methotrexate for treatment of a persistent ectopic pregnancy

Abbreviation: hCG, human chorionic gonadotropin.

*Stovall TG, Ling FW. Single-dose methotrexate: an expanded clinical trial. Am J Obstet Gynecol 1993;168:1759-62; discussion 1762–5.

†Barnhart K, Hummel AC, Sammel MD, Menon S, Jain J, Chakhtoura N. Use of "2-dose" regimen of methotrexate to treat ectopic pregnancy. Fertil Steril 2007;87:250–6.

‡Rodi IA, Sauer MV, Gorrill MJ, Bustillo M, Gunning JE, Marshall JR, et al. The medical treatment of unruptured ectopic pregnancy with methotrexate and citrovorum rescue: preliminary experience. Fertil Steril 1986;46:811–3.

failure OR, 1.71; 95% CI, 1.04–2.82), the single-dose regimen is associated with a decreased risk of adverse effects (OR, 0.44; 95% CI, 0.31–0.63) (55). However, a more recent systematic review of randomized controlled trials showed similar rates of successful resolution with the single-dose and multiple-dose regimens (relative risk [RR], 1.07; 95% CI, 0.99–1.17) and an increased risk of adverse effects with the multiple-dose protocol (RR, 1.64; 95% CI, 1.15–2.34) (56).

Single-Dose Versus Two-Dose

A systematic review and meta-analysis of three randomized controlled trials showed similar rates of successful resolution for the two-dose and single-dose protocols (RR, 1.09; 95% CI 0.98–1.20) and comparable risk of adverse effects (RR, 1.33; 95% CI, 0.92–1.94) (56). However, in two of the three trials included in the review, the two-dose regimen was associated with greater success among women with high initial hCG levels. In the first trial, there was a nonstatistically significant trend toward greater success for the two-dose regimen in the subgroup with an initial hCG level greater than 5,000 mIU/mL (80.0% versus 58.8%, P=.279) (RR, 0.74; 95% CI, 0.47–1.16) (57). The second trial reported a statistically significant higher success rate for the two-dose regimen versus the single-dose regimen in patients with initial serum hCG levels between 3,600 mIU/mL and 5,500 mIU/mL (88.9% versus 57.9%, P=.03) (OR 5.80; 95% CI, 1.29–26.2) (58).

▶ What surveillance is needed after methotrexate treatment?

After administration of methotrexate treatment, hCG levels should be serially monitored until a nonpregnancy level (based upon the reference laboratory assay) is reached (51). Close monitoring is required to ensure disappearance of trophoblastic activity and to eliminate the possibility of persistent ectopic pregnancy. During the first few days after treatment, the hCG level may increase to levels higher than the pretreatment level but then should progressively decrease to reach a nonpregnant level (51). Failure of the hCG level to decrease by at least 15% from day 4 to day 7 after methotrexate administration is associated with a high risk of treatment failure and requires additional methotrexate administration (in the case of the single-dose or two-dose regimen) or surgical intervention (51). Methotrexate treatment failure in patients who did not undergo pretreatment uterine aspiration should raise concern for the presence of an abnormal intrauterine gestation. In these patients, uterine aspiration should be considered before repeat methotrexate administration or surgical management, unless there is clear evidence of a tubal ectopic pregnancy. Ultrasound surveillance of resolution of an ectopic pregnancy is not routinely indicated because findings do not predict rupture or time to resolution (59, 60). Resolution of serum hCG levels after medical management is usually complete in 2–4 weeks but can take up to 8 weeks (55). The resolution of hCG levels is significantly faster in patients successfully treated with the two-dose methotrexate regimen compared with the single-dose regimen (25.7±13.6 versus 31.9±14.1 days; P>.025) (57).

▶ What are the potential adverse effects of systemic methotrexate administration?

Adverse effects of methotrexate usually are dependent on dose and treatment duration. Because methotrexate affects rapidly dividing tissues, gastrointestinal problems (eg, nausea, vomiting, and stomatitis) are the most common adverse effects after multiple doses. Vaginal spotting is expected. It is not unusual for women treated with methotrexate to experience abdominal pain 2–3 days after administration, presumably from the cytotoxic effect of the drug on the trophoblastic tissue. In the absence of signs and symptoms of overt tubal rupture and significant hemoperitoneum, abdominal pain usually can be managed expectantly by monitoring a woman's hemoglobin level and intraperitoneal fluid amount with transvaginal ultrasonography.

Elevation of liver enzymes is a less commonly reported adverse effect and typically resolves after discontinuing methotrexate use (61). Alopecia also is a rare adverse effect of the low doses used to treat ectopic pregnancy. Cases of pneumonitis also have been reported, and women should be counseled to report any fever or respiratory symptoms to their physicians (62).

▶ How should women be counseled regarding the treatment effects of methotrexate?

Patients treated with methotrexate should be counseled about the risk of ectopic pregnancy rupture; about avoiding certain foods, supplements, or drugs that can decrease efficacy; and about the importance of not becoming pregnant again until resolution has been confirmed. It is important to educate patients about the symptoms of tubal rupture and to emphasize the need to seek immediate medical attention if these symptoms occur. Vigorous activity and sexual intercourse should be avoided until confirmation of resolution because of the theoretical risk of inducing rupture of the ectopic pregnancy. Additionally, practitioners should limit pelvic and ultrasound examinations when possible. Patients should be advised to avoid folic acid supplements, foods

that contain folic acid, and nonsteroidal antiinflammatory drugs during therapy because these products may decrease the efficacy of methotrexate. Avoidance of narcotic analgesic medications, alcohol, and gas-producing foods are recommended so as not to mask, or be confused with, escalation of symptoms of rupture. Sunlight exposure also should be avoided during treatment to limit the risk of methotrexate dermatitis (63).

Before treatment with methotrexate, women should be counseled about the potential for fetal death or teratogenic effects when administered during pregnancy. The product labeling approved by the U.S. Food and Drug Administration recommends that women avoid pregnancy during treatment and for at least one ovulatory cycle after methotrexate therapy (63). Methotrexate is cleared from the serum before the 4–12 weeks necessary for the resolution of the ectopic gestation and ovulation in the next cycle (64, 65). However, there are reports of methotrexate detectable in liver cells 116 days past exposure (66). Limited evidence suggests that the frequency of congenital anomalies or early pregnancy loss is not elevated in women who have become pregnant shortly after methotrexate exposure (66). However, perhaps based on the timing of methotrexate's clearance from the body, some experts continue to recommend that women delay pregnancy for at least 3 months after the last dose of methotrexate (67).

▶ *How does methotrexate treatment affect subsequent fertility?*

Patients can be counseled that available evidence, although limited, suggests that methotrexate treatment of ectopic pregnancy does not have an adverse effect on subsequent fertility or on ovarian reserve. A prospective observational study noted no difference in anti-müllerian hormone levels or reproductive outcomes after administration of methotrexate (68). Furthermore, a systematic review of women undergoing fertility treatment found no significant differences in the mean number of oocytes retrieved during the cycles before and after methotrexate administration (69).

▶ *Who are candidates for surgical management of ectopic pregnancy?*

In clinically stable women in whom a nonruptured ectopic pregnancy has been diagnosed, laparoscopic surgery or intramuscular methotrexate administration are safe and effective treatments. The decision for surgical management or medical management of ectopic pregnancy should be guided by the initial clinical, laboratory, and radiologic data as well as patient-informed choice based on a discussion of the benefits and risks of each approach. Surgical management of ectopic pregnancy is required when a patient is exhibiting any of the following: hemodynamic instability, symptoms of an ongoing ruptured ectopic mass (such as pelvic pain), or signs of intraperitoneal bleeding.

Surgical management is necessary when a patient meets any of the absolute contraindications to medical management listed in Box 1 and should be considered when a patient meets any of the relative contraindications. Surgical management should be employed when a patient who initially elects medical management experiences a failure of medical management. Surgical treatment also can be considered for a clinically stable patient with a nonruptured ectopic pregnancy or when there is an indication for a concurrent surgical procedure, such as tubal sterilization or removal of hydrosalpinx when a patient is planning to undergo subsequent in vitro fertilization.

Surgical management generally is performed using laparoscopic salpingectomy (removal of part or all of the affected fallopian tube) or laparoscopic salpingostomy (removal of the ectopic pregnancy while leaving the affected fallopian tube in situ). Laparotomy typically is reserved for unstable patients, patients with a large amount of intraperitoneal bleeding, and patients in whom visualization has been compromised at laparoscopy.

▶ *How do medical management and surgical management of ectopic pregnancy compare in effectiveness and risk of complications?*

Medical management of ectopic pregnancy avoids the inherent risks of surgery and anesthesia. However, compared with laparoscopic salpingectomy, medical management of ectopic pregnancy has a lower success rate and requires longer surveillance, more office visits, and phlebotomy. Randomized trials that compared medical management of ectopic pregnancy with methotrexate to laparoscopic salpingostomy have demonstrated a statistically significant lower success rate with the use of single-dose methotrexate (relative rate for success, 0.82; 95% CI, 0.72–0.94) and no difference with the use of multidose methotrexate (relative rate for success, 1.8; 95% CI, 0.73–4.6) (70). Comparing systemic methotrexate with tube-sparing laparoscopic surgery, randomized trials have shown no difference in overall tubal preservation, tubal patency, repeat ectopic pregnancy, or future pregnancies (70).

Medical management of ectopic pregnancy is cost effective when laparoscopy is not needed to make the diagnosis and hCG values are less 1,500 mIU/mL (71). Surgical management of ectopic pregnancy is more cost

effective if time to resolution is expected to be prolonged, or there is a relatively high chance of medical management failure, such as in cases with high or increasing hCG values or when embryonic cardiac activity is detected (72, 73).

How do salpingostomy and salpingectomy compare in effectiveness and fertility outcomes in the management of ectopic pregnancy?

The decision to perform a salpingostomy or salpingectomy for the treatment of ectopic pregnancy should be guided by the patient's clinical status, her desire for future fertility, and the extent of fallopian tube damage. Randomized controlled trials that compared salpingectomy with salpingostomy for the management of ectopic pregnancy have found no statistically significant difference in the rates of subsequent intrauterine pregnancy (RR, 1.04; 95% CI, 0.899–1.21) or repeat ectopic pregnancy (RR, 1.30; 95% CI, 0.72–2.38) (74). In contrast, cohort study findings indicate that salpingostomy is associated with a higher rate of subsequent intrauterine pregnancy (RR, 1.24; 95% CI, 1.08–1.42) but also with an increased risk of repeat ectopic pregnancy (10% versus 4%; RR, 2.27; 95% CI, 1.12–4.58) compared with salpingectomy (74).

In general, salpingectomy is the preferred approach when severe fallopian tube damage is noted and in cases in which there is significant bleeding from the proposed surgical site. Salpingectomy can be considered in cases of desired future fertility when the patient has a healthy contralateral fallopian tube. However, salpingostomy should be considered in patients who desire future fertility but have damage to the contralateral fallopian tube and in whom removal would require assisted reproduction for future childbearing. When salpingostomy is performed, it is important to monitor the patient with serial hCG measurement to ensure resolution of ectopic trophoblastic tissue. If there is concern for incomplete resection, a single prophylactic dose of methotrexate may be considered (45).

Who are candidates for expectant management of diagnosed ectopic pregnancy?

There may be a role for expectant management of ectopic pregnancy in specific circumstances. Candidates for successful expectant management of ectopic pregnancy should be asymptomatic; should have objective evidence of resolution (generally, manifested by a plateau or decrease in hCG levels); and must be counseled and willing to accept the potential risks, which include tubal rupture, hemorrhage, and emergency surgery. If the initial hCG level is less than 200 mIU/mL, 88% of patients will experience spontaneous resolution; lower spontaneous resolution rates can be anticipated with higher hCG levels (75). In a single small randomized trial of women with hCG levels less than 2,000 mIU/mL, expectant management was not associated with a statistically significant lower treatment success than single-dose methotrexate for the management of ectopic pregnancy (59% versus 76%, respectively) (RR, 1.3; 95% CI, 0.9–1.8) (76). Reasons for abandoning expectant management include intractable or significantly increased pain, insufficient decrease of hCG levels, or tubal rupture with hemoperitoneum.

Summary of Recommendations

The following recommendations are based on good and consistent scientific evidence (Level A):

- In clinically stable women in whom a nonruptured ectopic pregnancy has been diagnosed, laparoscopic surgery or intramuscular methotrexate administration are safe and effective treatments. The decision for surgical management or medical management of ectopic pregnancy should be guided by the initial clinical, laboratory, and radiologic data as well as patient-informed choice based on a discussion of the benefits and risks of each approach.
- Surgical management of ectopic pregnancy is required when a patient is exhibiting any of the following: hemodynamic instability, symptoms of an ongoing ruptured ectopic mass (such as pelvic pain), or signs of intraperitoneal bleeding.

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- Serum hCG values alone should not be used to diagnose an ectopic pregnancy and should be correlated with the patient's history, symptoms, and ultrasound findings.
- If the concept of the hCG discriminatory level is to be used as a diagnostic aid in women at risk of ectopic pregnancy, the value should be conservatively high (eg, as high as 3,500 mIU/mL) to avoid the potential for misdiagnosis and possible interruption of an intrauterine pregnancy that a woman hopes to continue.
- The decision to perform a salpingostomy or salpingectomy for the treatment of ectopic pregnancy

should be guided by the patient's clinical status, her desire for future fertility, and the extent of fallopian tube damage.

- The choice of methotrexate protocol should be guided by the initial hCG level and discussion with the patient regarding the benefits and risks of each approach. In general, the single-dose protocol may be most appropriate for patients with a relatively low initial hCG level or a plateau in hCG values, and the two-dose regimen may be considered as an alternative to the single-dose regimen, particularly in women with an initial high hCG value.
- Failure of the hCG level to decrease by at least 15% from day 4 to day 7 after methotrexate administration is associated with a high risk of treatment failure and requires additional methotrexate administration (in the case of the single-dose or two-dose regimen) or surgical intervention.
- Patients can be counseled that available evidence, although limited, suggests that methotrexate treatment of ectopic pregnancy does not have an adverse effect on subsequent fertility or on ovarian reserve.
- There may be a role for expectant management of ectopic pregnancy in specific circumstances.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- The minimum diagnostic evaluation of a suspected ectopic pregnancy is a transvaginal ultrasound evaluation and confirmation of pregnancy. Serial evaluation with transvaginal ultrasonography, or serum hCG level measurement, or both, often is required to confirm the diagnosis.
- A woman with a pregnancy of unknown location who is clinically stable and has a desire to continue the pregnancy, if intrauterine, should have a repeat transvaginal ultrasound examination, or serial measurement of hCG concentration, or both, to confirm the diagnosis and guide management.
- Medical management with methotrexate can be considered for women with a confirmed or high clinical suspicion of ectopic pregnancy who are hemodynamically stable, who have an unruptured mass, and who do not have absolute contraindications to methotrexate administration.
- After administration of methotrexate treatment, hCG levels should be serially monitored until a nonpregnancy level (based upon the reference laboratory assay) is reached.
- Patients treated with methotrexate should be counseled about the risk of ectopic pregnancy rupture; about avoiding certain foods, supplements, or drugs that can decrease efficacy; and about the importance of not becoming pregnant again until resolution has been confirmed.

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Tubal ectopic pregnancy. ACOG Practice Bulletin No. 193. American College of Obstetricians and Gynecologists. Obstet Gynecol 2018; 131:e91–103.

The MEDLINE database, the Cochrane Library, and ACOG's own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 2000 and September 2017. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

I	Evidence obtained from at least one properly designed randomized controlled trial.
II-1	Evidence obtained from well-designed controlled trials without randomization.
II-2	Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

FLEISHER DECLARATION: EXHIBIT C

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ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician–Gynecologists

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Committee on Practice Bulletins—Obstetrics. This Practice Bulletin was developed by the American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics in collaboration with Jimmy Espinoza, MD, MSc; Alex Vidaeff, MD, MPH; Christian M. Pettker, MD; and Hyagriv Simhan, MD.

INTERIM UPDATE: The content of this Practice Bulletin has been updated as highlighted (or removed as necessary) to include limited, focused editorial corrections to platelet counts, diagnostic criteria for preeclampsia (Box 2), and preeclampsia with severe features (Box 3).

Gestational Hypertension and Preeclampsia

Hypertensive disorders of pregnancy constitute one of the leading causes of maternal and perinatal mortality worldwide. It has been estimated that preeclampsia complicates 2–8% of pregnancies globally (1). In Latin America and the Caribbean, hypertensive disorders are responsible for almost 26% of maternal deaths, whereas in Africa and Asia they contribute to 9% of deaths. Although maternal mortality is much lower in high-income countries than in developing countries, 16% of maternal deaths can be attributed to hypertensive disorders (1, 2). In the United States, the rate of preeclampsia increased by 25% between 1987 and 2004 (3). Moreover, in comparison with women giving birth in 1980, those giving birth in 2003 were at 6.7-fold increased risk of severe preeclampsia (4). This complication is costly: one study reported that in 2012 in the United States, the estimated cost of preeclampsia within the first 12 months of delivery was $2.18 billion ($1.03 billion for women and $1.15 billion for infants), which was disproportionately borne by premature births (5). This Practice Bulletin will provide guidelines for the diagnosis and management of gestational hypertension and preeclampsia.

Background

Risk Factors

A variety of risk factors have been associated with increased probability of preeclampsia (Box 1) (6–12). Nonetheless, it is important to remember that most cases of preeclampsia occur in healthy nulliparous women with no obvious risk factors. Although the precise role of genetic–environmental interactions on the risk and incidence of preeclampsia is unclear, emerging data suggest the tendency to develop preeclampsia may have some genetic component (13–16).

Definitions and Diagnostic Criteria for Hypertensive Disorders of Pregnancy

Preeclampsia (With and Without Severe Features)

Preeclampsia is a disorder of pregnancy associated with new-onset hypertension, which occurs most often after 20 weeks of gestation and frequently near term. Although often accompanied by new-onset proteinuria, hypertension and other signs or symptoms of preeclampsia may present in some women in the absence of proteinuria (17). Reliance on maternal symptoms may be occasionally problematic in clinical practice. Right upper quadrant or epigastric

Box 1. Risk Factors for Preeclampsia

Nulliparity
Multifetal gestations
Preeclampsia in a previous pregnancy
Chronic hypertension
Pregestational diabetes
Gestational diabetes
Thrombophilia
Systemic lupus erythematosus
Prepregnancy body mass index greater than 30
Antiphospholipid antibody syndrome
Maternal age 35 years or older
Kidney disease
Assisted reproductive technology
Obstructive sleep apnea

pain is thought to be due to periportal and focal parenchymal necrosis, hepatic cell edema, or Glisson's capsule distension, or a combination. However, there is not always a good correlation between the hepatic histopathology and laboratory abnormalities (18). Similarly, studies have found that using headache as a diagnostic criterion for preeclampsia with severe features is unreliable and nonspecific. Thus, an astute and circumspect diagnostic approach is required when other corroborating signs and symptoms indicative of severe preeclampsia are missing (19, 20). Of note, in the setting of a clinical presentation similar to preeclampsia, but at gestational ages earlier than 20 weeks, alternative diagnoses should to be considered, including but not limited to thrombotic thrombocytopenic purpura, hemolytic–uremic syndrome, molar pregnancy, renal disease or autoimmune disease.

Although hypertension and proteinuria are considered to be the classical criteria to diagnose preeclampsia, other criteria are also important. In this context, it is recommended that women with gestational hypertension in the absence of proteinuria are diagnosed with preeclampsia if they present with any of the following severe features: thrombocytopenia (platelet count less than 100,~~000~~ $\times$ 10^9/L); impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (to twice the upper limit of normal concentration); severe persistent right upper quadrant or epigastric pain and not accounted for by alternative diagnoses; renal insufficiency (serum creatinine concentration greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease); pulmonary edema; or new-onset headache unresponsive to acetaminophen and not accounted for by alternative diagnoses or visual disturbances (Box 2). *Gestational hypertension* is defined as a systolic blood pressure of 140 mm Hg or more or a diastolic blood pressure of 90 mm Hg or more, or both, on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure (21). Women with gestational hypertension with severe range blood pressures (a systolic blood pressure of 160 mm Hg or higher, or diastolic blood pressure of 110 mm Hg or higher) should be diagnosed with preeclampsia with severe features. These severe ranges of blood pressure or any of the severe features listed in Box 3 increase the risk of morbidity and mortality (22).

Box 2. Diagnostic Criteria for Preeclampsia

Blood pressure

- Systolic blood pressure of 140 mm Hg or more or diastolic blood pressure of 90 mm Hg or more on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure
- Systolic blood pressure of 160 mm Hg or more or diastolic blood pressure of 110 mm Hg or more. (Severe hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy).

and

Proteinuria

- 300 mg or more per 24 hour urine collection (or this amount extrapolated from a timed collection) or
- Protein/creatinine ratio of 0.3 ~~mg/dL~~ or more or
- Dipstick reading of 2+ (used only if other quantitative methods not available)

Or in the absence of proteinuria, new-onset hypertension with the new onset of any of the following:

- Thrombocytopenia: Platelet count less than 100,~~000~~ $\times$ 10^9/L
- Renal insufficiency: Serum creatinine concentrations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease
- Impaired liver function: Elevated blood concentrations of liver transaminases to twice normal concentration
- Pulmonary edema
- New-onset headache unresponsive to medication and not accounted for by alternative diagnoses or visual symptoms

Box 3. Preeclampsia with Severe Features

- Systolic blood pressure of 160 mm Hg or more, or diastolic blood pressure of 110 mm Hg or more on two occasions at least 4 hours apart (unless antihypertensive therapy is initiated before this time)
- Thrombocytopenia (platelet count less than 100,000 $\times$ 10^9/L
- Impaired liver function that is not accounted for by alternative diagnoses and as indicated by abnormally elevated blood concentrations of liver enzymes (to more than twice the upper limit normal concentrations), or by severe persistent right upper quadrant or epigastric pain unresponsive to medications
- Renal insufficiency (serum creatinine concentration more than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease)
- Pulmonary edema
- New-onset headache unresponsive to medication and not accounted for by alternative diagnoses
- Visual disturbances

Proteinuria during pregnancy is defined as 300 mg/dL of protein or more in a 24-hour urine collection (21, 23) or a protein -to-creatinine ratio of 0.30 or more (24). When quantitative methods are not available or rapid decisions are required, a urine protein dipstick reading can be substituted. However, dipstick urinalysis has high false–positive and false–negative test results. A test result of 1+ proteinuria is false–positive in 71% of cases compared with the 300 mg cutoff on 24-hour urine collection, and even 3+ proteinuria test results may be false–positive in 7% of cases. Using the same 24-hour urine collection standard, the false–negative rate for dipstick urinalysis is 9% (25). If urinalysis is the only available means of assessing proteinuria then overall accuracy is better using 2+ as the discriminant value (25, 26).

Gestational Hypertension

Gestational hypertension is defined as a systolic blood pressure 140 mm Hg or more or a diastolic blood pressure of 90 mm Hg or more, or both, on two occasions at least 4 hours apart after 20 weeks of gestation, in a woman with a previously normal blood pressure (21). Gestational hypertension is considered severe when the systolic level reaches 160 mm Hg or the diastolic level reaches 110 mm Hg, or both. On occasion, especially when faced with severe hypertension, the diagnosis may need to be confirmed within a shorter interval (minutes) than 4 hours to facilitate timely antihypertensive therapy (27). Gestational hypertension occurs when hypertension without proteinuria or severe features develops after 20 weeks of gestation and blood pressure levels return to normal in the postpartum period (21). It appears that this diagnosis is more of an exercise of nomenclature than a pragmatic one because the management of gestational hypertension and that of preeclampsia without severe features is similar in many aspects, and both require enhanced surveillance. Outcomes in women with gestational hypertension usually are good, but the notion that gestational hypertension is intrinsically less concerning than preeclampsia is incorrect. Gestational hypertension is associated with adverse pregnancy outcomes (17) and may not represent a separate entity from preeclampsia (28). Up to 50% of women with gestational hypertension will eventually develop proteinuria or other end-organ dysfunction consistent with the diagnosis of preeclampsia, and this progression is more likely when the hypertension is diagnosed before 32 weeks of gestation (29, 30). Although investigators have reported a higher perinatal mortality rate in women with nonproteinuric hypertension compared with proteinuric preeclampsia (31), in a cohort of 1,348 hypertensive pregnant patients, the women with proteinuria progressed more frequently to severe hypertension and had higher rates of preterm birth and perinatal mortality; however, women without proteinuria had a higher frequency of thrombocytopenia or liver dysfunction (17). Women with gestational hypertension who present with severe-range blood pressures should be managed with the same approach as for women with severe preeclampsia. Gestational hypertension and preeclampsia may also be undistinguishable in terms of long-term cardiovascular risks, including chronic hypertension (32).

Hemolysis, Elevated Liver Enzymes, and Low Platelet Count Syndrome

The clinical presentation of hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome is one of the more severe forms of preeclampsia because it has been associated with increased rates of maternal morbidity and mortality (33). Although different diagnostic benchmarks have been proposed (34), many clinicians use the following criteria (35) to make the diagnosis: lactate dehydrogenase (LDH) elevated to 600 IU/L or more, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevated more than twice the upper limit of normal, and the platelets count less than 100,000 $\times$ 10^9/L. Although HELLP syndrome is mostly a third-trimester condition, in 30% of cases it is

first expressed or progresses postpartum. Furthermore, HELLP syndrome may have an insidious and atypical onset, with up to 15% of the patients lacking either hypertension or proteinuria (36). In HELLP syndrome, the main presenting symptoms are right upper quadrant pain and generalized malaise in up to 90% of cases and nausea and vomiting in 50% of cases (35, 37).

Eclampsia

Eclampsia is the convulsive manifestation of the hypertensive disorders of pregnancy and is among the more severe manifestations of the disease. Eclampsia is defined by new-onset tonic-clonic, focal, or multifocal seizures in the absence of other causative conditions such as epilepsy, cerebral arterial ischemia and infarction, intracranial hemorrhage, or drug use. Some of these alternative diagnoses may be more likely in cases in which new-onset seizures occur after 48–72 hours postpartum (38) or when seizures occur during administration of magnesium sulfate.

Eclampsia is a significant cause of maternal death, particularly in low-resource settings. Seizures may lead to severe maternal hypoxia, trauma, and aspiration pneumonia. Although residual neurologic damage is rare, some women may have short-term and long-term consequences such as impaired memory and cognitive function, especially after recurrent seizures or uncorrected severe hypertension leading to cytotoxic edema or infarction (39). Permanent white matter loss has been documented on magnetic resonance imaging (MRI) after eclampsia in up to one fourth of women, however, this does not translate into significant neurologic deficits (39).

Eclampsia often (78–83% of cases) is preceded by premonitory signs of cerebral irritation such as severe and persistent occipital or frontal headaches, blurred vision, photophobia, and altered mental status. However, eclampsia can occur in the absence of warning signs or symptoms (40, 41). Eclampsia can occur before, during, or after labor. Of note, a significant proportion of women (20–38%) do not demonstrate the classic signs of preeclampsia (hypertension or proteinuria) before the seizure episode (42). Headaches are believed to reflect the development of elevated cerebral perfusion pressure, cerebral edema, and hypertensive encephalopathy (43).

The term preeclampsia implies that the natural history of patients with persistent hypertension and significant proteinuria during pregnancy is to have tonic–clonic seizures if no prophylaxis if instituted. However, the results of two randomized placebo-controlled trials indicate that seizure occurred in only a small proportion of patients with preeclampsia (1.9%) (44) or severe preeclampsia (3.2%) (45) allocated to the placebo arm of both studies. It is also noteworthy that there is a significant proportion of patients who had abrupt-onset eclampsia without warning signs or symptoms (40). In a nationwide analysis of cases of eclampsia in the United Kingdom, it was noted that in 38% of eclamptic cases the seizure occurred without any prior documentation of either hypertension or proteinuria in the hospital setting (46). Thus, the notion that preeclampsia has a natural linear progression from preeclampsia without severe features to preeclampsia with severe features and eventually to eclamptic convulsions is inaccurate.

Nervous system manifestations frequently encountered in preeclampsia are headache, blurred vision, scotomata, and hyperreflexia. Although uncommon, temporary blindness (lasting a few hours to as long as a week) also may accompany preeclampsia with severe features and eclampsia (47). Posterior reversible encephalopathy syndrome (PRES) is a constellation of a range of clinical neurologic signs and symptoms such as vision loss or deficit, seizure, headache, and altered sensorium or confusion (48). Although suspicion for PRES is increased in the setting of these clinical features, the diagnosis of PRES is made by the presence of vasogenic edema and hyperintensities in the posterior aspects of the brain on magnetic resonance imaging. Women are particularly at risk of PRES in the settings of eclampsia and preeclampsia with headache, altered consciousness, or visual abnormalities (49). Another condition that may be confused with eclampsia or preeclampsia is reversible cerebral vasoconstriction syndrome (50). Reversible cerebral vasoconstriction syndrome is characterized by reversible multifocal narrowing of the arteries of the brain with signs and symptoms that typically include thunderclap headache and, less commonly, focal neurologic deficits related to brain edema, stroke, or seizure. Treatment of women with PRES and reversible cerebral vasoconstriction syndrome may include medical control of hypertension, antiepileptic medication and long-term neurologic follow-up.

Pathophysiology

Several mechanisms of disease have been proposed in preeclampsia (1, 51, 52) including the following: chronic uteroplacental ischemia (53), immune maladaptation (53), very low-density lipoprotein toxicity (53), genetic imprinting (53), increased trophoblast apoptosis or necrosis (54, 55), and an exaggerated maternal inflammatory response to deported trophoblasts (56, 57). More recent observations suggest a possible role for imbalances of angiogenic factors in the pathogenesis of preeclampsia (58). It is possible that a combination of some of these purported mechanisms may be responsible

for triggering the clinical spectrum of preeclampsia. For example, there is clinical (59, 60) and experimental evidence (61, 62) suggesting that uteroplacental ischemia leads to increased circulating concentrations of antiangiogenic factors and angiogenic imbalances (63).

Vascular Changes

In addition to hypertension, women with preeclampsia or eclampsia typically lack the hypervolemia associated with normal pregnancy; thus, hemoconcentration is a frequent finding (64). In addition, the interaction of various vasoactive agents, such as prostacyclin (vasodilator), thromboxane A_2 (potent vasoconstrictor), nitric oxide (potent vasodilator), and endothelins (potent vasoconstrictors) results in another significant change described in preeclampsia: intense vasospasm. Attempts to correct the contraction of the intravascular space in preeclampsia with vigorous fluid therapy are likely to be ineffective and could be dangerous because of the frequent capillary leak and decreased colloid oncotic pressure often associated with preeclampsia. Aggressive fluid therapy may result in elevation of the pulmonary capillary wedge pressure and increased risk of pulmonary edema. A study using invasive hemodynamic monitoring in women with preeclampsia found that before intravenous fluid therapy, women with preeclampsia had hyperdynamic ventricular function with low pulmonary capillary wedge pressure (65). However, after aggressive fluid therapy, the pulmonary capillary wedge pressure increased significantly above normal levels (65) with increased risk of pulmonary edema.

Hematologic Changes

Various hematologic changes also may occur in women with preeclampsia, especially in preeclampsia with severe features. Thrombocytopenia and hemolysis may occur and may reach severe levels as part of HELLP syndrome. Thrombocytopenia results from increased platelet activation, aggregation, and consumption (66) and is a marker of disease severity. A platelet count less than 150,000 $\times$ 10^9/L is found in approximately 20% of patients with preeclampsia, varying from 7% in cases without severe manifestations to 50% in cases with severe manifestations (67). However, reduced platelet counts significant liver dysfunction, or there is suspected are not found in all cases of preeclampsia or eclampsia (68). Interpretation of hematocrit levels in preeclampsia should take into consideration that hemolysis and hemoconcentration may occur (69). In some cases, the hematocrit may not appear decreased despite hemolysis because of baseline hemoconcentration. Lactate dehydrogenase is present in erythrocytes in high concentration. High serum concentrations of LDH (more than 600 IU/L) may be a sign of hemolysis (34, 35).

Hepatic Changes

Hepatic function may be significantly altered in women with preeclampsia with severe features. Alanine aminotransferase and AST may be elevated. Aspartate aminotransferase is the dominant transaminase released into the peripheral circulation in liver dysfunction due to preeclampsia and is related to periportal necrosis. The fact that AST is increased to a greater extent than ALT, at least initially, may help in distinguishing preeclampsia from other potential causes of parenchymal liver disease in which ALT usually is higher than AST. Increased serum levels of LDH in preeclampsia are caused by hepatic dysfunction (LDH derived from ischemic, or necrotic tissues, or both) and hemolysis (LDH from red blood cell destruction). Increase in bilirubin secondary to significant hemolysis may develop only in the late stages of the disease. Similarly, alterations in hepatic synthetic function, as reflected by abnormalities of prothrombin time, partial prothrombin time, and fibrinogen, usually develop in advanced preeclampsia. Evaluation of these coagulation parameters is probably only useful when the platelet count is below 150,000 $\times$ 10^9/L, there is significant liver dysfunction, or there is suspected placental abruption (70).

Renal Changes

The histopathologic renal changes classically described in preeclampsia as glomerular endotheliosis consist of swollen, vacuolated endothelial cells with fibrils, swollen mesangial cells, subendothelial deposits of protein reabsorbed from the glomerular filtrate, and tubular casts (71, 72). Proteinuria in preeclampsia is nonselective, as a result of increased tubular permeability to most large-molecular-weight proteins (albumin, globulin, transferrin, and hemoglobin). Urinary calcium decreases because of an increased tubular reabsorption of calcium.

In women with preeclampsia, contraction of the intravascular space secondary to vasospasm leads to worsening renal sodium and water retention (73). The normal increase in renal blood flow and glomerular filtration rate and the expected decrease in serum creatinine may not occur in women with preeclampsia, especially if the disease is severe. Preeclampsia with severe features may include acute renal deterioration as part of the clinical spectrum. Oliguria in severe preeclampsia is a consequence of intrarenal vasospasm with an approximate 25% reduction in glomerular filtration rate. In these patients, transient oliguria (less than 100 mL over 4 hours) is a common observation in labor or the first 24 hours of the postpartum period. Plasma concentrations of uric acid normally increase in late pregnancy, and this is thought to be due to increased rates of fetal or placental

production, or both, decreased binding to albumin, and a decrease in uric acid clearance. The serum uric acid concentration increases to a greater extent in preeclampsia (74). The most commonly accepted explanation for hyperuricemia in preeclampsia, besides increased production, is the increased reabsorption and decreased excretion of uric acid in the proximal renal tubules.

Fetal Consequences

As a result of impaired uteroplacental blood flow secondary to failure of physiologic transformation of the spiral arteries or placental vascular insults, or both, manifestations of preeclampsia also may be seen in the fetal–placental unit (63). Abnormalities in the placental bed and subsequent failure of physiologic transformation of the spiral arteries in the first or early second trimester (75, 76) limit the blood flow to the uteroplacental unit. Additional mechanisms for chronic uteroplacental ischemia include placental vascular insults (77, 78). Among women with preeclampsia, clinical manifestations that follow from this uteroplacental ischemia include fetal growth restriction, oligohydramnios, placental abruption, and nonreassuring fetal status demonstrated on antepartum surveillance. Consequently, fetuses of women with preeclampsia are at increased risk of spontaneous or indicated preterm delivery.

Clinical Considerations and Recommendations

▶ ***Are there screening methods that are useful to identify women at risk of developing hypertensive disorders of pregnancy?***

Several studies have evaluated the role of biochemical markers or a combination of biochemical and biophysical markers in the prediction of preeclampsia in the first and second trimesters of pregnancy (79). Regardless of the parameters used, screening for preeclampsia in low-risk women is associated with very low positive predictive values ranging from 8% to 33% (79). Thus, most screen–positive patients will not develop the disease and any prophylactic intervention in the screen-positive group would unnecessarily expose a large number of patients who would not benefit from these interventions.

In general, the sensitivity and specificity for the prediction of early-onset preeclampsia using first-trimester (80–82) and second-trimester biochemical (81, 83) or biophysical parameters (84–87) are better than for late-onset preeclampsia. The reason for this is still unclear but it is possible that the timing of the insults to the fetal supply line or the fetal response to these insults may be different between early-onset and late-onset preeclampsia. Even so, there is limited evidence that an accurate prediction of early-onset preeclampsia can be followed by interventions that improve maternal or fetal outcome.

Regardless of the index or combinations of indices used, uterine artery Doppler studies alone have a low predictive value for the development of early-onset preeclampsia and an even lower value for late-onset preeclampsia (88). Extensive work has identified some angiogenic factors (soluble fms-like tyrosine kinase-[sFlt-1], placental growth factor [PlGF], and soluble endoglin) in the second trimester as likely tools for the prediction of early-onset preeclampsia. However, no single test reliably predicts preeclampsia and further prospective investigation is required to demonstrate clinical utility. In the first trimester of pregnancy, it has been reported that a combination of low maternal serum concentrations of PlGF, high uterine artery pulsatility index, and other maternal parameters, identified 93.1% of patients who would develop preeclampsia requiring delivery before 34 weeks of gestation (82). However, the results of this study are based on mathematical modeling derived from a nested case−control study applied to a large cohort of almost 7,800 patients in which PlGF was measured only in the case−control group. The calculated positive predictive value was only 21.2%, indicating that approximately 79% of the women in the screen-positive group would not develop hypertensive disorders during pregnancy (82). Of note, a similar algorithm underperformed in a subsequent randomized trial performed by the same research group (89). Thus, biomarkers and ultrasonography cannot accurately predict preeclampsia and should remain investigational.

▶ ***Are there prevention strategies for reducing the risk of hypertensive disorders of pregnancy?***

Strategies to prevent preeclampsia have been studied extensively over the past 30 years. To date, no intervention has been proved unequivocally effective at eliminating the risk of preeclampsia. With regard to nutritional interventions, evidence is insufficient to demonstrate effectiveness for vitamins C and E (90), fish oil (91), garlic supplementation (92), vitamin D (93), folic acid (94) or sodium restriction (95) for reducing the risk of preeclampsia. A meta-analysis of 13 trials (15,730 women) reported a significant reduction in preeclampsia with calcium supplementation, with the greatest effect among women with low-baseline calcium intake (96). Yet, this is not the case in the United States or other developed countries. Likewise, data do not support

effectiveness of bed rest and, thus, it should not routinely be recommended (97).

Investigators hypothesized that an imbalance in prostacyclin and thromboxane A_2 metabolism was involved in the pathogenesis of preeclampsia, leading to the initial studies of aspirin for preeclampsia prevention because of its preferential inhibition of thromboxane A_2 at lower doses (98, 99). In a recent meta-analysis of aggregate data from 45 randomized trials, only a modest reduction in preeclampsia was noted when low-dose aspirin was started after 16 weeks of gestation (relative risk [RR], 0.81; 95% CI, 0.66–0.99) but a more significant reduction in severe preeclampsia (RR, 0.47; 95% CI, 0.26–0.83) and fetal growth restriction (RR, 0.56; 95% CI, 0.44–0.70) was demonstrated when low-dose aspirin was started before 16 weeks of gestation (100). In contrast, in pooled individual data from 31 high-quality randomized trials, the beneficial effects of low-dose aspirin were consistent, whether treatment was started before or after 16 weeks of gestation (101). Women with any of the high-risk factors for preeclampsia (previous pregnancy with preeclampsia, multifetal gestation, renal disease, autoimmune disease, type 1 or type 2 diabetes mellitus, and chronic hypertension) and those with more than one of the moderate-risk factors (first pregnancy, maternal age of 35 years or older, a body mass index [BMI; calculated as weight in kilograms divided by height in meters squared] of more than 30, family history of preeclampsia, sociodemographic characteristics, and personal history factors) should receive low-dose (81 mg/day) aspirin for preeclampsia prophylaxis initiated between 12 weeks and 28 weeks of gestation (optimally before 16 weeks of gestation) and continuing until delivery (Table 1).

In a recent multicenter, double blind, placebo-controlled trial, pregnant women at increased risk of preterm preeclampsia (less than 37 weeks of gestation) were randomly assigned to receive aspirin, at a higher dose (150 mg/day), or placebo from 11 weeks to 14 weeks of gestation until 36 weeks of gestation (89). Preterm preeclampsia occurred in 1.6% of the participants in the aspirin group, as compared with 4.3% in the placebo group (odds ratio, 0.38; 95% CI, 0.20−0.74; P=.004). The authors also reported that there were no significant differences in the incidence of neonatal adverse outcomes between groups. The authors concluded that low-dose aspirin in women at high risk of preeclampsia was associated with a lower incidence for preterm preeclampsia. However, there were no differences in the rates of term preeclampsia between study groups. Of note, as a possible study limitation, the prevalence of preterm preeclampsia in the placebo group was one half of that expected for a high-risk population based on first-trimester parameters (89).

The use of metformin for the prevention of preeclampsia has been suggested. In a meta-analysis of five randomized controlled trials comparing metformin treatment (n=611) with placebo and control (n=609), no difference in the risk of preeclampsia was found (combined/pooled risk ratio, 0.86; 95% CI, 0.33–2.26); P=.76; I^2=66%) (102). Because preeclampsia was a secondary outcome in most studies in this meta-analysis, the effect of metformin needs to be assessed by a study designed to evaluate the reduction in the prevalence of preeclampsia as a primary endpoint. In the meantime, the use of metformin for the prevention of preeclampsia remains investigational, as is the use of sildenafil and statins (103–105). These drugs are not recommended for this indication outside of the context of clinical trials.

▶ ***What is the optimal treatment for women with gestational hypertension or preeclampsia?***

Delivery Versus Expectant Management

At the initial evaluation, a complete blood count with platelet estimate, serum creatinine, LDH, AST, ALT, and testing for proteinuria should be obtained in parallel with a comprehensive clinical maternal and fetal evaluation. In the settings of diagnostic dilemmas, such as in the evaluation of possible preeclampsia superimposed upon chronic hypertension, a uric acid test may be considered. Fetal evaluation should include ultrasonographic evaluation for estimated fetal weight and amount of amniotic fluid, as well as fetal antepartum testing. Subsequent management will depend on the results of the evaluation and gestational age. The decision to deliver must balance the maternal and fetal risks.

Continued observation is appropriate for a woman with a preterm fetus if she has gestational hypertension or preeclampsia without severe features (21). There are no randomized controlled trials in this population, but retrospective data suggest that without severe features, the balance should be in favor of continued monitoring until delivery at 37 0/7 weeks of gestation in the absence of abnormal antepartum testing, preterm labor, preterm prelabor rupture of membranes (also referred to as premature rupture of membranes) or vaginal bleeding, for neonatal benefit (106). The risks associated with expectant management in the late preterm period include the development of severe hypertension, eclampsia, HELLP syndrome, placental abruption, fetal growth restriction and fetal death; however, these risks are small and counterbalanced by the increased rates of admission to the neonatal intensive care unit, neonatal respiratory complications and neonatal death that would be associated with delivery before 37 0/7 weeks of gestation (39). In the

Table 1. Clinical Risk Factors and Aspirin Use*

Level of Risk	Risk Factors	Recommendation
High†	• History of preeclampsia, especially when accompanied by an adverse outcome • Multifetal gestation • Chronic hypertension • Type 1 or 2 diabetes • Renal disease • Autoimmune disease (ie, systemic lupus erythematosus, the antiphospholipid syndrome)	Recommend low-dose aspirin if the patient has one or more of these high-risk factors
Moderate‡	• Nulliparity • Obesity (body mass index greater than 30) • Family history of preeclampsia (mother or sister) • Sociodemographic characteristics (African American race, low socioeconomic status) • Age 35 years or older • Personal history factors (eg, low birth weight or small for gestational age, previous adverse pregnancy outcome, more than 10-year pregnancy interval)	Consider low-dose aspirin if the patient has more than one of these moderate-risk factors§
Low	• Previous uncomplicated full-term delivery	Do not recommend low-dose aspirin

*Includes only risk factors that can be obtained from the patient's medical history. Clinical measures, such as uterine artery Doppler ultrasonography, are not included.

†Single risk factors that are consistently associated with the greatest risk of preeclampsia. The preeclampsia incidence rate would be approximately 8% or more in a pregnant woman with one or more of these risk factors.

‡A combination of multiple moderate-risk factors may be used by clinicians to identify women at high risk of preeclampsia. These risk factors are independently associated with moderate risk of preeclampsia, some more consistently than others.

§Moderate-risk factors vary in their association with increased risk of preeclampsia.

Modified from LeFevre, ML. U.S. Preventive Services Task Force. Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med 2014;161(11):819–26.

HYPITAT trial, women with gestational hypertension and preeclampsia without severe features after 36 weeks of gestation were allocated to expectant management or induction of labor. The latter option was associated with a significant reduction in a composite of adverse maternal outcome including new-onset severe preeclampsia, HELLP syndrome, eclampsia, pulmonary edema, or placental abruption (RR, 0.71; 95% CI, 0.59–0.86) (107). In addition, no differences in rates of neonatal complications or cesarean delivery were reported by the authors (107).

Continued monitoring of women with gestational hypertension or preeclampsia without severe features consists of serial ultrasonography to determine fetal growth, weekly antepartum testing, close monitoring of blood pressure, and weekly laboratory tests for preeclampsia. The frequency of these tests may be modified based on clinical findings and patient symptoms. Following the initial documentation of proteinuria and the establishment of the diagnosis of preeclampsia, additional quantifications of proteinuria are no longer necessary. Although the amount of proteinuria is expected to increase over time with expectant management, this change is not predictive of perinatal outcome and should not influence the management of preeclampsia (108, 109). Women should be advised to immediately report any persistent, concerning, or unusual symptoms. In women with gestational hypertension without severe features, when there is progression to preeclampsia with severe features, this progression usually takes 1–3 weeks after diagnosis, whereas in women with preeclampsia without severe features, the progression to severe

preeclampsia could happen within days (72). Gestational hypertension and preeclampsia are known risk factors for fetal death and antenatal testing is indicated. However, limited-to-no data exist regarding when to start testing, the frequency of testing, and which test to use. In women with gestational hypertension or preeclampsia without severe features at or beyond 37 0/7 weeks of gestation, delivery rather than expectant management upon diagnosis is recommended.

Preeclampsia with severe features can result in acute and long-term complications for the woman and her newborn. Maternal complications include pulmonary edema, myocardial infarction, stroke, acute respiratory distress syndrome, coagulopathy, renal failure, and retinal injury. These complications are more likely to occur in the presence of preexistent medical disorders. The clinical course of preeclampsia with severe features is characterized by progressive deterioration of maternal and fetal condition. Therefore, delivery is recommended when gestational hypertension or preeclampsia with severe features (Box 3) is diagnosed at or beyond 34 0/7 weeks of gestation, after maternal stabilization or with labor or prelabor rupture of membranes. Delivery should not be delayed for the administration of steroids in the late preterm period.

In women with preeclampsia with severe features at less than 34 0/7 weeks of gestation, with stable maternal and fetal condition, expectant management may be considered. Two randomized controlled trials of delivery versus expectant management of preterm preeclampsia with severe features demonstrated that expectant management is associated with higher gestational age at delivery and improved neonatal outcomes (110, 111). These observations were reiterated by a Cochrane systematic review (112). The limited available randomized data are consistent with observational evidence suggesting that expectant management of early preeclampsia with severe features prolongs pregnancy by 1–2 weeks, has low maternal risk, and improves neonatal outcomes (113). In contrast, in a multicenter randomized controlled trial in Latin America, the authors found no neonatal benefit with expectant management of preeclampsia with severe features from 28 weeks to 34 weeks of gestation (114). These different results may reflect the limitations in neonatal intensive care in low-resource settings.

Embarking on a course of expectant management necessitates adherence to principles of shared decision making with discussions of maternal and fetal risks and benefits, appropriate resources (levels of care), and ongoing vigilant surveillance. Close maternal and fetal clinical monitoring is necessary, and laboratory testing (complete blood count including platelets, liver enzymes, and serum creatinine) should be performed serially (115).

The expectant management of preeclampsia with severe features before 34 0/7 weeks of gestation is based on strict selection criteria of those appropriate candidates and is best accomplished in a setting with resources appropriate for maternal and neonatal care (116). Because expectant management is intended to provide neonatal benefit at the expense of maternal risk, expectant management is not advised when neonatal survival is not anticipated. During expectant management, delivery is recommended at any time in the case of deterioration of maternal or fetal condition, which may include some of the criteria in Box 4. Indications for expedited delivery irrespective of gestational age after maternal stabilization are described in Box 4 (115).

If delivery is indicated at less than 34 0/7 weeks of gestation, administration of corticosteroids for fetal lung maturation is recommended (115); however, delaying delivery for optimal corticosteroid exposure may not always be advisable. Maternal or fetal deterioration may preclude completion of the course of steroid treatment. Previously, fetal growth restriction was considered an indication for delivery. In the setting of normal fetal parameters (eg, amniotic fluid volume, Doppler findings, antenatal fetal testing), continuation of expectant management may be reasonable in the absence of other, aforementioned maternal and fetal criteria.

Inpatient Versus Outpatient Management

Ambulatory management at home is an option only for women with gestational hypertension or preeclampsia without severe features and requires frequent fetal and maternal evaluation. Hospitalization is appropriate for women with severe features and for women in whom adherence to frequent monitoring is a concern. Because assessment of blood pressure is essential for this clinical condition, health care providers are encouraged to follow the recommendations from regulatory bodies regarding the proper technique for blood pressure measurement. Having a blood pressure cuff that is too small or too large may result in erroneous evaluations. To reduce inaccurate readings, an appropriate size cuff should be used (length 1.5 times upper arm circumference or a cuff with a bladder that encircles 80% or more of the arm). The blood pressure level should be taken with an appropriately-sized cuff with the patient in an upright position after a 10-minute or longer rest period. For patients in the hospital, the blood pressure can be taken with either the patient sitting up or in the left lateral recumbent position with the patient's arm at the level of the heart (117). The patient should not use tobacco or caffeine for 30 minutes preceding the measurement

Box 4. Conditions Precluding Expectant Management

Maternal

- Uncontrolled severe-range blood pressures (persistent systolic blood pressure 160 mm Hg or more or diastolic blood pressure 110 mm Hg or more not responsive to antihypertensive medication
- Persistent headaches, refractory to treatment
- Epigastric pain or right upper pain unresponsive to repeat analgesics
- Visual disturbances, motor deficit or altered sensorium
- Stroke
- Myocardial infarction
- HELLP syndrome
- New or worsening renal dysfunction (serum creatinine greater than 1.1 mg/dL or twice baseline)
- Pulmonary edema
- Eclampsia
- Suspected acute placental abruption or vaginal bleeding in the absence of placenta previa

Fetal

- Abnormal fetal testing
- Fetal death
- Fetus without expectation for survival at the time of maternal diagnosis (eg, lethal anomaly, extreme prematurity)
- Persistent reversed end-diastolic flow in the umbilical artery

Abbreviation: HELLP, hemolysis, elevated liver enzymes, and low platelet count.
In some cases, a course of antenatal steroids can be considered depending on gestational age and maternal severity of illness.
Data from Balogun OA, Sibai BM. Counseling, management, and outcome in women with severe preeclampsia at 23 to 28 weeks' gestation. Clin Obstet Gynecol 2017;60:183–9.

because these agents can temporarily lead to increased blood pressure (118).

If home management is selected, frequent fetal and maternal evaluation are required. No randomized trials have determined the best tests for fetal or maternal evaluation. Among women with gestational hypertension or preeclampsia without severe features, expectant management up to 37 0/7 weeks of gestation is recommended, during which frequent fetal and maternal evaluation is recommended. Fetal monitoring consists of ultrasonography to determine fetal growth every 3–4 weeks of gestation and amniotic fluid volume assessment at least once weekly. In addition, an antenatal test one-to-two times per week for patients with gestational hypertension or preeclampsia without severe features is recommended.

Maternal evaluation consists primarily of frequent evaluation for either the development of or worsening of preeclampsia. In women with gestational hypertension or preeclampsia without severe features, weekly evaluation of platelet count, serum creatinine, and liver enzyme levels is recommended. In addition, for women with gestational hypertension, once weekly assessment of proteinuria is recommended. However, these tests should be repeated sooner if disease progression is a concern. In addition, women should be asked about symptoms of preeclampsia with severe features (eg, severe headaches, visual changes, epigastric pain, and shortness of breath). Blood pressure measurements and symptom assessment are recommended serially, using a combination of in-clinic and ambulatory approaches, with at least one visit per week in-clinic.

Intrapartum Management

In addition to appropriate management of labor and delivery, the two main goals of management of women with preeclampsia during labor and delivery are 1) prevention of seizures and 2) control of hypertension.

Seizure Prophylaxis

The prevention of eclampsia is empirically based on the concept of timely delivery, as previously discussed, once preeclampsia has been diagnosed. A significant body of evidence attests to the efficacy of magnesium sulfate to prevent seizures in women with preeclampsia with severe features and eclampsia. In the Magpie study, a randomized placebo-controlled trial with 10,110 participants (two thirds originating from developing countries), the seizure rate was reduced overall by more than one half with this treatment. It is interesting to note that the reduction in the rate of eclampsia was not statistically significant in the subset of women enrolled in high-resource countries in the Western world (RR, 0.67; 95% CI, 0.19–2.37) (44). In a subsequent systematic review that included the Magpie study and five other studies, magnesium sulfate compared with placebo more than halved the risk of eclampsia (RR, 0.41; 95% CI, 0.29–0.58), reduced the risk of placental abruption (RR, 0.64; 95% CI, 0.50–0.83), and reduced the risk of maternal mortality albeit nonsignificantly (RR, 0.54; 95% CI, 0.26–1.10). There were no differences in maternal morbidity or perinatal mortality. A quarter of women reported adverse effects with magnesium sulfate, primarily hot flushes, and the rate of cesarean delivery was increased by 5% when magnesium sulfate was used (119).

There is no consensus regarding the prophylactic use of magnesium sulfate for the prevention of seizures in women with gestational hypertension or preeclampsia without severe features. Two small randomized trials (total n=357) allocated women with preeclampsia without severe features to either placebo or magnesium sulfate and reported no cases of eclampsia among women allocated to placebo and no significant differences in the proportion of women that progressed to severe preeclampsia (120, 121). However, given the small sample size, the results of these studies cannot be used for clinical guidance (122, 123).

The rate of seizures in preeclampsia with severe features without magnesium sulfate prophylaxis is four times higher than in those without severe features (4 in 200 versus 1 in 200). It has been calculated that 129 women need to be treated to prevent one case of eclampsia in asymptomatic cases, whereas in symptomatic cases (severe headache, blurred vision, photophobia, hyperreflexia, epigastric pain), the number needed to treat is 36 (124). The evidence regarding the benefit-to-risk ratio of magnesium sulfate prophylaxis is less supportive of routine use in preeclampsia without severe features (122). The clinical decision of whether to use magnesium sulfate for seizure prophylaxis in patients with preeclampsia without severe features should be determined by the physician or institution, considering patient values or preferences, and the unique risk-benefit trade-off of each strategy. Although the benefit-to-risk ratio for routine prophylaxis is less compelling for patients in high resource settings, it is recommended that magnesium sulfate should be used for the prevention and treatment of seizures in women with gestational hypertension with severe features and preeclampsia with severe features or eclampsia (124, 125).

Magnesium sulfate is more effective than phenytoin, diazepam, or nimodipine (a calcium-channel blocker used in clinical neurology to reduce cerebral vasospasm) in reducing eclampsia and should be considered the drug of choice in the prevention of eclampsia in the intrapartum and postpartum periods (119, 126, 127). Benzodiazepines and phenytoin are justified only in the context of antiepileptic treatment or when magnesium sulfate is contraindicated or unavailable (myasthenia gravis, hypocalcemia, moderate-to-severe renal failure, cardiac ischemia, heart block, or myocarditis).

There are still sparse data regarding the ideal dosage of magnesium sulfate. Even the therapeutic range of 4.8–9.6 mg/dL (4–8 mEq/L) quoted in the literature is questionable (128, 129). Although there is a relationship between toxicity and plasma concentration of magnesium, with higher infusion rates increasing the potential for toxicity, the accurate magnesium concentration clinically effective in prevention of eclampsia has not been established. Seizures occur even with magnesium at a therapeutic level, whereas several trials using infusion rates of 1 g/hour, frequently associated with subtherapeutic magnesium levels, were able to significantly reduce the rate of eclampsia or recurrent convulsions (44, 130). Further complicating aspects are that steady magnesium levels are reached more slowly during the antepartum period than postpartum period. Larger volume of distribution and higher BMI also affect the dosage and duration needed to reach adequate circulating levels. It has been reported in patients with a high BMI (especially greater than 35) that the antepartum level of magnesium may remain subtherapeutic for as long as 18 hours after infusion initiation when an intravenous loading dose of 4.5 g followed by 1.8 g/hour is used (131). However, infusion rates in excess of 2 g/hour have been associated with increased perinatal mortality in a systematic review of randomized studies of magnesium sulfate used for tocolysis (132). These data may be considered supportive for the regimen generally preferred in the United States (intravenous [IV] administration of a 4–6 g loading dose over 20–30 minutes, followed by a maintenance dose of 1–2 g/hour). For women requiring cesarean delivery (before onset of labor), the infusion should ideally begin before surgery and continue during surgery, as well as for 24 hours afterwards. For women who deliver vaginally, the infusion should continue for 24 hours after delivery. In case of difficulties with establishing venous access, magnesium sulfate can be administered by intramuscular (IM) injection, 10 g initially as a loading dose (5 g IM in each buttock), followed by 5 g every 4 hours. The medication can be mixed with 1 mL of xylocaine 2% solution because the intramuscular administration is painful. The rate of adverse effects is also higher with the intramuscular administration (44). The adverse effects of magnesium sulfate (respiratory depression and cardiac arrest) come largely from its action as a smooth muscle relaxant. Deep tendon reflexes are lost at a serum magnesium level of 9 mg/dL (7 mEq/L), respiratory depression occurs at 12 mg/dL (10 mEq/L), and cardiac arrest at 30 mg/dL (25 mEq/L). Accordingly, provided deep tendon reflexes are present, more serious toxicity is avoided. (Table 2) Because magnesium sulfate is excreted almost exclusively in the urine, measuring urine output should be part of the clinical monitoring, in addition to monitoring of respiration status and tendon reflexes. If renal function is impaired, serum magnesium levels will increase quickly, which places the patient at risk of significant adverse effects. In patients with mild renal failure (serum creatinine 1.0–1.5 mg/dL) or oliguria (less than 30 mL urine output per hour for more than 4 hours), the loading dose of 4–6 g should be followed by

Table 2. Serum Magnesium Concentration and Toxicities

Serum Magnesium Concentration			
mmol/L	mEq/L	mg/dL	Effect
2–3.5	4–7	5–9	Therapeutic range
>3.5	>7	>9	Loss of patellar reflexes
>5	>10	>12	Respiratory paralysis
>12.5	>25	>30	Cardiac arrest

Data from Duley L. Magnesium sulphate regimens for women with eclampsia: messages from the Collaborative Eclampsia Trial. Br J Obstet Gynaecol 1996;103:103–5 *and* Lu JF, Nightingale CH. Magnesium sulfate in eclampsia and pre-eclampsia: pharmacokinetic principles. Clin Pharmacokinet 2000;38:305–14.

a maintenance dose of only 1 gm/hour. Using a lower loading dose, such as 4 g, may be associated with subtherapeutic levels for at least 4 hours after loading (133). In cases with renal dysfunction, laboratory determination of serum magnesium levels every 4 hours becomes necessary. If the serum level exceeds 9.6 mg/dL (8 mEq/L), the infusion should be stopped and serum magnesium levels should be determined at 2-hour intervals. The infusion can be restarted at a lower rate when the serum level decreases to less than 8.4 mg/dL (7 mEq/L) (133). The serum concentration of magnesium is related to the occurrence of adverse effects and toxicities (see Table 2) (128, 134). Patients at risk of impending respiratory depression may require tracheal intubation and emergency correction with calcium gluconate 10% solution, 10 mL IV over 3 minutes, along with furosemide intravenously to accelerate the rate of urinary excretion.

Antihypertensive Approach: Drugs and Thresholds for Treatment

The objectives of treating severe hypertension are to prevent congestive heart failure, myocardial ischemia, renal injury or failure, and ischemic or hemorrhagic stroke. Antihypertensive treatment should be initiated expeditiously for acute-onset severe hypertension (systolic blood pressure of 160 mm Hg or more or diastolic blood pressure of 110 mm Hg or more, or both) that is confirmed as persistent (15 minutes or more). The available literature suggests that antihypertensive agents should be administered within 30–60 minutes. However, it is recommended to administer antihypertensive therapy as soon as reasonably possible after the criteria for acute-onset severe hypertension are met. Intravenous hydralazine or labetalol and oral nifedipine are the three agents most commonly used for this purpose (see Table 3). A recent Cochrane systematic review that involved 3,573 women found no significant differences regarding either efficacy or safety between hydralazine and labetalol or between hydralazine and calcium channel blockers (135). Thus, any of these agents can be used to treat acute severe hypertension in pregnancy (135, 136). Although parenteral antihypertensive therapy may be needed initially for acute control of blood pressure, oral medications can be used as expectant management is continued. Oral labetalol and calcium channel blockers have been commonly used. One approach is to begin an initial regimen of labetalol at 200 mg orally every 12 hours and increase the dose up to 800 mg orally every 8–12 hours as needed (maximum total 2,400 mg/d). If the maximum dose is inadequate to achieve the desired blood pressure goal, or the dosage is limited by adverse effect, then short-acting oral nifedipine can be added gradually.

Monitoring for Disease Progression

Because the clinical course of gestational hypertension or preeclampsia without severe features can evolve during labor, all women with gestational hypertension or preeclampsia without severe features who are in labor must be monitored for early detection of progression to severe disease. This should include monitoring of blood pressure and symptoms during labor and delivery as well as immediately after delivery. Magnesium sulfate therapy should be initiated if there is progression to preeclampsia with severe features. The evidence regarding the benefit-to-risk ratio of magnesium sulfate prophylaxis is less supportive of routine use in preeclampsia without severe features (122). The clinical decision of whether to use magnesium sulfate for seizure prophylaxis in patients with preeclampsia without severe features should be determined by the physician or institution, considering patient values or preferences and the unique risk-benefit trade-off of each strategy.

Mode of Delivery

The mode of delivery in women with gestational hypertension or preeclampsia (with or without severe features) should be determined by routine obstetric considerations. Vaginal delivery often can be accomplished, but with labor induction in preeclampsia with severe features this is less likely with decreasing gestational age at diagnosis. The likelihood of cesarean delivery at less than 28 weeks of gestation could be as high as 97%, and at 28–32 weeks of gestation as high as 65% (137–139). For gestational hypertension or preeclampsia without severe features, vaginal delivery is preferred (137–139). Retrospective studies comparing induction of labor with cesarean delivery in women with preeclampsia with severe features remote from term concluded that induction of labor was reasonable and was not harmful to low-birth-weight infants (140, 141). The decision to perform cesarean delivery should be

Table 3. Antihypertensive Agents Used for Urgent Blood Pressure Control in Pregnancy

Drug	Dose	Comments	Onset of Action
Labetalol	10–20 mg IV, then 20–80 mg every 10–30 minutes to a maximum cumulative dosage of 300 mg; or constant infusion 1–2 mg/min IV	Tachycardia is less common with fewer adverse effects. Avoid in women with asthma, preexisting myocardial disease, decompensated cardiac function, and heart block and bradycardia.	1–2 minutes
Hydralazine	5 mg IV or IM, then 5–10 mg IV every 20–40 minutes to a maximum cumulative dosage of 20 mg; or constant infusion of 0.5–10 mg/hr	Higher or frequent dosage associated with maternal hypotension, headaches, and abnormal fetal heart rate tracings; may be more common than other agents.	10–20 minutes
Nifedipine (immediate release)	10–20 mg orally, repeat in 20 minutes if needed; then 10–20 mg every 2–6 hours; maximum daily dose is 180 mg	May observe reflex tachycardia and headaches	5–10 minutes

Abbreviations: IM, intramuscularly; IV, intravenously.

individualized, based on anticipated probability of vaginal delivery and on the nature and progression of preeclampsia disease state.

Anesthesia Considerations

With improved techniques over the past decades, regional anesthesia has become the preferred technique for women with preeclampsia with severe features and eclampsia for labor and delivery. A secondary analysis of women with preeclampsia with severe features in a randomized trial of low-dose aspirin reported that epidural anesthesia was not associated with an increased rate of cesarean delivery, pulmonary edema, or renal failure (142). Also, in a prospective study, the incidence and severity of hypotension did not appear to be increased with spinal anesthesia for cesarean delivery in women with preeclampsia with severe features (n=65) compared with women without preeclampsia (143).

When the use of spinal or epidural anesthesia in women with preeclampsia with severe features was compared in a randomized trial (144), the incidence of hypotension was higher in the spinal group (51% versus 23%) but was easily treated and of short duration (less than 1 minute). General anesthesia carries more risk to pregnant women than regional anesthesia does because of the risk of aspiration, failed intubation because of pharyngolaryngeal edema, and stroke secondary to increased systemic and intracranial pressures during intubation and extubation (145, 146). However, neuraxial anesthesia and analgesia are contraindicated in the presence of a coagulopathy because of the potential for hemorrhagic complications (147). Thrombocytopenia also increases the risk of epidural hematoma. There is no consensus in regard to the safe lower-limit for platelet count and neuraxial anesthesia. The literature offers only limited and retrospective data to address this issue, but a recent retrospective cohort study of 84,471 obstetric patients from 19 institutions combined with a systematic review of the medical literature support the assertion that the risk of epidural hematoma from neuraxial anesthetics in a parturient patient with a platelet count of more than 70×10^9/L is exceptionally low (less than 0.2%) (148). Extrapolating this expanded data to previous recommendations (149) would suggest that epidural or spinal anesthesia is considered acceptable, and the risk of epidural hematoma is exceptionally low, in patients with platelet counts of 70×10^9/L or more provided that the platelet level is stable, there is no other acquired or congenital coagulopathy, the platelet function is normal, and the patient is not on any antiplatelet or anticoagulant therapy (148, 149).

Magnesium sulfate has significant anesthetic implications because it prolongs the duration of nondepolarizing muscle relaxants. However, women with preeclampsia who require cesarean delivery should

continue magnesium sulfate infusion during the delivery. This recommendation is based on the observation that magnesium sulfate half-life is 5 hours and that discontinuation of the infusion of magnesium sulfate before cesarean delivery would only minimally reduce magnesium concentration at the time of delivery while possibly increasing the risk of seizure (150). Women with preeclampsia with severe features undergoing cesarean delivery remain at risk of developing eclampsia. The induction of general anesthesia and the stress of delivery may even reduce the seizure threshold and increase the likelihood of eclampsia in the immediate postpartum period if the infusion of magnesium sulfate is stopped during delivery.

Postpartum Hypertension and Postpartum Headache

Postpartum hypertension and preeclampsia are either persistent or exacerbated hypertension in women with previous hypertensive disorders of pregnancy or a new-onset condition. It is important to increase the awareness among health care providers and to empower patients to seek medical advice if symptoms that precede eclampsia, hypertensive encephalopathy, pulmonary edema, or stroke are noted in the postpartum period. Most women who present with eclampsia and stroke in the postpartum period have these symptoms for hours or days before presentation (151–154). Some common medications and substances used in the postpartum period may potentially aggravate hypertension through three major mechanisms: volume retention, sympathomimetic activation, and direct vasoconstriction. Of particular interest are nonsteroidal antiinflammatory drugs (NSAIDs), which are frequently prescribed as postpartum analgesics. These medications decrease prostaglandins leading to a lack of vasodilation and increased sodium retention. Nonsteroidal anti-inflammatory medications should continue to be used preferentially over opioid analgesics; however, women with chronic hypertension may theoretically require intensification of blood pressure monitoring and regimen adjustments when on these medications. Overall, data support the safe use of NSAIDs in postpartum patients with blood pressure issues. In a randomized trial comparing use of ibuprofen to acetaminophen in postpartum patients with preeclampsia with severe features, ibuprofen did not lengthen the duration of severe-range blood pressures (155). In a cohort of 399 patients with preeclampsia with severe features, there was no association of NSAID use with postpartum blood pressure elevations (156). Further, another cohort study of postpartum patients on magnesium for seizure prophylaxis for preeclampsia did not show differences in blood pressure, antihypertensive requirements, or other adverse events for patients managed with NSAIDs in the postpartum period (157, 158).

▶ *What is the optimal treatment for eclampsia?*

The initial steps in the management of a woman with eclampsia are basic supportive measures such as calling for help, prevention of maternal injury, placement in lateral decubitus position, prevention of aspiration, administration of oxygen, and monitoring vital signs including oxygen saturation. Only subsequently is attention directed to the administration of magnesium sulfate. Most eclamptic seizures are self-limited. Magnesium sulfate is not necessary to arrest the seizure but to prevent recurrent convulsions.

During eclamptic seizures, there are usually prolonged fetal heart rate decelerations, even fetal bradycardia, and sometimes an increase in uterine contractility and baseline tone. After a seizure, because of maternal hypoxia and hypercarbia, the fetal heart rate tracing may show recurrent decelerations, tachycardia, and reduced variability. However, only after maternal hemodynamic stabilization should one proceed with delivery. Furthermore, maternal resuscitation is usually followed by normalization of the fetal tracing.

Cochrane reviews, including data originating from developing countries, indicate a significant reduction in recurrent seizures and eclampsia-related maternal mortality with the use of magnesium sulfate. Magnesium sulfate administered intramuscularly or intravenously is superior to phenytoin, diazepam, or lytic cocktail (usually chlorpromazine, promethazine, and pethidine) and also is associated with less maternal and neonatal morbidity (126, 159, 160). Thus, these data support the use of magnesium sulfate as the drug of choice to prevent recurrent seizures in women with eclampsia. In the rare cases of an extremely agitated patient, IV clonazepam 1 mg, diazepam 10 mg, or midazolam may be used for sedation to facilitate the placement of the IV lines and Foley catheter, and the collection of blood specimens. These drugs should be used cautiously and only if absolutely necessary because they inhibit laryngeal reflexes, increasing the risk of aspiration and also may depress the central respiratory centers leading to apnea.

Women with eclampsia should be delivered in a timely fashion. However, eclampsia by itself is not an indication for cesarean delivery. Once the patient is stabilized, the method of delivery should depend, in part, on factors such as gestational age, fetal presentation, and the findings of the cervical examination. A high rate of failure may be anticipated with induction or augmentation in pregnancies less than 30 weeks of gestation if the

patient is not in active labor and the Bishop score is unfavorable. In these cases, it may be preferable to opt for cesarean delivery without further delay. However, patients that adequately progress in labor could be allowed to continue labor even after an eclamptic seizure.

It has been proposed that when convulsions recur, a further 2–4 grams of magnesium sulfate could be administered IV over 5 minutes (130). In cases refractory to magnesium sulfate (still seizing at 20 minutes after the bolus or more than two recurrences), a health care provider can use sodium amobarbital (250 mg IV in 3 minutes), thiopental, or phenytoin (1,250 mg IV at a rate of 50 mg/minute). Endotracheal intubation and assisted ventilation in the intensive care unit are appropriate in these circumstances. Head imaging should also be considered because most of cases refractory to magnesium sulfate therapy may prove to have abnormal findings on brain imaging (161).

▶ *What is the management of acute complications for preeclampsia with HELLP?*

The clinical course of HELLP syndrome often is characterized by progressive and sometimes sudden deterioration in maternal and fetal condition. Considering the serious nature of this entity, with increased rates of maternal morbidity and mortality, many authors have concluded that women with HELLP syndrome should be delivered regardless of their gestational age. Because the management of patients with HELLP syndrome requires the availability of neonatal and obstetric intensive care units and personnel with special expertise, patients with HELLP syndrome who are remote from term should receive care at a tertiary care center (116, 162).

It has been hypothesized that the antiinflammatory and immunosuppressive effects of corticosteroids may modify some of the proinflammatory features of preeclampsia with severe features and favorably affect the clinical course. Several randomized controlled trials of high-dose corticosteroid treatment for antepartum or postpartum stabilization of HELLP syndrome have been conducted. The use of corticoids in the management of HELLP syndrome compared with placebo or no treatment was reviewed in a Cochrane Database Systematic Review, which included 11 randomized trials (550 women) (163). There was no difference in the risk of maternal death, severe maternal morbidity, or perinatal or infant death. The only effect of treatment on individual outcomes was improved platelet count (standardized mean difference [SMD] 0.67; 95% CI, 0.24−1.10). The authors concluded that the evidence is insufficient to support the use of corticosteroids for attenuation of the disease process in HELLP syndrome (163).

Very close monitoring is required in HELLP syndrome until delivery and in the postpartum period, with laboratory testing at least at 12-hour intervals. Aspartate aminotransferase levels more than 2,000 IU/L or LDH more than 3,000 IU/L suggest an increased mortality risk. In the natural history of HELLP syndrome there is an inverse relationship between the trends in platelet values and liver enzymes level. During the aggravation slope in the disease evolution, platelet count usually decreases at an average rate of approximately 40% per day, whereas the liver enzymes values tend to increase. The lowest observed platelet count occurs at a mean of 23 hours after delivery. The disease may achieve peak intensity during the first 2 days after delivery, including a downward trend in hematocrit. If the platelet count continues to drop and liver enzymes to increase after 4 days postpartum, the validity of the initial diagnosis of HELLP syndrome should be reassessed. With supportive care alone, 90% of patients with HELLP syndrome will have platelet count more than 100,000 $\times$ 10^9/L and reversed trend (decrease) in liver enzymes values within 7 days after delivery. Not infrequently, a rebound phenomenon in platelet count follows reaching values of 400,000–871,000 $\times$ 10^9/L (164). Women with HELLP syndrome are also at increased risk of pulmonary edema, acute respiratory distress syndrome and renal failure (165).

▶ *What are the risks of subsequent cardiovascular disease among women with hypertensive disorders of pregnancy and are there prevention strategies that modify this risk?*

Women with a history of preeclampsia continue to have an elevated risk of cardiovascular disease in subsequent years. Several systematic reviews and meta-analyses have linked preeclampsia with an increased risk of cardiovascular disease (hypertension, myocardial infarction, congestive heart failure), cerebrovascular events (stroke), peripheral arterial disease, and cardiovascular mortality later in life, with an estimated doubling of odds compared with women unaffected by preeclampsia (166–168). Meta-regression analysis reveals a graded relationship between the severity of preeclampsia or eclampsia and the risk of cardiac disease (mild: RR, 2.00; 95% CI, 1.83–2.19; moderate: RR, 2.99; 95% CI, 2.51–3.58; severe: RR, 5.36; 95% CI, 3.96–7.27, $P<.0001$) (169). The risk is even higher (4–8 times the risk for women with normal pregnancies) in women with recurrent preeclampsia (170) and women with early-onset preeclampsia or preeclampsia requiring preterm delivery (171). More recent evidence suggests that all hypertensive conditions in pregnancy are associated with later cardiovascular disease with an approximately doubling of the rate of incident cardiovascular disease and a five times higher rate of hypertension (172).

The mechanisms that account for an increased risk of cardiovascular disease in women with a history of preeclampsia are not yet well understood, but endothelial dysfunction, which has been linked to atherosclerosis, persists in women with a history of preeclampsia many years after an affected pregnancy (173). A study of cardiovascular risk factors present before and after pregnancy suggested that nearly one half of the elevated risk of future hypertension after preeclampsia can be explained by prepregnancy risk factors (174). Yet, it may be possible that the stress incurred to the cardiovascular system during gestation triggers a biological response that would otherwise not have occurred despite any genetic predisposition or risk factors (172). It remains unclear if cardiovascular changes associated with preeclampsia during pregnancy causally lead to cardiovascular remodeling increasing the risk of cardiovascular disease later in life or if preeclampsia is a manifestation of an underlying increased risk of cardiovascular disease (for example, a common genetic–environmental risk factor(s) interaction [such as hyperlipidemia, obesity, diabetes mellitus, or renal disease] that predisposes women to develop preeclampsia during pregnancy and cardiovascular diseases later in life) (175). Preventive strategies to be considered by patients and health care providers may warrant closer long-term follow-up and lifestyle modifications to better manage risk factors for cardiovascular disease (eg, achieving healthful weight, exercise, diet, smoking cessation), for which women and their primary care providers may maintain ongoing care and vigilance.

Summary of Recommendations

The following recommendations are based on good and consistent scientific evidence (Level A):

- Women with any of the high-risk factors for preeclampsia (previous pregnancy with preeclampsia, multifetal gestation, renal disease, autoimmune disease, type 1 or type 2 diabetes mellitus, and chronic hypertension) and those with more than one of the moderate-risk factors (first pregnancy, maternal age of 35 years or older, a body mass index of more than 30, family history of preeclampsia, sociodemographic characteristics, and personal history factors) should receive low-dose (81 mg/day) aspirin for preeclampsia prophylaxis, initiated between 12 weeks and 28 weeks of gestation (optimally before 16 weeks of gestation) and continuing until delivery.
- In women with gestational hypertension or preeclampsia without severe features at or beyond 37 0/7 weeks of gestation, delivery rather than expectant management upon diagnosis is recommended.
- Magnesium sulfate should be used for the prevention and treatment of seizures in women with gestational hypertension and preeclampsia with severe features or eclampsia.
- Nonsteroidal anti-inflammatory medications should continue to be used preferentially over opioid analgesics. Postpartum patients on magnesium for seizure prophylaxis for preeclampsia did not show differences in blood pressure, antihypertensive requirements, or other adverse events for patients managed with NSAIDs in the postpartum period.

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- Delivery is recommended when gestational hypertension or preeclampsia with severe features is diagnosed at or beyond 34 0/7 weeks of gestation, after maternal stabilization or with labor or prelabor rupture of membranes. Delivery should not be delayed for the administration of steroids in the late preterm period.
- The expectant management of preeclampsia with severe features before 34 0/7 weeks of gestation is based on strict selection criteria of those appropriate candidates and is best accomplished in a setting with resources appropriate for maternal and neonatal care. Because expectant management is intended to provide neonatal benefit at the expense of maternal risk, expectant management is not advised when neonatal survival is not anticipated. During expectant management, delivery is recommended at any time in the case of deterioration of maternal or fetal condition.
- Antihypertensive treatment should be initiated expeditiously for acute-onset severe hypertension (systolic blood pressure of 160 mm Hg or more or diastolic blood pressure of 110 mm Hg or more, or both) that is confirmed as persistent (15 minutes or more). The available literature suggests that antihypertensive agents should be administered within 30–60 minutes. However, it is recommended to administer antihypertensive therapy as soon as reasonably possible after the criteria for acute-onset severe hypertension are met.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- It is recommended that women with gestational hypertension in the absence of proteinuria are

diagnosed with preeclampsia if they present with any of the following severe features: thrombocytopenia (platelet count less than 100,000 × 10^9/L); impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (to twice the upper limit of normal concentration); severe persistent right upper quadrant or epigastric pain and not accounted for by alternative diagnoses; renal insufficiency (serum creatinine concentration more than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease); pulmonary edema, or new-onset headache unresponsive to acetaminophen and not accounted for by alternative diagnoses, or visual disturbances.

- Women with gestational hypertension who present with severe-range blood pressures should be managed with the same approach as for women with severe preeclampsia.
- Among women with gestational hypertension or preeclampsia without severe features, expectant management up to 37 0/7 weeks of gestation is recommended, during which frequent fetal and maternal evaluation is recommended. Fetal monitoring consists of ultrasonography to determine fetal growth every 3–4 weeks of gestation, and amniotic fluid volume assessment at least once weekly. In addition, an antenatal test one-to-two times per week for patients with gestational hypertension or preeclampsia without severe features is recommended.
- Epidural or spinal anesthesia is considered acceptable, and the risk of epidural hematoma is exceptionally low, in patients with platelet counts 70 × 10^9/L or more provided that the platelet level is stable, there is no other acquired or congenital coagulopathy, the platelet function is normal, and the patient is not on any antiplatelet or anticoagulant therapy.

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The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to locate relevant articles published between January 1985–June 2018. Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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Pregnancy and Heart Disease

Maternal heart disease has emerged as a major threat to safe motherhood and women's long-term cardiovascular health. In the United States, disease and dysfunction of the heart and vascular system as "cardiovascular disease" is now the leading cause of death in pregnant women and women in the postpartum period (1, 2) accounting for 4.23 deaths per 100,000 live births, a rate almost twice that of the United Kingdom (3, 4). The most recent data indicate that cardiovascular diseases constitute 26.5% of U.S. pregnancy-related deaths (5). Of further concern are the disparities in cardiovascular disease outcomes, with higher rates of morbidity and mortality among nonwhite and lower-income women. Contributing factors include barriers to prepregnancy cardiovascular disease assessment, missed opportunities to identify cardiovascular disease risk factors during prenatal care, gaps in high-risk intrapartum care, and delays in recognition of cardiovascular disease symptoms during the puerperium. The purpose of this document is to 1) describe the prevalence and effect of heart disease among pregnant and postpartum women; 2) provide guidance for early antepartum and postpartum risk factor identification and modification; 3) outline common cardiovascular disorders that cause morbidity and mortality during pregnancy and the puerperium; 4) describe recommendations for care for pregnant and postpartum women with preexisting or new-onset acquired heart disease; and 5) present a comprehensive interpregnancy care plan for women with heart disease.

Background

Emerging Trends in Cardiovascular Disease

Cardiovascular disease affects approximately 1–4% of the nearly 4 million pregnancies in the United States each year. The incidence of pregnancy in women with congenital heart disease and acquired heart disease is on the rise (6). In developed countries, maternal morbidity and mortality secondary to congenital heart disease have remained relatively stable at 11% and 0.5% (7), respectively; however, the United States experienced a significant linear increase in maternal congenital heart disease (6.4 to 9.0 per 10,000 delivery hospitalizations) from 2000 to 2010 (8), and maternal deaths due to acquired heart disease remain high. From 2002 to 2011, 22.2% of maternal deaths in Illinois were due to cardiovascular disease, 97.1% of which were related to acquired heart disease (9). This rising trend in maternal deaths related to cardiovascular disease appears to be due to acquired heart disease (10).

The most common presentations of maternal acquired heart disease during pregnancy and the postpartum periods are heart failure, myocardial infarction, arrhythmia, or aortic dissection (11, 12). Diagnosis can be challenging because the overlap of cardiovascular symptoms with those of normal pregnancy may lead to delays in diagnosis and subsequent care (10). If cardiovascular disease were to be considered in the differential diagnosis by treating health care providers, it is estimated that a quarter or more of maternal deaths could be prevented (10, 13, 14). A recent study of maternal cardiovascular mortality in Illinois found that 28.1% of maternal cardiac deaths were potentially deemed preventable due to health care provider issues, patient features (eg, nonadherence, obesity) (9), and health care system factors related to access. In the United Kingdom, a 2015 report on maternal mortality concluded that substandard health care accounted for more than 50% of cardiac deaths, half of which were considered avoidable (15).

Risk Factors for Cardiovascular Disease Across the Maternity Care Continuum

There are four key risk factors linked to cardiovascular disease-related maternal mortality:

1. Race/Ethnicity: Non-Hispanic black women have a 3.4 times higher risk of dying from cardiovascular disease-related pregnancy complications compared with non-Hispanic white women independent of other variables (5). Between 2011 and 2013, there were 43.5 pregnancy-related deaths per 100,000 live births for non-Hispanic black women compared with 11.0 and 12.7 pregnancy-related deaths per 100,000 live births for Hispanic and non-Hispanic white women, respectively (5). This disparity can be explained in part by exposure to structural, institutional, and systemic barriers that contribute to a higher rate of comorbidities.
2. Age: Age older than 40 years increases the risk of heart disease-related maternal death 30 times the risk for women younger than 20 years (16, 17).
3. Hypertension: Hypertensive disorders affect up to 10% of pregnancies and can lead to maternal morbidity and mortality. Severe and early-onset hypertension during pregnancy put women at an increased risk of cardiac compromise during or following delivery (18–20). In pregnancies complicated by hypertension, the incidence of myocardial infarction and heart failure is 13-fold and 8-fold higher, respectively, than in healthy pregnancies (18).
4. Obesity: Prepregnancy obesity increases maternal death risk due to a cardiac cause (21), especially if associated with moderate-to-severe obstructive sleep apnea (22). In the United Kingdom from 2006 to 2008, 60% of maternal deaths in which the body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) was known were in overweight or obese women (15).

The presence of one or more of these risk factors should raise the threshold for suspicion that a patient is at-risk for maternal heart disease and pregnancy-related morbidity and mortality (23).

Social Determinants of Disparities in Cardiovascular Disease in Health and Health Care

Increased rates of cardiovascular disease-related complications among women of color are explained, in part, by racial and ethnic bias in the provision of health care and health system processes (24). Patient, physician, and health system-level factors can affect outcomes. Physician implicit and explicit bias and overt racism often can result in missed diagnoses or inappropriate treatment. Health system barriers to efficient triage based on symptom severity, language barriers, and differences in cultural humility are important factors that must be investigated to understand fully the pervasiveness of disparities that women of color face when encountering the health care system (25). Moreover, women of color may have experienced injustice in health care processes, leading to mistrust of the medical system. These factors contribute to a disproportionately higher rate of pregnancy-associated complications among women of color which, in turn, places these women not only at a greater risk of cardiovascular events in the postpartum period but also increase their lifetime risk of cardiovascular disease. Thus, it is important to improve education for these women and their trusted lay sources of information by emphasizing the value of medical care and the importance of healthy dietary habits and regular exercise. Non-Hispanic black women are more likely to develop gestational diabetes mellitus, preeclampsia, and have a preterm delivery or low-birthweight infant compared with non-Hispanic white women (23, 26). These health disparities often are amplified by missed opportunities to identify cardiovascular disease risk factors before pregnancy and limited access to cardiac-related care algorithms during intrapartum and postpartum care (23, 27). Additionally, the higher rate of obesity among racial and ethnic nonwhite groups independently contributes to disparities in the development of adverse pregnancy outcomes leading to long-term risk of cardiovascular disease. A higher prevalence of postpartum weight retention and persistence of high-glucose levels among women with gestational diabetes mellitus places them at increased risk of cardiovascular disease (28, 29).

Physiologic Changes in Pregnancy That Affect Cardiovascular Stress

Pregnancy is a natural stress test because the cardiovascular system undergoes structural and hemodynamic adaptations to sustain a high-volume load. An understanding of these physiologic changes is essential for health care providers.

Hemodynamic Changes

Antepartum. Because of increases in estrogen and progesterone and the activation of the renin-angiotensin-aldosterone system, pregnancy causes a continuous increase in cardiac output and plasma volume and a decrease in maternal systemic vascular resistance (30). Blood pressure initially decreases but increases in the third trimester (31, 32) (Table 1). Uterine mechanical compression of the inferior vena cava can occur during the second and third trimesters, potentially reducing venous return to the right ventricle, causing a postural hypotensive syndrome (33) and exacerbating lower-extremity edema. These changes are amplified in women with multiple gestations.

Intrapartum and Postpartum. During labor and after delivery, there are dramatic changes in cardiac output, heart rate, blood pressure, and plasma volume (34, 35). Although heart rate and blood pressure normally decrease within 48 hours postpartum, blood pressure may increase again between days 3–6 due to fluid shifts (36) (Table 1). During this period, clinicians should monitor patients for hypertensive complications and those related to fluid overload (37). Increased hydrostatic pressure and decreased colloid osmotic pressure render women with cardiovascular disease susceptible to pulmonary edema at the time of delivery and immediately postpartum, particularly in women with severe cardiovascular disease and excessive intravenous fluid administration or preeclampsia, or both. Increased maternal plasma atrial natriuretic peptide levels in the first week postpartum allow for postpartum diuresis (38). Maternal hemodynamics generally return to a prepregnancy state 3–6 months after delivery.

Structural Changes

The heart ventricles adapt to the plasma volume increase during pregnancy. Left ventricular end diastolic volume increases by approximately 10% (39) and left and right ventricular mass increase by approximately 50% and 40%, respectively (40). Reports of ejection fraction during pregnancy are varied. Ejection fractions in some women show no change, (39) although others decrease

Table 1. Cardiovascular Changes in a Normal Pregnancy*

	First Trimester	Second Trimester	Third Trimester	Stage 1 Labor	Stage 2 Labor	Early Postpartum	3–6 months Postpartum
Cardiac output	↑5–10%	↑↑35–45%		↑30%	↑↑50%	↑↑↑60–80% immediately, then rapidly decreases within the first hour	Return to prepregnancy values
Heart rate	↑3–5%	↑10–15%	↑15–20%	During uterine contractions: ↑40–50%		↓5–10% within 24 hours; continues to decrease throughout the first 6 weeks	Return to prepregnancy values
Blood pressure	↓10%	↓5%	↑5%	During uterine contractions: ↑SBP 15–25% ↑DBP 10–15%		↓SBP 5–10% within 48 hours; may increase again between days 3–6 due to fluid shifts	Return to prepregnancy values
Plasma volume	↑	↑↑40–50%		↑	↑↑	↑↑↑500 mL due to autotransfusion	Return to prepregnancy values

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure.

*Hemodynamic changes that occur during pregnancy, labor, and postpartum (compared with prepregnancy) should be understood to identify early interventions (such as blood pressure control and diuresis) that may be needed to prevent clinical deterioration in a woman with cardiovascular disease.

Data from Kuhn JC, Falk RS, Langesaeter E. Haemodynamic changes during labour: continuous minimally invasive monitoring in 20 healthy parturients. Int J Obstet Anesth 2017;31:74–83; Ouzounian JG, Elkayam U. Physiologic changes during normal pregnancy and delivery. Cardiol Clin 2012;30:317–29; Sanghavi M, Rutherford JD. Cardiovascular physiology of pregnancy. Circulation 2014;130:1003–8; Shen M, Tan H, Zhou S, Smith GN, Walker MC, Wen SW. Trajectory of blood pressure change during pregnancy and the role of pre-gravid blood pressure: a functional data analysis approach. Sci Rep 2017;7:6227; Sohnchen N, Melzer K, Tejada BM, Jastrow-Meyer N, Othenin-Girard V, Irion O, et al. Maternal heart rate changes during labour. Eur J Obstet Gynecol Reprod Biol 2011;158:173–8; and Walters BN, Walters T. Hypertension in the puerperium [letter]. Lancet 1987;2:330.

(41, 42). Importantly, approximately 20% of women have diastolic dysfunction at term, which may be associated with dyspnea on exertion (41, 43). Structural changes of the maternal heart return to baseline before 1 year postpartum.

Hematologic, Coagulation, and Metabolic Changes

Hematologic, coagulation, and metabolic changes in pregnancy are important contributors to cardiovascular risk. Although intensified erythropoiesis in pregnancy increases red blood cell mass by 20–30%, this increase is proportionally lower than the increase in plasma volume, resulting in physiologic anemia from hemodilution. Because severe anemia may be associated with heart failure and myocardial ischemia, hemoglobin or hematocrit levels should be checked each trimester in women with cardiovascular disease. Pregnancy is associated with physiologic and anatomic changes that increase the risk of thromboembolism, including hypercoagulability, venous stasis, decreased venous outflow, compression of the inferior vena cava and pelvic veins by the enlarging uterus, and decreased mobility (44). Pregnancy also alters the levels of coagulation factors normally responsible for hemostasis. The overall effect of these changes is an amplified thrombogenic state with an increased risk of thromboembolism. Certain disorders, such as antiphospholipid antibody syndrome and high-risk thrombophilia and smoking, further increase the risk of thrombosis and embolism during pregnancy. From a metabolic standpoint, pregnancy is a catabolic state that leads to insulin resistance and an atherogenic lipid profile with elevated serum fatty acids.

Signs and Symptoms of Heart Disease

Normal pregnancy and postpartum symptoms and signs can overlap with findings reflective of underlying heart disease (Table 2). Health care providers should become familiar with the signs and symptoms of cardiovascular disease as an important step toward improving maternal outcomes.

Clinical Considerations and Recommendations

▶ ***What are the prerequisites of pregnancy preparation and prepregnancy counseling for patients with known heart disease?***

Whenever possible, optimization of maternal health status should be attempted and achieved before pregnancy. Risk to a woman's heart and cardiovascular system engendered by pregnancy depends upon the specific type of heart disease and clinical status of the patient. Women with known cardiovascular disease (Table 3) should be evaluated by a cardiologist ideally before pregnancy or as early as possible during the pregnancy for an accurate diagnosis and assessment of the effect pregnancy will have on the underlying cardiovascular disease, to assess the potential risks to the woman and fetus, and to optimize the underlying cardiac condition. A detailed history, including family history and any current cardiovascular symptoms, physical examination, and review of medical records, including prior cardiovascular testing and interventions, should be obtained (45–48). A comprehensive cardiovascular family history should include inquiry about structural, vascular, or rhythm disorders and sudden unexpected death. Clues to a familial cardiac condition may include prior cardiac surgery, myocardial infarction, stroke, aortic dissection, and sudden death. Upon confirmation of family history of cardiovascular disease, health care providers should ask whether genetic testing has been performed. A known gene mutation, such as *MYH7* for cardiomyopathy, may have implications for a patient's individual risk of developing cardiomyopathy and may alert the patient and care team to plan postpartum surveillance and to screen offspring (49).

Patients with moderate and high-risk cardiovascular disease should be managed during pregnancy, delivery, and the postpartum period in medical centers with a multidisciplinary Pregnancy Heart Team (Table 4) that includes obstetric providers, maternal–fetal medicine subspecialists, cardiologists, and an anesthesiologist at a minimum. Ad hoc members may include cardiac surgeons, interventional cardiologists, cardiac imaging specialists, electrophysiologists, pulmonary hypertension and heart failure specialists, adult congenital cardiologists, emergency physicians, intensivists, neonatologists, geneticists, mental health specialists, primary care physicians, other medical specialists, advanced practice providers and specialized nurses, midwives, or pharmacists. The members of the Pregnancy Heart Team (Table 4) should work together to assess and counsel the patient regarding the individualized risks of her underlying cardiac condition should she become pregnant, the potential risk of transmission of congenital heart or genetic disease to the child, and the need for increased medical surveillance during the antepartum, parturition, and postpartum phases of pregnancy (Table 3).

A triad of cardiovascular risk screening, patient education, and multidisciplinary team planning has been suggested to optimize outcomes in women with known cardiovascular disease (50). It is imperative to

Table 2. How to Differentiate Common Signs and Symptoms of Normal Pregnancy Versus Those That Are Abnormal and Indicative of Underlying Cardiac Disease

	ROUTINE CARE	CAUTION*†	STOP†‡
	Reassurance	Nonemergent Evaluation	Prompt Evaluation Pregnancy Heart Team
History of CVD	None	None	Yes
Self-reported symptoms	None or mild	Yes	Yes
Shortness of breath	No interference with activities of daily living; with heavy exertion only	With moderate exertion, new-onset asthma, persistent cough, or moderate or severe OSA§	At rest; paroxysmal nocturnal dyspnea or orthopnea; bilateral chest infiltrates on CXR or refractory pneumonia
Chest pain	Reflux related that resolves with treatment	Atypical	At rest or with minimal exertion
Palpitations	Few seconds, self-limited	Brief, self-limited episodes; no lightheadedness or syncope	Associated with near syncope
Syncope	Dizziness only with prolonged standing or dehydration	Vasovagal	Exertional or unprovoked
Fatigue	Mild	Mild or moderate	Extreme
Vital signs	Normal		
HR (beats per minute)	<90	90–119	≥120
Systolic BP (mm Hg)	120–139	140–159	≥160 (or symptomatic low BP)
RR (per minute)	12–15	16–25	≥25
Oxygen saturation	>97%	95–97%	<95% (unless chronic)
Physical examination	Normal		
JVP	Not visible	Not visible	Visible >2 cm above clavicle
Heart	S3, barely audible soft systolic murmur	S3, systolic murmur	Loud systolic murmur, diastolic murmur, S4
Lungs	Clear	Clear	Wheezing, crackles, effusion
Edema	Mild	Moderate	Marked

Abbreviations: BP, blood pressure; CVD, cardiovascular disease; CXR, chest x-ray; HR, heart rate; JVP, jugular venous pressure; OSA, obstructive sleep apnea; RR, respiratory rate.

*If unclear, any combination of factors in the yellow column that add up to 4 or more should prompt further evaluation.

†Data in this column from Afshan B. Hameed, Christine H. Morton, and Allana Moore. Improving Health Care Response to Cardiovascular Disease in Pregnancy and Postpartum. Developed under contract #11-10006 with the California Department of Public Health, Maternal, Child and Adolescent Health Division. Published by the California Department of Public Health, 2017. Available at https://www.cmqcc.org/resources-toolkits/toolkits/improving-health-care-response-cardiovascular-disease-pregnancy-and.

‡History of CVD or signs and symptoms in the red column should lead to urgent evaluation by the Pregnancy Heart Team.

§Should raise concern about heart failure and should promptly be evaluated.

Modified from Thorne S. Pregnancy and native heart valve disease. Heart 2016;102:1410–7.

Table 3. Modified World Health Organization Pregnancy Risk Classification for Women With Preexisting Cardiovascular Disease

Modified WHO Pregnancy Risk Classification (Risk of Pregnancy by medical condition) Suggested follow-up	Specific Cardiac Lesions	Pregnancy Care Delivery Location

mWHO Risk Class I
No detectable increased risk of maternal mortality and no or mild increase in morbidity
(2–5% risk of maternal cardiac event rate)
Follow-up: Cardiology evaluation once or twice during pregnancy
	• Uncomplicated, small, or mild
	  ○ Pulmonary stenosis
	  ○ Patient ductus arteriosus
	  ○ Mitral valve prolapse
	• Successfully repaired simple lesions (atrial or ventricular septal defect, patent ductus arteriosus, anomalous pulmonary venous drainage)
	• Atrial or ventricular ectopic beats, isolated
		• Prepregnancy/pregnancy counseling
		• Care at local hospital
		• Delivery at local hospital*

mWHO Risk Class II Small increased risk of maternal mortality or moderate increase in morbidity (6–10% maternal cardiac event rate) Follow-up: Cardiology, every trimester	• Unoperated atrial or ventricular septal defect • Repaired Tetralogy of Fallot or aortic coarctation • Most arrhythmias (supraventricular arrhythmias) • Turner syndrome without congenital cardiac disease	• Prepregnancy/pregnancy counseling • Pregnancy Heart Team* consultation/ counseling • Care at local hospital • Delivery at local hospital*
mWHO Risk Classes II and III Intermediate increased risk of maternal mortality or moderate to severe increase in morbidity (11–19% maternal cardiac event rate) Follow-up: Cardiology, every trimester	• Mild left ventricular impairment (EF >45%) • Hypertrophic cardiomyopathy • Native or bioprosthetic valve disease not considered mWHO Risk Class I or IV (mild mitral stenosis, moderate aortic stenosis) • Marfan or other HTAD syndrome without aortic dilation • Aorta <45 mm in bicuspid aortic valve pathology • Repaired coarctation without residua (non-Turner) • Atrioventricular septal defect	• Prepregnancy/pregnancy counseling • Pregnancy heart team* consultation/ counseling • Care at an appropriate level hospital (critical members of the Pregnancy Heart Team* available depending on cardiac disease) • Delivery at an appropriate level hospital*†
Pre-mWHO Risk Class III Significantly increased risk of maternal mortality or severe morbidity (20–27% maternal cardiac event rate) Follow-up: Cardiology, every 1–2 months	• Moderate left ventricular impairment (EF 30–45%) • Previous peripartum cardiomyopathy without any residual left ventricular impairment • Mechanical valve • Systemic right ventricle with good or mildly decreased ventricular function • Uncomplicated Fontan circulation, • Unrepaired cyanotic heart disease • Other complex heart disease • Moderate mitral stenosis • Severe asymptomatic aortic stenosis • Moderate aortic dilation (40–45 mm in Marfan syndrome or other HTAD; 45–50 mm in bicuspid aortic valve; Turner syndrome ASI 20–25 mm/m^2; Tetralogy of Fallot <50 mm) • Ventricular tachycardia	• Prepregnancy/pregnancy counseling • Pregnancy Heart Team* consultation/ counseling • Care at an appropriate level hospital† • Delivery at an appropriate level hospital*†

(*continued*)

Table 3. Modified World Health Organization Pregnancy Risk Classification for Women With Preexisting Cardiovascular Disease (*continued*)

Modified WHO Pregnancy Risk Classification (Risk of Pregnancy by medical condition) Suggested follow-up	Specific Cardiac Lesions	Pregnancy Care Delivery Location
mWHO Risk Class IV Pregnancy contraindicated Discuss induced abortion Extremely high risk of maternal mortality or severe morbidity (>27% maternal cardiac event rate) Follow-up: Cardiology follow-up every month (minimum)	▪ Pulmonary arterial hypertension ▪ Severe systemic ventricular dysfunction (EF <30%, NYHA III-IV) ▪ Previous peripartum cardiomyopathy with any residual left ventricular dysfunction ▪ Severe mitral stenosis ▪ Severe symptomatic aortic stenosis ▪ Systemic right ventricle with moderate to severely decreased ventricular function ▪ Severe aortic dilation (>45 mm in Marfan syndrome or other HTAD; >50 mm in bicuspid aortic valve; Turner syndrome ASI >25 mm/m^2; Tetralogy of Fallot >50 mm) ▪ Vascular Ehlers-Danlos ▪ Severe (re)coarctation ▪ Fontan circulation with any complication	▪ Pregnancy Heart Team* consultation/ counseling ▪ Care at an appropriate level hospital† (critical members of the Pregnancy Heart Team* available depending on cardiac disease) ▪ Delivery at an appropriate level hospital*‡

Abbreviations: ASI, aortic size index; EF, ejection fraction; HTAD, hereditary thoracic aortic disease; mWHO, modified World Health Organization; NYHA, New York Heart Association.

*Pregnant women with a positive cardiac history or findings, or both, should receive prenatal, intrapartum, and postpartum care in a hospital setting that represents an appropriate maternal level of care that is at Level II or higher depending upon the specific cardiac lesion(s) that are present. "The goal of regionalized maternal care is for pregnant women at high risk to receive care in facilities that are prepared to provide the required level of specialized care, thereby reducing maternal morbidity and mortality in the United States." (Levels of maternal care. Obstetric Care Consensus No. 2. American College of Obstetricians and Gynecologists. Obstet Gynecol 2015;125:502–15).

†**mWHO Risk Class III.** Critical members of the Pregnancy Heart Team available depending on cardiac disease. For example: A mechanical valve patient requires care at a center with cardiologist/maternal–fetal medicine team who monitor and adjust anticoagulation weekly, delivery at a center with obstetric anesthesia, and advance cardiac care options including access to emergency cardiac surgery should acute prosthetic valve thrombosis necessitate emergency intervention.

‡**mWHO Risk Class IV.** For example, a severe pulmonary hypertension patient requires care and delivery at a center with maternal–fetal medicine, obstetric and cardiac anesthesia, a pulmonary hypertension specialist, and advanced heart failure care options, such as ventricular assist device and extracorporeal membrane oxygenator management.

Adapted from Thorne S, MacGregor A, Nelson-Piercy C. Risks of contraception and pregnancy in heart disease. Heart 2006;92:1520–5).

identify cardiac conditions associated with significantly increased maternal mortality or severe morbidity. Pregnancy is not recommended for women in modified World Health Organization (WHO) pregnancy risk category IV (Table 3) (51–53). Discussion of cardiovascular disease with the woman should include the possibilities that 1) pregnancy can contribute to a decline in cardiac status that may not return to baseline after the pregnancy; 2) maternal morbidity or mortality is possible; and 3) fetal risk of congenital heart or genetic conditions, fetal growth restriction, preterm birth, intrauterine fetal demise, and perinatal mortality is higher when compared with risk when cardiovascular disease is not present (54–56).

Approximately one third of cardiac patients will require medication during pregnancy (57), and special emphasis should be placed on agents to be avoided, and when feasible, switching to safer alternatives before pregnancy (see Table 5). Certain medications, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone antagonists should be avoided if possible because of the risk of potential fetal adverse effects (58). However, there may be cardiac conditions that are controlled only by medications or interventions that have potential teratogenic effects that must be used during pregnancy despite known risk to the fetus, such as warfarin in a patient with a mechanical valve prosthesis (57). In these circumstances, the

Table 4. The Pregnancy Heart Team

	Modified WHO Pregnancy Risk Classification I	Modified WHO Pregnancy Risk Classification II	Modified WHO Pregnancy Risk Classifications III and IV
Pregnancy Heart Team Members	Obstetrician, family medicine practitioner, internist	Obstetrician, family medicine practitioner, internist	Obstetrician, family medicine practitioner, maternal–fetal medicine subspecialist, internist, obstetric anesthesiologist, cardiology subspecialists in adult congenital/aortopathy*, heart rhythm*, heart failure*, pulmonary hypertension*, and cardiac imaging*
		Maternal–fetal medicine subspecialist	
	Cardiologist consultation	Cardiologist consultation	Interventional cardiologist*
			Cardiac surgeon*
			Neonatologist*
			Geneticist*
			Mental health specialist*
			Pharmacist*

Abbreviation: WHO, World Health Organization.

*Ad Hoc members of a Pregnancy Heart Team

specialists who constitute the Pregnancy Heart Team (Table 4) should review the risks, benefits, and alternative therapeutic options with the patient and document in the medical record a summary of what is discussed and recommended. Patients should be encouraged not to stop any medications until they have reviewed management options with their care team.

Although the goal of prepregnancy counseling is to identify and modify risks to improve pregnancy outcome, the individual's choices will be conditional upon her values and preferences, and patient autonomy must be ensured. A collaborative discussion with shared decision making should take place between the Pregnancy Heart Team (Table 4), the patient, and her family. A personalized approach estimating the maternal and fetal hazards related to the patient's specific cardiac disorder and the patient's pregnancy plans can provide anticipatory guidance to help support her decision making. For some patients, the prepregnancy evaluation may suggest a pregnancy risk that is unacceptable (Table 3). For those women, reproductive alternatives, such as surrogacy or adoption, and effective contraceptive methods should be discussed (58).

▶ ***Why is risk assessment indicated, what types are recommended, and which patients should be referred to centers with a high level of care?***

A key area of competence and expertise for obstetric care providers is the ability to differentiate between common symptoms of pregnancy and those suggestive of cardiovascular disease. Maternal mortality reviews indicate that most women who die from cardiovascular disease had either undiagnosed cardiovascular disease or new-onset cardiovascular disease of pregnancy, specifically peripartum cardiomyopathy. Therefore, all women should be assessed for cardiovascular disease in the antepartum and postpartum periods using the California Improving Health Care Response to Cardiovascular Disease in Pregnancy and Postpartum toolkit algorithm (Fig. 1). Use of this algorithm could have identified individuals as high risk requiring further cardiac evaluation and referral in 88% of maternal deaths (50). Patients with concerning symptoms or signs of cardiovascular disease should undergo consultation with a Pregnancy Heart Team (Table 4).

Risk Assessment of the Pregnant or Postpartum Patient With Known Cardiovascular Disease

Risk assessment can be accomplished using one of the several available risk stratification models, such as the Canadian Cardiac Disease in Pregnancy risk index (CARPREG II) (a comprehensive scoring system that incorporates general cardiac factors, specific cardiac lesions, and process of care factors), the Zwangerschap bij Aangeboren HARtAfwijkingen (ZAHARA) (a weighted risk score for congenital heart disease patients), and the modified World Health Organization (WHO) classification of maternal cardiovascular risk (54–56, 59). Among these, the modified WHO

Table 5. Cardiac Medications With Potential Pregnancy and Lactation Influence

Drug	Teratogenic	Fetal Effects	Breastfeeding
Inotropic Agents			
Dopamine	No	No adverse fetal effects	Probably compatible, may inhibit prolactin release
Dobutamine	No	No adverse fetal effects	Probably compatible
Epinephrine	No	No adverse fetal effects when used acutely	Probably compatible
Vasodilators			
Nitroprusside	No	Potential for fetal cyanide toxicity with high doses	Possibly hazardous
Hydralazine	No	Relatively safe for the fetus	Probably compatible
Nitroglycerin	No	No adverse fetal effects Observe for risks of methemoglobinemia	Possibly hazardous
Ephedrine sulfate	No	No adverse fetal effects when used acutely	Possibly hazardous with chronic use
Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers			
	Yes	Contraindicated Associated with fetal renal failure, growth restriction, malformations and death	Probably compatible No published information
Beta-blockers			
Propranolol	No	May increase risk of growth restriction	Probably compatible
Labetalol	No	No adverse fetal effects	Probably compatible
Atenolol	No	May increase risk of growth restriction	Probably compatible Limited information
Metoprolol	No	May increase risk of growth restriction	Probably compatible
Esmolol	No	May cause beta blockage in fetus	Probably compatible No published information
Carvedilol	Limited Information	May increase risk of growth restriction	Probably compatible No published information
Calcium Channel Blockers			
Verapamil	No	No adverse fetal effects	Probably compatible
Nifedipine	No	No adverse fetal effects	Probably compatible
Diltiazem	No	No adverse fetal effects	Probably compatible Limited information
Amlodipine	No	No adverse fetal effects Limited human information, animal data suggest risk	Probably compatible Limited information
Antiarrhythmic Agents			
Lidocaine	No	No adverse fetal effects	Probably compatible
Procainamide	No Limited human information	Limited human information	Probably compatible Limited information
Phenytoin	Yes	Potential for early hemorrhagic disease of the newborn	Probably compatible

(*continued*)

Table 5. Cardiac Medications With Potential Pregnancy and Lactation Influence (*continued*)

Drug	Teratogenic	Fetal Effects	Breastfeeding
Amiodarone	No	May be associated with fetal thyroid toxicity	Hazardous
Flecainide	Yes	Limited human information	Probably compatible
	Limited human information		Limited information
Sotalol	No	Human data suggest fetal risk	Possibly hazardous
	Limited human information		
AV Node Blocking Agents			
Adenosine	No Information	No adverse fetal effects	Probably compatible
			No published information
Digoxin	No	No adverse fetal effects	Probably Compatible
Anticoagulants and Anti-Thrombotics			
Warfarin	Yes	Risk of fetal hemorrhage	Probably compatible
Low-molecular-weight heparin	No	No adverse fetal effects	Probably compatible
		Does not cross placenta	
Unfractionated heparin	No	No adverse fetal effects	Probably compatible
		Does not cross placenta	
Clopidogrel	No	Limited human information	Probably compatible
	Limited human information		No published information
Direct Factor Xa Inhibitors (rivaroxaban or apixaban)			
	No	Product labeling warns about abnormal bleeding risk	Possibly hazardous
		Crosses placenta	No published information
Diuretics			
Hydrochlorothiazide	No	No adverse fetal effects	Probably compatible
Furosemide	No	No adverse fetal effects	Probably compatible
			No published information

* For additional information on an individual medication's risk with breastfeeding, see https://toxnet.nlm.nih.gov/lactmed.htm.

Data from Hale TW. Hale's medications and mothers' milk: a manual of lactational pharmacology. 18th ed. New York (NY): Springer; 2019 and Briggs GG, Freeman RK, Towers CV, Forinash AB. Drugs in pregnancy and lactation. 11th ed. Philadelphia (PA): Wolters Kluwer; 2017.

risk assessment model is most widely accepted and validated in pregnant women with known cardiovascular disease (Table 3). The modified WHO pregnancy risk classification stratifies cardiovascular disease into 5 groups and informs the health care provider of the frequency of cardiology evaluation recommended. All pregnant and postpartum women with known or suspected cardiovascular disease should proceed with further evaluation by a Pregnancy Heart Team (Table 4) consisting of a cardiologist and maternal–fetal medicine subspecialist, or both, and other subspecialists as necessary. The goal is to establish a multidisciplinary comprehensive plan of care for the pregnancy, delivery, and postpartum periods. A mechanism for local, regional, and high-level facility referral should be in place for all labor and delivery units, particularly those with limited resources, in the event the need for consultation or emergency transfer arises. Referral to a hospital setting that represents an appropriate maternal level of care dependent upon the specific cardiac lesion (Table 3) is recommended for all pregnant patients with moderate- to high-risk cardiac conditions (modified WHO risk classes III and IV) because outcomes are

significantly better for women in these facilities (8, 60). Complex congenital heart disease patients should be managed, to the extent possible, at advanced care centers with congenital heart disease expertise.

▶ ***What are the indicated tests and how should these tests be interpreted for the pregnant patient with possible heart disease?***

Testing of maternal cardiac status is warranted during pregnancy or postpartum in women who present with symptoms such as shortness of breath, chest pain, or palpitations and known cardiovascular disease whether symptomatic or asymptomatic, or both. Factors linked to cardiovascular disease, such as family history and underlying medical conditions, play an important role in assessing the risk of cardiovascular disease (Fig. 1). The type of testing and urgency of evaluation depends on the underlying cardiac condition and symptoms at the time of presentation (Table 2; Fig. 1).

Natriuretic Peptides

Brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) are natriuretic peptides (referred to collectively as BNP in this document). Elevated levels can be suggestive of heart failure. Although BNP reference ranges vary among laboratories, assays, age, gender, and BMI, in general a BNP level of greater than 100 pg/mL and an NT-proBNP level greater than 450 pg/mL suggest the diagnosis of heart failure in nonpregnant patients (61). Brain natriuretic peptide levels in healthy women increase twofold during pregnancy (62) with a further increase early after delivery, (63) but values remain within normal range. Levels of BNP increase significantly in pregnant women with shortness of breath related to heart failure from left ventricular systolic dysfunction, (64) diastolic dysfunction, (65) and hypertensive disorders, including preeclampsia. (66)

Natriuretic peptides should be measured in the presence of new clinical symptoms or suggestive signs of heart failure to prevent delayed diagnosis. It may be helpful to obtain a baseline BNP level during pregnancy in women at high risk of or with known heart disease, such as dilated cardiomyopathy and congenital heart disease (Fig. 1). Serial determinations of BNP levels throughout each trimester and in the early postpartum period may assist in clinical decision making. Normal or low BNP levels are useful in excluding cardiac decompensation during pregnancy (67–69), and increasing BNP levels from the second trimester of pregnancy appear to predict adverse events (67, 70).

Cardiac Troponin I, Troponin T, and "High-Sensitivity" Troponin

Cardiac troponin I, troponin T, and "high-sensitivity" troponin are specific and sensitive biomarkers of myocardial injury (71). The diagnosis of acute coronary syndrome associated with pregnancy is similar to that in the general adult population, including comparable symptoms, electrocardiogram abnormalities, and elevations in biomarkers such as troponin (72). All pregnant and postpartum patients with chest pain should undergo standard troponin testing and an electrocardiogram to evaluate for acute coronary syndrome. Cardiology consultation should be obtained as clinically indicated. It should be noted that troponin I may be mildly elevated in the early postpartum period (73) in women with preeclampsia with severe features and in other noncardiac conditions, such as acute pulmonary embolisms or chronic renal disease (74).

Electrocardiogram

An electrocardiogram should be performed in pregnant women presenting with chest pain, shortness of breath, or palpitations to assess for features of ischemia, infarction, or arrhythmias. Normal pregnancy-related physiologic changes in maternal heart rate and chest wall shape cause benign nonpathologic electrocardiogram changes (75). Nonspecific ST-wave and T-wave abnormalities are found in up to 14% of pregnancies, usually occur in the left precordial leads, resolve after delivery, and may recur with subsequent pregnancies. Any rhythm abnormalities noted on electrocardiogram should prompt further evaluation.

Chest Radiograph

A chest radiograph with abdominal shield (76) should be considered as an important early test in pregnant or postpartum women presenting with shortness of breath to evaluate cardiac or pulmonary etiology.

Echocardiogram

An echocardiogram should be performed in pregnant or postpartum women with known or suspected congenital heart disease (including presumed corrected cardiac malformations), valvular and aortic disease, cardiomyopathies, and those with a history of exposure to cardiotoxic chemotherapy (eg, doxorubicin hydrochloride). Women with pulmonary hypertension or unexplained oxygen desaturation should have an echocardiogram before pregnancy, when pregnancy is confirmed, and during and after pregnancy. If there is doubt about the etiology as well as presence and severity of pulmonary hypertension, cardiac catheterization should be performed (52). The frequency of clinical and echocardiographic follow-up during pregnancy and postpartum is individualized. Cardiac chamber enlargement,

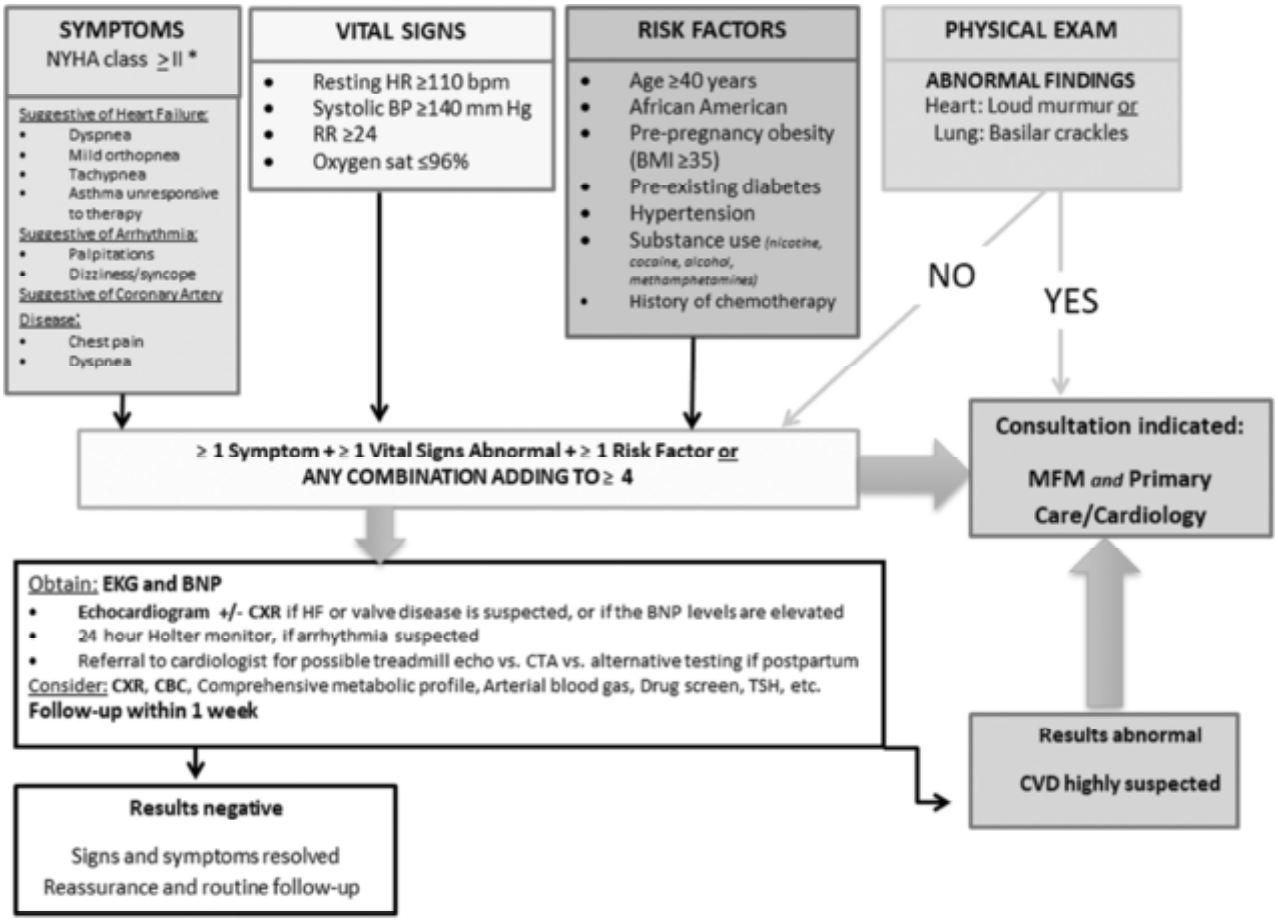

Figure 1. Cardiovascular Disease Assessment in Pregnant and Postpartum Women. *The NYHA Functional Classification is available at http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp. Abbreviations: BMI, body mass index; BNP, brain natriuretic peptide; BP, blood pressure; CBC, complete blood count; CVD, cardiovascular disease; CXR, chest x-ray; EKG, electrocardiogram; HR, heart rate; MFM, maternal–fetal medicine; TSH, thyroid stimulating hormone; NYHA, New York Heart Association; RR, respiratory rate. (Modified from California Department of Public Health, 2017; supported by Title V funds. Developed in partnership with California Maternal Quality Care Collaborative Cardiovascular Disease in Pregnancy and Postpartum Taskforce. Visit www.CMQCC.org for details.)

concentric cardiac remodeling, diastolic dysfunction, valvular annular dilatation with regurgitation, and small asymptomatic pericardial effusion are frequent normal echocardiogram findings during late gestation. (41, 77–79)

Exercise Stress Test

An exercise stress test is an important predictor of a woman's ability to tolerate pregnancy. An exercise stress test provides an objective assessment of maternal functional capacity and facilitates the identification of exercise-induced arrhythmias (52). An exercise stress test should be performed in patients with known heart disease who plan pregnancy (80). International guidelines recommend submaximal exercise testing (80% of predicted maximal heart rate) in asymptomatic patients with suspected heart disease if already pregnant (80).

Computed Tomography

Computed tomography should be performed in pregnant or postpartum women presenting with chest pain when pulmonary embolism or acute aortic dissection is suspected. Iodinated contrast materials are not teratogenic or carcinogenic but cross the placenta and can produce transient depressive effects on the developing fetal thyroid gland. It is recommended that contrast agents be used only when absolutely required to obtain additional diagnostic information that will affect care. Less than 1% of iodinated contrast administered to a lactating woman is excreted into breast milk and absorbed through the infant's gastrointestinal tract. Therefore, breastfeeding can be continued without interruption after administration of iodinated contrast (81).

Magnetic Resonance Imaging

Magnetic resonance imaging is used rarely in the urgent or emergent evaluation of cardiovascular concerns during pregnancy because imaging is less available and is more time consuming than computerized tomography. However, it is the preferred imaging modality in pregnant women to assess aortic dimension and for assessment of ventricular function and wall motion when echocardiography is nondiagnostic. When elective cross-sectional imaging is needed during pregnancy, a discussion with a cardiac imaging specialist to assist with choosing the most appropriate study and protocol is recommended to evaluate the patient optimally. There are no reported adverse maternal or fetal effects from magnetic resonance imaging during pregnancy (82). Reference values for cardiac magnetic resonance imaging indices during normal pregnancy and the postpartum state have been reported (40). Gadolinium, the contrast agent used for magnetic resonance imaging, should be limited in pregnant patients. It may be used as a contrast agent only if it significantly improves diagnostic performance and is expected to improve fetal or maternal outcome. Breastfeeding should not be interrupted after gadolinium contrast is administered (81).

Holter Monitor or Prolonged Cardiac Monitoring Device

A Holter monitor (24-hour to 48-hour ambulatory electrocardiogram monitoring) or a prolonged cardiac monitoring device (such as wireless patch cardiac monitor) is helpful for assessing symptoms of palpitations, lightheadedness, and syncope during pregnancy (83).

D-dimer

D-dimer is not recommended as part of routine evaluation of cardiac disease in pregnancy or the postpartum period (44).

▶ *Which types of preexisting maternal cardiac disease have the greatest effect on pregnancy and the postpartum period?*

Evidence of underlying or overt cardiovascular disease can present initially either during pregnancy or in the first days, weeks, and months postpartum. Women with any high-risk cardiovascular disease, such as pulmonary hypertension, congenital heart disease, noncongenital valvular disease, dilated hypertrophic or peripartum cardiomyopathy, aortic disorders, or coronary artery disease should be monitored during pregnancy and the postpartum period by a cardiologist with expertise in the management of such patients or a Pregnancy Heart Team (Table 4) if institutionally available. A plan for management during pregnancy, labor, and postpartum should be decided and recorded in the medical and prenatal records.

Pulmonary Arterial Hypertension

Pulmonary arterial hypertension is defined as a mean pulmonary arterial pressure more than 25 mm Hg at rest. It can be either idiopathic or caused by various disorders. Pulmonary arterial hypertension carries an increased risk of maternal mortality, reported to range from 9% to 28% (84–86). Despite improved prognosis in women with pulmonary arterial hypertension, low-risk patients might not be identified easily. Therefore, all women with severe pulmonary arterial hypertension should be advised against pregnancy. Health professionals caring for women with pulmonary arterial hypertension should ensure that women who are at risk of pregnancy understand these hazards and receive effective contraception. Induced abortion should be discussed if pregnancy occurs (80, 87). If a woman with severe pulmonary hypertension elects to proceed with or continue pregnancy, medical therapy for pulmonary hypertension can be initiated or modified during pregnancy (Table 5).

Congenital Heart Disease

Congenital heart disease encompasses multiple cardiac structural lesions. Many patients with congenital heart disease require additional specialized care while pregnant. Regular follow-up is required, the frequency of which depends on the type of the disease and the patient response to pregnancy (Table 3). Patients with high-risk lesions, such as those associated with pulmonary hypertension (eg, Eisenmenger syndrome), severe left-sided heart obstruction, severe ventricular dysfunction, cyanosis, failing Fontan circulation, and lesions associated with complex arrhythmias are counseled to avoid pregnancy or to proceed with surgical correction before pregnancy to allow for a lower-risk future pregnancy. The implications of maternal congenital heart disease on the fetus, including potential inheritance, should be discussed. In addition, certain genetic disorders are associated with congenital heart disease (eg, Noonan syndrome, Down syndrome, Holt-Oram syndrome, 22q11 microdeletion) and, therefore, prepregnancy genetic consultation and testing is recommended. Congenital heart disease in the woman should prompt fetal echocardiography, and conversely, identification of congenital heart disease in a fetus or neonate may prompt screening for parental congenital heart disease.

Noncongenital Valvular Disease

Noncongenital valvular disease, (examples include rheumatic valvular disease, mitral valve prolapse, bioprosthetic valve prosthesis, or valve disease related to infective endocarditis), requires specialized evaluation. A transthoracic echocardiogram and an exercise stress test generally are recommended for patients with moderate-to-severe valve disease (such as valve stenosis or severe regurgitation), associated ventricular dysfunction, or pulmonary hypertension. Women with asymptomatic valve disease should be monitored by a cardiologist and may require additional testing or care during pregnancy. The frequency of monitoring necessary is indicated in the patient's modified WHO classification (Table 3). Ideally, symptomatic severe valve disease should be treated before pregnancy.

Mechanical Valve Prostheses

During pregnancy, mechanical valve prostheses and some cardiac lesions require therapeutic anticoagulation, which carries an increased risk for the woman and fetus. A detailed discussion about anticoagulation options and risks, frequency, and type of monitoring is best performed and documented before pregnancy. Regular monitoring and medication adjustment to confirm therapeutic levels is required (80, 88, 89). All pregnant patients with mechanical and bioprosthetic valves should be maintained on daily low-dose (81 mg) aspirin during pregnancy (90). Endocarditis prophylaxis should be administered around the time of delivery in high-risk patients (see "Intrapartum Management Principles") (88, 91).

Preexisting Dilated Cardiomyopathy

Prepregnancy assessment will include a baseline BNP level, transthoracic echocardiogram to assess ejection fraction, and hemodynamics, as well as an exercise stress test to assess functional capacity. The cause of the cardiomyopathy should be evaluated. Prepregnancy genetic consultation is recommended for patients with familial dilated cardiomyopathy. Cardiomyopathy related to prior unrecognized peripartum cardiomyopathy also should be considered. Women with preexisting dilated cardiomyopathy have a high rate (25–40%) of major adverse cardiovascular events, mainly heart failure, during pregnancy (92, 93). Patients should be counseled to avoid pregnancy or consider induced abortion if they have severe heart disease, including an ejection fraction less than 30% or class III/IV heart failure, severe valvular stenosis, Marfan syndrome with aortic diameter more than 45 mm, bicuspid aortic valve with aortic diameter more than 50 mm, or pulmonary arterial hypertension (Table 3) (80). Furthermore, women with ejection fractions between 30% and 45% also should be counseled regarding an increased risk of adverse cardiac events during pregnancy, such as heart failure or arrhythmia (94). Once pregnancy occurs, medication changes (Table 5) and follow-up frequency are dependent on cardiac and functional status.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy is the most common genetic cardiac disease, with a prevalence of 2%. An analysis of pregnancy outcomes in such patients reported that cardiovascular complications are common and can be predicted by prepregnancy status, facilitating prepregnancy counseling and targeted antenatal care (95). Prepregnancy cardiovascular and genetic consultations are recommended for patients with hypertrophic cardiomyopathy.

Aortic Aneurysmal Disease and Dissection

Aortic aneurysmal disease and dissection in women of childbearing age generally are triggered genetically and are familial, syndromic, congenital, or inflammatory. Before pregnancy, a thorough cardiovascular specialty consultation to assess the cause, size, and location of the aneurysm is recommended. This consultation should include imaging with echocardiography and either computerized tomography or magnetic resonance imaging to evaluate the entire aorta. Although most dissections in young patients occur in the ascending aorta, the descending thoracic or abdominal aorta also can be affected. The cause, location, and size of the aortic aneurysm will influence counseling before and management during pregnancy. For example, all patients with vascular Ehlers-Danlos syndrome are advised to avoid pregnancy. The risk of aortic dissection associated with these conditions is increased during pregnancy and postpartum because of hormonal and hemodynamic changes on the aorta. No aortic dimension guarantees a safe pregnancy in a patient with aortopathy. The aortic size threshold for intervention before pregnancy depends on the cause of aortic aneurysmal disease (Table 6) (6, 80, 96). Even after ascending aorta replacement, aortic dissection can affect the remaining native aorta, so patients with prior operative intervention also should be monitored closely. During pregnancy, patients with aortic aneurysmal disease often are treated with beta-blocker therapy and should be seen regularly with repeat aortic imaging. The frequency of follow-up and imaging depends on the underlying disorder and aortic aneurysm location and dimension (Table 6). Surgical or percutaneous intervention for aortic aneurysm or dissection during

pregnancy or postpartum rarely is needed and should occur only for an aortic emergency. Type and timing of invasive maternal interventions and the preferred mode of delivery should be made by the Pregnancy Heart Team (Table 4).

Atrial Arrhythmias

Atrial arrhythmias that cause palpitations are a common indication for cardiac evaluation during pregnancy. Any pregnant woman who presents with an arrhythmia should undergo evaluation to assess the cause and the possibility of underlying structural heart disease. The most common arrhythmias during pregnancy are premature atrial beats and paroxysmal supraventricular tachycardia, usually atrioventricular-nodal reentrant tachycardia that can be successfully treated with medication. Atrial fibrillation and flutter during pregnancy often occur in women with structural heart disease. Management is individualized depending on the effect of the arrhythmia and the presence of underlying cardiac disease (55).

Ventricular Arrhythmias

Ventricular arrhythmias are rarely encountered during pregnancy. If detected, a search for a cause and underlying structural heart disease is appropriate. The most common type of ventricular tachycardia that occurs in the absence of structural heart disease is right ventricular outflow tract ventricular tachycardia. This form of ventricular tachycardia initially may be identified during pregnancy because it is catecholamine sensitive, and it often can be treated successfully with beta-blockers or verapamil. Women with the long QT syndrome are at risk of ventricular tachycardia, especially in the postpartum period. Treatment with beta-blocker therapy throughout pregnancy and postpartum is appropriate. Acute treatment of sustained ventricular arrhythmias in pregnant women is similar to that in nonpregnant women. In women with structural heart disease and ventricular tachycardia, the risk versus benefit of antiarrhythmic drug therapy, an implantable cardioverter-defibrillator, and ablation should be reviewed with a Pregnancy Heart Team (Table 4) in conjunction with an electrophysiologist with expertise in managing patients with arrhythmias during pregnancy (80, 97).

▶ *How should women at high risk of peripartum cardiomyopathy be identified, assessed, and managed?*

Peripartum cardiomyopathy occurs in 25–100 per 100,000 live births in the United States (98). It is characterized as a nonischemic cardiomyopathy presenting late in pregnancy or the first few months postpartum (99, 100) with a decrease in the left ventricular ejection fraction to less than 45% and no previous history of

Table 6. Management Strategies in Pregnant Women With Aortopathy

Marfan Syndrome	Surveillance Frequency	Suggested Mode of Delivery
Normal-sized aorta	Each trimester	Vaginal
Dilated ascending aorta <40 mm	4–6 weeks	Vaginal
Ascending aorta 40–45 mm	4 weeks	Cesarean
Ascending aorta >45 mm	Prophylactic aortic surgery before or during pregnancy for rapid growth	Cesarean

Bicuspid Aortic Valve	Surveillance Frequency	Suggested Mode of Delivery
Ascending aorta <45 mm	4–6 weeks	Vaginal
Ascending aorta 45–50 mm	4 weeks	Cesarean
Ascending aorta >50 mm	Aortic surgery before or during pregnancy for rapid growth	Cesarean

Modified from Elkayam U, Goland S, Pieper PG, Silversides CK. High-risk cardiac disease in pregnancy: part II. J Am Coll Cardiol 2016;68:502–16.

cardiac disease. The etiology remains uncertain. Although an autoimmune pathogenesis has been postulated (101), recent work has focused on vascular (102) and genetic etiologies (103).

Most women eventually recover myocardial function. For the remainder, chronic cardiomyopathy and heart failure persist. The overall rate of death or cardiac transplantation for women presenting with peripartum cardiomyopathy is 5–10% by 1 year postpartum (104, 105). Peripartum cardiomyopathy disproportionately affects non-Hispanic black women as evidenced by an increased incidence (106) and a lower rate of complete myocardial recovery (104, 107–110). Other risk factors for peripartum cardiomyopathy include increased maternal age, multifetal pregnancies, gestational hypertension, and preeclampsia. Women with a history of peripartum cardiomyopathy have a risk as high as 20% of experiencing a recurrence during subsequent pregnancies (111–113).

Pregnant or postpartum women who present with shortness of breath, chest discomfort, palpitations, arrhythmias, or fluid retention should be evaluated for peripartum cardiomyopathy. An echocardiogram is generally the most important diagnostic test. This evaluation also applies to women who are thought to have a hypertensive disorder of pregnancy. Consultation with a cardiologist is recommended to assist in management of peripartum cardiomyopathy, and referral to an appropriate level facility should be considered to allow multidisciplinary care by a Pregnancy Heart Team (Table 4). Medical management of peripartum cardiomyopathy follows the same general principles as management of heart failure with a reduced ejection fraction. Treatment with bromocriptine to improve myocardial recovery in peripartum cardiomyopathy remains investigational and requires further study (98, 114, 115). Breastfeeding should not be discouraged in women with peripartum cardiomyopathy because there are no data to suggest it negatively affects maternal cardiac status.

For women with peripartum cardiomyopathy who are pregnant at the time of peripartum cardiomyopathy diagnosis, timing and mode of delivery should be individualized, weighing the maternal risks of continuing pregnancy against the perinatal morbidity and mortality associated with preterm birth, and documented by a Pregnancy Heart Team (Table 4). Women presenting with shock (hypotension, tachycardia, or end-organ compromise) should be transferred to an appropriate level facility for consideration of a ventricular assist device support and transplant options. Vaginal delivery is a reasonable consideration for many women with peripartum cardiomyopathy because vaginal delivery results in less maternal morbidity and improved neonatal outcomes (116).

Predicted outcomes of women with peripartum cardiomyopathy can be stratified by the severity of left ventricular dysfunction at presentation because women with a lower left ventricular ejection fraction have poorer outcomes (117). In the North American Registry Investigations of Pregnancy-Associated Cardiomyopathy (104), women with an initial ejection fraction less than 30% had less myocardial recovery and higher rates of left ventricular assist device implantation, cardiac transplantation, and death. In contrast, nearly 90% of women with an initial ejection fraction of more than 30% had complete myocardial recovery.

▶ ***How should acute coronary events, including maternal cardiac arrest, be managed during pregnancy?***

Acute Myocardial Infarction and Acute Coronary Syndrome

Ischemic heart disease complicates 8 per 100,000 hospitalizations for pregnancy and postpartum care (118). Maternal death occurs in 5–11% of affected patients with the highest risk in the peripartum period, a rate that is 3–4 times more than that of nonpregnant age-matched women (17, 119).

Acute coronary syndrome implies suspicion of myocardial oxygen deprivation culminating in myocardial injury and necrosis. The spectrum of myocardial ischemia includes stable angina, unstable angina, and myocardial infarction. Increased cardiac output, enhanced stroke volume, and hypercoagulability favor the development or unmasking of underlying coronary artery disease. Risk factors for acute coronary syndrome during pregnancy (120) include traditional and pregnancy-specific features (see Box 1).

Box 1. Risk Factors for Acute Coronary Syndrome During Pregnancy

- Maternal age more than 30 years
- Non-Hispanic black race
- Elevated body mass index
- Diabetes mellitus
- Tobacco use
- Hyperlipidemia
- Strong family history of cardiovascular disease
- Hypertensive disorders of pregnancy
- History of coronary artery dissection
- Blood transfusion
- Peripartum infection

Acute coronary syndrome can be caused by coronary atherosclerosis, dissection, embolism, spasm, arteritis, and coronary artery occlusion related to aortic dissection. The differential diagnosis also should include takotsubo (stress) cardiomyopathy (119, 120). Coronary artery dissection is the most common cause of pregnancy-associated acute coronary syndrome and, although it can happen at any time during pregnancy, typically occurs in the early postpartum period (119, 121, 122). Coronary angiography remains the standard for diagnosis in patients with ST-segment elevation myocardial infarction. The noninvasive approach, however, is preferred in stable patients with preserved global left ventricular function because of the risk of complications, such as iatrogenic coronary dissection associated with coronary angiography and other interventions (119, 122, 123).

Every pregnant or postpartum patient with chest pain or cardiac symptoms should have consideration of acute coronary syndrome. Patients who have an acute coronary syndrome can present with typical (chest pain or shortness of breath) or atypical (vomiting, reflux, or diaphoresis) symptoms that mimic physiological changes of pregnancy or a pregnancy-related condition such as preeclampsia, or both. Some patients present with hemodynamic compromise, arrhythmia, or cardiogenic shock. Elevated troponins have sensitivity and specificity for myocardial damage. Electrocardiographic changes revealing ST-segment elevations or depression are pathological and suggest acute myocardial infarction or ischemia. The differential diagnosis includes pericarditis, pulmonary embolism, and electrolyte abnormalities.

Acute coronary syndrome during pregnancy is best managed by a medical team such as a Pregnancy Heart Team (Table 4). Management of the maternal condition should receive priority. While maternal evaluation and initial therapy are proceeding, an unstable patient should be placed in a left lateral tilt ranging from 30–90 degrees. Fetal monitoring and corticosteroids to enhance fetal lung maturation are recommended for appropriate gestational ages. Initial medical management usually includes oxygen supplementation, nitrates, aspirin, intravenous unfractionated heparin, and beta-blocker therapy. If symptoms persist, coronary angiography is the preferred test and should be performed without delay. The type of intervention should be individualized based on the etiology of acute coronary syndrome, patient characteristics, and facilities available at the presenting medical center. The goal is to restore coronary blood flow promptly to accomplish tissue reperfusion, which is best accomplished by percutaneous coronary intervention if the cause is atherosclerotic coronary disease. The results of percutaneous coronary intervention in women with coronary dissection are, however, suboptimal and associated with high risk of propagation of the existing dissection. For this reason, a conservative approach is recommended in stable patients with coronary artery dissection (123).

When a patient with acute myocardial infarction presents to a medical center that does not have interventional cardiac catheterization facilities, options include emergent transfer to a center that has these capabilities or emergent thrombolysis in patients with ST-elevation myocardial infarction, or both, with subsequent planned transfer. Complications of maternal acute coronary syndrome include heart failure, cardiogenic shock, ventricular arrhythmias, recurrent myocardial infarction, and death. Data regarding timing and mode of delivery are limited.

Maternal Cardiac Arrest

Although maternal cardiac arrest occurs infrequently, the health care provider should be prepared to manage this situation in any health care facility (124). Maternal cardiac arrest etiologies include pregnancy-related and nonpregnancy-related conditions. The American Heart Association recommends the use of an alphabetical categorization for the differential diagnosis of maternal cardiac arrest that underscores the importance of a broad-based approach (125) (see Box 2).

Among the various etiologies for maternal cardiac arrest in patients admitted for delivery, hemorrhage is the most common (38.1%), followed by amniotic fluid embolism (13.3%) (126). Approximately 10% of pregnant or postpartum women with acute coronary syndrome and 4% with venous thromboembolism experience a maternal cardiac arrest (126).

An obstetric care provider is among the members of a multidisciplinary team that should be assembled immediately with the announcement of a facility alert "maternal code" (125). A health care facility that deals with obstetric patients should have 24-hour access to an experienced maternal code team. Management of cardiac arrest in the pregnant or postpartum patient requires familiarity with the physiologic adaptations of pregnancy that affect the execution of interventions dictated by basic and advanced cardiac life support. There are six key concepts to emphasize for the pregnant cardiac arrest patient:

1. Increased oxygen demand coupled with alteration in pharyngeal/laryngeal landmarks and a greater tendency toward aspiration upon loss of consciousness necessitate prioritization of bag mask ventilation with 100 percent oxygen and early intubation with a small endotracheal tube by an experienced health care provider (6–7 mm) (125).

2. Aortocaval compression by a uterus larger than 20 weeks of gestation should be reduced with a one-handed or two-handed manual left uterine displacement maneuver very early in the resuscitation process while the patient remains in the full supine position on a backboard to maximize cardiac compression efforts (127, 128).
3. Simultaneous concurrent interventions are recommended in contrast to a sequential approach used in nonpregnant populations (128) (See Fig. 2).
4. Preparations for fetal delivery should be initiated in parallel with maternal resuscitative efforts.
5. Perform high-quality chest compressions on a backboard at a rate of 100–120 per minute using the same landmarks over the mid-lower sternum as left lateral uterine displacement is accomplished.
6. Oxygenation remains a primary goal using a ratio of 30:2 chest compressions/ventilation efforts initially supplied by bag mask ventilation with 100% oxygen.

Otherwise intervention is similar to management of cardiac arrest in the nonpregnant state. Defibrillation pads are placed to enable rhythm analysis. Use of an automated external defibrillator may facilitate rhythm analysis when rescuers are less acquainted with this task. Use of an automated external defibrillator, however, does not obviate the requirement for resuscitation skill training (128). Although there is only a theoretical risk of electrocution from defibrillation, fetal monitors should be removed to allow maternal status to guide resuscitation interventions. Prompt biphasic defibrillation should be performed for appropriate shockable rhythms with reassessment of rhythm/pulse every 2 minutes, taking care to minimize interruptions in chest compressions. Although there can be a reluctance to use medications during pregnancy, the gravity of maternal cardiac arrest is such that medications should be used in resuscitation. Epinephrine is the vasopressor of choice and should be administered by intravenous or intraosseous access above the diaphragm. A timekeeper should keep the resuscitation team aware of the time that has transpired since cardiac arrest (125).

Perimortem Cesarean Delivery/ Resuscitative Hysterotomy

When initial interventions are unsuccessful, the American Heart Association recommends timely consideration of perimortem cesarean delivery or resuscitative hysterotomy (129) when the uterus is sized 20 weeks of gestation or more. Because achieving the shortest time from cardiac arrest to delivery clearly enhances maternal and neonatal outcomes, efforts should be made to facilitate delivery as rapidly as possible from cardiac arrest, with the target to deliver within a 4–5-minute window. When return of spontaneous circulation is very unlikely, or arrest is unwitnessed, postponing delivery 4–5 minutes is not necessary (128, 130). Preparations to undertake resuscitative hysterotomy should begin immediately during the first minute of maternal cardiac arrest or apparent rapidly declining maternal cardiac function. Health care providers should be aware that there is no obvious threshold for either death or damage at 4 minutes. Instead there is a progressive decrease in the likelihood of injury-free survival for the woman and fetus with lengthening time since cardiac arrest (131). Survival curves for women and newborns have shown 50% injury-free survival rates with perimortem cesarean as late as 25 minutes after maternal cardiac arrest (131); therefore, delivery may be of benefit even if it does not occur within 4 minutes.

Box 2. Alphabetical Categorization for the Differential Diagnosis of Maternal Cardiac Arrest

- A (anesthetic complications, accidents)
- B (bleeding)
- C (cardiovascular disorders)
- D (drugs such as magnesium sulfate)
- E (embolism including venous thromboembolism and amniotic fluid embolism)
- F (fever including sepsis)
- G (general including metabolic and electrolyte)
- H (hypertensive disorders including stroke)

Ideally, perimortem cesarean delivery should occur at the site of the arrest because transport compromises cardiopulmonary resuscitation and also leads to further time delay (124). Initiation of perimortem cesarean delivery requires a scalpel, which usually is contained in the code cart's perimortem cesarean delivery kit (125). A vertical skin incision may be fastest to accomplish and provides more options for further exploratory surgery. If return of cardiac function has not occurred with perimortem cesarean delivery, alternatively open-chest direct cardiac massage can be attempted (128). Cardiopulmonary bypass and extracorporeal membrane oxygenation have been successfully employed for etiologies requiring time-limited cardiopulmonary support, such as local anesthetic drug toxicity, acute cardiac decompensation related peripartum cardiomyopathy, and acute respiratory distress syndrome (128).

The infrequency of maternal cardiac arrest underscores the need for regular team training and practice of

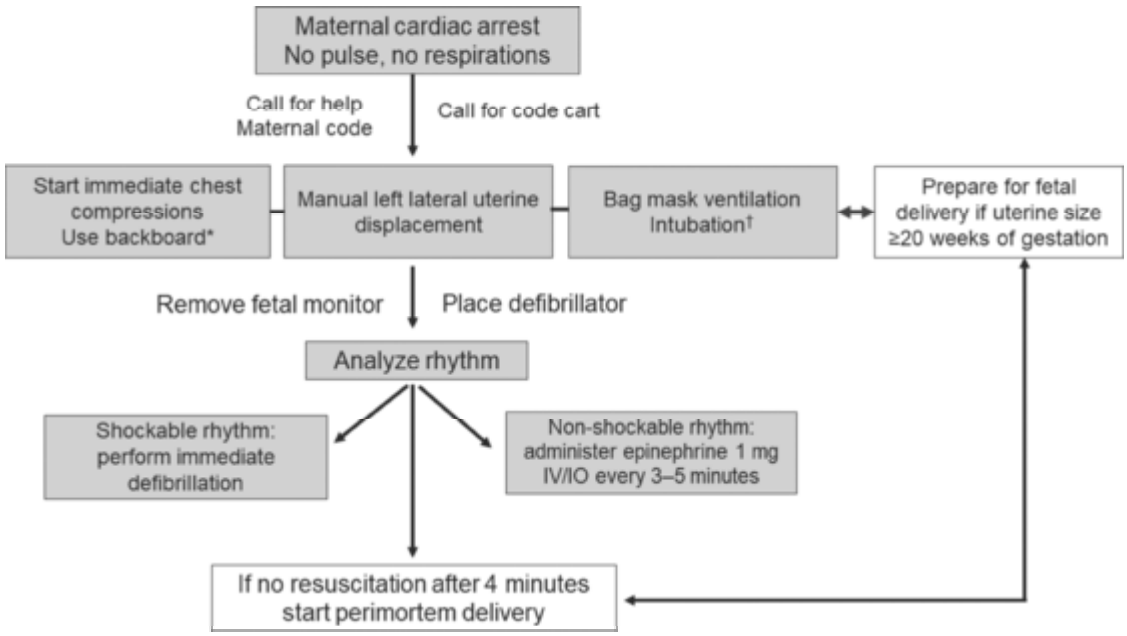

Figure 2. Maternal Resuscitation Algorithm. Abbreviations: IO, Intraosseous; IV, intravenous. *High-quality chest compressions on a backboard are performed at a rate of 100–120 per minute. †Prioritization of bag mask ventilation with 100 percent oxygen. Oxygenation remains a primary goal using a ratio of 30:2 (chest compressions/ventilation efforts). (Modified from Zelop CM, Einav S, Mhyre JM, Martin S. Cardiac arrest during pregnancy: ongoing clinical conundrum. Am J Obstet Gynecol 2018;219:52–61.)

resuscitation skills and scenarios through simulation training (128).

▶ ***What are the general approaches to pregnancy management antepartum, intrapartum, and postpartum for the patient with cardiovascular disease?***

Antepartum Management Principles

Pregnant women with cardiac disease should give birth at a hospital with the appropriate maternal level of care (60). The resources needed to minimize maternal and fetal complications should be anticipated, outlined, and documented before delivery. A comprehensive plan of care for the pregnancy, delivery, and postpartum periods should be available readily in the medical record and easily accessible to all health care providers involved with the woman's care. Women with complex congenital or noncongenital heart disease should be treated by a Pregnancy Heart Team (Table 4) (52, 80, 132) and should undergo comprehensive cardiac diagnostic evaluation as directed by the team and the diagnosis. In women with congenital heart disease, screening fetal echocardiogram is indicated at 18–22 weeks of gestation because the risk of congenital heart defect in the fetus is estimated at 4–10% (133, 134). Fetal growth assessment by either serial clinical examination or ultrasonography should be considered because fetal growth restriction occurs in many types of maternal congenital and acquired cardiac lesions (133, 135).

Women with chronic medical conditions, such as pregestational diabetes or chronic hypertension, can develop cardiac and other vascular complications of their disease (46, 47). Daily low-dose aspirin prophylaxis is recommended in women at high risk of preeclampsia and should be initiated between 12–28 weeks of gestation and continued until delivery. Similar prophylaxis should be considered for women with more than one of several moderate risk factors for preeclampsia (136). The precise blood pressure level at which antihypertensive therapy is indicated during pregnancy in women with cardiovascular disease continues to be debated. The use of blood pressure-lowering medications is recommended for secondary prevention of recurrent cardiovascular disease events in nonpregnant patients with clinical cardiovascular disease (defined as coronary heart disease, congestive heart failure, and stroke) and an average systolic blood pressure of 130 mm Hg or higher or an average diastolic blood pressure of 80 mm Hg or higher (137). Few clinical trials on this topic have been conducted in pregnancy and the evidence is limited (47). Prompt treatment of severe hypertension (systolic blood pressure more than 160 mm Hg and diastolic blood pressure more than

110 mm Hg) is recommended to prevent complications (47, 138). Left ventricular hypertrophy with impairment of diastolic function may develop in the setting of long-term hypertension. This scenario may place the pregnant woman at risk of cardiogenic pulmonary edema due to the baseline volume increase in pregnancy and after intravenous fluid boluses. Pulmonary edema in the patient with preeclampsia may be cardiogenic or noncardiogenic in origin or a combination of both. Echocardiography can help differentiate between the two entities. An echocardiogram should be performed in any pregnant or postpartum patient with pulmonary edema possibly due to peripartum cardiomyopathy or preeclampsia.

In general, regular physical activity during pregnancy and postpartum improves or maintains physical fitness, helps with weight management, reduces the risk of gestational diabetes in obese women, and enhances psychologic well-being. During pregnancy complicated by cardiac disease, the woman should be carefully evaluated by a Pregnancy Heart Team (Table 4) before recommendations are made regarding physical activity participation (139) to ensure that a patient does not have a cardiac reason to avoid exercise.

Intrapartum Management Principles

A detailed delivery plan should be determined between 20–30 weeks of gestation and recorded in the medical record. An individualized plan through shared decision making with the patient and the Pregnancy Heart Team (Table 4) is recommended. This strategy should include management of induction, delivery, and postpartum concerns and a surveillance plan. Women with stable cardiac disease can undergo a vaginal delivery at 39 weeks of gestation, with cesarean delivery reserved for obstetric indications (140). Some patients with very high-risk cardiac conditions may not be able to tolerate the fluctuations in cardiac output or Valsalva efforts that occur during vaginal delivery. For many of these patients, regional anesthesia during labor may provide sufficient pain relief (thereby minimizing catecholamine release and resultant cardiac output fluctuations) to render a vaginal delivery feasible. A Pregnancy Heart Team (Table 4) should determine which patients are not candidates for vaginal delivery or require assisted second stage of labor during pregnancy. In the absence of spontaneous onset of labor or indicated delivery before term, scheduled induction of labor for pregnant women with cardiac disease between 39–40 weeks of gestation may be considered with input from the Pregnancy Heart Team.

Anticoagulation must be carefully reviewed and managed by the Pregnancy Heart Team during pregnancy and adjusted appropriately at the time of neuraxial anesthesia and delivery. For women who are receiving prophylactic low-molecular-weight heparin, discontinuation is recommended at least 12 hours before scheduled induction of labor or cesarean delivery. A 24-hour interval is recommended for patients on an adjusted-dose regimen (44, 141, 142). For unfractionated heparin doses of 7,500 units subcutaneously twice a day or more, a 12-hour interval as well as evaluation of coagulation status with laboratory testing are recommended. Women receiving anticoagulation therapy may be converted from warfarin or low-molecular-weight heparin to the shorter half-life unfractionated heparin in anticipation of delivery, depending upon the institution's protocol. An alternative may be to stop anticoagulation and induce labor within 24 hours, if clinically appropriate. If conversion to unfractionated heparin is planned, timing should be based upon the likelihood of spontaneous labor with the goal of minimizing the time without anticoagulation coverage. This approach is especially important in a patient with a mechanical valve prosthesis (44, 88, 119).

The most common intrapartum cardiac complications include pulmonary edema or arrhythmias (54, 59, 133). These patients require a high level of surveillance and care. For women with a history of arrhythmias and for those who develop an arrhythmia during pregnancy, intrapartum cardiac monitoring is recommended. (52). Pulmonary edema usually can be prevented by maintaining a meticulous fluid balance. Expert consensus is that antibiotic prophylaxis administered at the time of delivery is reasonable for the subset of patients at increased risk of developing infective endocarditis, such as those with a history of previous infective endocarditis, and for patients at high risk of experiencing an adverse outcome from infective endocarditis (88, 91).

Obstetric Anesthesia Principles

Cardiac disease patients may require an elevated level of monitoring and anesthetic care for all obstetric procedures (eg, dilation and curettage or evacuation or cerclage) as well as vaginal or cesarean delivery. Consultation with an anesthesiologist should be performed antepartum for anesthetic, cardiac, and obstetric risk assessment and planning.

Under the direction of an anesthesiologist, cardiac disease patients undergoing vaginal delivery should be offered epidural labor analgesia, and cardiac disease patients undergoing cesarean delivery should have neuraxial anesthesia, if possible. Cardiovascular events (usually arrhythmia) are significantly decreased with epidural use (143). Exceptions for neuraxial anesthesia include the usual anesthetic contraindications and patients receiving pharmacologic anticoagulation as noted above (141, 142, 144). Consideration also should be

given to modifying neuraxial anesthesia management for patients at risk of cardiovascular decompensation related to reduction of systemic vascular resistance. Such patients include those with left ventricular outflow tract obstruction or cyanotic congenital heart disease.

Immediate Postpartum Management Principles

The postpartum period is a time of heightened risk of cardiovascular disease-related maternal morbidity and mortality (80) as evidenced by a threefold increase in the rate of postpartum hospitalizations for chronic heart disease in the past decade (14). Among cardiovascular disease-related mortality, peripartum cardiomyopathy (25–100 per 100,000 live births) is identified as the leading (23%) cause of late postpartum death (10, 144). Aortic dissection and acute coronary syndromes typically are diagnosed in the early postpartum period and are associated with a high risk of maternal mortality (15, 145–147). The incidence of acute coronary syndrome is estimated at 2.7–8.1 per 100,000 deliveries, a rate known to be threefold to fourfold higher during the pregnancy and postpartum periods compared with nonpregnant women matched for age (15, 17, 118, 119, 148). Cardiac disease is particularly linked to late maternal death as long as 1 year postpartum (10).

Women with cardiac disease are at high risk of immediate complications during the early puerperium (first 7 days after delivery) and as long as 6 months postpartum (26). This risk is compounded by the common concurrence of immediate postpartum obstetric complications, such as hypertensive disorders, hemorrhage, and infection. An elevated level of care or a prolonged period of monitoring may be necessary, particularly for patients at risk of cardiogenic pulmonary edema and arrhythmias or in the setting of concurrent obstetric or surgical complications. Consideration should be given to careful and frequent monitoring of the signs and symptoms of cardiovascular disease (Table 2) using pulse oximetry, lung auscultation, the recording of fluid balance, and for the development of shortness of breath or cough. Cardiovascular testing may be appropriate and individualized to presenting features. Early consultation with a cardiologist and possible transfer of the patient to a facility with a higher level of care should be expedited if maternal complications related either to known disease or to new-onset, acquired maternal heart disease develop at any time during the course of care.

Each facility should review the available venous thromboembolism risk assessment protocols and adopt and implement one of them in a systematic way to reduce the incidence of venous thromboembolism in the postpartum period (44). Cesarean delivery, particularly when complicated by postpartum hemorrhage or infection, as well as medical factors or pregnancy complications, increases the risk of venous thromboembolism. Although current evidence is insufficient to recommend universal adoption of pharmacologic prophylaxis for venous thromboembolism after cesarean delivery, for selected high-risk patients in whom significant risk factors persist after delivery, prophylaxis may be considered (44). If thromboprophylaxis is considered, evidence suggests that in women with a BMI of 35 or more, weight-based dosage (0.5 mg/kg enoxaparin every 12 hours) compared to fixed dosage will achieve significantly higher anti-Xa concentrations within the adequate prophylaxis range ($P<.01$) (149, 150). However, the optimal dose, route, and duration of thromboprophylaxis need further evaluation. In the absence of clear, randomized controlled trial evidence, practitioners can rely on consensus-derived clinical practice guidelines or recommendations from national and international societies (44).

Pharmacologic Considerations

Health care providers should be aware of cardiac medications with obstetric implications (Table 5) as well as obstetric medications with cardiac implications (Table 7). Obstetrician–gynecologists and other health care providers should consult lactation pharmacology resources for current information on individual medications because inappropriate advice often can lead women to discontinue breastfeeding unnecessarily (151).

▶ ***How should in-hospital postpartum care be altered for women with or at risk of cardiovascular disease?***

Postpartum Considerations After Delivery Hospitalization

Complications are frequently encountered in the days, weeks, and months after delivery in women with known cardiovascular disease and in those with latent cardiovascular disease. Women with multiple risk factors for cardiovascular disease (See Box 3) may be particularly at risk of manifesting symptoms for the first time during their postpartum course. A postpartum follow-up visit (early postpartum visit) with either the primary care provider or cardiologist is recommended within 7–10 days of delivery for women with hypertensive disorders or 7–14 days of delivery for women with heart disease/cardiovascular disorders. Ideally, future pregnancy intentions and commensurate contraceptive needs should be discussed before delivery or hospital discharge and reassessed at each postpartum visit.

Table 7. Obstetric Medications With Cardiac Influences

Drug	Cardiovascular Side Effects	Cardiac Conditions Contraindicated	Special Considerations
Corticosteroids (Betamethasone or Dexamethasone)	Fluid retention Electrolyte disturbance Hypertension	Use with caution in patients with heart failure or hypertension	Recent history of myocardial infarction; risk of left ventricular free wall rupture
Hydroxyprogesterone	Fluid retention Electrolyte disturbance Hypertension	Use with caution in patients with cardiac dysfunction	
Prostaglandin (PGE_2)	None reported		
Misoprostol	Rare		
Oxytocin	Arrhythmias Hypotension		Titrate carefully and avoid rapid intravenous bolus
Magnesium Sulfate	Hypotension Vasodilation Syncope	Caution in patients with heart block	Titrate carefully in hypertrophic obstructive cardiomyopathy and stenotic valvular lesions especially aortic stenosis
Terbutaline	Tachycardia Hypotension Arrhythmias Myocardial ischemia	Hypertrophic obstructive cardiomyopathy Patients at risk of arrhythmias or ischemia Stenotic valvular lesions especially mitral stenosis	Do not use beyond 48–72 hours
Methylergonovine	Coronary artery vasospasm Hypertension Arrhythmias	Coronary artery disease or risk for ischemia Aortopathies	Do not give intravenously
Carboprost Tromethamine	Hypertension Palpitations Tachycardia Vasodepressor syncope Pulmonary hypertension	Pulmonary hypertension Cyanotic congenital heart disease Pulmonary edema	Can cause bronchospasm Do not give intravenously
Tranexamic Acid			Use with caution in uncorrected cardiovascular disease due to thrombosis

Data from Facts & Comparisons. St. Louis (MO): Wolters Kluwer Health, Inc; 2019. Available at: http://fco.factsandcomparisons.com/lco/action/home. Retrieved January 22, 2019.

Optimal care for women with known cardiovascular disease during this critical period requires a team-based approach, such as with a Pregnancy Heart Team (23, 47, 138), and a cardiovascular disease risk assessment by a maternal care provider (Fig. 1). Mortality reviews indicate that cardiovascular disease signs and symptoms are not recognized readily by the patient, family, or the health care provider and that there are delays in access to health care related to transportation or other financial barriers (10). All postpartum women with cardiovascular disease and those identified as at high risk of cardiovascular disease should be educated on their individual risk. They should be instructed when and how to seek medical care and be provided with phone numbers and a printed or electronic copy of their discharge summary, including an explanation of signs and symptoms that should

prompt timely assessment. These women benefit from an early outpatient visit within 7–14 days after delivery to facilitate overall assessment of well-being and symptoms or functional status, or both. To facilitate patient adherence to appointments, it is important to address barriers to care, such as socioeconomic variability, insurance status, access to health care, and physical distance to the nearest hospital.

Contraceptive options, including immediate postpartum placement of long-acting reversible contraceptive methods, should be discussed in the prenatal period, and plans to execute should be implemented before hospital discharge to minimize the risk of short-interval recurrent pregnancy.

Breastfeeding has important short-term and long-term health benefits for the woman. Cardiac patients should be encouraged to breastfeed during the postpartum hospital stay and in the outpatient setting because most medications are considered safe (Table 5) (152). Breastfeeding has favorable effects not only on hypertension through positive effects on the maternal vasculature but fosters a favorable lipid and hormonal milieu along with improved mother-infant bonding (153). Women whose cumulative lifetime duration of breastfeeding is 6–12 months are 10% less likely to develop cardiovascular disease (154).

It is important to emphasize that the overwhelming majority of cardiovascular disease mortality occurs beyond the conventional postpartum period, including the first 42 days after delivery (10). Thus, a long-term care plan is crucial. Women identified as high risk (Fig. 1) should be evaluated at 3 months in a comprehensive cardiovascular postpartum visit. Payment models that provide health care coverage for the 3-month visit for these high-risk patients should be developed. This 3-month comprehensive cardiovascular postpartum visit with the Pregnancy Heart Team, the obstetrician–gynecologist, or other primary care provider should be individualized to each patient and should include a history of pertinent symptoms, a physical examination, an assessment of height and weight (BMI), waist circumference, heart rate, respiratory rate, blood pressure, and oxygen saturation. Laboratory testing, including fasting blood glucose or hemoglobin A_{1c}, and a complete lipid profile should be considered. Patients should have a yearly follow-up with their primary care physician. Health care providers should establish and maintain an ongoing partnership with a cardiologist or primary care physician, or both, who will be available for future care. Bundled payments for maternity care should be expanded to include this intensive classification (as many as three visits in the first 3 months postpartum) for a more individualized approach to these women. Ongoing collaborative care of the woman with cardiovascular disease or at risk of future cardiovascular disease is essential to reducing morbidity and mortality, optimizing the woman's health in preparation for future pregnancies, and promoting long-term cardiovascular health (26, 139).

▶ ***What are the contraceptive options and considerations for women with heart or cardiovascular disease, or both?***

Contraception Considerations

Decisions regarding the most appropriate contraceptive option for a woman require discussion of her future pregnancy desires and personal preferences, as well as critical assessment of the patient's underlying disease and the relative risks and benefits of the contraceptive option considered. The Centers for Disease Control and Prevention and the World Health Organization have established a four-tier scale related to medical eligibility criteria for contraceptive use that provides clinicians an assessment of the relative risks and benefits of contraceptive methods in various medical settings (155–157). Clinicians can access this detailed clinical guidance at https://www.cdc.gov/reproductivehealth/contraception/pdf/summary-chart-us-medical-eligibility-criteria_508tagged.pdf. See also the American College of Obstetricians and Gynecologists' For More Information web page.

Intrauterine devices are the recommended nonpermanent option for women with high-risk cardiovascular conditions (155, 158). Intrauterine devices are highly effective and reliable long-acting reversible contraception. Multiple intrauterine device options (copper and progestin containing) are available based on patient preference, contraindications, and desire for future fertility. Annual failure rates with intrauterine devices use are less than 1%, and duration of action ranges from 3 to 10 years depending on the device used. Intrauterine device placement can be undertaken in the clinician's office and poses minimal risk for women with underlying cardiac disease (155, 158). Although expulsion rates are increased (10–27%) with placement at the time of delivery, immediate postpartum intrauterine device placement after delivery of the placenta is also a consideration for women with high-risk cardiac disease to ensure there is no gap in contraceptive protection (159). Women should be counseled about the increased expulsion risk as well as signs and symptoms of expulsion (159).

Progestin-only contraceptives (oral, depot medroxyprogesterone acetate injection, or implant) are potentially effective alternatives for women with cardiac disease. The progestin-only pill is limited primarily to use in the immediate postpartum period in lactating women. This option, however, has lower efficacy (more than 9% failure rate) for pregnancy prevention (155, 160, 161). Intramuscular depot medroxyprogesterone acetate is a highly

Box 3. Risk Factors for Maternal Cardiovascular Disease

- Non-Hispanic black race
- Older age (more than 40 years)
- Obesity
- Hypertensive disorders of pregnancy (preeclampsia, eclampsia, or hemolysis, elevated liver enzymes, and low platelet count syndrome)
- Chronic disease (chronic hypertension or pregestational diabetes mellitus)
- Obstructive sleep apnea (moderate to severe)
- History of preterm delivery
- Strong family history of heart disease
- Exposure to cardiotoxic drugs

effective contraceptive modality and appears to be a safe option for women with valvular heart disease, cardiomyopathy, and well-controlled hypertension (155, 162). For women receiving therapeutic anticoagulation, depot medroxyprogesterone acetate injections theoretically can increase risk of hematoma formation. Reversible bone loss, diminution of protective high-density lipoprotein, and increased triglycerides have been noted secondary to the hypoestrogenic effect of depot medroxyprogesterone acetate (163, 164). The progestin implant is highly efficacious and appears to be a safe option for most women with hypertension or known cardiac disease. Use in women with current or previous ischemic heart disease or cerebrovascular accident is limited secondary to increased concern for thrombosis (155). There also may be risk of hematoma formation at the time of insertion or removal, or both, in women who are anticoagulated.

Combined hormonal contraception (eg, oral, ring, or patch), although effective, may pose significant risk for women depending on the patient's underlying cardiac condition because of the estrogen component. The use of combined hormonal contraception in women with poorly controlled hypertension, aged more than 35 years, who are smokers, or who have migraine with aura, is associated with increased risks for exacerbation of high blood pressure, cardiovascular events, such as stroke and acute myocardial infarction, and thromboembolic events (155, 161, 162, 165–169). For women with valvular heart disease, especially those with complicated valvular pathology, combined hormonal contraception may increase the risk of arterial thrombosis and other adverse cardiovascular consequences. Use of combined hormonal contraception in the setting of cardiomyopathy can be associated with fluid retention, which can exacerbate heart failure (170). Because of these concerns, alternative contraceptive options should be considered in women with prothrombogenic states, uncontrolled hypertension, ischemic heart disease, and complicated valvular heart disease (155).

Barrier, fertility awareness-based, and other nonhormonal methods used to lessen the risk of fertilization, although safe, have high risk of contraceptive failure. Therefore, these methods are suboptimal for women who do not desire further childbearing or who have significant cardiovascular disease in which pregnancy is ill-advised or contraindicated. Estimated annual failure rates vary according to the method used. The fertility-awareness method has a failure rate of 24%; withdrawal, 22%; spermicide use, 28%; male condom, 18%; female condom, 21%; sponge, 12–24%; and diaphragm, 12% (155, 160, 171).

Emergency contraception is available for women with contraindications to use of combined hormonal contraception (155, 161). The presence of cardiovascular disease is not a contraindication to the use of emergency contraception (155, 161). Progestin-only emergency contraceptive methods are generally better tolerated and are more efficacious than combined regimens and may be preferred in the setting of cardiovascular disease. Insertion of a copper intrauterine device is an effective method of emergency contraception when inserted within 5 days after unprotected intercourse. The copper intrauterine device provides ongoing contraception and should be made available to patients at high risk of pregnancy morbidity and mortality (158).

Permanent sterilization is one of the most effective contraceptive options for reproductive-aged women who have completed childbearing, especially for women with high-risk cardiac conditions or cardiovascular disease. Paternal vasectomy is a highly effective approach for male sterilization with low complications and failure rates of less than 1% (155, 172, 173). Limitations of vasectomy include the potential for pregnancy in the setting of a nonmonogamous relationship or a sexual relationship with a new partner. Female sterilization may be performed by several approaches (eg, laparoscopy, minilaparotomy, and in combination with cesarean delivery) (172). Although laparoscopy is an effective and safe approach for sterilization, the need for general anesthesia and pneumoperitoneum (with resultant increased intraperitoneal pressure) can alter cardiac and pulmonary function and thereby impose challenges for women with certain critical cardiac abnormalities (174, 175). Low-pressure laparoscopy does not appear to mitigate these operative physiologic effects (176). Minilaparotomy with tubal ligation can be performed under regional anesthesia and may minimize intraoperative risks in women with cardiac disease (172).

▶ ***What are the long-term considerations and implications after pregnancy for women with cardiovascular disease?***

There are immediate and long-term continuity of care considerations for women with congenital or acquired heart and cardiovascular disease. Specific and immediate considerations include the following:

- Ensure proper cardiology follow-up is initiated during pregnancy or postpartum.
- Acknowledge the effect of a chronic diagnosis and possible need for long-term medication use. Consider 3-month prescriptions (or longer) if clinically appropriate (177).
- Refer patients with cardiovascular disease to lactation services when breastfeeding presents challenges, which often arise because of preterm delivery (178).
- Be mindful of the mental health implications of cardiovascular disease during the postpartum period and beyond. Preterm birth also is associated with maternal depression, anxiety, and posttraumatic stress disorder (179). Of note, most medications used to treat these disorders are compatible with breastfeeding, even in conjunction with cardiac medications. Mobilize all available resources to support the patient and her family during this time as indicated.
- Discuss future pregnancy intentions and provide a commensurate form of contraception.
- Screen patients routinely at postpartum follow-up visits for depressive symptoms and evidence of posttraumatic stress disorder and refer to social services or psychologic services, or both, as indicated (179).

These are priorities early in the puerperium because many women lose health insurance beyond the first 42 days postpartum. These steps are especially relevant in the postpartum period when women with cardiovascular disease are focused on newborn care and are less likely to prioritize their own health.

Continuity of Care Considerations for Women With Cardiovascular Disease Risk Factors

Acute (gestational hypertension, preeclampsia) and chronic hypertensive disorders of pregnancy are important identifiers of patients at risk of cardiovascular disease (23). Gestational hypertension and preeclampsia increase the risk of future cardiovascular disease by severalfold, and the risk is even higher in women with recurrent preeclampsia, preterm birth at less than 37 weeks of gestation, or intrauterine growth restriction (29, 180–186). Not only do women with hypertensive disorders of pregnancy have a substantially higher risk of future cardiovascular disease, they also have a threefold to fourfold increase in the risk of chronic hypertension, a 4.2-fold increase in the risk of heart failure, an 81% increase in the risk of stroke, a 5-fold to 12-fold increased risk of developing end-stage renal disease, and double the risk of atrial arrhythmias, coronary heart disease, and mortality when compared with women with normotensive pregnancies (184, 187). Exposure to severe maternal preeclampsia is an independent risk factor for long-term cardiovascular morbidity in offspring born at term (188).

The presence of gestational complications reliably identifies women with underlying, often unrecognized, cardiovascular risk factors (189, 190). Because approximately 20% of women have one or more of these complications (191), risk screening is recommended (192) within the first year postpartum (191). Cardiovascular assessment and follow-up at 3 months postpartum is recommended for women with the following conditions:

- Hypertension, chronic/essential or hypertensive disorder of pregnancy (ie, gestational hypertension, preeclampsia, eclampsia, hemolysis, elevated liver enzymes, and low platelet syndrome, chronic hypertension [with or without superimposed preeclampsia])
- Gestational diabetes mellitus
- Intrauterine fetal growth restriction (particularly less than the 5th percentile for gestational age or less than 2,500 g at term)
- Idiopathic preterm birth
- Placental abruption
- Obesity/excessive pregnancy weight gain/postpartum weight retention
- Sleep disorders/moderate-to-severe obstructive sleep apnea (193–197)
- Maternal age older than 40 years

Cardiovascular risk screening within 3 months postpartum includes a detailed medical history (including history of cardiovascular disease), postpartum medication monitoring (such as antihypertensive medication), a physical examination, and basic biochemical testing (see Box 4).

After cardiovascular screening is complete, women should be counseled with regard to their identified risk factors. The goal of targeted cardiovascular risk assessment and patient education is to promote patient self-awareness and self-initiation of preventive actions. The American Heart Association's Life's Simple 7 describes

Box 4. Postpartum Cardiovascular Risk Screening

Medical history

- Smoking (number of cigarettes per day, number of years smoked)
- Physical activity (times per week, duration)
- Breast feeding (how long)
- History of hypertension, diabetes, or cardiovascular disease
- First degree family history of cardiovascular disease, hypertension, or diabetes

Physical examination

- Resting blood pressure and heart rate
- Body mass index and waist circumference

Biochemical testing

- Cholesterol/lipid profile
- Fasting glucose (or oral glucose tolerance testing if patient had gestational diabetes)
- Urine protein assessment (protein:creatinine ratio)

Nutrition assessment

seven steps to achieve a healthy lifestyle (198). Tests for borderline or elevated blood pressure or lipid abnormalities, or both, should be repeated after 6–12 months of lifestyle modification and, if persistently elevated, initiation of pharmacologic treatment should be considered.

Ongoing Postpartum Care After the 3-Month Cardiovascular Assessment Visit

Continuing follow-up as indicated after the 3-month comprehensive cardiovascular postpartum evaluation provides the opportunity for counseling, planning, and intervention to optimize underlying medical conditions to improve future pregnancy outcomes and cardiovascular health. If not already managed, contraceptive needs can be considered, managed, or modified as needed. In addition to the usual prepregnancy topics such as folic acid usage, restoration to prepregnancy weight should be emphasized because not achieving it increases the risk of future pregnancy complications (199). Weight management strategies include referral to a registered dietitian, peer support, improved access to opportunities for physical activity, and programs that provide child care at no or low cost. Women with pregnancy complications, such as preeclampsia and gestational diabetes, should be counseled regarding the risks of future cardiovascular disease and overt diabetes, respectively. In any future pregnancy, patients with a history of prior preeclampsia should be considered for low-dose aspirin prophylaxis (136). For those who have previous gestational diabetes mellitus, early screening in the next pregnancy is recommended (200). Finally, given the benefits for the infant and the cardiometabolic benefits for the woman (201), breastfeeding should be recommended, and community support identified, to increase breastfeeding success after future pregnancies. During the postpartum period, health care providers may include a primary care provider and various other specialists, and communication across the clinical team should continue. However, because coordinated care can be challenging among many different specialists and subspecialists (202), the patient must be educated about her individualized cardiovascular risk, and a recommended plan of care for future pregnancies should be developed in collaboration with cardiologist colleagues. During postpartum care, opportunities should be developed to expand shared decision making whereby clinicians can understand their patients' goals, values, and preferences for health care and to facilitate a mutually suitable evaluation and management plan for future pregnancies (202).

For More Information

The American College of Obstetricians and Gynecologists has identified additional resources on topics related to this document that may be helpful for ob-gyns, other health care providers, and patients. You may view these resources at www.acog.org/More-Info/PregnancyAndHeartDisease.

These resources are for information only and are not meant to be comprehensive. Referral to these resources does not imply the American College of Obstetricians and Gynecologists' endorsement of the organization, the organization's website, or the content of the resource. The resources may change without notice.

Summary of Recommendations and Conclusions

The following recommendations and conclusions are based on limited or inconsistent scientific evidence (Level B):

- Referral to a hospital setting that represents an appropriate maternal level of care dependent upon the specific cardiac lesion is recommended for all pregnant patients with moderate- to high-risk cardiac conditions (modified WHO risk classes III and IV) because outcomes are significantly better for women in these facilities.

- It may be helpful to obtain a baseline BNP level during pregnancy in women at high risk of or with known heart disease, such as dilated cardiomyopathy and congenital heart disease.
- All pregnant and postpartum patients with chest pain should undergo standard troponin testing and an electrocardiogram to evaluate for acute coronary syndrome.
- Patients should be counseled to avoid pregnancy or consider induced abortion if they have severe heart disease, including an ejection fraction less than 30% or class III/IV heart failure, severe valvular stenosis, Marfan syndrome with aortic diameter more than 45 mm, bicuspid aortic valve with aortic diameter more than 50 mm, or pulmonary arterial hypertension.

The following recommendations and conclusions are based primarily on consensus and expert opinion (Level C):

- Health care providers should become familiar with the signs and symptoms of cardiovascular disease as an important step toward improving maternal outcomes.
- Women with known cardiovascular disease should be evaluated by a cardiologist ideally before pregnancy or as early as possible during the pregnancy for an accurate diagnosis and assessment of the effect pregnancy will have on the underlying cardiovascular disease, to assess the potential risks to the woman and fetus, and to optimize the underlying cardiac condition.
- Patients with moderate and high-risk cardiovascular disease should be managed during pregnancy, delivery, and the postpartum period in medical centers with a multidisciplinary Pregnancy Heart Team that includes obstetric providers, maternal–fetal medicine subspecialists, cardiologists, and an anesthesiologist at a minimum.
- Discussion of cardiovascular disease with the woman should include the possibilities that 1) pregnancy can contribute to a decline in cardiac status that may not return to baseline after the pregnancy; 2) maternal morbidity or mortality is possible; and 3) fetal risk of congenital heart or genetic conditions, fetal growth restriction, preterm birth, intrauterine fetal demise, and perinatal mortality is higher when compared with risk when cardiovascular disease is not present.
- A personalized approach estimating the maternal and fetal hazards related to the patient's specific cardiac disorder and the patient's pregnancy plans can provide anticipatory guidance to help support her decision making. For some patients, the prepregnancy evaluation may suggest a pregnancy risk that is unacceptable. For those women, reproductive alternatives, such as surrogacy or adoption, and effective contraceptive methods should be discussed.
- All women should be assessed for cardiovascular disease in the antepartum and postpartum periods using the California Improving Health Care Response to Cardiovascular Disease in Pregnancy and Postpartum toolkit algorithm.
- All pregnant and postpartum women with known or suspected cardiovascular disease should proceed with further evaluation by a Pregnancy Heart Team consisting of a cardiologist and maternal–fetal medicine subspecialist, or both, and other subspecialists as necessary.
- Testing of maternal cardiac status is warranted during pregnancy or postpartum in women who present with symptoms such as shortness of breath, chest pain, or palpitations and known cardiovascular disease whether symptomatic or asymptomatic, or both.
- An echocardiogram should be performed in pregnant or postpartum women with known or suspected congenital heart disease (including presumed corrected cardiac malformations), valvular and aortic disease, cardiomyopathies, and those with a history of exposure to cardiotoxic chemotherapy (eg, doxorubicin hydrochloride).
- Congenital heart disease in the woman should prompt fetal echocardiography, and conversely, identification of congenital heart disease in a fetus or neonate may prompt screening for parental congenital heart disease.
- Women with asymptomatic valve disease should be monitored by a cardiologist and may require additional testing or care during pregnancy. The frequency of monitoring necessary is indicated in the patient's modified WHO classification.
- Any pregnant woman who presents with an arrhythmia should undergo evaluation to assess the cause and the possibility of underlying structural heart disease.
- Pregnant or postpartum women who present with shortness of breath, chest discomfort, palpitations, arrhythmias, or fluid retention should be evaluated for peripartum cardiomyopathy. An echocardiogram is generally the most important diagnostic test.
- Every pregnant or postpartum patient with chest pain or cardiac symptoms should have consideration of acute coronary syndrome.
- Although maternal cardiac arrest occurs infrequently, the health care provider should be prepared to manage this situation in any health care facility.

- The infrequency of maternal cardiac arrest underscores the need for regular team training and practice of resuscitation skills and scenarios through simulation training.
- Women with complex congenital or noncongenital heart disease should be treated by a Pregnancy Heart Team.
- Women with stable cardiac disease can undergo a vaginal delivery at 39 weeks of gestation, with cesarean delivery reserved for obstetric indications.
- Health care providers should be aware of cardiac medications with obstetric implications as well as obstetric medications with cardiac implications.
- A postpartum follow-up visit (early postpartum visit) with either the primary care provider or cardiologist is recommended within 7–10 days of delivery for women with hypertensive disorders or 7–14 days of delivery for women with heart disease/cardiovascular disorders.
- All postpartum women with cardiovascular disease and those identified as at high risk of cardiovascular disease should be educated on their individual risk.
- Decisions regarding the most appropriate contraceptive option for a woman require discussion of her future pregnancy desires and personal preferences, as well as critical assessment of the patient's underlying disease and the relative risks and benefits of the contraceptive option considered.
- Intrauterine devices are the recommended nonpermanent option for women with high-risk cardiovascular conditions.

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The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 2010–February 2019. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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FLEISHER DECLARATION: EXHIBIT E

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician–Gynecologists

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Prelabor Rupture of Membranes

Preterm birth occurs in approximately 10% of all births in the United States and is a major contributor to perinatal morbidity and mortality (1–3). Prelabor rupture of membranes (PROM) that occurs preterm complicates approximately 2–3% of all pregnancies in the United States, representing a significant proportion of preterm births, whereas term PROM occurs in approximately 8% of pregnancies (4–6). The optimal approach to assessment and treatment of women with term and preterm PROM remains challenging. Management decisions depend on gestational age and evaluation of the relative risks of delivery versus the risks (eg, infection, abruptio placentae, and umbilical cord accident) of expectant management when pregnancy is allowed to progress to a later gestational age. The purpose of this document is to review the current understanding of this condition and to provide management guidelines that have been validated by appropriately conducted outcome-based research when available. Additional guidelines on the basis of consensus and expert opinion also are presented. This Practice Bulletin is updated to include information about diagnosis of PROM, expectant management of PROM at term, and timing of delivery for patients with preterm PROM between 34 0/7 weeks of gestation and 36 6/7 weeks of gestation.

Background

The definition of *prelabor rupture of membranes* is rupture of membranes before the onset of labor. Membrane rupture before labor that occurs before 37 weeks of gestation is referred to as "preterm prelabor rupture of membranes." Management of preterm and term PROM is influenced by gestational age and the presence of complicating factors such as clinical infection, abruptio placentae, labor, or abnormal fetal testing. An accurate assessment of gestational age and knowledge of the maternal, fetal, and neonatal risks are essential to appropriate evaluation, counseling, and care of patients with PROM.

Etiology of Prelabor Rupture of Membranes

Membrane rupture may occur for a variety of reasons. Although membrane rupture at term can result from a normal physiologic weakening of the membranes combined with shearing forces created by uterine contractions, preterm PROM can result from a wide array of pathologic mechanisms that act individually or in concert (7, 8). Intraamniotic infection has been shown to be commonly associated with preterm PROM, especially at earlier gestational ages (9, 10).

A history of preterm PROM is a major risk factor for preterm PROM or preterm labor in a subsequent pregnancy (11–13). Additional risk factors associated with preterm PROM are similar to those associated with spontaneous preterm birth and include short cervical length, second-trimester and third-trimester bleeding, low body mass index, low socioeconomic status, cigarette smoking, and illicit drug use (14–17). Although each of these risk factors is associated with preterm PROM, the condition often occurs in the absence of recognized risk factors or an obvious cause.

Term Prelabor Rupture of Membranes

At term, PROM complicates approximately 8% of pregnancies and generally is followed by the prompt

onset of spontaneous labor and delivery (6). In a large randomized trial, one half of women with term PROM who were managed expectantly had an interval of membrane rupture to delivery of 33 hours, and 95% gave birth within 94–107 hours of membrane rupture with the use of oxytocin or prostaglandin when, during expectant management, induction was indicated or an endpoint of 4 days of expectant management was reached (18). The most significant maternal consequence of term PROM is intrauterine infection, the risk of which increases with the duration of membrane rupture.

Preterm Prelabor Rupture of Membranes

Regardless of obstetric management or clinical presentation, birth within 1 week of membrane rupture occurs in at least one half of patients with preterm PROM (8). Latency after membrane rupture is inversely correlated with the gestational age at membrane rupture (19). Cessation of amniotic fluid leakage with restoration of normal amniotic fluid volume may infrequently occur in the setting of spontaneous preterm PROM but can be associated with favorable outcomes (20–22).

Among women with preterm PROM, clinically evident intraamniotic infection occurs in 15–35% of cases and postpartum infection occurs in approximately 15–25% of cases. The incidence of infection is higher at earlier gestational ages (9, 23–25). Abruptio placentae complicates 2–5% of pregnancies with preterm PROM (26, 27).

The most significant risks to the fetus after preterm PROM are complications of prematurity. Respiratory distress has been reported to be the most common complication of preterm birth (28, 29). Sepsis, intraventricular hemorrhage, and necrotizing enterocolitis also are associated with prematurity but are less common near term. Preterm PROM has been associated with an increased risk of neurodevelopmental impairment (30–32), and early gestational age at membrane rupture also has been associated with an increased risk of neonatal white matter damage (33). However, there are no data that suggest that immediate delivery after presentation with PROM will avert these risks. A large cohort study suggests that prolonged latency duration, when adjusted for gestational age, does not worsen neonatal prognosis with respect to survival, survival without morbidity, and early-onset sepsis (34).

Periviable Prelabor Rupture of Membranes

Rupture of the membranes before viability occurs in less than 1% of pregnancies. The probability of neonatal death and morbidity associated with PROM decreases with longer latency and advancing gestational age (35, 36). In a review of periviable PROM occurring between 14 weeks of gestation and 24 weeks of gestation, perinatal deaths were more or less equally divided between stillbirths and neonatal deaths. Neonatal survival rates in patients expectantly managed for periviable PROM were much higher following membrane rupture after 22 weeks of gestation compared with membrane rupture before 22 weeks of gestation (57.7% versus 14.4%, respectively) (37). A second retrospective study of patients between 20 weeks of gestation and 24 weeks of gestation with periviable PROM who elected expectant management showed similar results, with neonatal survival of 22% of the newborns of patients with membrane rupture before 22 weeks of gestation and 58% for those with membrane rupture at 22 and 23 weeks of gestation (36). Most studies of second-trimester and periviable PROM are retrospective and include only expectantly managed cases. Thus, they likely overestimate survival rates because of selection bias. Survival data may vary by institution.

Significant maternal complications that occur after periviable PROM include intraamniotic infection, endometritis, abruptio placentae, and retained placenta (37). One center found that 14% of women with periviable PROM experienced significant maternal morbidity, including sepsis, transfusion, hemorrhage, infection, acute renal injury, and readmission (38). Although it occurs infrequently, life-threatening maternal infection may complicate expectant management of periviable PROM. Maternal sepsis is reported in approximately 1–5% of cases (36–38), and isolated maternal deaths due to infection have been reported in this setting.

Latency periods appear to be prolonged with second-trimester preterm PROM compared with PROM during later gestational ages. However, 40–50% of patients with periviable PROM will give birth within the first week and approximately 70–80% will give birth within 2–5 weeks after membrane rupture (36, 37, 39, 40).

The rate of pulmonary hypoplasia after preterm PROM before 24 weeks of gestation varies widely among reports and may be subject to variable reporting but is in the range of 2–20%. (35, 41–43). Pulmonary hypoplasia is associated with a high risk of mortality (37) but is rarely lethal when rupture of membranes occurs at or after 23–24 weeks of gestation (44), presumably because alveolar growth adequate to support postnatal development already has occurred. Early gestational age at membrane rupture and low residual amniotic fluid volume are the primary determinants of the incidence of pulmonary hypoplasia (46, 47). One retrospective cohort study demonstrated that persistent oligohydramnios in

cases of periviable PROM may correlate with lower survival rates and adverse neurodevelopmental outcomes (48). Prolonged oligohydramnios also can result in fetal deformations, including Potter-like facies (eg, low-set ears and epicanthal folds) and limb contractures or other positioning abnormalities. The reported frequency of skeletal deformations varies widely (1.5–38%) but many of these resolve with postnatal growth and physical therapy (37, 49).

Clinical Considerations and Recommendations

▶ *How is prelabor rupture of membranes diagnosed?*

Most cases of PROM can be diagnosed on the basis of the patient's history and physical examination. Examination should be performed in a manner that minimizes the risk of introducing infection. Because digital cervical examinations increase the risk of infection and add little information to results available with speculum examination, they generally should be avoided unless the patient appears to be in active labor or delivery seems imminent (50, 51). Sterile speculum examination provides an opportunity to inspect for cervicitis and prolapse of the umbilical cord or fetal parts, assess cervical dilatation and effacement, and obtain cultures as appropriate.

The diagnosis of membrane rupture typically is confirmed by conventional clinical assessment, which includes the visualization of amniotic fluid passing from the cervical canal and pooling in the vagina, a simple pH test of vaginal fluid, or arborization (ferning) of dried vaginal fluid, which is identified under microscopic evaluation. The normal pH of vaginal secretions is generally 3.8–4.5 whereas amniotic fluid usually has a pH of 7.1–7.3. False-positive test results may occur in the presence of blood or semen, alkaline antiseptics, certain lubricants, trichomonas, or bacterial vaginosis. Alternatively, false-negative test results may occur with prolonged membrane rupture and minimal residual fluid.

In equivocal cases, additional tests may aid in the diagnosis. Ultrasonographic examination of amniotic fluid volume may be a useful adjunct but is not diagnostic. Fetal fibronectin is a sensitive but nonspecific test for ruptured membranes; a negative test result suggests intact membranes, but a positive test result is not diagnostic of PROM (52). Several commercially available tests for amniotic proteins are currently on the market, with reported high sensitivity for PROM (53, 54). However, false-positive test result rates of 19–30% have been reported in patients with clinically intact membranes and symptoms of labor (55, 56). These tests are appealing in light of the requirements of regulatory bodies related to Clinical Laboratory Improvement Amendments of 1988 quality standards on the point-of-care methods of clinical assessment such as Nitrazine and fern testing. The studies evaluating these protein tests are problematic because most of them use conventional clinical assessment (pooling, ferning, pH) as controls or gold standards for the diagnosis of rupture of membranes, calling into question their utility in equivocal cases (53, 54, 57, 58). Additionally, the U.S. Food and Drug Administration released a letter to health care providers in response to adverse events related to their use, including 13 fetal deaths and multiple reports of health complications in pregnant women. The U.S. Food and Drug Administration letter reminded health care providers that these tests should not be used without other clinical assessments because of concerns about "misuse, overreliance, and inaccurate interpretation of lab test results from rupture of membranes tests used to detect rupture of membranes in pregnant women. These can lead to serious adverse events, including fetal death, infection, and other health complications in pregnant women." (59) At most these test kits should be considered selectively relative to standard methods of diagnosis.

If the diagnosis remains unclear after a full evaluation, and if the benefits of the procedure outweigh the risks, membrane rupture can be diagnosed with ultrasonographically guided transabdominal instillation of indigo carmine dye, followed by the passage of blue-dyed fluid into the vagina, which is documented by a stained tampon or pad that is removed 20–30 minutes later. It is important to note that maternal urine also will turn blue or blue-green and should not be confused with amniotic fluid. Recent shortages of indigo carmine dye have complicated the availability of this procedure, and alternatives, such as fluorescein, have been suggested (60).

▶ *What does initial management involve once prelabor rupture of membranes has been confirmed?*

In all patients with PROM, gestational age, fetal presentation, and fetal well-being (61) should be determined. The examination should evaluate for evidence of intrauterine infection and abruptio placentae. If results are not already available and if an indication for treatment is not already present, culture for group B streptococci (GBS) should be obtained when expectant management is being considered.

In patients with preterm PROM, an initial period of electronic fetal heart rate monitoring and uterine activity

monitoring offers the opportunity to identify abnormal fetal heart rate tracings and to evaluate for contractions (62). Management after confirmation of the diagnosis of PROM is dependent primarily on gestational age and is discussed in more detail in the following paragraphs. Abnormal fetal testing or evidence of intraamniotic infection are indications for delivery. Vaginal bleeding should raise concern for abruptio placentae, which should prompt consideration of delivery, with the decision based on fetal status, the amount of bleeding, and gestational age. In general, digital examination should be used sparingly and judiciously.

▶ *What is the optimal method of initial management for a patient with prelabor rupture of membranes at term?*

Gestational age and fetal position should be confirmed, and fetal heart rate monitoring should be used, to assess fetal status. Group B streptococcal prophylaxis should be given based on prior culture results or intrapartum risk factors if cultures have not been performed previously (63).

A meta-analysis of 23 randomized controlled trials (8,615 women) found that induction of labor reduced the time from rupture of membrane to birth and the rates of chorioamnionitis or endometritis, or both, and also reduced admission to the neonatal intensive care unit without increasing the rates of cesarean birth or operative vaginal delivery (6). The largest of these trials also found that women viewed induction of labor more positively than expectant management (18). Induction of labor with vaginal prostaglandins has been shown to be equally effective for labor induction compared with oxytocin but was associated with higher rates of chorioamnionitis (18). Infection also is a concern with mechanical methods of cervical ripening, such as the Foley catheter balloon, but there are insufficient data on which to base a firm recommendation for mechanical methods of cervical ripening in the setting of PROM. One trial comparing Foley catheter balloon with oxytocin to oxytocin alone in women with PROM demonstrated an increased risk with Foley balloon (8% compared with 0%, $P<.01$), though this was not seen in another similar trial (64, 65). A meta-analysis of four trials suggests that use of prophylactic antibiotics may reduce infection morbidity, but prompt induction of labor was not standard care in either study. Thus, there is insufficient evidence to justify the routine use of prophylactic antibiotics with PROM at term in the absence of an indication for GBS prophylaxis (66, 67).

Meta-analysis data indicate that patients with term PROM benefit from induction of labor compared with expectant management. Induction may help reduce infection in the woman and neonate without increasing the risk for cesarean birth (6). For women with PROM at 37 0/7 weeks of gestation or more, if spontaneous labor does not occur near the time of presentation in those who do not have contraindication to labor, labor induction should be recommended, although the choice of expectant management for a short period of time may be appropriately offered. In the cases in which expectant management is chosen, given that nearly 80% and 95% of patients start labor spontaneously within 12 hours and 24 hours respectively, a period of 12–24 hours of expectant management is reasonable as long as the clinical and fetal conditions are reassuring, and the patient is adequately counseled regarding the risks of prolonged PROM and the limitations of available data. For women who are GBS positive, administration of antibiotics for GBS prophylaxis should not be delayed while awaiting labor, and immediate induction rather than expectant management is recommended (63). During induction of labor with oxytocin, a sufficient period of adequate contractions (at least 12–18 hours) should be allowed for the latent phase of labor to progress before diagnosing failed induction and moving to cesarean birth (68–72).

▶ *When is delivery recommended for the preterm fetus in the presence of prelabor rupture of membranes?*

Abnormal results from fetal testing, clinical intraamniotic infection, and significant abruptio placentae are clear indications for delivery. Otherwise, gestational age is a primary factor when considering delivery versus expectant management (Box 1).

However, the optimal gestational age for delivery is unclear and controversial. A meta-analysis of 12 randomized controlled trials, including 3,617 women, concluded there was evidence to guide clinical practice toward expectant management regarding the risks and benefits of expectant management versus delivery in the setting of preterm PROM (73). Although there was no difference in neonatal sepsis between women who gave birth immediately compared with those managed expectantly, immediate birth had higher risks for neonatal respiratory distress, need for ventilation, neonatal mortality, neonatal intensive care unit admission, and likelihood of cesarean birth. In patients with no contraindications to continuing the pregnancy, such as abnormal results from fetal testing or intrauterine infection, expectant management likely provides benefit for the woman and newborn. Patients with preterm PROM before 34 0/7 weeks of gestation should be managed expectantly if no maternal or fetal contraindications exist (73, 74).

Box 1. Management of Prelabor Rupture of Membranes by Gestational Age Categories in Patients With Normal Antenatal Testing

Term (37 0/7 weeks of gestation or more)

- GBS prophylaxis as indicated
- Treat intraamniotic infection if present
- Proceed toward delivery (induction or cesarean as appropriate/indicated)

Late Preterm (34 0/7–36 6/7 weeks of gestation)

- Expectant management or proceed toward delivery (see text) (induction or cesarean as appropriate/indicated)
- Single-course of corticosteroids, if steroids not previously given, if proceeding with induction or delivery in no less than 24 hours and no more than 7 days, and no evidence of chorioamnionitis*
- GBS screening and prophylaxis as indicated
- Treat intraamniotic infection if present (and proceed toward delivery)

Preterm (24 0/7–33 6/7 weeks of gestation)

- Expectant management
- Antibiotics recommended to prolong latency if there are no contraindications
- Single-course of corticosteroids; insufficient evidence for or against rescue course
- Treat intraamniotic infection if present (and proceed to delivery)
- A vaginal–rectal swab for GBS culture should be obtained at the time of initial presentation and GBS prophylaxis administered as indicated.
- Magnesium sulfate for neuroprotection before anticipated delivery for pregnancies <32 0/7 weeks of gestation, if there are no contraindications†

Periviable (Less than 23–24 weeks of gestation)‡,§

- Patient counseling; consider neonatology and maternal–fetal medicine consultation
- Expectant management or induction of labor
- Antibiotics may be considered as early as 20 0/7 weeks of gestation
- GBS prophylaxis is not recommended before viability‖
- Corticosteroids are not recommended before viability‖
- Tocolysis is not recommended before viability‖
- Magnesium sulfate for neuroprotection is not recommended before viability†,‖

Abbreviation: GBS, group B streptococci.
*Do not delay delivery for steroids; steroids should not be administered for an imminent cesarean birth.
†Magnesium sulfate for neuroprotection in accordance with one of the larger studies.
‡The combination of birth weight, gestational age, and sex provide the best estimate of chances of survival and should be considered in individual cases.
§Periviable birth. Obstetric Care Consensus No. 6. American College of Obstetricians and Gynecologists. 2017;130:187–99.
‖May be considered for pregnant women as early as 23 0/7 weeks of gestation.

At 34 0/7 weeks of gestation and before 37 0/7 weeks of gestation, delivery has traditionally been recommended for all women with ruptured membranes. However, a recent large randomized trial of 1,839 women that evaluated immediate delivery (shortly after diagnosis and preferably within 24 hours) versus expectant management in patients with PROM between 34 0/7 weeks of gestation and 36 6/7 weeks of gestation suggests benefits to expectant management (75). Expectant management was according to local practice at participating centers, with 73% of patients managed in a hospital setting. There was no significant difference in the primary outcome—neonatal sepsis—or in the secondary outcome of composite neonatal morbidity. Infants in the immediate delivery group had higher rates of respiratory distress (relative risk [RR], 1.6; 95% CI, 1.1–2.3) and mechanical ventilation (RR, 1.4; 95% CI, 1.0–1.8) and spent more days in intensive care (4 days versus 2 days). However, maternal adverse outcomes, such as hemorrhage and infection, were approximately twofold higher with expectant management, although the rate of cesarean birth was lower (RR, 1.4; 95% CI, 1.2–1.7). According to the authors, the findings suggest that if expectant management is chosen, it should include careful monitoring of symptoms and signs of

maternal infection, chorioamnionitis, and antepartum hemorrhage. This monitoring may be done best in a hospital setting. An individual participant data meta-analysis of three trials showed similar results, with no difference in composite adverse neonatal outcome or neonatal sepsis when comparing expectant management with immediate delivery. In addition, immediate delivery resulted in higher rates of respiratory distress syndrome, intensive care admission, and cesarean birth (76). Either expectant management or immediate delivery in patients with PROM between 34 0/7 weeks of gestation and 36 6/7 weeks of gestation is a reasonable option, although the balance between benefit and risk, from both maternal and neonatal perspectives, should be carefully considered, and patients should be counseled clearly. Care should be individualized through shared decision making, and expectant management should not extend beyond 37 0/7 weeks of gestation. Latency antibiotics are not appropriate in this setting.

▶ *What general approaches are used in cases of preterm prelabor rupture of membranes managed expectantly?*

Expectant management of preterm PROM generally consists of hospital admission with periodic assessment for infection, abruptio placentae, umbilical cord compression, fetal well-being, and labor. There is no consensus on the optimal frequency of assessment, but an acceptable strategy would include periodic ultrasonographic monitoring of fetal growth and periodic fetal heart rate monitoring. A temperature elevation may indicate intrauterine infection. Prompt diagnosis of intraamniotic infection in preterm pregnancy requires a high index of suspicion because early signs and symptoms may be subtle. In the absence of fever, other clinical criteria, such as abdominal or fundal tenderness and maternal or fetal tachycardia, have variable sensitivity and specificity for diagnosing infection. Serial monitoring of leukocyte counts and other markers of inflammation have not been proved to be useful and are nonspecific when there is no clinical evidence of infection, especially if antenatal corticosteroids have been administered (77). Specific treatment considerations regarding tocolytics, corticosteroids, antibiotics, magnesium sulfate, and timing of delivery are discussed in detail below.

For cases of expectant management of periviable PROM, it is reasonable to evaluate and monitor such patients for a short period looking for signs of abnormalities as above. After a period of assessment in the hospital, outpatient management may be possible, as there is less concern for timely intervention for a periviable fetus. Expectant management of periviable PROM has significant maternal risks that are important to monitor carefully when choosing outpatient management. Such outpatient expectant management should involve frequent temperature evaluations, clear counseling on how to monitor for the signs and symptoms of abnormalities (eg, abdominal pain, vaginal bleeding, abnormal discharge), and frequent evaluations by a health care provider. Hospitalization often occurs around the time of viability when intervention for fetal indications is desired.

The use of 17-hydroxyprogesterone caproate to extend latency in cases of preterm PROM has been evaluated in two randomized trials. One trial involving 1,523 patients was stopped when a planned interim analysis suggested futility in continuing (78). There was no significant difference in interval to delivery or in composite adverse perinatal outcome, indicating that 17-hydroxyprogesterone caproate should not be used in patients with preterm PROM specifically for the purpose of extending latency. The second trial was stopped prematurely because of poor enrollment after 21 patients. This trial also did not find any benefit from 17-hydroxyprogesterone caproate (79). There are no data regarding the utility or safety of using vaginal progesterone in cases of preterm PROM. Given this lack of data and the theoretical risk of introducing infection with the administration of a daily vaginal drug in the presence of ruptured membranes, the use of vaginal progesterone is cases of preterm PROM is not recommended.

▶ *Should tocolytic agents be considered for patients with preterm prelabor rupture of membranes?*

The use of tocolytic agents in the setting of preterm PROM is controversial, and practice patterns among specialists vary widely (80). There are insufficient data to support or refute the use of tocolytic therapy in the setting of preterm PROM. A meta-analysis of eight trials evaluating the efficacy of tocolytic agents in preterm PROM is of limited use because women were only treated in two of the trials (81, 82) with latency antibiotics and corticosteroids, both of which have become part of standard management (83). The use of tocolytic therapy was associated with a longer latency period and a lower risk of delivery within 48 hours but also was associated with a higher risk of chorioamnionitis in pregnancies before 34 0/7 weeks of gestation. In summary, tocolytic agents may be associated with

a prolongation of pregnancy and an increased risk of chorioamnionitis without proven maternal or neonatal benefit, although their use has not been evaluated adequately with latency antibiotics and corticosteroids. In the setting of ruptured membranes with active labor, although tocolytic therapy has not been shown to prolong latency or improve neonatal outcomes, data are limited. Tocolytic agents can be considered in preterm PROM for steroid benefit to the neonate, especially at earlier gestational ages, or for maternal transport but should be used cautiously and avoided if there is evidence of infection or abruption. Tocolytic therapy is not recommended in the setting of preterm PROM between 34 0/7 weeks of gestation and 36 6/7 weeks of gestation.

▶ *Should antenatal corticosteroids be administered to patients with preterm prelabor rupture of membranes?*

The use of antenatal corticosteroids after preterm PROM has been evaluated in a number of clinical trials and has been shown to reduce neonatal mortality, respiratory distress syndrome, intraventricular hemorrhage, and necrotizing enterocolitis (84–86). Current data suggest that antenatal corticosteroids are not associated with increased risks of maternal or neonatal infection regardless of gestational age. A single course of corticosteroids is recommended for pregnant women between 24 0/7 weeks of gestation and 33 6/7 weeks of gestation and may be considered for pregnant women who are at risk of preterm birth within 7 days, including for those with ruptured membranes, as early as 23 0/7 weeks of gestation (87–89). A Cochrane meta-analysis reinforces the beneficial effect of this therapy regardless of membrane status and concludes that a single course of antenatal corticosteroids should be considered routine for all preterm deliveries (84).

Recent data indicate that administration of betamethasone in the late preterm period between 34 0/7 weeks of gestation and 36 6/7 weeks of gestation reduces respiratory morbidity in newborns (90). Although a subgroup analysis was not done, approximately 22% of study patients had preterm PROM. A single course of corticosteroids is recommended for pregnant women between 34 0/7 weeks of gestation and 36 6/7 weeks of gestation at risk of preterm birth within 7 days and who have not received a previous course of antenatal corticosteroids if proceeding with induction or delivery in no less than 24 hours and no more than 7 days (89). Late preterm administration of antenatal corticosteroids is not indicated in women diagnosed with clinical chorioamnionitis. Furthermore, delivery should not be delayed, and antenatal corticosteroids should not be used in the late preterm period (89).

There are no data that support the use of corticosteroids before viability, and administration of corticosteroids in this setting is not currently recommended. Weekly administration of corticosteroids has been associated with a reduction in birth weight and head circumference and is not recommended (91–93). Whether to administer a rescue course of corticosteroids with PROM at any gestational age is controversial, and there is insufficient evidence to make a recommendation for or against. A retrospective cohort study and a secondary analysis of a prospective cohort study suggest that corticosteroids do not increase the risk of chorioamnionitis (94, 95). If used as a rescue course, corticosteroids could be provided as early as 7 days from the prior dose, if indicated by the clinical scenario. A single repeat course of antenatal corticosteroids can be considered in women with preterm PROM who are less than 34 0/7 weeks of gestation, are at risk of preterm delivery within 7 days, and whose prior course of antenatal corticosteroids was administered more than 14 days previously. However, delivery should not be delayed to achieve a rescue course.

▶ *Should magnesium sulfate for fetal neuroprotection be administered to patients with preterm prelabor rupture of membranes?*

Randomized controlled trials have demonstrated that maternal administration of magnesium sulfate used for fetal neuroprotection when birth is anticipated before 32 0/7 weeks of gestation reduces the risk of cerebral palsy in surviving infants (RR, 0.71; 95% CI, 0.55–0.91) (96). In the largest of these trials, 85% of the women enrolled had preterm PROM between 24 weeks of gestation and 32 weeks of gestation (97). Magnesium sulfate administration for this indication does not appear to affect latency interval (98). The optimal treatment regimen for fetal neuroprotection remains unclear, and different regimens were used in different trials. With respect to the use of magnesium sulfate for fetal neuroprotection, hospitals should develop uniform and specific guidelines for their departments regarding inclusion criteria, treatment regimens, concurrent tocolytic therapy, and monitoring in accordance with one of the larger trials (97, 99, 100). Regardless of the treatment regimen used, women with preterm PROM before 32 0/7 weeks of gestation who are thought to be at risk of imminent delivery should be considered candidates for fetal neuroprotective treatment with magnesium sulfate (101).

▶ *Should antibiotics be administered to patients with preterm prelabor rupture of membranes?*

Administration of broad-spectrum antibiotics prolongs pregnancy, reduces maternal and neonatal infections, and reduces gestational age-dependent morbidity (23, 102, 103). The optimal antibiotic regimen is unclear because multiple regimens have demonstrated benefit. Based on available information, to reduce maternal and neonatal infections and gestational-age-dependent morbidity, a 7-day course of therapy of latency antibiotics with a combination of intravenous ampicillin and erythromycin followed by oral amoxicillin and erythromycin is recommended during expectant management of women with preterm PROM who are at less than 34 0/7 weeks of gestation (23, 102). The regimen used in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network trial was intravenous ampicillin (2 g every 6 hours) and erythromycin (250 mg every 6 hours) for 48 hours followed by oral amoxicillin (250 mg every 8 hours) and erythromycin base (333 mg every 8 hours) (103). Some centers have replaced the use of erythromycin with azithromycin (such as a single oral dose of azithromycin 1 g) in situations in which erythromycin is not available or not tolerated, and this substitution is a suitable alternative (104, 105). One retrospective cohort study did not find a difference in latency or secondary outcomes such as neonatal survival, sepsis, or respiratory distress between the two medications (106). Another retrospective cohort study that also compared erythromycin and azithromycin likewise found no difference in latency (107). Further, there may be cost benefits to the use of azithromycin. (108) The use of amoxicillin–clavulanic acid has been associated with increased rates of necrotizing enterocolitis and it is not recommended (23, 102). Although there are no well-studied alternative regimens for women allergic to β-lactam antibiotics, it may be reasonable to consider another agent effective against GBS to replace the β-lactam agent. The choice of agent will be influenced by the severity of the reported allergic reaction and antibiotic susceptibility results of the GBS culture, if available (63). Patients with preterm PROM should be screened for GBS. Women with preterm PROM and a viable fetus who are candidates for intrapartum GBS prophylaxis should receive intrapartum GBS prophylaxis to prevent vertical transmission regardless of earlier antibiotic treatments (63, 109). Approaches for GBS prophylaxis should emphasize appropriate principles of antibiotic stewardship.

▶ *Should preterm prelabor rupture of membranes be managed with home care?*

Two small randomized controlled trials that compared hospitalization to home care of women with preterm PROM had insufficient power to demonstrate a meaningful difference in outcome because only 11–18% of the women were eligible for antepartum home care (110, 111). Because latency is frequently brief, infection may present suddenly, and the fetus is at increased risk of umbilical cord compression, hospitalization with surveillance of the woman and her fetus is recommended once viability has been reached. The outpatient management of preterm PROM with a viable fetus has not been studied sufficiently to establish safety and, therefore, is not recommended. Periviable PROM may be considered for home care after a period of assessment in the hospital, as discussed previously.

▶ *How should a patient with preterm prelabor rupture of membranes and a cervical cerclage be treated?*

There are no complete prospective studies with which to guide the care of women with preterm PROM who have a cervical cerclage. One randomized trial that was terminated early because of concern regarding lack of power during the interim analysis failed to determine differences in outcomes between removal and retention of cervical cerclage in preterm PROM (112). Results from retrospective studies have not been consistent, but generally have found that cerclage retention for more than 24 hours after preterm PROM is associated with pregnancy prolongation (113). Because of the nonrandomized nature of the reports, it is unclear how factors, such as labor or infection, contributed to decisions for cerclage removal, which may have yielded biased results. In some, but not all studies, cerclage retention with preterm PROM has been associated with increased rates of neonatal mortality from sepsis, neonatal sepsis, respiratory distress syndrome, and maternal chorioamnionitis (113, 114). A firm recommendation regarding whether a cerclage should be removed after preterm PROM cannot be made, and either removal or retention is reasonable. Regardless, if a cerclage remains in place with preterm PROM, prolonged antibiotic prophylaxis beyond 7 days is not recommended.

▶ *What is the optimal management of a patient with preterm prelabor rupture of membranes and herpes simplex virus infection or human immunodeficiency virus?*

Neonatal herpes simplex virus (HSV) infection usually results from maternal–fetal transmission during delivery.

The risk of vertical transmission with delivery in patients with subclinical shedding at the time of labor as a result of having acquired genital HSV in the third trimester is reported to be between 30% and 50%, compared with only 3% in cases of maternal symptomatic reactivation of HSV at the time of labor (115). The literature regarding expectant management of preterm PROM with active maternal HSV infection is limited to small case series and case reports (116, 117). All patients were treated with acyclovir, and cesarean birth was performed if lesions were present at the time of delivery. No cases of vertical transmission were reported.

There is no consensus on the gestational age at which the risk of prematurity in women with preterm PROM outweighs the potential risk of neonatal HSV infection. In the setting of PROM with recurrent active infection, expectant management is recommended before 34 0/7 weeks of gestation. Antiviral therapy should be initiated when expectant management is elected, and corticosteroids, antibiotics, and magnesium sulfate for neuroprotection should be provided as clinically indicated. The decision to use corticosteroids should be based on the balance between the risk of pulmonary immaturity and the risk of neonatal herpes. If active disease or prodromal symptoms are present at the onset of labor or when delivery is indicated, cesarean birth is recommended.

Optimal management of preterm PROM in the setting of primary HSV infection is less clear because of the increased risk of vertical transmission. Antiviral therapy is advocated, and if lesions are present at the time of delivery, cesarean birth is recommended. In general, cesarean birth is not recommended for women with a history of HSV infection but no active genital lesions or prodromal symptoms during labor (118). However, for women with a primary or nonprimary first-episode genital HSV infection during the third trimester of pregnancy, cesarean birth may be offered due to the possibility of prolonged viral shedding (119, 120).

The optimal management of the patient with human immunodeficiency virus (HIV) and preterm PROM also is uncertain because there are no adequate data from patients with prolonged rupture of membranes. Early observations showed that the duration of the interval between membrane rupture and labor correlated with risk of transmission to the newborn (121), but current data suggest that the duration the interval between membrane rupture and labor is not correlated with risk of vertical transmission in patients who receive highly active antiretroviral therapy, have a low viral load, and receive antepartum and intrapartum zidovudine (122, 123). Also, a series of 10 patients with preterm PROM who were managed expectantly while receiving antiretroviral therapy had no cases of HIV transmission to the newborn despite viral loads as high as 23,000 copies per mL. The latent periods ranged from 4 hours to 4 days in this series, and all had a cesarean birth (124).

The management of patients with HIV infection who have preterm PROM should be individualized with consideration of factors including gestational age, current antiretroviral regimen, and viral load. In cases involving a very early gestational age in which the patient is being treated with antiretroviral medications and the viral load is low, a period of expectant management is likely to be appropriate. In all cases, the patient should be managed in consultation with a physician with expertise in management of HIV in pregnancy. Furthermore, standard antepartum and intrapartum treatment guidelines should be followed, and management choices should be fully discussed with the patient (125).

▶ *How does care differ for patients with prelabor rupture of membranes that occurs before neonatal viability?*

Women presenting with PROM before neonatal viability should be counseled regarding the risks and benefits of expectant management versus immediate delivery. Counseling should include a realistic appraisal of neonatal outcomes (87). Immediate delivery (termination of pregnancy by induction of labor or dilation and evacuation) and expectant management should be offered. Physicians should provide patients with the most current and accurate information possible (87).

If the patient opts for expectant management and is clinically stable with no evidence of infection after evaluation, outpatient management and surveillance can be considered. Precautions should be reviewed with the patient, and the patient should come to the hospital if she develops symptoms of infection, labor, or abruptio placentae. Patients should monitor body temperatures. Typically, women with periviable PROM who have been cared for as outpatients are admitted to the hospital once the pregnancy has reached viability and the patient would accept interventions for delivery on behalf of the fetus.

Administration of antenatal corticosteroids and latency antibiotics for fetal maturation upon reaching viability is appropriate given that early delivery remains likely. Multiple ultrasonographic methods (such as thoracic measurements and ratios, flow velocities in pulmonary vessels, and three-dimensional estimations of lung volume) have been studied to evaluate pulmonary development in the antepartum period, but all are

of limited accuracy and cannot be considered sufficiently reliable for clinical management (47). Because most studies of antibiotic prophylaxis with preterm PROM enrolled patients only after 24 0/7 weeks of gestation, there are no adequate data to assess the risks and benefits of such treatment at earlier (periviable) gestational ages. However, it is reasonable to consider a course of broad-spectrum antibiotics for pregnancy prolongation in patients with periviable PROM who choose expectant management (87). There is no evidence to support the use of tocolytic agents in the setting of periviable PROM, and in this setting, it is not recommended.

▶ ***What is the expected outcome of prelabor rupture of membranes after second-trimester amniocentesis?***

In studies of women undergoing second-trimester amniocentesis for prenatal diagnosis of genetic disorders, the risk of PROM is less than 1% (126–128). In contrast to patients with spontaneous PROM in the second trimester, reaccumulation of normal amniotic fluid volume and favorable outcomes are expected. In one series of 11 patients with periviable PROM after genetic amniocentesis, there was one periviable pregnancy loss, reaccumulation of normal amniotic fluid occurred within 1 month in 72% of patients, and the perinatal survival rate was 91% (126).

After appropriate counseling, patients with periviable PROM after genetic amniocentesis typically are managed expectantly as outpatients. Precautions regarding symptoms of chorioamnionitis and miscarriage should be given. Regular follow-up visits with ultrasonographic examinations to assess amniotic fluid volume are recommended.

▶ ***How should a patient with a history of preterm prelabor of membranes be managed in future pregnancies?***

Patients with prior preterm PROM have an increased risk of recurrent PROM and preterm birth, and a detailed medical and obstetric history should be taken when patients have a history suggestive of these complications. However, there are few studies that examine interventions to prevent recurrent PROM. Women with prior preterm births should be counseled that short interpregnancy intervals, particularly those shorter than 6 months, may differentially and negatively affect subsequent pregnancy outcomes (129).

Patients with a history of preterm PROM were included in studies of progesterone supplementation for preterm birth recurrence reduction, but most studies did not report the specific proportion of women with PROM in the study group or separately analyze results in those patients (130, 131). However, given the potential benefit of progesterone therapy, women with a single gestation and a prior spontaneous preterm birth (due to either labor with intact membranes or preterm PROM) should be offered progesterone supplementation as clinically indicated to reduce the risk of recurrent spontaneous preterm birth.

Although vaginal ultrasonographic measurement of the cervix is a safe and reliable means of evaluating the risk of preterm birth related to cervical length, there have been no well-designed trials of cervical surveillance in women with a history of preterm PROM. Similar to the progesterone studies, trials that evaluated cervical assessment, vaginal progesterone, and cerclage included women with prior preterm PROM, but their specific data were not reported (132, 133). Thus, as with women with spontaneous preterm births, consideration can be given to transvaginal cervical length screening. Cerclage placement is associated with significant decreases in preterm birth outcomes, offers perinatal benefits, and may be considered in women with the following combination of history and ultrasonographic findings: a current singleton pregnancy, prior spontaneous preterm birth at less than 34 weeks of gestation, and short cervical length (less than 25 mm) before 24 weeks of gestation (134). There are no data on which to base a recommendation regarding the optimal gestational age for initiating surveillance or frequency of monitoring.

Summary of Recommendations and Conclusions

The following recommendations are based on good and consistent scientific evidence (Level A):

- ▶ Patients with preterm PROM before 34 0/7 weeks of gestation should be managed expectantly if no maternal or fetal contraindications exist.
- ▶ A single course of corticosteroids is recommended for pregnant women between 24 0/7 weeks of gestation and 33 6/7 weeks of gestation and may be considered for pregnant women who are at risk of preterm birth within 7 days, including for those with ruptured membranes, as early as 23 0/7 weeks of gestation.
- ▶ A single course of corticosteroids is recommended for pregnant women between 34 0/7 weeks of gestation and 36 6/7 weeks of gestation at risk of preterm birth within 7 days and who have not received a previous course of antenatal corticosteroids if proceeding with induction or delivery in no less than 24 hours and no more than 7 days.
- ▶ Women with preterm PROM before 32 0/7 weeks of gestation who are thought to be at risk of imminent

delivery should be considered candidates for fetal neuroprotective treatment with magnesium sulfate.

- To reduce maternal and neonatal infections and gestational-age-dependent morbidity, a 7-day course of therapy of latency antibiotics with a combination of intravenous ampicillin and erythromycin followed by oral amoxicillin and erythromycin is recommended during expectant management of women with preterm PROM who are at less than 34 0/7 weeks of gestation. Some centers have replaced the use of erythromycin with azithromycin in situations in which erythromycin is not available or not tolerated, and this substitution is a suitable alternative.
- Women with preterm PROM and a viable fetus who are candidates for intrapartum GBS prophylaxis should receive intrapartum GBS prophylaxis to prevent vertical transmission regardless of earlier antibiotic treatments.

The following recommendations and conclusions are based on limited and inconsistent scientific evidence (Level B):

- For women with PROM at 37 0/7 weeks of gestation or more, if spontaneous labor does not occur near the time of presentation in those who do not have contraindication to labor, labor induction should be recommended, although the choice of expectant management for a short period of time may be appropriately offered.
- Either expectant management or immediate delivery in patients with PROM between 34 0/7 weeks of gestation and 36 6/7 weeks of gestation is a reasonable option, although the balance between benefit and risk, from both maternal and neonatal perspectives, should be carefully considered, and patients should be counseled clearly. Care should be individualized through shared decision making, and expectant management should not extend beyond 37 0/7 weeks of gestation. Latency antibiotics are not appropriate in this setting.
- In the setting of ruptured membranes with active labor, although tocolytic therapy has not been shown to prolong latency or improve neonatal outcomes, data are limited. Tocolytic agents can be considered in preterm PROM for steroid benefit to the neonate, especially at earlier gestational ages, or for maternal transport but should be used cautiously and avoided if there is evidence of infection or abruption. Tocolytic therapy is not recommended in the setting of preterm PROM between 34 0/7 weeks of gestation and 36 6/7 weeks of gestation.
- Given the potential benefit of progesterone therapy, women with a single gestation and a prior spontaneous preterm birth (due to either labor with intact membranes or preterm PROM) should be offered progesterone supplementation as clinically indicated to reduce the risk of recurrent spontaneous preterm birth.

The following conclusions are based primarily on consensus and expert opinion (Level C):

- The diagnosis of membrane rupture typically is confirmed by conventional clinical assessment, which includes the visualization of amniotic fluid passing from the cervical canal and pooling in the vagina, a simple pH test of vaginal fluid, or arborization (fern) of dried vaginal fluid, which is identified under microscopic evaluation.
- The outpatient management of preterm PROM with a viable fetus has not been studied sufficiently to establish safety and, therefore, is not recommended. Periviable PROM may be considered for home care after a period of assessment in the hospital.

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The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 2000 and March 2019. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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